ELSEVIER

Development of Primary Superficial Venous Insufficiency: The Ascending Theory. Observational and Hemodynamic Data From a 9-Year Experience

Eugenio Bernardini,[1] Paola De Rango,[2] Riccardo Piccioli,[1] Carlo Bisacci,[1] Valentino Pagliuca,[1] Giuseppe Genovese,[1] and Roberto Bisacci,[1] Perugia, Italy

Background: Hemodynamic principles suggest that primary venous insufficiency follows the hydrostatic column of venous pressure of the limbs, and therefore, venous reflux begins at the lower points and rises upwards. To test the hypothesis of an ''ascending development'' of reflux, we carried an observational study to analyze the natural evolution of lower limb venous insufficiency.

Methods: During 9-year period patients with primary superficial venous disease who refused treatment were followed prospectively with 6-month scheduled clinical and duplex ultrasound examinations. Localization, stage, and evolution of the venous patterns were compared.

Results: A total of 104 limbs in 99 patients were analyzed (12 males, 92 female; mean age 48.7 years). Prevalence of reflux was ($p < 0.001$) more frequent along great-saphenous and its tributaries (78/104, 75%) than nonsaphenous veins. The time of re-examination ranged from 1 to 13 years (mean 4 ± 3.1 years). With the exception of six remaining stable, all the veins showed a progression of insufficiency (94%); 47 involved deep circulation. In all the worsened refluxes, an extension to reach one or more venous segments at an upper level, uninvolved before, was found. There was no downward oriented pattern of progression. There was no significant difference in age, gender, and type of vein between the stable and progressive diseases.

Conclusions: Natural history of primary venous insufficiency is that of a progressive disease, which begins at lower levels of the limbs and develops in an antegrade manner as venous stasis is higher where force of gravity is higher. This data do not support the aggressive and widespread treatment of terminal valve as first approach, but need to be supported by larger studies.

INTRODUCTION

The pathogenesis and pathophysiology leading to development and progression of primary venous insufficiency are largely unknown. According to the traditional ''retrograde theory,'' the primary source of chronic venous disease is the incompetence of valves above the saphenofemoral junction (SFJ), which in turn produces dilatation and valvular incompetence sequentially in the greater saphenous vein (GSV) and its tributaries in a retrograde manner.[1] However, refluxes are often found below competent terminal valves, especially in youngsters,[2] and in up to 67% of patients,[3-10] saphenous reflux exists without SFJ (26.6-67%)[2-10] or saphenopopliteal junction incompetence (42%).[4]

Hemodynamic scientific laws (Newton gravitational and fluid mechanics laws)[11,12] do not support such a ''retrograde'' development of venous reflux from upper to lower levels, and suggest that the natural history of primary venous insufficiency is

[1]*Interuniversitary Phlebology Center, University of Perugia, Perugia, Italy.*

[2]*Unit of Vascular and Endovascular Surgery, University of Perugia, Perugia, Italy.*

Correspondence to: Paola De Rango, Unit of Vascular and Endovascular Surgery, University of Perugia, Ospedale S. Maria della Misericordia, Via G Dottori, 06100 Perugia, Italy, E-mail: pderango@unipg.it, plderango@gmail.com

Ann Vasc Surg 2010; 24: 709-720
DOI: 10.1016/j.avsg.2010.01.011

more likely determined by the hydrostatic column of venous pressure. Accordingly, the development of venous insufficiency in lower limbs follows the gravity gradient: the lower the limb level, the higher the gravity force, the higher the hydrostatic pressure causing venous incompetence and reflux to begin. When started at a lower point, the reflux can subsequently evolve uprising in accordance with the pressure gradient. The latest segment of the vein to be involved would be the terminal valve (i.e. SFJ, saphenopopliteal junction).

Several reports have also found that venous wall dilatation occurring in sites of venous reflux is due to changes in collagen and elastin content and does not have correlations with the site and function of valves. According to these findings, ''wall weakening'' is the initiating factor of primary reflux that, therefore, might not develop in a retrograde manner beginning from the terminal valve but, more likely, following a reverse, upward directed, pattern.[13-15]

To test the hypothesis of ''ascending development'' of primary venous insufficiency for which the terminal/junctional valve represents the last stage of a venous reflux that advances from lower levels, we carried out an observational study. The purpose was to analyze the natural evolution of reflux over the time in a series of patients with lower limb primary venous insufficiency left untreated.

PATIENTS AND METHODS

During a 9-year period (1997-2006) data on patients referred for primary venous insufficiency to the vascular laboratory at a single venous service serving 1,800 patients were prospectively entered in a customized database. The main offered treatment option was sclerotherapy.

All the patients who refused treatment, treatment was not offered, or was delayed at their first visit because in the meantime they were receiving cure on the contralateral leg were followed up to evaluate the evolution of their venous disease. After the first evaluation, patients were given elastic compression (12-18 mmHg), and clinical and duplex ultrasound follow-up every 6 months was planned. Use of flavonoid was optional, and no standardized medical therapy regimen was used. Only patients who complied with follow-up and had at least two duplex imaging and clinical functional evaluations were included in the present study. Totally incompetent superficial veins (reflux extended along the entire venous axis and encompassing the terminal valve to reach deep circulation) were excluded because the evolution of the disease was not assessable at this terminal stage. Patients with deep venous incompetence, pregnancy, a history of deep or superficial venous thrombosis, or who refused follow-up were also excluded. Recurrences after a destructive treatment (surgery) were not exclusion criteria because these involved new venous segments; recanalizations after previous therapy (sclerotherapy injection, laser therapy, etc.) were excluded because these treatments could have affected the spontaneous evolution of the venous patterns.

Hemodynamic Assessment and Definitions

The anatomic or functional classification and definitions introduced by Franceschi[16,17] were used to define patterns of venous insufficiency.

Anatomical Definitions

R1, deep venous pathways; R2, saphenous trunks; R3, saphenous trunk branches; and R4, venous branches allowing saphenous trunks to intercommunicate (e.g., Giacomini's vein).

Functional Definitions

Antegrade flow (A+), flow whose direction is physiological. Retrograde flow (A−), flow whose direction is the reverse of physiological direction. Reflux (R+), any flow going from the deep venous to the superficial venous system (Reflux Rx−R2) and from the superficial saphenous trunk to the saphenous branches (Reflux R2−R3); R−, not-reflux flow from the deep veins. Finally, according to Valsalva maneuvers to test competence under induced pressure: V+, with incompetent valves; V−, with competent valves.

To define the site of reflux, the following hemodynamic patterns were identified:

1. Physiologic venous drainage.
2. Reflux along nonsaphenous branches.
3. Reflux along saphenous axis and/or saphenous branches:
    - Reflux R3 (saphenous collateral branch R3 involvement, single or multiple segment).
    - Reflux R2 (along saphenous trunk).
    - Reflux R3−R2 (involving both, the collateral branch and saphenous trunk).
    - Reflux R2−R1 (from the saphenous vein to the deep circulation either through an incompetent junction or through a perforator vein).

- Reflux R3—R2—R1 (reflux detected on collateral branch, saphenous trunk, and deep venous circulation).[16]

To assess patterns of reflux, site of venous incompetence and the involvement of terminal saphenous valves, color-flow duplex ultrasound scans using a 7.5-13 MHz linear array transducer (ESAOTE AU 530 and ESAOTE CARIS PLUS) was used. All the examinations were performed by a single Operator (E.B.) with validated venous ultrasound experience and were blinded to previews patients' charts and results. The presence of reflux was investigated and located with patients in standing positions. Reflux was defined as any reverse flow (R1—R2, R2—R3 or R1—R3) lasting more than 1.0 seconds that does not follow the physiological sequence of venous drainage (R3—R2—R1 or R3—R1) and turns back to the starting point without being drained (i.e., ''venous-venous shunt'' that can no longer achieve one-directional venous drainage from the superficial to the deep system, and permits the creation of a true dead volume circulating in a closed circuit perpetuating a vicious cycle).

To evaluate valve competence, venous flow was examined below and above the valve plane and throughout the entire extension of the veins and their tributaries in longitudinal and transverse views using Color and pulsed Doppler signals.[18,19] Reflux was induced by firm manual compression of the limb 10 cm distal to the vein segment under investigation and was followed by sudden release. Valsalva maneuver was also part of saphenous junction (SJ) reflux evaluation. Terminal valve incompetence at SJ level was defined in the presence of both compression-release test and Valsalva maneuver positives. SJ reflux with negative compression-release test was considered indicative of terminal valve competence, independent from the Valsalve positive or negative results. Stress tests, as voluntary contraction (active foot dorsiflexion and relaxation; tip-toe position) and isometric reflex contractions (Parana' maneuvers)[16,17] were sometimes employed to elicit a reflux when a standard stimulus was needed to evaluate reflux parameters (briefly, in Parana' maneuvers changes of venous flow during isometric contractions of the lower limbs in stationary standing position are measured when the examiner slightly pushes the patient's waist forward to induce disequilibrium).[16,17] These stress tests present a good reliability and reproduce the real physiologic hemodynamic conditions during walking.

The anatomic locations of the site and the extension of reflux at any visit were carefully recorded on an anatomic chart, thereby allowing accurate sequential comparisons.

Depending on its location, reflux was separated as proximal (thigh) if located above the knee veins or distal if involved the below-knee veins (leg). Within each level (thigh and leg), three different longitudinal segments were considered to record reflux: upper, medium, and lower (Fig. 1). Therefore, the overall lower limb was divided in 6 segments (with the lowest labeled the first), and the location and progression of venous insufficiency was evaluated for each segment. Varicose veins were categorized as being ''primary'' if presenting without previous surgery or ''recurrent'' if developing after previous surgical intervention, usually saphenofemoral or saphenopopliteal ligation with or without stripping.

The selected patients were also classified in accordance with the Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification criteria.[20]

Color Duplex assessment with dynamic maneuvers was repeated at each follow-up visit. The evolution of venous insufficiency was defined ''ascending'' if there was any new reflux appearing in one or more previously competent segment located above. The ascension could involve either the same type of vein (R3) or a vein of different type (R2) at an above level. The evolution was defined ''retrograde'' when a new reflux appeared in one or more competent venous segment located at a below level.

Statistical Analysis

Descriptive statistics were used for the analysis of the venous reflux. Prevalences of refluxes and changes in reflux patterns were compared using χ^2 test or Fisher exact test, when required. Values of $p < 0.05$ were used for significance.

RESULTS

A total of 104 limbs (99 patients) with comprehensive baseline duplex patterns of leg veins were available for repeated duplex ultrasound and hemodynamic evaluation of the evolution of a non-treated primary superficial venous disease. Representing 10.1% of the overall untreated population ($n = 1{,}020$) over the study period, these were patients who were offered a treatment at their first visit, but for various reasons treatment was postponed or refused. There were 12 male and 92 female patients with a mean age of 48.7 years, ranging from 22 to 79 years. The following algorithm describes the selected cases, according to the CEAP classification

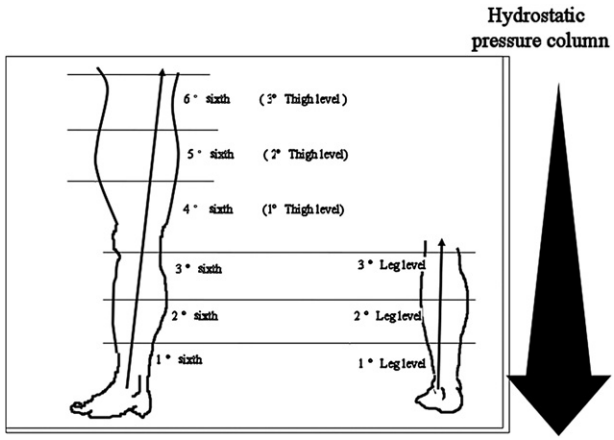

Fig. 1. On the left: six anatomical segments of the leg. On the right strength and direction of the hydrostatic pressure column in static conditions; following the gravity forces, the pressure column increases from the top to the bottom.

criteria ($C_{S1,2,3,6}$,E_P,A_s,P_r).[20] All the selected patients presented with classic clinical symptoms of chronic venous insufficiency. The majority of limbs (74%) were in the clinical class 2 (C2) showing simple varicose veins; 10.6% were with reticular veins or telangiectasias (C1), 5.8% with edema (C3), 7.7% with lipodermatosclerosis and/or other skin changes (C4), and 1.9% with active ulcer (C6). In all the cases, the etiology was primary (Ep) and the Anatomical distribution was located to the superficial system (As) as inclusion criteria. Finally, the pathophysiology was due to reflux in all the cases (Pr).

At the baseline evaluation, no involvement of deep circulation was present as an exclusion criterion, and 11 patients did not show any evident reflux despite symptoms (all draining veins). In the others, pattern of saphenous ($n = 54$), saphenous branches ($n = 27$) and nonsaphenous ($n = 12$) refluxes were recorded. Of the 12 refluxes detected in nonsaphenous veins, nine were recurrences after previous surgery. Prevalence of reflux was more frequently detected along in GSV and its tributaries (78/104, 75%) than nonsaphenous veins (12/104, 11.5%): $p < 0.001$, OR 23; 95% CI 10.20-52.84. The involvement of small saphenous vein ($n = 2$) and accessory saphenous vein ($n = 1$) were negligible, and these refluxes were analyzed together with GSV for a total of 81 Saphenous vessels involvement.

Thirteen saphenous refluxes were located only in the saphenous trunk (R2), 27 in the collateral branches (R3), 41 in both the saphenous and collateral trunks (R2−R3 refluxes), and 16 had reflux extended up to the saphenofemoral junction, but the terminal valve was never involved. The prevalence of reflux in different veins is shown in Table I. Different locations and hemodynamic of reflux at baseline are also shown in Tables II and III.

Table I. Baseline localization of reflux in 104 venous patterns

Veins involved	Number	%
Normal pattern	11	10
GSV trunk (R2)	51	49
GSV branch (R3)	27	26
Accessory saphenous	1	0.9
SSV	2	1.9
Nonsaphenous	12	11
Primary	3	2.9
Recurrent after stripping	9	8.6

GSV, great saphenous vein; SSV, small saphenous vein.

Table II. Baseline evaluation: site of reflux

Level	Leg (below-knee)	Thigh	Leg and thigh
GSV trunk (R2)	5	35	11
GSV branch (R3)	27	—	
Accessory saphenous	—	—	1
SSV	2	—	—
Nonsaphenous	—	—	—
Primary	1	—	2
Recurrent after stripping	1	—	8

GSV, great saphenous vein; SSV, small saphenous vein.

The time of re-examination ranged from 1 year to 13 years (mean 4 ± 3.1 years), with 30 limbs reaching 1 year, 12 2-year, 11 3-year, 14 4-year, 9 4-year, and 28 6-year or more follow-up. During the period of observation in all the veins, a progression of the reflux occurred with the exception of six GSV in which R2 refluxes remained stable, without any extension along R2 or to the R1 and R2 network. There was no significant difference in age (mean 50.6 years vs. 53.17 years, $p = 0.5$) and gender (1/12 or 8.3% progression in males vs. 5/92 or 5.4% in females $p = 0.53$) between the stable and progressive diseases. The progression in saphenous veins (93%) and nonsaphenous veins (100%) was similar ($p = 0.7$). Examples are shown in Figures 2 and 3. According to CEAP, there were 5.8% C1, 56.7% C2, 27.9% C3, 7.7% C4, and 1.9% C6.

There was no reflux extending from above to below venous segments either along R2, R3 or

Table III. Baseline evaluation: hemodynamic pattern of reflux by site

Reflux pattern	Leg (below-knee)	Thigh	Leg and thigh
Isolated R2	7		6
Isolated R3	27	—	
R2—R3	—	—	41
Nonsaphenous	2	—	10
No reflux		11	

R2, saphenous trunk; R3, saphenous branch.

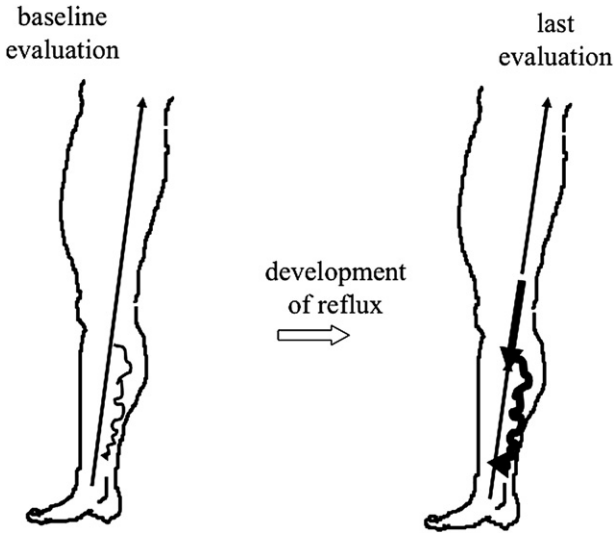

Fig. 2. Examples of reflux development along saphenous axis as detected in seven limbs. On the left, baseline no-reflux flow on saphenous trunk (black arrow along the thigh with the top upward); varicosities of saphenous branch at the below-knee level. On the right, progression of reflux to involve the 4° segment (thigh) and the saphenous axis (bold black arrow with inverted top to the bottom).

nonsaphenous veins. In 57 (58%) veins, progressing refluxes extended to involve (after a mean of 4.49 ± 3.27 years) a single sixth segment above; in 41 (42%) the rising (after a mean of 3.34 ± 2.77 years) was by more than a single segment.

Eleven veins, formerly without reflux flows, showed reflux involving R2 trunk. In five, the reflux started in a R3 branch and then, at a later stage, the evolution involved the above saphenous trunk (reflux R3—R2) for one or more segments. In the other six, the reflux directly started in the saphenous trunk (R2) at the leg level and evolved along another R2-sixth segment above at a further evaluation.

Of the 27 incompetences originally limited to collateral branch (R3 refluxes), 9 extended from partial to whole R3 segment involvement,

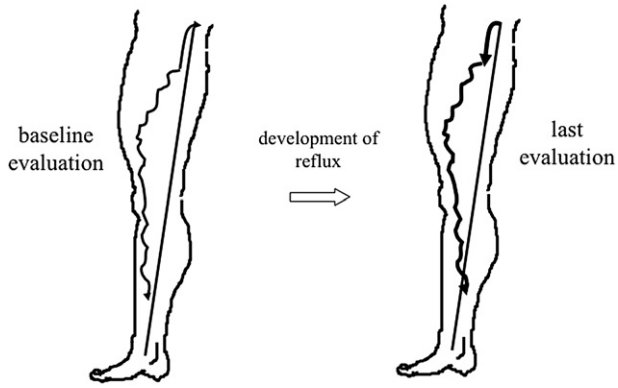

Fig. 3. Example of accessory saphenous vein reflux evolution as detected in one patient. On the left (baseline assessment), initial reflux flow (R3) without involvement of great saphenous trunk (R2). On the right (last assessment), development of retrograde flow to involve great saphenous trunk (Reflux R2—R3).

ascending for 1 or more segments along this. In the other 18, R3 reflux extended into the saphenous trunk above (R3—R2). Details of progression are shown in Table IV.

Overall, 47 involvement of deep circulation occurred (R1), 36 along saphenous veins and 11 from nonsaphenous veins. Along the saphenous axis, two deep involvements come from originally isolated R2 refluxes, three from isolated R3 refluxes, and 31 from R2—R2 refluxes. Specifically, all the 16 incompetences that involved the SFJ at basal evaluation progressed into the deep circulation (reflux R2—R1 or R3—R2—R1) by arising through the terminal valve. In addition, all but one of the 12 nonsaphenous refluxes progressed into deep circulation through a perforator vein in the thigh.

In a subgroup of 15 patients, three to five scheduled Ultrasound-staged examinations were available. A step-by-step segmental pattern of the ascension of the reflux either in saphenous or nonsaphenous axis could be verified. Starting with initial disease limited in a distal venous segment, an upward sixth by sixth evolution progressively developed. In five cases, a single upward segment involvement; in four cases, a two segment above progression; and in six, a progression of more than three above segments were recorded, as shown in Figures 4-6.

DISCUSSION

The original hypothesis of a retrograde pattern of evolution for primary venous insufficiency beginning from the terminal valve and progressing

Table IV. Longitudinal evolution

Veins involved	Number at baseline	Number with evolution	%	Type of evolution
Normal pattern	11	11	100	To R2
GSV trunk (R2)	51	45	88	To extended R2
GSV branch (R3)	27	27	100	18 to R2 9 to extended R3
Accessory saphenous	1	1	100	
SSV	2	2	100	
Nonsaphenous	12	12	100	
Involvement of deep circulation (R1)	—	47		2 from isolated R2 3 from isolated R3 31 from R2-R3 11 nonsaphenous

GSV, great saphenous vein; SSV, small saphenous vein.

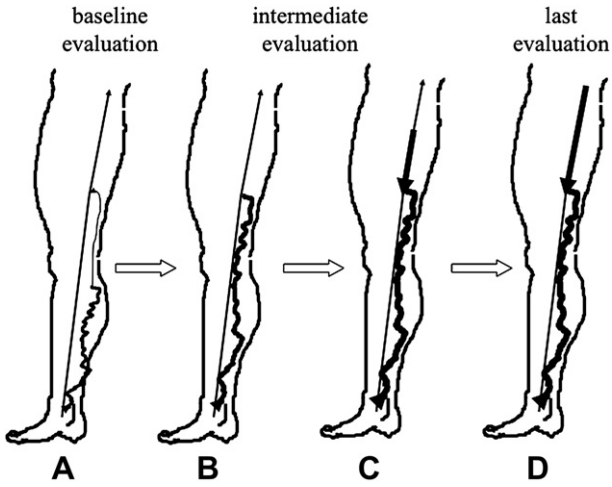

Fig. 4. Four step development of reflux along saphenous axis as detected in nine limbs. From the left to the right: varicosities in saphenous branch at the below-knee level with baseline no-reflux flow on saphenous axis (black arrow along the leg with the top upward); development of retrograde flow to involve the 4° sixth segment of the branch; progression of reflux to involve the 5° sixth segment of saphenous axis above (bold arrow with inverted top to the bottom); progression of reflux along saphenous axis up to the 6° segment and the terminal valve.

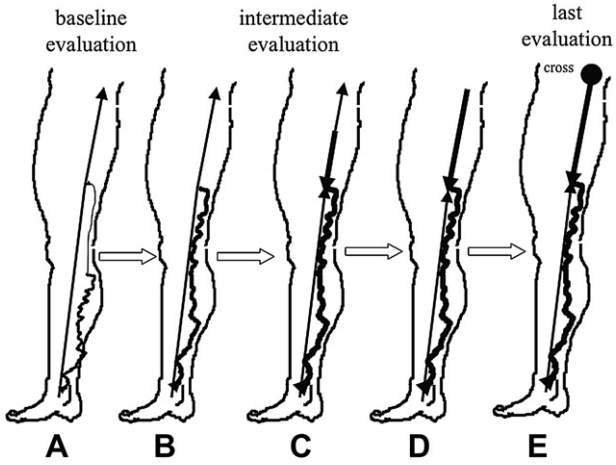

Fig. 5. Saphenous vein: step-by-step progressive evolution of reflux as detected in two limbs: From the left to the right: **A** baseline assessment: initial reflux flow (R3) localized within the 2° and 3° segments and without involvement of great saphenous trunk (R2); **B** ascending evolution of reflux to include 2°, 3°, and 4° segments; **C** following involvement of the saphenous trunk at upper levels: 5° segment, and, subsequently, **(D)** 6° segment (reflux R2-R3); **(E)** last assessment: development of reflux flow to involve the terminal valve and the deep circulation (reflux R1—R2—R3). SFJ, saphenofemoral junction.

from above-to-below levels along the leg could not be confirmed by our data. In 94% of the 104 veins observed over a 9-year period, venous insufficiency evolved and all the progressions, when occurred, extended to reach one or more venous segments at an upper level uninvolved before. The longitudinal analysis of this series of patients suggested that when venous refluxes were detectable in patients at both below-the-knee and thigh levels, those at lower levels were pre-existent and preliminary to those at the thigh. However, larger studies population are needed to definitely clarify the natural history of primary varicose vein disease.

Other literature data disagree with the retrograde traditional hypothesis of venous reflux, somewhat of which our study supports. Labropoulos et al., analyzed the origin of lower-limb primary reflux by examining three groups: 40 healthy young patients, 20 patients with prominent nonvaricose

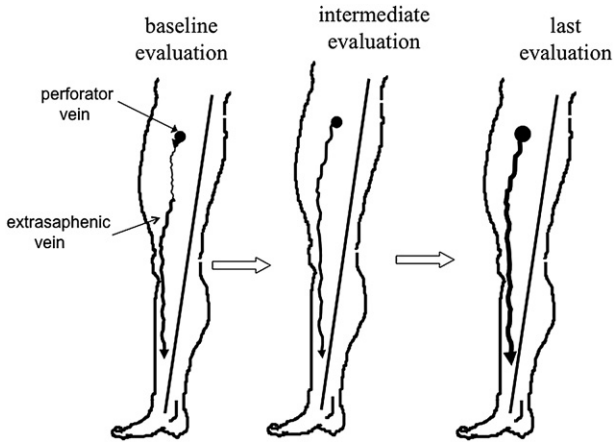

Fig. 6. Nonsaphenous vein: step-by-step progressive evolution of reflux as detected in four limbs. On the left (baseline assessment): initial reflux flow (R3) localized within the 2°, 3°, and 4° segments and without involvement of great saphenous trunk (R2). On the middle ascending evolution of reflux to include 2°, 3°, 4°, and 5° segment and involving the whole nonsaphenous vein R3. On the right (last assessment), development of retrograde flow to involve deep circulation through a perforator vein (reflux R1–R3).

veins, and 20 patients with varicose veins.[8] Significantly more reflux was reported in the below-knee segment of saphenous vein (68%), whereas SJ was involved in 32% of cases. Authors suggested that reflux might progress in multiple manners following either retrograde, ascending, or also multicentric direction patterns.

Engelhorn et al., who analyzed 590 extremities in women with varicose veins and at early stages of disease found that the large preponderance of the disease was distal and segmental, whereas SJ was involved in only 5% of cases.[9]

In the last recent years, there has been a growing renewed interest toward an ascending or multifocal development of varicose veins due to improvements in hemodynamic and ultrasound knowledge. Several studies and appealing venous treatment methods (as the ASVAL [ambulatory selective varices ablation under local anesthesia])[21] have been published[2,8-10,21-27] to support this concept, as synthesized in Table V. However, there are no studies large enough to provide strong evidence against the traditional retrograde evolution in the natural history of venous disease (one only study included more than 2,000 limbs[2]). In addition, published studies at this regard are not uniform, and heterogeneous populations have been analyzed.[2,8-10,21-27] Difficulties in recruitment, assessment and following patients with symptoms or signs of venous insufficiency, most of them receiving one or more types of treatment (misleading the natural evolution of the disease) obstacle the conduction of large population studies on this issue.

Partly due to the lack of large longitudinal studies on the natural history, the pathophysiologic mechanisms that lead to the development and progression of reflux in primary superficial venous insufficiency still remain largely unknown. However, the physiology of venous reflux as a retrograde phenomenon seems weakly reasonable since it contrasts with the basic physic laws and gravity forces. Indeed, according to the retrograde theory that has been conventionally believed,[1] the incompetence of femoral valves should be the initiating factor in promoting reflux in primary venous disease; after this occurrence and because the venous pressure in the lower limbs is increased in the upright posture due to hydrostatic reasons, the reflux develops in a retrograde manner.

Conversely, hemodynamic and physical principles support that the natural history of venous insufficiency follows more likely an ''ascending evolution'':

According to static fluid laws, under the action of gravity a liquid exerts a resultant vertical force which equals the liquid weight; the pressure exerted by a static fluid depending on the depth of the fluid and the acceleration of gravity (Fluid Pressure Calculation [Fluid column height] in the relationship: $\Delta P = \rho gh$, where $\rho = m/V$ = fluid density, g = acceleration of gravity, h = depth of fluid].[11,12] The hydrostatic pressure gradient is directed downwards according to the gravity gradient (higher gravity at lower levels). The length and height of venous reflux is directly proportional to hydrostatic pressure (height of a column of water between the heart and ankle; Fig. 7). Accordingly, venous stasis is higher at lower levels where force of gravity is higher and vein dilatation with valve incompetence and reflux most likely begin at lower levels and develop in an antegrade manner. In static conditions (upright posture), a fluid pressure gradient of about 42-45 mm Hg can be measured between the ankle and the groin. Depending on the height of the patients (thereby of the height of a column of water between the heart and ankle), at parity of fluid density, the gravity force would provide at the groin a pressure of 46.25 mm Hg in an hypothetical patient of 178 cm height and of 42.5 mm Hg in a patient of 163 cm height; the corresponding values at the ankle would be 95 mm Hg and 87.5 mm Hg, in patients of 178 and 163 cm height, respectively (Fig. 7A).

Table V. Literature review on the ascending theory (by publication year)

Author	Year	Settings	Main findings	Population *N*
Labropoulos et al.[8]	1997	Observational study on where does reflux start	Significantly more reflux for calf saphenous vein (68%) than for the thigh or the SFJ (38%)	220
Cooper et al.[10]	2003	Distribution of varicosites patterns	Primary varicose veins develop as ''spreading incompetence'' from one focal point while SFJ function is preserved	480
Labropoulos et al.[22]	2004	SFJ Reflux in normal saphenous trunk	SFJ normal diameter in 21%, dilated in 62% and varicose in 17% chronic venous diseases	1500
Engelhorn et al.[9]	2005	Varicosities patterns in women	The large preponderance of the varicose disease was distal and segmental while saphenous junction was involved in only 5% of cases	590
Labropoulos et al.[27]	2005	Reflux progression study	Reflux extension: antegrade and retrograde fashion; in continuity and separately from the preexisting disease	116
Labropoulos et al.[24]	2006	Perforator veins reflux patterns	Reflux in perforators veins develops in ascending fashion through the superficial veins, at reentry points and at new sites	158
Caggiati et al.[23]	2006	Age related varicose vein anatomy	Varicose disease in young patients may progressively evolve in antegrade fashion, spreading from nonsphenous vein (SFJ reflux in 38% young and in 59% elder patients)	100
Bernardini et al.[25]	2007	Echo-sclerosis hemodynamic conservative (ESEC) technique	55% SFJ incompetences reversal with sclerotherapy directed in the subostial saphenous vein trunk or in saphenous branches	980
Pittaluga et al.[2]	2008	Classification of saphenous refluxes	Antegrade development of SVI, probably starting from the suprafascial venous network. Presence of SFJ incompetence correlates with older age	2275
Pittaluga et al.[21]	2009	Ambulatory selective varices ablation under local anesthesia (ASVAL) procedure	Ablation of varicose reservoir with conservation of a refluxing SV is effective treatment in >2/3 cases suggesting ascending evolution of venous insufficiency	303

SFJ, saphenous femoral junction; SV, saphenous vein; SVI, saphenous vein incompetence.

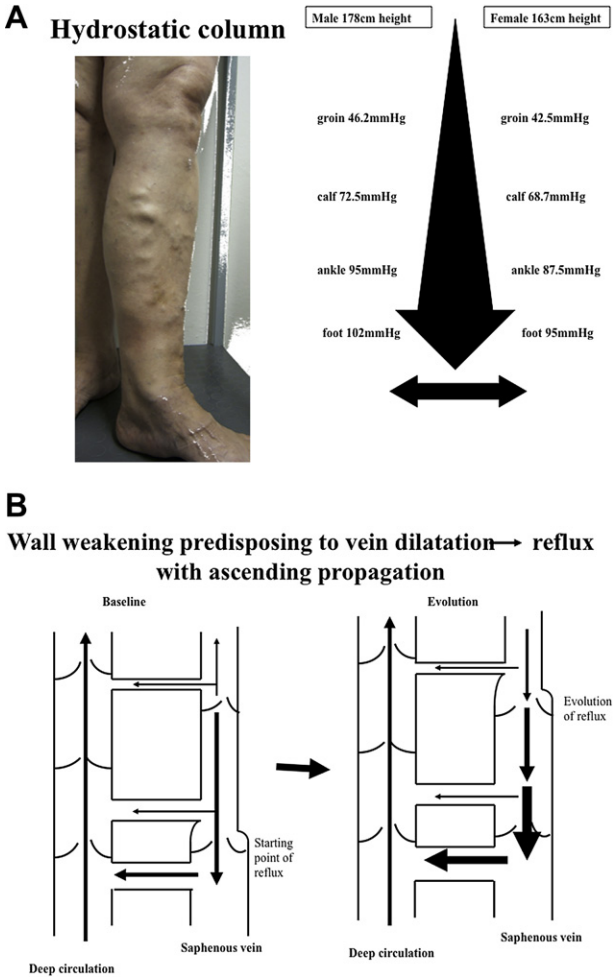

Fig. 7. A In upright posture, the increase in hydrostatic pressure is proportional to the height of the column, as the height of the hydrostatic column is not affected by venous valve activity. Pressure values are higher at the bottom and decrease while uprising at above levels where the column is shorter. Here are shown hypothetic values of pressure gradient calculated for a male patient of 178 cm (on the left) and a female patient 163 cm height (on the right), respectively, in static conditions. A static fluid pressure gradient of about 42-45 mm Hg can be measured between the ankle and the groin. Depending on the height of the patient, at parity of fluid density, the gravity force would provide at the groin a pressure of 46.25 mm Hg (in a patient of 178 cm height) and of 42.5 mm Hg (in a patient of 163 cm height); the corresponding values at the ankle would be 95 mm Hg and 87.5 mm Hg. This values are applicable in static conditions when a continuous hydrostatic column weights on all the legs. During muscular contraction, the height (and therefore the weight) of the hydrostatic column is also affected by the extent of valve competence influencing reflux in the phase of muscular relaxation (diastole). In conditions of muscular relaxation after contraction, venous valves indeed will be closed in a competent system, permitting a fragmentation of the hydrostatic column, whereas valves incompetence along the superficial veins will determine the formation of higher hydrostatic columns. **B** Wall weakening associated with high pressure values at the bottom levels will allow a vein dilatation with detachment of the valves and vein incompetence in a upward progression. Progressive vein dilatation → valve incompetence → reflux uprises following the longitudinal distribution of the highest hydrostatic pressure values. Reflux causes further increase in venous pressure in the superficial venous circulation with varicose vein appearance and increased flow through perforating vessels (re-entry) into the deep circulation still competent. On the left, initial superficial venous disease; on the right, evolution of the disease.

In the development of the venous insufficiency, the lower the level, the higher the gravity force, the earlier the veins dilate (Laplace law), the valves separate and the reflux develops. Although varicose disease is associated with weakness of the vein wall, clinical manifestations occur only under certain orthostatic hemodynamic conditions. A primary wall abnormality (weakening) either along saphenous trunk or venous branches may be a predisposing factor necessary but not sufficient by itself to promote vein dilatation and reflux development in the absence of increased local pressure. Vein dilation under localized hyperpressurization in turn produces veins valve incompetence, and the formation of a reflux that proceeds upwards according to the longitudinal distribution of local hydrostatic pressure weight (Fig. 7B). Hydrostatic columns of different heights create the necessary gradient for the development of reflux. At the opposite, it is difficult to understand why should reflux develop in a retrograde manner, starting from the terminal valve of the thigh where the gravity and the pressure weight are lower and junction valves are intact (as in more than half patients with primary venous insufficiency).[3-9] Favored by hydrostatic factors, primary venous insufficiency is most likely an ascending evolving disease.[2-9,21-27]

It is also a common finding in clinical practice that varicosities are most often seen in the medial and posteromedial aspect of the calf.[8,9,28] Because of the increased hydrostatic pressure levels, the lowest limb level represents not only the starting point but also the point of more severe reflux responsible for developing the earliest symptoms and signs of venous insufficiency. The continuous increase in hydrostatic pressure allows progressive enlargement and valve insufficiency of the above venous axis that, if not treated, will propagate upwards following the hydrostatic pressure gradient, and

finally will involve the terminal valve at junctions in a later time. In this study, we observed 16 limbs in which saphenous junctions were involved but terminal valves were still competent (negative compression-release test and positive Valsalva); only in a subsequent stage, both the Valsalva and compression maneuvers become positive. This indicated that a greater and huge pressure (both, Valsalva and compression tests positive) is required to dilate and make incompetent the terminal valve in previously incompetent veins.

In this series of 104 veins, there were no occurrences of retrograde progression of reflux along R2, R3, or extrasaphenous veins below the level of starting point of reflux, either in contiguity or not. In our experience, we found that sometimes telangiectasias could develop in contiguity, transversely, and also slight below the reflux starting point. However, these varicosities were all directly dependent from the original point of reflux and belonged to that draining venous system already involved by the disease. Therefore, our data do not support that, even after an antegrade evolution, a development of varicosities below the starting point by contiguity might be initiated.

The progression of venous insufficiency is usually segmental; in this experience, 41 of 98 evolutions occurred by a single sixth segment, although there were 57 veins in which the reflux ascended more, depending on the time of assessment and other potential cofactors (the exact timing and rate of progression was not the aim of the present study).

Because of the ascending and segmental evolution of primary venous insufficiency, localized venous treatment at a lower level in an early stage could be helpful to prevent or slow down the further progression of the disease to the end stage with terminal valve damage. Our data, as well as other previous experiences, [2-9,21,25-29] do not support the widespread surgical treatment of SFJ in an early stage of primary varicose vein disease. As valve incompetence predominates in areas that would be anticipated to suffer the greatest pressures (lower legs), an initial treatment localized at these lower points may be warranted. There is also evidence that even in case of terminal valve involvement, the vein continence may be restored without valve surgery.[3,7,21,25,26]

Previous studies described the possibility of reflux elimination as an hemodynamic consequence of procedures performed without any direct action on the junctional valve.[16,17,21,25-29] The approach could be directed on the subostial7 incompetent saphenous vein (either collaterals or saphenous trunk) or may be entirely performed outside the saphenous axis (fully preservation of saphenous vein as with the ASVAL[21]). The shown efficacy of these methods is strictly dependent from the ascending progression of venous disease.[25,29] The efficacy in preservation of a refluxing SFJ has been recently emphasized by the ASVAL method.[21] Authors found that the ablation of the varicose reservoir by phlebectomy of venous collaterals, while fully preserving saphenous vein and also conserving a refluxing SFJ, was effective in the treatment of signs and symptoms in 303 patients with superficial venous insufficiency. Nonsignificant or none reflux was obtainable in more than two-thirds of cases.[21] According to hemodynamic concept of venous disease,[16,17] the selective interruption of the hydrostatic pressure column, localized at the reflux sites, allows to decrease the pressure weight on the veins below, as the height of the hydrostatic column is shortened (the breakage splits the single longer hydrostatic column in two shorter columns, each with a lower weight). At the same time, after such interruption, venous flow will be likely redirected through collateral branches or perforating veins (named ''reentry'' perforating veins) in a physiologic one-way (superficial to deep) pattern. These recovered re-entry flows can allow an efficient venous drainage of the above varicose segments previously hyperpressurized as they were overflowed from the reflux point that has now been interrupted. These hemodynamic corrected and physiologically redirected low-pressure flows can therefore permit depressurization and shrinkage of the upward superficial varicose segment up to the above valve that will recover continence (segmental venous insufficiency recover). In the same way, the terminal valve at the SFJ may be also recovered when the subostial saphenous vein shrinks after the interruption of the weight pressure at a level below. If hemodynamic abnormalities are not corrected by breaking the pressure column, the increase of hydrostatic pressure within the varicose veins with the time will get worse and will propagate upward (following the longitudinal hydrostatic pressure gradient) causing progressive vein dilatation, valve detachment with incompetence, and development of reflux into the above venous axis.

This is partially in accordance with the hemodynamic concept of causality of venous insufficiency Cure Conservatrice et Haemodinamique de l' Insuffisance Veineuse en Ambulatorie (CHIVA)[16,17,30] that claimed to treat the varicose vein by creating a draining (low resistance) venous system as varicose veins may regress after the hemodynamic alteration is corrected. However, in disagreement with

classical hemodynamic venous surgery, our study (ascending theory) suggests that the treatment should be directed at the lower leg levels where hemodynamics is mainly altered and not at the SFJ.

Limitations of the present study include the small sample of vessels at study to assess the natural history of the disease. This is not a large population-based study and our findings cannot be generalizable to all the patients with chronic venous disease. Furthermore, the referral of patients to our center (sclerotherapy service) could have introduced selection bias: patients motivated to perform sclerotherapy could be the majority of our attendant population, whereas those who do not like this approach could have been missed. A bias in the selection of our population with primary superficial venous disease could have been occurred. However, we believe that our patients may be representative of a common general population referring for venous symptoms in a general venous service (real world). Our center indeed was not a tertiary referring service and treatment was not selectively applied to specific subgroups of population with venous disease (e.g., young, females, pregnant, stroke patients, etc.).

At the same time, studies including large unselected population (e.g., young without symptoms of venous insufficiency) could underestimate the evolution of the disease because of the low prevalence and are often impractical to manage for long-term analysis.

We did not provide precise rate and timing of progression of reflux, and only in a few patients we detailed the progressive staging of the disease; however, our aim was the assessment of the pattern of venous disease evolution and not to detail the whole natural history for which other study design are needed.

Finally, we did not use a medical control group to compare the population neither any specific medical therapy was applied. However, medical therapy generally shows a limited effect, if any, on the evolution of primary venous disease, and in any case it cannot influence the pattern of evolution.

CONCLUSION

The natural history of long-standing primary superficial vein insufficiency is that of progressive deterioration with extension of reflux to other previously competent segments of the superficial veins or to the deep circulation. An ascending (upward directed) more than retrograde and anti-gravity (downward directed) evolution of primary venous insufficiency is likely because venous stasis is higher where force of gravity is higher.

Development of reflux appears to begin particularly in the below-knee segment of the veins where the hydrostatic pressure is higher and to become evident in the upper veins levels only at a later stage following the longitudinal hydrostatic pressure gradient (the highest is near to the ground). Because of the segmental and ascending evolution of primary venous insufficiency, localized correction of reflux at a lower level in an early stage could prevent or slow down the further progression of the disease. Selective treatment in the lower veins might be appropriate as a primary therapeutic option in most patients before predictable deterioration will occur.

However, for a better understanding of the pathogenesis and development of primary venous reflux in lower limbs, and to provide more strength to the ascending theory, prospective longitudinal, large population-based studies, also detailing the timing of the natural history of the disease, are needed.

REFERENCES

1. Ludbrook J, Beale G. Femoral venous valves in relation to varicose veins. Lancet 1962;1:79-81.
2. Pittaluga P, Chastane S, Rea B, Barbe R. Classification of saphenous refluxes: implications for treatment. Phlebology 2008;23:2-9.
3. Wong JK, Duncan JL, Nichols DM. Whole-leg duplex mapping for varicose veins: observations on patterns of reflux in recurrent and primary legs, with clinical correlation. Eur J Vasc Endovasc Surg 2003;25:267-275.
4. Abu-Own A, Scurr JH, Coleridge Smith PD. Saphenous vein reflux withou incompetence at the saphenofemoral junction. Br J Surg 1994;81:1452-1454.
5. Perrin MR, Labropoulos N, Leon LR, Jr. Presentation of the patient with recurrent varices after surgery (REVAS). J Vasc Surg 2006;43:327-334.
6. García-Gimeno M, Rodríguez-Camarero S, Tagarro-Villalba S, et al. Duplex mapping of 2036 primary varicose veins. J Vasc Surg 2009;49:681-689.
7. Cappelli M, Molino Lova R, Ermini S, Zamboni P. Hemodynamics of the sapheno-femoral junction. Patterns of reflux and their clinical implications. Int Angiol 2004;23:25-28.
8. Labropoulos N, Giannoukas AD, Delis K, et al. Where does venous reflux start? J Vasc Surg 1997;26:736-742.
9. Engelhorn CA, Engelhorn AL, Cassou MF, Salles-Cunha SX. Patterns of saphenous reflux in women with primary varicose veins. J Vasc Surg 2005;41:645-651.
10. Cooper DG, Hillman-Cooper CS, Barker SG, Hollingsworth SJ. Primary varicose veins: the saphenofemoral junction, distribution of varicosities and patterns of incompetence. Eur J Vasc Endovasc Surg 2003;25:53-59.
11. Genick Bar—Meir. Basics of Fluid Mechanics, 2008. pp 51-62. Available at http://www.potto.org/downloadsFM.php.
12. Massey B, Ward-Smith J. Mechanics of Fluids. 8th ed. London: Taylor & Francis, 2005.

13. Pascarella L, Schmid Schonbein GW. Causes of telangiectasias, reticular veins and varicose veins. Semin Vasc Surg 2005;18:2-4.
14. Venruri M, Bonavina L, Annoni F, Colombo L, Butera C, Perachia A. Biochemical assay of collagen and elastin in the normal and varicose vein wall. J Surg Res 1996;60: 245-248.
15. Travers JP, Brookes CE, Evans J, et al. Assessment of wall structure and composition of varicose veins with reference to collagen, elastin and smooth muscle cell content. Eur J Vasc Endovasc Surg 1996;11:230-237.
16. Franceschi C. Theory and practice of the conservative hemodynamic treatment of incompetent and varicose veins in ambulatory patients. Armançon Ed. Précy-Sous-Thil. France. 1993- Théorie et practique de la cure conservatrice de l'insuffisance veineuse en ambulatorie. Vol 1. Armançon Ed., Précy-Sous-Thil, France, 1988.
17. Escribano JM, Juan J, Bofill R, Maeso J, Rodríguez-Mori A, Matas M. Durability of reflux-elimination by a minimal invasive CHIVA procedure on patients with varicose veins: a 3-year prospective case study. Eur J Vasc Endovasc Surg 2003;25:159-163.
18. Coleridge-Smith P, Labropoulos N, Partsch H, Myers K, Nicolaides A, Cavezzi A. Duplex ultrasound investigation of the veins in chronic venous disease of the lower limbs—UIP consensus document. Part I: Basic principles. Eur J Vasc Endovasc Surg 2006;31:83-92.
19. Khilnani NM, Min RJ. Duplex ultrasound for superficial venous insufficiency. Tech Vasc Interv Radiol 2003;6: 111-115.
20. Eklöf B, Rutherford RB, Bergan JJ, et al American Venous Forum International Ad Hoc Committee for Revision of the CEAP Classification. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg 2004;40:1248-1252.
21. Pittaluga P, Chastanet S, Rea B, Barbe R. Midterm results of the surgical treatment of varices by phlebectomy with conservation of a refluxing saphenous vein. J Vasc Surg 2009;50:107-118.
22. Labropoulos N, Leon L, Engelhorn CA, et al. Saphenofemoral junction reflux in patients with a normal saphenous trunk. Eur J Vasc Endovasc Surg 2004;28:595-599.
23. Caggiati A, Rosi C, Heyn R, Franceschini M, Acconcia MC. Age-related variations of varicose veins anatomy. J Vasc Surg 2006;44:1291-1295.
24. Labropoulos N, Tassiopoulos AK, Bhatti AF, Leon L. Development of reflux in the perforator veins in limbs with primary venous disease. J Vasc Surg 2006;43:558-562.
25. Bernardini E, Piccioli R, De Rango P, Bisacci C, Pagliuca V, Bisacci R. Echo-sclerosis hemodynamic conservative: a new technique for varicose vein treatment. Ann Vasc Surg 2007;21:535-543.
26. Pittaluga P, Chastanet S, Guex JJ. Great saphenous vein stripping with preservation of sapheno-femoral confluence: hemodynamic and clinical results. J Vasc Surg 2008;47: 1300-1304.
27. Labropoulos N, Leon L, Kwon S, et al. Study of the venous reflux progression. J Vasc Surg 2005;41:291-295.
28. Labropoulos N, Kang SS, Mansour MA, Giannoukas AD, Buckman J, Baker WH. Primary superficial vein reflux with competent saphenous trunk. Eur J Vasc Endovasc Surg 1999;18:201-206.
29. Bernardini E, Piccioli R, De Rango P, Bisacci C, Pagliuca V, Bisacci R. Ambulatory and hemodynamic treatment of venous insufficiency by ultrasound-guided sclerotherapy: 14 year results. Phlebologie 2007;4:186-195.
30. Carandina S, Mari C, De Palma M, et al. Varicose vein stripping versus haemodynamic correction (CHIVA): a long term randomised trial. Eur J Vasc Endovasc Surg 2008;35: 230-237.