**<http://www.cvphysiology.com/Blood%20Pressure/BP004.htm>**

**Vascular Compliance**

The ability of a blood vessel wall to expand and contract passively with changes in pressure is an important function of large arteries and veins. This ability of a vessel to distend and increase volume with increasing **transmural pressure**(inside minus outside pressure) is quantified as vessel compliance (C), which is the change in volume (ΔV) divided by the change in pressure (ΔP).



The volume-pressure relationship (i.e., compliance) for an artery and vein are depicted in Figure 1. Two important characteristics stand out. First, the slope is not linear because the blood vessel wall is a heterogeneous tissue. Therefore, compliance decreases at higher pressures and volumes (i.e., vessels become "stiffer" at higher pressures and volumes). Second, at lower pressures, the compliance of a vein is about 10 to 20-times greater than an artery. Therefore, veins can accommodate a large changes in [blood volume](http://www.cvphysiology.com/Blood%20Pressure/BP025.htm) with only a small change in pressure. However, at higher pressures and volumes, venous compliance (slope of compliance curve) becomes similar to arterial compliance. This makes veins suitable for use as arterial by-pass grafts.



There is no single compliance curve for a blood vessel. For example, vascular smooth muscle contraction, which increases[vascular tone](http://www.cvphysiology.com/Blood%20Flow/BF002.htm), reduces vascular compliance (Figure 2); conversely, smooth muscle relaxation increases compliance. This is particularly important in the venous vasculature for the regulation of [venous pressure](http://www.cvphysiology.com/Blood%20Pressure/BP020.htm) and [cardiac preload.](http://www.cvphysiology.com/Cardiac%20Function/CF007.htm) Contraction of smooth muscle in arteries reduces their compliance, thereby decreasing arterial blood volume and increasing arterial blood pressure.  Another example of changing compliance is reduced aortic compliance with age or disease (e.g., arteriosclerosis). When this occurs, there is a qualitatively similar downward shift in the compliance curves as shown in Figure 2 for veins. Such compliance changes in the aorta are responsible in large part for the increase in aortic [pulse pressure](http://www.cvphysiology.com/Blood%20Pressure/BP003.htm) with advanced age or arterial disease.

Compliance, as depicted in Figure 1, represents static compliance that is generated by expanding a vessel by a known volume and measuring the change in pressure at steady-state. However, prior to achieving a steady-state pressure, the pressure will actually be initially higher than the steady-state pressure when the volume of fluid is first added. The transient fall in pressure at a constant volume is called [stress relaxation](http://www.cvphysiology.com/Blood%20Pressure/BP027.htm) and is related to the viscous properties of biological tissues. If the initial pressure increase is used instead of the steady-state pressure when the vessel volume is suddenly increased, the compliance will be lower (i.e., the vessel will appear more stiff). Therefore, the compliance of the vessel is also dependent upon the rate by which the change in volume occurs – i.e., there is a [dynamic component to compliance](http://www.cvphysiology.com/Blood%20Pressure/BP027.htm).

[**http://college.holycross.edu/faculty/kprestwi/physiology/phys\_class\_notes/Phys\_Lect5\_Circulation/Phys\_Lect5\_Circulation\_PDF/Phys06\_03\_Vasculature.pdf**](http://college.holycross.edu/faculty/kprestwi/physiology/phys_class_notes/Phys_Lect5_Circulation/Phys_Lect5_Circulation_PDF/Phys06_03_Vasculature.pdf)

## Starling's hypothesis

*n.*

The hypothesis that fluid filtration through capillary membranes is dependent on the balance between the pressure the blood places onthe membranes and the osmotic pressure of the membranes.

The American Heritage® Medical Dictionary Copyright © 2007, 2004 by Houghton Mifflin Company. Published by [**Houghton Mifflin Company**](http://medical-dictionary.thefreedictionary.com/_/gr.aspx?url=-eref-trade.hmco.com/). All rights reserved.

## Starling's hypothesis, law

the law relating to the passage of fluid out of a capillary depending on the hydrostatic and osmotic pressures of the blood and thesame pressures of tissue fluid, the net effect of the opposing pressures determining the direction and rate of flow.

Saunders Comprehensive Veterinary Dictionary, 3 ed. © 2007 Elsevier, Inc. All rights reserved

# Influence of peripheral arterial disease on capillary pressure in the foot[☆](http://www.jvascsurg.org/article/S0741-5214%2803%2900603-7/abstract#article-footnote-☆)

Jurgen C de Graaff, MD, PhD

,

Dirk Th Ubbink, MD, PhD

,

Joost A van der Spruit, MD

,

Sjoerd M Lagarde, MD

,

Michael J.H.M Jacobs, MD, PhD

Open Archive

DOI: [http://dx.doi.org/10.1016/S0741-5214(03)00603-7](http://dx.doi.org/10.1016/S0741-5214%2803%2900603-7)

## [showArticle Info](http://www.jvascsurg.org/article/S0741-5214%2803%2900603-7/abstract)

* [**Abstract**](http://www.jvascsurg.org/article/S0741-5214%2803%2900603-7/abstract)
* [Full Text](http://www.jvascsurg.org/article/S0741-5214%2803%2900603-7/fulltext)
* [Images](http://www.jvascsurg.org/action/showFullTextImages?pii=S0741-5214%2803%2900603-7)
* [References](http://www.jvascsurg.org/article/S0741-5214%2803%2900603-7/references)

## Abstract

### Background

Capillary perfusion and transmural pressure are delicately regulated by microvascular constriction mechanisms, which are activated upon a change in posture. Capillary flow is known to be disturbed in patients with severe peripheral arterial disease. To date, however, the influence of this disease on capillary pressure is unknown.

### Methods

Capillary pressure in the nail fold of the hallux, ankle, and toe blood pressures were measured in the sitting and supine positions in 8 patients with intermittent claudication (F2), in 7 patients with rest pain and/or ischemic ulcers (F3-4), and in 12 age-matched healthy controls (F0). Red blood cell velocity, laser Doppler flux, and continuous blood pressure of the second toe were measured simultaneously. Toe, ankle, and brachial pressure were measured after the experiment in both positions.

### Results

Capillary pressure did not increase significantly with increasing disease severity (F0, F2, and F3-4) in supine (P = .37; medians, 17, 21, and 14 mm Hg, respectively) and sitting (P = .96; medians, 59, 60, and 60 mg Hg, respectively) positions, whereas toe systolic pressure did, both in supine (P < .001; medians, 91, 49, and 14 mm Hg, respectively) and sitting (140, 104, and 64 mm Hg, respectively) positions. Nutritive skin perfusion (red blood cell velocity) decreased with increasing disease severity (F0, F2, and F3-4) while supine (P = .005; medians, .19, .20, and .04 mm/s, respectively) and while sitting (P = .06; medians, .22, .15, and .04 mm/s, respectively).

### Conclusions

An increase in orthostatic pressure increases both toe and capillary pressures. Arterial insufficiency of the leg seems to leave the capillary pressure unscathed. Apparently, arteriolar vasodilation compensates for the lower arterial pressure in both positions, even in patients with rest pain and low nutritive perfusion.

[☆](http://www.jvascsurg.org/article/S0741-5214%2803%2900603-7/abstract#back-article-footnote-☆)Supported by grant 96-113 from The Netherlands Heart Foundation.

[☆](http://www.jvascsurg.org/article/S0741-5214%2803%2900603-7/abstract#back-article-footnote-☆)Competition of interest: none.

© 2003 The Society for Vascular Surgery and The American Association for Vascular Surgery. Published by Elsevier Inc.

**http://www.ncbi.nlm.nih.gov/books/NBK54123/**



### FIGURE 3

The revised Starling principle. (Left) In the classic Starling model, fluid flux across permeability pathways is driven by the difference in hydrostatic pressure (Δ*P*) and colloid osmotic pressure (ΔΠ), between the capillary lumen (c) and the interstitial compartment (i), as in [Figure 2](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig2/?report=objectonly). (Right) In the revised Starling model, fluid flux is driven by the pressure differences between the capillary lumen and the relatively protein-free, volume-restricted space between endothelial cells (intercellular cleft). In this case, the principle barrier to fluid permeability is the glycocalyx network that restricts fluid entry to the intercellular space.



## Regulation of Endothelial Barrier Function.

[Show details](http://www.ncbi.nlm.nih.gov/books/NBK54123/__NBK54123_dtls__)

* [Contents](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/)

Haut du formulaire

Search term



 

Bas du formulaire

[< Prev](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/ch1/)[Next >](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/ch3/)

# Chapter 2Structure and Function of Exchange Microvessels

[Go to:](http://www.ncbi.nlm.nih.gov/books/NBK54123/)

## MICROVASCULAR BLOOD–TISSUE EXCHANGE

The circulatory system delivers oxygen and nutrients to tissues and removes CO2 and other metabolic wastes from tissues, a process conducted at two levels: the macrovasculature and microvasculature [[262](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b262)]. The macrovasculature is composed of arteries and veins, large capacity vessels responsible for transporting blood rapidly toward or away from organs. The microvasculature consists of three types of small vessels: arterioles, capillaries, and venules. These microvessels form a network that regulates local blood perfusion and conducts blood–tissue exchange [[262](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b262), [415](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b415)] ([Figure 1](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig1/?report=objectonly)).



#### [FIGURE 1](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig1/?report=objectonly)

Architecture of a microvascular bed. Blood flow to capillaries is supplied by arterioles, resistance vessels that are surrounded by vascular smooth muscle. Blood entering the capillary bed is controlled by contraction or dilation of arterioles and precapillary [(more...)](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig1/?report=objectonly)

Arterioles are resistance microvessels enveloped by vascular smooth muscle that via contraction or relaxation controls the vessel caliber and thus the volume of blood flow. When arterioles dilate, downstream blood flow is increased. When arterioles contract, blood flow to the downstream microvascular bed (capillaries) is reduced or may be shunted through metarterioles directly to the venous circulation, bypassing the capillary bed. Humoral factors (such as vasopressin and angiotensin) or metabolic factors (such as tissue pH and nitric oxide) can cause vasoconstriction or vasodilation thereby controlling the level of perfusion to meet the metabolic demand of tissues.

While arterioles are a key determinant of local blood flow, which controls the volume for exchange, the exchange process mainly occurs downstream of arterioles in capillaries and postcapillary venules [[262](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b262)]. The walls of these microvessels are thin, mainly composed of endothelial cells and lack vasomotor function due to the absence of continuous smooth muscle. Although other types of cells, such as pericytes, fibroblasts, and smooth muscle cells, are found in the outer wall of capillaries and postcapillary venules, they vary in composition, extent, and function depending upon anatomical location within the microvasculature, as well as organ or tissue type. In the microvasculature of most organs, including the lungs, heart, skeletal muscle, and gut, the walls of capillaries are formed by a continuous (without fenestration) layer of endothelial cells that closely connect to each other, permitting water and solutes <3 nm in molecular radius to pass through freely and restricting the passage of larger molecules. Molecules of >3 nm can move across the endothelium partially and selectively [[262](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b262)]. The relatively high basal permeability and the large surface area of these microvessels provide an efficient means for blood–tissue exchange.

In short, the conventional concept regarding fluid and solute exchange in the microcirculation is that arterioles do not participate in the exchange process. Only capillaries and postcapillary venules are considered to be exchange microvessels, where capillaries serve as the major site for fluid passage, and postcapillary venules are the primary location for leukocyte diapedesis and plasma protein leakage, processes often seen under stimulated or inflammatory conditions.

[Go to:](http://www.ncbi.nlm.nih.gov/books/NBK54123/)

## PHYSICAL FORCES GOVERNING FLUID FILTRATION

In 1896, Ernest H. Starling stated [[428](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b428)], “whereas capillary pressure determines transudation, the osmotic pressure of the proteids of the serum determines absorption. Moreover, if we leave the fric-tional resistance of the capillary wall to the passage of fluid through it out of account, the osmotic attraction of the serum for the extravascular fluid will be proportional to the force expended in the production of this latter, so that, at any given time, there must be a balance between the hydrostatic pressure of the blood in the capillaries and the osmotic attraction of the blood for the surrounding fluids.”

Starling proposed that fluid movement across the capillary wall is driven by the difference in the hydrostatic pressure (Δ*P*) generated by the circulating blood fluid and the colloid osmotic pressure (ΔΠ) exerted by plasma proteins within the vascular lumen relative to that of the interstitial (extravascular) compartment ([Figure 2](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig2/?report=objectonly)). This theory was verified and further established by Eugene Landis in 1932 [[251](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b251), [252](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b252)], leading to the classic Starling–Landis equation:



1

where *J*v is the fluid volume filtration rate (mL/s), *A* is endothelial surface area (cm2), *P*c is blood fluid hydrostatic pressure inside the capillary (mm Hg), *P*i is hydrostatic pressure in the interstitium outside the capillary (mm Hg), Πp is colloid osmotic (oncotic) pressure of the plasma (mm Hg), and Πi is interstitial oncotic pressure (mm Hg). In addition,*L*p is the hydraulic conductivity, a coefficient describing the permeation property of capillary wall to water (cm/s/mm Hg), and σ is the reflection coefficient, which describes the molecular sieving property of the capillary wall (σ = 0 means completely permeable without reflection back; σ = 1 means completely impermeable with 100% reflection back). For example, the reflection coefficient of albumin is ∼0.7, meaning that it can cross the capillary wall but its passage is highly restricted. The Starling principle is commonly summarized as:



2

where Δ*P* = *P*c − *P*i, determined by capillary blood pressure (ranging 12–45 mm Hg) relative to the tissue interstitium, and ΔΠ = Πp − Πi, dictated by the difference in concentration of plasmaproteins inside and outside of a capillary. The major source of microvessel transmural oncotic pressure is albumin, with lesser contributions from globulins. Under normal physiological conditions, there is virtually no protein present in the tissue interstitial compartment, while in the blood, the concentration of albumin is 4.5 g/dL and for globulins is 2.5 g/dL. Hence, there is inward-directed microvascular oncotic pressure across the microvessel wall (25–28 mm Hg), as well as outward-directed hydrostatic pressure (12–45 mm Hg) [[264](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b264), [374](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b374)].



#### [FIGURE 2](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig2/?report=objectonly)

Hydrodynamic forces governing fluid flow across the microvessel wall (The Starling–Landis model). Fluid movement across capillary walls (flux per unit area; *J*v/*A*) is driven by Starling forces: the difference in hydrostatic pressure (Δ[(more...)](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig2/?report=objectonly" \t "object)

In the microvasculature under dynamic conditions, the hydrostatic pressure is higher at the arteriolar end (35–45 mm Hg) than that at the venular end (12–15 mm Hg) ([Figure 2](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig2/?report=objectonly)) [[264](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b264)]. Thus, upstream of the capillary network near the arterioles, Δ*P* > ΔΠ, driving fluid filtration out of the vessels into the tissue, while at the downstream of capillaries near the venular end, Δ*P* < ΔΠ, favoring absorption of fluid back into the vessel lumen ([Figure 2](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig2/?report=objectonly)). In this way, vital nutrients are filtered into the tissues, and byproducts of metabolism are drawn out of the tissues into the venous blood. Under normal physiological conditions, ΔΠ also decreases modestly toward the distal end of the microvascular bed, as plasma proteins are filtered into the interstitial space. However, under pathophysiological conditions, where *L*p is increased, large quantities of proteins accumulate in the interstitial space producing an osmotic/oncotic “sucking” force that drives fluid flow into the tissue and prevents fluid absorption back into the circulation (edema).

Recently, the conventional filtration–absorption model has been challenged by many experiments indicating the absence or transient nature of reabsorption. In particular, Levick and Michel [[34](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b34)] demonstrated that tissue fluid balance could not be maintained by downstream reabsorption in skin more than 10 cm below heart level where venous capillary pressure exceeds oncotic pressure. This is supported by the finding that in the cutaneous venous capillaries or venules at heart level, the interstitial hydrostatic pressure is negative (*P*i = 2 mm Hg) and the interstitial oncotic pressure is relatively high (Πi = 15.7 mm Hg) so that Δ*P* > ΔΠ, and hence according to this model, no reabsorption can occur.

Most recently, it has been proposed that the Starling principle should be revised to account for the glycocalyx as the principle permeability barrier [[204](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b204), [304](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b304)]. Based on physiological evidence produced by Adamson et al. [[7](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b7), [97](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b97)], Curry, Levick and Michel [[96](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b96), [264](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b264)] proposed a modified version of the Starling principle by revising [Eq. (1)](http://www.ncbi.nlm.nih.gov/books/NBK54123/#e1) to the following:



3

Note the major difference between [Eq. (1)](http://www.ncbi.nlm.nih.gov/books/NBK54123/#e1) and [Eq. (3)](http://www.ncbi.nlm.nih.gov/books/NBK54123/#e1) is that Πi is replaced with Πg, the oncotic pressure of the thin layer of interstitial fluid residing between endothelial cells (the intercellular cleft) immediately beneath the glycocalyx network that covers the endothelial surface. In this model, the glycocalyx forms a semipermeable barrier that separates the microvessel luminal compartment from the fluid residing within the [albumin-restricted] space between adjacent endothelial cells ([Figure 3](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig3/?report=objectonly)). Thus, ΔΠ now represents the oncotic pressure difference across the glycocalyx, rather than across the endothelium.



#### [FIGURE 3](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig3/?report=objectonly)

The revised Starling principle. (Left) In the classic Starling model, fluid flux across permeability pathways is driven by the difference in hydrostatic pressure (Δ*P*) and colloid osmotic pressure (ΔΠ), between the capillary lumen [(more...)](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig3/?report=objectonly)

The glycocalyx is a network of glycoproteins and polysaccharides that protects the luminal surface of microvascular endothelium ([Figure 4](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig4/?report=objectonly)) [[38](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b38), [438](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b438), [461](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b461)]. The thickness of the endothelial glycocalyx varies by tissue type, from 20 nm to 3000 nm. The glycocalyx is heavily negatively charged and functions to repel blood cells and selectively attracts or repels plasma components according to electrostatic charge. The major components of the endothelial glycocalyx are proteoglycans and proteins with extensive branches of glycosaminoglycans (GAGs) that form the essential structure of the glycocalyx ([Figure 4](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig4/?report=objectonly)) [[264](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b264), [301](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b301)]. Proteoglycans include syndecans with transmembrane protein domains and glypicans with glycosylphosphatidylinositol groups that anchor the glycocalyx to endothelium, as well as soluble proteoglycans (perlecan, versican, decorin, biglycan, and mimecan) secreted by the endothelium and embedded within the glycocalyx network [[376](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b376), [438](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b438)]. Each proteoglycan core protein may be linked to one or more GAG sidechain composed of heparin sulfate, chondroitin sulfate, dermatan sulfate, or keratan sulfate chains. All are linear polymers of disaccharide subunits: sulfated or unsulfated glucuronic or galacturonic acid, linked to *N*-acetyl-glucosamine or *N*-acetyl-galactosamine. The majority of GAG sidechains for proteoglycans in the endothelial glycocalyx are heparin sulfate, which is 4 times more abundant than chondroitin sulfate. Hyaluronin (hyaluronic acid (HA)) is another type GAG chain polymer that is integral to the endothelial glycocalyx, but is not directly attached to a proteoglycan. HA chains may be either unattached or attached to membrane proteins on the surface of endothelium, contributing to the polysaccharide mesh of the glycocalyx. Integral membrane glycoproteins, including adhesion molecules (selectins, integrins, intercellular adhesion molecules (ICAMs), or platelet/endothelial adhesion molecule 1 (PECAM-1)) provide further structural support for attachment of the glycocalyx the endothelium. Surface expression of these adhesion molecules is dynamically regulated, altering the glycocalyx structure by providing more or less points of attachment to the endothelium and modifying endothelial barrier function. In addition, various soluble proteins secreted by the endothelium or deposited from the blood serum (e.g., albumin) become embedded in the glycocalyx. In some cases, protein deposition can alter microvascular permeability by modifying the charge composition of the glycocalyx. Albumin and other proteins binding further impedes transmural fluid flow by effectively increasing the transmural oncotic pressure above that predicted by the Starling equation, thereby reducing capillary fluid filtration. Consistent with this description, removal of the glycocalyx by enzymatic cleavage increases *L*p.



#### [FIGURE 4](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig4/?report=objectonly)

Structural components of the endothelial glycocalyx. The endothelial glycocalyx is an extensive network of proteins and polysaccharide polymers that cover the apical (luminal) surface of microvascular endothelium and contribute to barrier function. The [(more...)](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig4/?report=objectonly)

The relative presence and importance of the glycocalyx for microvascular fluid exchange varies according to tissue type [[264](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b264), [301](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b301)]. It is speculated that glycocalyx plays a particularly important role in restricting transmural fluid flow in discontinuous or fenestrated microvasculature, as in the liver or kidney. Extensively branching glycocalyx can extend into gaps and fenestrations, and thereby limit fluid flow through these openings in the microvessel wall. Curry and Adamson have also shown, through three-dimensional modeling of the endothelial cell–cell junctional ultrastructure in rat mesenteric microvessels, that the 100–300 μm pores that occur periodically between junction proteins create permeability pathways for fluid and solute flux that are too large to account for theapparent reflection coefficient of albumin (σ ≈ 0.9) [[97](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b97)]. Therefore, these investigators hypothesize that the glycocalyx is the principle permeability barrier to proteins across the endothelium in most vascular beds. The glycocalyx may also serve as a sensor of fluid flow in microvascular endothelium [[301](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b301)]. The glycocalyx is modified by shear stress and triggers production of nitric oxide, a potent intracellular signaling molecule that modifies endothelial permeability and barrier function.

[Go to:](http://www.ncbi.nlm.nih.gov/books/NBK54123/)

## SOLUTE TRANSPORT ACROSS THE MICROVASCULAR WALL

### Convection vs. Diffusion

Thus far, we have discussed the relevant hydrodynamic forces for fluid flux across the microvessel wall during filtration. For solutes (e.g., plasma proteins, salts), two major physical forces drive their movement across a semipermeable membrane: convective flow and solute diffusion (discussed below). For any given set of conditions, either one or the other mechanism will prevail. In most cases in the microvasculature, fluid movement (flux) occurs as a convective flow, the movement of a volume of fluid as a cohesive unit in which bulk fluid flow is driven by hydrostatic pressure, as described by the Starling–Landis relationship [[Eq. (1)](http://www.ncbi.nlm.nih.gov/books/NBK54123/#e1)]. The hydrostatic pressure gradient (Δ*P*) is opposed by the oncotic pressure gradient (ΔΠ), which decreases fluid flow (*J*v) via filtration.

As bulk fluid flow proceeds, plasma proteins (and other solutes) are dragged along in the moving current, a phenomenon called solvent drag [[22](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b22)]. Bulk flow of fluid through a pore is capable of moving dissolved solute particles, irrespective of the solute concentration gradient that otherwise drives solute flux. Hence, any dissolved particle present in the blood may be moved across the endothelium by solvent drag, provided that the size of the permeability pathway is sufficient to permit passage of the solute, determined by the solute reflection coefficient (σ). As fluid filtration proceeds along the length of the microvascular bed, fluid and albumin are exuded into the tissue interstitial compartment. This leads to a condition where Δ*P* is increasingly diminished across the length of the microvessel ([Figure 2](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig2/?report=objectonly)). At the same time, accumulation of plasma proteins in the interstitium via solute drag increases Πi and decreases the oncotic driving force for fluid reabsorption (−ΔΠ). According to the Starling–Landis model, the conditions present in real biological situations in microvessels dictate that fluid filtration will persist and that reabsorption is not possible. Clearly, this is not the case, in that under normal physiological conditions, organs and tissues are not maintained in a chronically swollen state. In fact, the measured *P*i in vivo is typically negative, and yet fluid and solute reabsorption still occurs in the distal microvasculature. The glycocalyx model and the modified Starling–Landis model accounts for the absence of fluid efflux in the distal microvasculature in real tissues, however, other forces are necessary to drive reabsorption of fluid and solutes [[97](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b97)]. This discrepancy was noted by Starling, who indicated that under conditions of decreased capillary fluid pressure, osmotic forces can temporarily drive reabsorption of salts and water into the blood. When fluid flow becomes sufficiently slowed, as occurs in the distal microvessels, then the prevailing flux mechanism becomes solute diffusion, which then drives fluid reabsorption. Pappenheimer [[337](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b337)] suggested that under conditions where the net thermodynamic force driving fluid flow (Δ*P* − ΔΠ) is near 0, there will be insufficient energy for laminar shear forces to overcome fluid viscosity, and hence bulk fluid flow will not occur. Under these conditions, solutes can diffuse passively across the endothelium along their concentration gradients. Diffusion across a semipermeable membrane is described by Fick's law:



4

where diffusive flux of a solute (*J*s) is driven by the solute concentration gradient (Δ*C*), according to the diffusion coefficient (*D*) and the surface area of the exchange membrane (*A*), across the distance (Δ*x*) over which the concentration gradient is dissipated. *D* is determined by the barrier permeability (*P*s) to a specific solute, and is inversely proportional to the square root of the solute's molecular mass. This relationship is alternatively expressed as



5

Osmotically active particles (e.g., sugars, salts, amino acids, proteins) attract water, and therefore any net flux of these kinds of solutes across the endothelium is accompanied by a proportional flux of water. This is based on the osmotic pressure, which is proportional to the average thermal kinetic energy of solutes in solution [[176](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b176)]. In a two-compartment system of dilute salt solutions (i.e., physiological concentrations) separated by a semipermeable membrane (freely permeable to water, and not to solutes), the osmotic pressure (*P*osm) exerted by the salt particles in each compartment is proportional to the salt concentration and the absolute temperature (Kelvin) (Van't Hoff's law):



6

where *C* is the salt concentration, *R* is the ideal gas constant and *T* is the absolute temperature. This pressure tends to expand the compartment volume, drawing water molecules into the compartment. In the two-compartment model, if unrestricted by the outer compartment walls, water will be drawn into the compartment of greater salt concentration until the thermal kinetic energy of salts is equalized on both sides (i.e., equal salt concentrations). Based on these principles of osmotic pressure, diffusion of an osmolyte across a semipermeable membrane also causes water flux.

Salt and other solute (e.g., sugars, amino acids) diffusion across endothelium occurs through open intercellular pathways (pores), or may be facilitated by transport proteins residing in the endothelial membrane. This model of permeability is based on Fick's law, yet differs from that originally described by Fick where solute permeability includes partitioning into and diffusion across an artificial lipid membrane with no pores or transporters. Kedem and Katchalsky [[225](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b225)] accordingly adapted Fick's law to describe solute movement across a porous membrane:



7

where diffusive flux (*J*d) is proportional to the solute concentration gradient (Δ*C*) and the permeability coefficient–surface area product (PS). In real microvasculature, solute fluxes (*J*s) are driven by both solvent drag (convection; *J*c) and diffusion such that



8

Therefore, by incorporating solvent drag forces into Starling's law [[Equation (1)](http://www.ncbi.nlm.nih.gov/books/NBK54123/#e1)], solute flux (*J*s) becomes [[225](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b225)]:



9

In real microvasculature diffusion-driven solute, fluxes are short lived and will proceed until the concentration of proteins [oncotic pressure] due to reduced interstitial volume is sufficient to oppose the osmotic force of solute diffusion [[97](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b97)]. In most situations, transvascular solute flux is predominantly driven by convective fluid flow.

### The Capillary Pore Theory

The permeable state of the exchange microvascular wall results from the presence of pores in the endothelium that selectively filters plasma components and retains particles that are too large to pass. In 1951, Pappenheimer, Renken and Borrero [[338](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b338)] published the “pore theory” of capillary permeability. This classical pore theory is based on the principles that molecular movement is affected by steric restriction based on sieving and molecular size. In pore theory, permeability pathways are assumed to be long cylindrical pores through the endothelium ([Figure 6](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig6/?report=objectonly)), with ideal fluid flow behavior as described by Poiseuille's law, where hydraulic conductivity (*K*F) is a function of fluid viscosity (η) and pore radius (*r*):



10

Based on the measured hydraulic conductivity of individual tracer molecules of various size injected into the dog paw or cat leg, Garlick and Renkin [[149](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b149)] inferred that endothelial permeability pathways consist of small (4 nm) vs. large (80 nm) pores ([Figure 5](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig5/?report=objectonly)). Smaller pores were predicted to occur at approximately 0.2% of the microvascular surface area, while the decreased permeability to albumin and other large tracers indicated that larger pores are far less abundant [[377](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b377)]. Using this classical two-pore model, one can reasonably account for hydraulic permeability observed in most physiological situations. Some investigators have necessarily refined the original 2-pore model, by adjusting the predicted large pore size (25–30 nm) to fit permeability measurements conducted in various tissues [[301](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b301), [377](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b377)]. The physical pathways represented by these pores are uncertain. While the existence of small pores is believed to represent permeability pathways between endothelials at cell–cell junctions, the nature of large pores is somewhat disputed. Speculatively, large pores may represent leaks or gaps that occur infrequently (0.003–0.01% total surface area) and with less consistency than small pores.



#### [FIGURE 6](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig6/?report=objectonly)

Lymphatic microvessel contraction. Light microscope images show a contractile lymphatic microvessel undergoing peristaltic dilation (left panel) or contraction (right panel), driving lymphatic flow away from the tissue interstitium and toward the lymph [(more...)](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig6/?report=objectonly)



#### [FIGURE 5](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig5/?report=objectonly)

Pore theory of capillary permeability. (Top) Pore theory predicts the existence of three type of pores that exist in capillary endothelium: small pores represent the normal permeability pathways for fluid and solute flux through intercellular junctions; [(more...)](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig5/?report=objectonly)

Not long after the inception of the two-pore model, ultrastructural studies of endothelium revealed the existence of endothelial vesicles and transendothelial pores that extend across the endothelial cell interior, in addition to physical passages through intercellular junctions [[336](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b336), [377](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b377)].Therefore, large pore phenomena may represent movement of fluid and solutes in intracellular vesicles via transcytosis ([Figure 5](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig5/?report=objectonly)). Hence, at least three distinct pathways may account for fluid and solute permeability across the microvascular endothelium. Conventional understanding is that transendothelial pores, rather than vesicles, account for most fluid flux across microvessel walls. This is based on the assumption that the effects of solvent drag, i.e., indiscriminant and nonspecific flux of particles proportional to fluid flow, can only be seen in a true transendothelial pore and not in a vesicle-mediated transport system [[377](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b377)].

Modern interpretations of pore theory indicate that the endothelial glycocalyx is responsible for the sieving properties described by pore theory [[377](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b377)]. In this explanation, the glycocalyx serves as a size- and charge-selective filter. The glycocalyx is a meshwork that includes caverns and passages of various sizes, which, taken together, can be modeled as a system of pores of uniform size. The glycocalyx covers the endothelial luminal surface and extends across cell–cell junctions, serving a filter for both transcellular and paracellular hydraulic permeability pathways.

Morphologically, increased endothelial permeability is correlated with several cellular events. Increased vesicle trafficking can be observed by fluorescence microscopy. Endothelial contraction can also be seen in response to a number of compounds that increase permeability. In this case, it is believed that increased cytoskeletal tension pulls apart cell–cell junctions, causing permeability pores to open. In some cases, investigators have shown that the margins of endothelial cells recede, revealing infrequent, yet enormous visible gaps between endothelial cells. However, these gaps are much larger than the large pores predicted by classical pore theory. Transcellular pores, based on vesiculo-vacuolar organelles (VVOs) (discussed in a subsequent chapter), are also detected; however, the contribution of these structures to hydraulic permeability is uncertain. A more widely accepted explanation for hydraulic permeability is pore or gap formation occurring primarily at cell–cell junctions.

[Go to:](http://www.ncbi.nlm.nih.gov/books/NBK54123/)

## PHYSIOLOGICAL FACTORS AFFECTING FLUID/SOLUTE FLUX

Under physiological conditions, the transvascular movement of fluid and solutes is mainly controlled by three factors: hemodynamics (dictated by the Starling forces), lymphatic drainage (removal of excessive fluid and proteins from tissues), and the barrier (permeability) property of the endothelium.

### Hemodynamics

Microvascular fluid exchange is strongly affected by blood flow. Blood flow in larger microvessels occurs in a laminar fashion and is faster (4.6 mm/s in arterioles; 2.6 mm/s in venules) than in capillaries (0.3 to 1 mm/s) [[262](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b262), [405](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b405)]. Flow through capillaries is much more restricted. Because capillaries are smaller in diameter (5–6 μm) than red blood cells (8 μm), red blood cells travel single-file through capillaries, by uniform stacking and bending in the “parachute” configuration [[262](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b262)]. Flow through capillaries is also intermittent, controlled by contraction or vasodilation of precapillary, terminal arterioles. Periodic contraction and vasodilation in microvascular beds (vasomotion) causes the flow through capillaries to increase and subside approximately every 15 sec. Thus, significant periods exist for capillaries where luminal hydrostatic pressure is substantially lower than arterial pressure. These conditions decrease Starling forces, favoring reabsorption. In contrast, increased blood flow through arteriole vasodilation increases capillary luminal pressure and increases filtration. Many signaling molecules and/or byproducts of metabolism increase both arteriole vasodilation and capillary permeability. This has the combined effect of increasing both hydrostatic pressure (*P*c) and hydraulic conductivity (*L*p), with both increasing capillary fluid filtration. Therefore, when studying microvessel permeability, one must be careful to distinguish the components of transcapillary fluid flux that are due to increased permeability from those due to arteriole vasodilation and increased blood flow.

### Lymphatic Drainage

Fluid and plasma components that flux across the microvessel wall and are not reabsorbed will accumulate in the tissue interstitial space. In most tissues, lymphatic microvessels are responsible for drainage of excess fluids and solutes (proteins, etc.) that enter the interstitial space ([Figure 2](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig2/?report=objectonly)) [[262](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b262)]. A few tissues, including bone, cartilage, tendons, ligaments, placenta, and the central nervous system do not have lymphatic vessels [[40](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b40), [265](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b265), [439](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b439)]. For example, in the brain, excess fluid is removed through the arachnoid space to the ventricles, into the cerebrospinal fluid, and then returned to the blood circulation. In most other tissues, prelymphatic channels [[265](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b265)] shunt excess fluid into initial lymphatic microvessels that are located near the perivascular space of blood microvessels. Initial lymphatic microvessels are formed of juxtaposed endothelial cells surrounded by a discontinuous basement membrane and absence of peripheral contractile cells (i.e., parietal cells or smooth muscle cells) [[262](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b262)]. Lymphatic endothelial cells show minimal expression of cell–cell junction proteins. Rather, lymphatic endothelial cell–cell interfaces extend overlapping flap-like projections that are loosely associated with each other. These flaps are arranged to open in the presence of excess extravascular fluid to allow drainage and to close under normal physiological conditions to prevent backflow. Initial lymphatic microvessels are easily distinguished from blood capillaries because of their irregular nonrounded morphology. Initial lymphatic microvessels form an extensively branched network that feeds into the contractile lymphatic microvessels. Contractile lymphatic vessels ([Figure 6](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig6/?report=objectonly)) have a rounded morphology and are surrounded by vascular smooth muscle. Lymphatic flow is driven by regular peristaltic contraction of vascular smooth muscle, which pushes fluid through a series of one-way valves within contractile lymphatic vessels. Peristaltic flow returns lymphatic fluid to the lymph nodes, and then through the thoracic ducts into the venous circulation. In skeletal muscle, lymphatic vessels also rely upon skeletal muscle contraction to drive lymphatic flow. In a normal balanced circulatory system, the outflow of fluid via the lymphatic system matches the net influx of fluid into the tissue from the blood circulation and maintains normal homeostatic fluid volume and pressure in the tissue interstitial space. If the lymphatic flow becomes obstructed, or if peristaltic contraction is prevented, excess fluid will accumulate in the interstitial space, a condition known as lymphedema. Lymphedema occurs in certain disease conditions, the most common of which is elephantiasis caused by a parasitic infection that obstructs lymphatic drainage [[349](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b349)].

### Endothelial Barrier Properties

The exchange microvessel wall consists of a 1-μm thick monolayer of closely juxtaposed endothelial cells [[40](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b40), [262](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b262)]. Adjacent microvascular endothelial cells are joined together at cell–cell (intercellular) junctions, forming the continuous tubular structure of the microvessel lumen. The apical surface of the endothelium exposed to the vessel lumen bears surface glycoproteins (the glycocalyx). The basolateral side of the endothelium is attached to a basement membrane (basal lamina) composed of collagen fibrils, laminin, fibronectin, and glycosaminoglycans. Endothelial cells are anchored to the basement membrane and to the surrounding matrix via cell surface integrins localized at focal adhesions. This structure is semipermeable to water and nonlipophilic molecules and provides size- and charge-selectivity for solute transport across the microvessel wall. The permeability properties of the endothelial barrier are regulated through interactions of endothelial cells, basement membrane and supporting matrix and cells in the surrounding tissue. Barrier dysfunction is often described as increased permeability or hyperpermeability. The consequence of barrier dysfunction is excessive flux of blood fluid, proteins, or cells into the tissue, a pathophysiological process underlying many disease states or injurious conditions.

### Leukocytes and Endothelial Barriers

Endothelial hyperpermeability is a generalized response to inflammation that occurs following trauma, pathogen infection, or chronic disease states [[247](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b247), [289](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b289)]. A hallmark of inflammation is extravasation of leukocytes from the blood to the tissue across the microvascular endothelium [[71](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b71), [267](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b267), [330](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b330), [383](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b383)]. Leukocytes are white blood cells circulating in the blood that include lymphocytes (T-cells, B-cells, and natural killer cells), monocytes, and polymorphonuclear granulocytes (neutrophils, eosinophils, and basophils) [[268](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b268), [317](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b317)]. Lymphocytes are responsible for the adaptive immune response, which includes production of antibodies against specific antigens, and targeted destruction of pathogens based on antigen recognition [[317](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b317)]. Monocytes and granulocytes, mainly, neutrophils, provide innate immune responses to destroy pathogens, such as bacteria by engulfing them or producing oxygen radicals or enzymes capable of digesting pathogens. Endothelial hyperpermeability, including opening of cell–cell junctions and/or increased vesicle-mediated transcytosis facilitates the movement of leukocytes across the endothelium. In addition, chemical factors secreted by activated blood cells can increase or prolong endothelial hyperpermeability during inflammation [[55](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b55), [364](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b364)]. Polymorphonuclear neutrophils (PMNs) present in the blood circulation migrate toward compromised tissues and initiate a generalized immune response [[189](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b189), [330](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b330)]. If encountered, PMNs will attack and engulf bacteria into intracellular compartments filled with chemicals (e.g., oxygen-free radicals) and digestive proteases (e.g., metalloproteinases) that dismember and kill the bacteria. PMNs can also migrate across the microvascular endothelium and become activated within the extravascular tissue.

Neutrophil extravasation is a multi-stage process: rolling, activation, adhesion, and transmigration, requiring complex interactions of PMNs or other leukocytes with the microvascular endothelium ([Figure 7](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig7/?report=objectonly)) [[62](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b62), [125](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b125), [126](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b126), [166](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b166), [245](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b245), [268](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b268)]. Normal blood flow velocity is extremely fast in microvascular beds (≥1 mm/sec), preventing sustained interactions of blood cells with the microvessel wall. Under normal physiological conditions, leukocytes in the blood circulation will contact the microvessel wall and interact temporarily through interactions of membrane surface receptors and integral membrane glycoproteins present on both leukocyte and endothelial surfaces. Leukocytes (and platelets) express selectins on the cell surface that bind to sialylated and fucosylated glycoproteins on the endothelial surface, reducing the velocity of leukocytes by approximately 100-fold and causing leukocyte “rolling” along the endothelium [[125](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b125), [518](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b518)].



#### [FIGURE 7](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig7/?report=objectonly)

The stages of neutrophil extravasation. Neutrophil transmigration is a sequential process of (1) rolling along the microvessel wall, (2) firm adhesion to the endothelium (via interactions with cell surface adhesion molecules), (3) diapedesis (transmigration) [(more...)](http://www.ncbi.nlm.nih.gov/books/NBK54123/figure/fig7/?report=objectonly)

Leukocyte transendothelial migration occurs in response to bacterial invasion or tissue inflammatory injury. In the presence of a compromised microvascular endothelial barrier, leukocytes can become immobilized by firm adhesion to the microvessel luminal surface [[255](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b255)]. This process requires more stable attachment to the endothelium and involves increased expression of adhesion molecules [[166](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b166), [192](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b192)], including selectins: endothelial (E)-selectin and platelet (P)-selectin expressed on the surface of endothelium, binding to leukocyte cell surface glycoproteins including P-selectin glycoprotein ligand 1 (PSGL-1) [[125](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b125), [126](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b126), [268](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b268)]. Firm adhesion is then mediated by binding between leukocyte cell–surface integrins (discussed in a subsequent chapter) and additional cell adhesion molecules on the endothelial surface [[125](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b125), [126](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b126), [166](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b166), [192](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b192), [268](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b268)]. Firm adhesion and interactions of endothelial and leukocyte surface adhesion molecules facilitate leukocyte transmigration across the endothelial wall [[20](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b20)].

In general, PMNs are the first leukocyte cell type to arrive at the site of barrier dysfunction [[330](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b330)]. After and/or during transmigration across the microvessel wall, PMNs will become activated and undergo a respiratory burst, characterized by release of granule secretions of numerous compounds [[267](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b267)]. Many of these secretions (e.g., oxygen-free radicals, proteases, nitric oxide, leukotrienes, prostaglandins, cytokines) induce endothelial hyperpermeability [[267](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b267), [364](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b364)] and can attack and liquify tissue surrounding the compromised vasculature (pus formation) [[330](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b330)]. PMNs also secrete chemokines or induce endothelial expression of chemokines [[307](http://www.ncbi.nlm.nih.gov/books/n/c00025isp013/reflist1/#b307)] to attract other leukocytes (macrophages, monocytes, and immune cells) to the site of inflammation. Hence, leukocyte activation and migration across the endothelium are both cause and consequence of endothelial hyperpermeability and barrier dysfunction.

[Copyright](http://www.ncbi.nlm.nih.gov/books/about/copyright/) © 2011 by Morgan & Claypool Life Sciences.

Bookshelf ID: NBK54123