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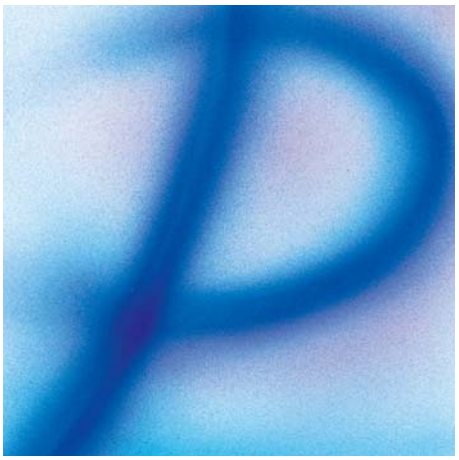

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AIMS AND SCOPE

Phlebolymphology is an international scientific journal entirely devoted to venous and lymphatic diseases.

The aim of *Phlebolymphology* is to provide doctors with updated information on phlebology and lymphology written by well-known international specialists.

Phlebolymphology is scientifically supported by a prestigious editorial board.

Phlebolymphology has been published four times per year since 1994, and, thanks to its high scientific level, was included in the EMBASE and Elsevier BIOBASE databases.

Phlebolymphology is made up of several sections: editorial, articles on phlebology and lymphology, review, news, and congress calendar.

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Phlebolymphology

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PHLEBOLYMPHOLOGY

EDITORIAL

Laser ablation of the great saphenous vein is a technique whose use has expanded dramatically during the last few years. Endovenous techniques without groin incision and high ligation are certainly less invasive than conventional vein stripping, and seem to involve less risk of neovascularization. ***Steven Zimmet*** *from Austin, Texas, the immediate Past President of the American College of Phlebology, gives a well-balanced overview of laser ablation, including the mechanisms of action, technical details, results, adverse sequelae, and complications. Using tumescent anesthesia, this procedure can be performed in-office without general anesthesia or surgical incisions.*

Michel R. Boisseau*, Pharmacology Department of the University of Bordeaux, contributes an interesting basic research paper entitled "Recent findings in the pathogenesis of venous wall degradation". One of the central findings is that the leukocyte-mediated inflammatory chain-reaction is a key factor in the development of varicose veins. There is undoubtedly a vicious circle in which damage to venous walls to incompetent valves, which in turn results in further damage to the vein wall. Faced with this "chicken and egg" conundrum, Professor Boisseau favors the interesting view that it is not venous wall alterations that damage the valves, but rather the reverse.*

A survey, describing the role of Daflon 500 mg in the management of chronic venous insufficiency, is presented by ***Françoise Pitsch****, the driving force behind Phlebolymphology.*

Michael Kendler *and* ***Eva Haas*** *from Germany present an interesting pilot study on patients with "heavy leg syndrome", which is associated with subjective leg symptoms but no objective signs of venous disease (C0,1 S; En; An; Pn), and is also called "functional phlebopathy" (see Giuseppe Andreozzi. Prevalence of patients with chronic venous disease-related symptoms but without visible signs (described as Cos in the CEAP classification): the Italian experience. Phlebolymphology. 2006;13:28-34). In a quality-of-life analysis using the SF-12 questionnaire, the authors found that a global psychological score deviated significantly from that of a healthy population.*

Michael Dalsing*, the President of the American Venous Forum, presents an excellent overview of artificial venous valves in the treatment of the severe stages of deep venous insufficiency. Non-autogenous valve substitutes have failed in clinical evaluation. Hitherto, only valve cusps made of autogenous vein have shown promising results. It may be expected that some day this kind of "science fiction surgery" will offer a clinically important alternative treatment, at least for selected cases.*

The last contributions are reviews. ***Michèle Cazaubon****, Paris, reviews a leading article on chronic venous disease, published by a group of prestigious authors (Bergan JJ, Schmid-Schönbein GW, Coleridge Smith PD, Nicolaides AN, Boisseau MR, Eklof B) in a recent issue of the New England Journal of Medicine. Those who are specifically interested should read and digest this landmark paper.* ***Michel Perrin*** *reviews the recently published "Vein Book" (Elsevier), whose editor-in-chief, J-J Bergan, and 89 authors, have risen to the challenge of covering this vast topic in 617 pages, divided into 65 chapters, with over one thousand references. The result is outstanding.*

Enjoy your reading!

Hugo Partsch, MD

Endovenous laser ablation

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ABSTRACT

Endovenous laser ablation (EVLA) is a less invasive alternative to vein stripping. Outcomes seem equal to, or better than, those with stripping, with better quality of life scores in the post-operative period. EVLA has been shown to correct or significantly improve hemodynamic abnormality in patients with chronic venous insufficiency (CVI) with superficial venous reflux. Early reports suggest that endovenous ablation techniques, in contrast to surgical stripping, are associated with a low incidence of neovascularization.

A variety of wavelengths are being used to perform EVLA. While the initial chromophore is water or hemoglobin, depending on the wavelength used, carbon appears to be a secondary but key chromophore that is probably independent of wavelength.

The application of the principles of tumescent anesthesia to venous treatments, along with the development of endovenous ablation techniques, offer the possibility of treating the vast majority of patients with varicose veins in-office without general anesthesia or surgical incisions, while at the same time maximizing outcomes and minimizing recurrence.

INTRODUCTION

Saphenous vein reflux is the underlying primary abnormality in the majority of cases of superficial venous insufficiency. Thus, approaches to dealing with saphenofemoral junction and saphenous truncal incompetence have dominated the thinking of phlebologists. Trendelenburg described saphenofemoral junction ligation alone, without stripping of the incompetent saphenous vein, in the 1890s. The advantages of ligation alone over ligation and stripping, which are still extolled today,[1] include preservation of the saphenous trunk for possible future use as a bypass graft[2] and avoidance of saphenous nerve injury.[3] High ligation by itself is less

Keywords:
endovenous laser ablation, EVLA, EVLT, saphenous reflux.

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invasive, quicker and simpler to perform, and associated with an easier recovery when compared to vein stripping. While it is true it routinely "spares" the saphenous trunk,[4] the use of a diseased saphenous vein as a conduit has been associated with an increased risk of graft failure.[5] Most importantly, there is no longer any question that high ligation alone usually results in persistent reflux in the saphenous trunk.[6,7] Varicose recurrence is significantly reduced[7-9] and the re-operation rate is 60% to 70% less if the saphenous vein is stripped compared with ligation alone.[10,11] Also, after ligation alone, recurrence or residual communication with the junction in the groin was found in 80% of patients, while 34% also had mid-thigh perforator incompetence via the unstripped great saphenous vein (GSV).[12] As Neglen concluded, stripping of the GSV of the thigh is essential to minimizing recurrence that is caused by redevelopment of incompetent communication with the saphenofemoral confluence, and due to thigh perforator incompetence.[13] Simply put, the shortcomings of ligation alone outweigh its advantages.

It is important to note that recurrence is common even after ligation and stripping of the saphenous vein. While inadequate surgery of the saphenofemoral junction and progression of disease are mechanisms that explain some cases of recurrence, another important mechanism is neovascularization around the junction after venous surgery.[11,14] In fact, neovascularization has been reported as the principle cause of recurrence,[9] with neovascular channels of variable size, number, and tortuosity accounting for the reflux to recurrent varicosities in the majority of cases.[15] Though some have expressed doubt as to the veracity of true neovascularization, there is clear histological evidence that neovascularization is a cause of recurrent varicose veins.[16] Early reports suggest, in contrast, that endovenous ablation techniques are associated with a very low incidence of neovascularization.[17] It may be that the development of neovascularization is largely prevented by avoiding groin dissection and by preserving venous drainage in normal junctional tributaries.[18,19]

EVLA, like radiofrequency ablation and foam sclerotherapy, is a less invasive alternative to vein stripping. EVLA is indicated in an ambulatory patient with great, small or accessory saphenous vein reflux with surface varices and/or symptoms or complications related to superficial venous insufficiency. EVLA is routinely performed using dilute local anesthesia, with or without supplemental oral anxiolytics, in an office setting. Generally taking 30-60 minutes to perform, procedure times are dependent on the length of segment treated, experience of the operator, and whether ancillary procedures, such as ambulatory phlebectomy, are done. Regardless of how underlying saphenous incompetence is treated, ancillary treatments are typically needed to treat residual varices (*Figure 1*).

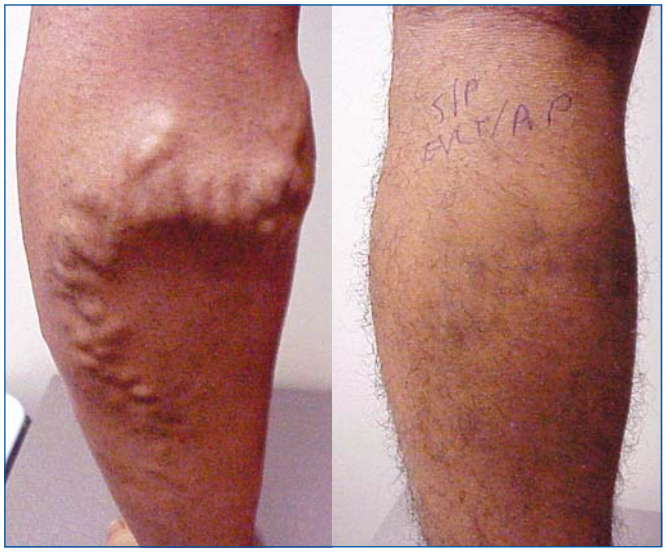

Figure 1. 26 y/o male before and 1 month after endovenous laser ablation of the great saphenous vein and ambulatory phlebectomy of varicose tributaries.

EFFICACY

Short- and mid-term studies of EVLA, regardless of wavelength used, seem remarkably consistent, typically reporting ablation of refluxing saphenous veins in 90% or more of cases.[18,20-23] EVLA of the saphenous vein has been shown to correct or significantly improve the hemodynamic abnormality and clinical symptoms of chronic venous insufficiency (CVI) in Clinical, Etiological, Anatomical, Pathophysiological (CEAP) clinical class 3-6 patients with superficial venous reflux.[24,25] Outcomes seem equal to or better than those of stripping, with better quality of life scores in the post-operative period compared to stripping.[20,25-27] High patient satisfaction rates have been reported.[18,28,29] The total cost (cost of the procedure plus societal cost) of endovenous procedures is likely equal to or lower than that of surgery.[27]

Early data on treatment of the GSV with 810 nm and 940 nm devices suggest treatment failure is uncommon

in patients treated with > 70 J/cm.[30,31] A withdrawal rate of 2 mm/sec at 14 watts delivers 70 J/cm.

MECHANISM OF ACTION

The following wavelengths are in current use for EVLA: 810, 940, 980, 1064, 1319, 1320, and 2068 nm. It has been postulated that vein wall injury is mediated both by direct effect and indirectly via laser-induced steam generated by heating of small amounts of blood within the vein.[32] Some have suggested that choice of wavelength greatly impacts results.[23]

The main chromophore of 1320 and 2078 nm lasers, at least initially, is water, while other wavelengths used for EVLA primarily target hemoglobin. Obviously it is imperative to thermally damage the vein wall adequately in order to obtain effective ablation. Some heating may occur by direct absorption of photon energy (radiation) by the vein wall as well as by convection from steam bubbles and conduction from heated blood. However, it is unlikely that these latter mechanisms account for the majority of impact on the vein. The maximum temperature of blood is 100°C. Laser treatment has been found to produce carbonization of the vein wall.[33] Carbonization of the laser tip, which occurs at about 300°C, is noted following EVLA, and seems to occur regardless of the wavelength used.[34] Carbonization of the laser fiber tip creates a point heat source and essentially reduces light penetration into tissue to zero.[34,35] Mordon et al stated "The steam produced by absorption of laser energy by the blood is a tiny fraction of the energy necessary to damage the vein wall and cannot be the primary mechanism of injury to the vein with endovenous laser. The carbonization and tract within the vein walls seen by histology following endovenous laser can only be the result of direct contact between the laser fiber tip and the vein wall."[36] Dr Rox Anderson, director of The Wellman Center for Photomedicine at Massachusetts General Hospital, reported that carbon appears to be a secondary but key chromophore that is probably independent of wavelength (*Figure 2*).[34] Note that fiber tip and shape may impact development of carbonization.[37]

Figure 2. Carbonization of 600-micron laser fiber tip secondary to endovenous laser ablation with a 1320 nm laser (Photo courtesy of Mark Forrestal, MD, FACPh).

TUMESCENT ANESTHESIA

EVLA should be performed under local anesthesia using large volumes of a dilute solution of lidocaine and epinephrine (average volume of 200-400 mL of 0.1% lidocaine with 1:1,000,000 epinephrine) that is buffered with sodium bicarbonate. This solution should be delivered either manually or with an infusion pump under ultrasound guidance so the vein is surrounded with the anesthetic fluid along the entire length of the segment to be treated (*Figure 3*). The benefits of tumescent anesthesia for endovenous ablation include:

- anesthesia,
- separation of vein to be treated from surrounding structures,
- thermal sink, which reduces peak temperatures in perivenous tissues,
- vein compression, which maximizes the effect of treatment on the vein wall.

Although the maximum safe dosage of lidocaine using the tumescent technique for venous procedures is not

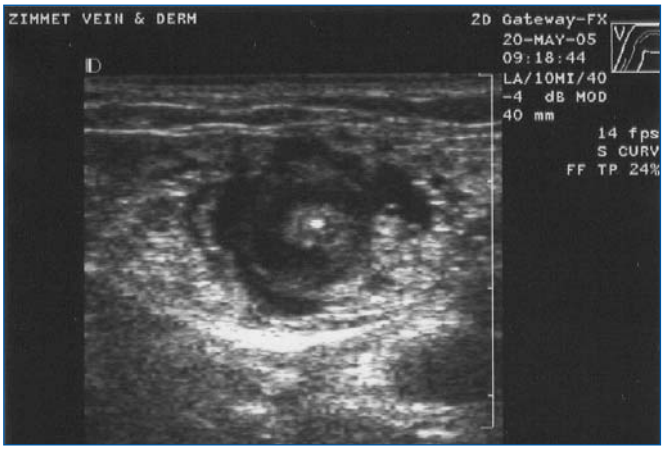

Figure 3. Transverse ultrasound image of tumescent anesthetic fluid surrounding centrally located great saphenous vein and laser fiber/sheath.

well studied, a dosage of 35 mg/kg is a reasonable estimate.

Using these parameters, tumescent anesthesia in the context of liposuction has been shown to be extraordinarily safe. More information is available at http://www.liposuction.com/pharmacology/drug_interact.php.

CONTRAINDICATIONS TO EVLA

Contraindications to EVLA technique are summerized in *Table I*.

Allergy to local anesthetic
Hypercoagulable states
Infection of the leg to be treated
Lymphedema
Nonambulatory patient
Peripheral arterial insufficiency
Poor general health
Pregnancy
Recent/active venous thromboembolism
Thrombus or synechiae in the vein to be treated
Tortuous great saphenous vein (it may be difficult to place the laser fiber)

Table I. Contraindications to endovenous laser.

ADVERSE SEQUELAE

Short-term pain and ecchymoses have been commonly observed after EVLA. Intermittent-pulsed laser fiber pullback has been reported, in a retrospective review, to cause significantly greater levels of post-operative pain and bruising, compared with a continuous pullback protocol.[38] Adding a short-stretch bandage for 3 days following intermittent mode EVLA substantially reduced patient-reported bruising and pain. Employing continuous mode pullback further reduced the severity of pain and bruising to such an extent that levels were similar to those reported by patients treated with radiofrequency ablation (*Tables II and III*). Preliminary reports suggest there may be some differences in postoperative course depending on wavelength used to perform EVLA.[22,39] However, this is based on sparse data with short-term follow-up.

PERIVENOUS THERMAL INJURY

Mean peak intravascular temperatures during EVLA (goat jugular vein, 12 watts, 1-second pulses, 1-second intervals), measured flush with the laser tip, averaged 729°C, while those 4 mm distal to the tip averaged 93°C.[40] However, the risk of collateral thermal injury depends on perivenous tissue heating, not intravascular temperature.

	Mild	Moderate	Severe
Pulsed: stockings (n=21)	28%	23%	49%
Pulsed: stockings + short-stretch bandage (n=8)	37%	50%	13%
Continuous: stockings + short-stretch bandage (n=16)	75%	25%	0%
Radiofrequency: stockings (n=16)	88%	12%	0%

Table II. Patient-rated post-operative bruising 3-7 days following pulsed endovenous laser ablation (EVLA) with class II stockings, pulsed EVLA with stockings plus short-stretch bandage, continuous mode EVLA with stockings and short-stretch bandage, and radiofrequency ablation with stockings.

	Mild	Moderate	Severe
Pulsed: stockings (n=21)	38%	39%	23%
Pulsed: stockings + short-stretch bandage (n=8)	50%	38%	12%
Continuous: stockings + short-stretch bandage (n=16)	81%	19%	0%
Radiofrequency: stockings (n=16)	75%	25%	0%

Table III. Patient-rated post-operative pain 3-7 days following pulsed endovenous laser ablation (EVLA) with class II stockings, pulsed EVLA with stockings plus short-stretch bandage, continuous mode EVLA with stockings and short-stretch bandage, and radiofrequency ablation with stockings.

Collagen has been noted to contract at about 50°C, while necrosis occurs between 70°C and 100°C.[41] The extent of thermal injury to tissue is strongly dependent on the amount and duration of heat the tissue is exposed to. Henriques and Moritz investigated the time-temperature response for tissue exposed to up to 70°C.[42] They found that skin could withstand temperature rises for very short exposure times, and that the response appears to be logarithmic as the exposure times become shorter. For example, an increase in body temperature to 58°C will produce cell destruction if the exposure is longer than 10 seconds. Tissues, however, can withstand temperatures up to 70°C if the duration of the exposure is maintained for less than 1 second. Li et al reported that heating endothelial cells to 48°C for 10 minutes did not induce cell death.[43] They also found that osteoblasts, after exposure for 10 minutes or less at 45°C, underwent transient and reversible changes. Another study found reversible tissue damage to the hind limb of mice after submersion in a waterbath at 44°C.[44]

A recent study measured peak temperature at the outer vein wall during EVLA in a live pig ear vein and in exposed hind limb veins.[45] EVLA settings ranged from 8 watts (1-2 second pulse durations), 10 watts (1-1.5 second pulse duration), 12 watts (0.5-1.5 second pulse duration) to 15 watts (0.5-1.0 second pulse duration), with and without tumescent anesthesia. Results demonstrate that peak temperatures ranged from 34.6°C to 49.1°C as a function of joules delivered, with lower peak temperatures obtained when tumescent fluid was present (*Figure 4*).

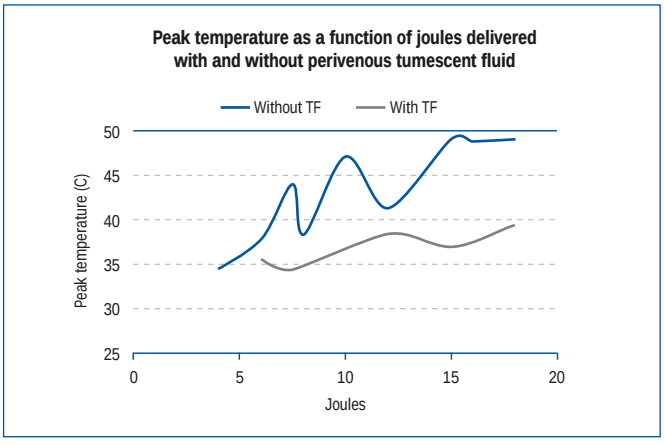

Figure 4. Adapted from Zimmet SE, Min RJ. Temperature changes in perivenous tissue during endovenous laser treatment in a swine model. J Vasc Interv Radiol. 2003;14:911-915 (ref 45).

Peak temperature measured during EVLA (63 patients, 980 nm, 15 watts, 1.5 sec pulses) at the outer vein wall in humans, 3 cm below the saphenofemoral junction, was 40.9°C and 49.8°C with and without tumescent fluid, respectively.[46] Similar results were reported from another human study during EVLA (12 patients, 810 nm, 12 W, 1 second pulses, 1 second intervals, tumescent technique), with peak temperatures of 43.3°C, 42.0°C, and 36.0°C at 3 mm, 5 mm, and 10 mm from the GSV, respectively.[47]

There appears to be a very rapid fall-off in temperature over short distances during EVLA. This is probably in contrast to radiofrequency energy where microwave heating occurs around the tissue-electrode interface. The animal and human data suggest that peak perivenous temperatures generated during endovenous laser are unlikely to cause permanent damage to perivenous tissue in most situations. The peak temperature generated is reduced with the use of perivenous tumescent fluid. These findings seem to explain the very low reported incidence of nerve injury and skin burns following EVLA. One study, using a 1064 nm Nd: YAG laser, reported a very high incidence of paresthesia in 36.5% and skin burns in 4.8%.[48] It should be noted that the amount of energy delivered was about three times higher than what is typically used and that treatment was done without tumescent anesthesia. Despite the low perivenous temperatures reported with EVLA, it is important to note that special caution is required when considering endovenous intervention in certain cases such as sciatic nerve varices.[49,50]

MAJOR COMPLICATIONS

Major complications following EVLA have been reported rarely. Rates of deep venous thrombosis (DVT), pooled from multiple series, are much lower than 1%.[17,18,20,28] One group reported an incidence of thrombus extension into the femoral vein of 7.7%.[51] However, in that study EVLA was done under general or spinal anesthesia. The fact that patients were not able to ambulate immediately post-operatively may have contributed to the high incidence of thrombus extension. There is a single report of an arteriovenous fistula that developed following EVLA of the short saphenous vein (SSV).[52] One patient developed septic thrombophlebitis following EVLA combined with open ligation of perforators and stab phlebectomy.[53] This resolved with antibiotic treatment and debridement.

ALTERNATIVE APPROACHES

EVLA and radiofrequency ablation (RFA)[54,55] both appear to be effective treatments for saphenous incompetence. Advantages of EVLA over RFA include shorter procedure times and lower per treatment cost. Reported occlusion rates of EVLA generally are slightly higher than those obtained with RFA.[56] Disadvantages of EVLA may include more bruising and discomfort in the early post-operative period, although this may be technique-dependent. Both techniques continue to undergo refinement, which will improve results. Both procedures, when performed using tumescent anesthesia, are associated with low complication rates.

Another emerging treatment for saphenous reflux is the use of foamed sclerosants delivered under ultrasound control. A gas, such as air or CO_2, can be mixed with liquid detergent sclerosants to create foam, estimated to be about four times more potent than the liquid form of the same agent. Early results suggest this may be a valuable modality, as it is quick and inexpensive to perform with reported short- and mid-term success rates of about 75% to 90%. There are many variables regarding foam (eg, type and amount of gas, technique used to create foam, concentration and type of sclerosant used, volume injected, etc). There may be a higher risk of deep vein thrombosis following foam sclerotherapy compared with standard sclerotherapy. Proper technique is important to minimize the risk of this complication. Other side effects reported following foam sclerotherapy include visual and neurological events. There is a published report of stroke following foam sclerotherapy (20 mL polidocanol foam) in a patient with a 1.8 cm patent foramen ovale.[57] Further experience and research with this modality will better delineate its risks as well as long-term efficacy.

CONCLUSION

Currently accepted principles of treatment of varicose veins serve to maximize outcomes from a hemodynamic and patient standpoint, while minimizing the risk of recurrence. Appropriate treatment of varicose veins begins with an accurate assessment of the underlying venous pathology and identification of sources of venous hypertension. The aims of treatment include elimination of the incompetent connections between the deep and superficial systems, as well as the obliteration of pathways of venous incompetence and incompetent varicose veins. It is evident that recurrence is reduced if the incompetent segment of the saphenous trunk is ablated.

Endovenous laser ablation is a less invasive alternative to vein stripping. Outcomes seem equal to or better than those of stripping, with better quality of life scores in the post-operative period. EVLA has been shown to correct or significantly improve hemodynamic abnormality in patients with chronic venous insufficiency with superficial venous reflux. Early reports suggest that endovenous ablation techniques, in contrast to surgical stripping, are associated with a low incidence of neovascularization.

The application of the principles of tumescent anesthesia to venous treatments, along with the development of endovenous ablation techniques, offer the possibility of treating the vast majority of patients with superficial venous insufficiency in-office without general anesthesia or surgical incisions, while at the same time maximizing outcomes and minimizing recurrence.

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Recent findings in the pathogenesis of venous wall degradation

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SUMMARY

Increased venous pressure in the erect position is a constant finding in patients with chronic venous disease. In the case of primary chronic venous disease, this increase in venous pressure is linked to venous reflux. A linear relationship exists between increased ambulatory venous pressure and skin ulceration.

The length of time a subject is exposed to elevated venous pressure is a major factor in the progression of venous disease and in the development of varicose veins. The development of an animal model of venous hypertension (VHT) has demonstrated venous valve damage at an early stage of the disease, associated with the development of a leukocyte-endothelium biochemical cascade reaction. According to a similar mechanism, this inflammatory chain reaction may extend to large veins, resulting in multilevel valvular deficiencies and increased VHT. Prolonged VHT has an impact on the capillary network, and can produce trophic (skin) changes. Factors that trigger leukocyte adhesion and migration in the venous endothelium are mainly related to slowing of blood flow, with a decrease in shear stress in the valvular sinuses and along the large veins, and lastly in the cutaneous venules. Valvular and subsequent luminal and medial hypoxia is also a triggering factor. Remodeling of the saphenous veins is related to migration of monocytes, T and B lymphocytes, and mast cells in particular. The latter transport growth factors such as transforming growth factor (TGFβ1). All these cells, including the endothelium and migratory and dedifferentiated smooth muscle cells, participate in setting up enzyme systems that act on the extracellular matrix (ECM), in particular zinc-dependent metalloproteinases (MMPs), which are produced in excess compared with their inhibitors. Collagen disorders (type III rather than type I), rarefaction of elastin, alternating cellular zones, and atrophic fibrous zones account for the macroscopic and sometimes exuberant appearance of varices. The wide variability from one subject to another in the progression of venous disease is related to many factors that promote venous disease, ranging from having to stand erect to familial genetic factors.

Keywords:
venous disease, varices, pathogenesis, histopathology, inflammation, leukocytes, remodeling, valvular alteration.

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In summary, alterations in venous valves induced by a leukocyte-mediated inflammatory process appear to be a key factor in the development of varicose veins, and can be inhibited by the micronized flavonoid fraction in Daflon (diosmin) 500 mg.

INTRODUCTION

Many causes of chronic venous disease (CVD) can be differentiated, but it is formally established that the most frequent one, primary venous disease, is linked to venous hypertension (VHT). The mechanisms responsible for venous return are complex, all the more so in that the force of gravity in the blood column in the erect position, venous distensibility, and pressure produced by abdominal exertion inhibit the return of blood to the heart in a subject in the standing position. Reflux is prevented by the venous valves, which protect against excessive distension of the venous wall, by facilitating appropriate emptying of the superficial venous network into the deep veins, and also protect distal tissues, especially the cutaneous tissue, which behaves "naively" with regard to VHT. Therefore, it is evident that venous valve incompetence, whose consequence is an increase in venous pressure, is the major cause of varicose vein disease, and subsequent venous insufficiency and skin disorders, including venous ulceration, the most serious complication. The historic studies by Nicolaides demonstrated a linear relationship between ambulatory venous pressure, measured at the ankle, and ulceration. Skin lesions, observed in stages 5 and 6 of the clinical, etiological, anatomical and pathophysiological (CEAP) classification, are most often associated with both superficial and deep venous reflux.[1] The mechanisms by which uncontrolled VHT produces venous wall dystrophy, remodeling that characterizes varices and microcirculatory skin alterations, have been partly elucidated.

Recent studies show that the link between valvular dysfunction and remodeling involves early activation of aseptic inflammation, which triggers cellular and enzymatic processes. The cellular processes are dynamic, related to VHT, and again it is the cells that determine *in situ* the biochemistry of the valvular apparatus and in the wall of the vein.[2,3]

These findings represent an appreciable step in the study of venous disease, and enable better definition of new therapeutic targets. Nevertheless, the wide variability in the expression of venous disease, the many factors that promote it, and the genetic factors that remain largely unknown, have opened the way to future research in this field.

The purpose of this article is to provide an updated account of our knowledge of the mechanisms involved in venous disease, by considering the venous valve and the venous wall, factors that promote this disease, and therapeutic prospects.

Background to the relationship between venous hypertension and valvular alterations

Incompetent venous valves

Spontaneous venous insufficiency does not exist in four-legged animals, because venous pressure in their paws is low. In humans in the standing position, venous pressure measured at the ankle reaches 85 mm Hg; but ambulation produces a fall to 25 mm Hg. Therefore, frequent and regular walking by healthy subjects provides effective protection against the pathologic effect of the blood column pressure in orthostatic posture, as a result of the "joint and muscle pump." This was true of our distant ancestors who had to walk long distances in search of food, and may still be true for a few isolated tribes of humans who live under primitive conditions. Since such conditions of life have disappeared, subjects who live under the conditions of "modern life" tend to remain standing or in the seated position longer, thus activating the muscle pump mechanism less. Consequently, they are subject to VHT for a longer time. It is the duration of the pressure exerted on the venous valves and venous wall that determines alterations, and is the essential factor in the development of CVD.

Figure 1 depicts the conditions under which venous valves operate. Venous valves in superficial, paratissular and perforating veins are closed when the subject is in the standing position, and during contraction of skeletal muscles, thus providing peripheral protection. These valves open when the deep venous system is emptied, creating a negative pressure gradient, and then they fill from the upper to the lower part of the vein, in particular emptying the microcirculatory plexuses of the skin. Thus, valvular incompetence in superficial veins is the key component of venous disease, and has been

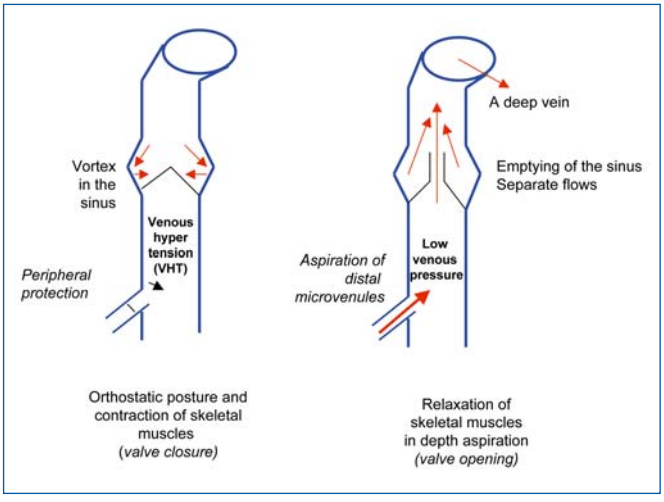


Figure 1. Alternating high and low venous pressures in the saphenous veins in orthostatic posture. Occurrence of venous hypertension (VHT), specific to human subjects.

observed by angioscopy,[4,5] showing retraction of the free borders, atrophy of the leaflets, and thickening of the opposite side of the wall. Furthermore, angioscopy has shown the frequency of alterations, sometimes in their early stages, in young subjects, with no marked alteration in the corresponding veins.[4] This finding has been confirmed by epidemiological studies on very young subjects, showing reflux in an appreciable percentage of subjects, as shown by duplex scanning (the Bochum study).[6] Thus, valvular incompetence may frequently occur prior to venous wall damage, and therefore would be a decisive factor in the progression of this disease.

Figure 2 depicts hemodynamic alterations corresponding to valvular incompetence, with the occurrence of reverse flow prolonging VHT in the periphery, especially if the perforator veins are incompetent. The resultant hemodynamic disorders affect activation of the endothelium, a key player in triggering the inflammatory cascade.

It is undisputed that obstruction is a less frequent cause of venous ulceration than has been recognized to date, the cause being reflux in the superficial venous system, the perforator veins, or the deep venous system (mean values of several studies) in 80% of cases, while the sequelae of venous thrombosis or trauma are mentioned in 20% of cases, and a congenital anomaly is noted in 2%.[7,8] CVD is maintained by an "axial reflux," from the thigh to the calf, in the superficial and deep vein axes.

But then how does venous valve dysfunction produce histological alterations?

Several theories have been proposed, and currently two poles of thought have received a certain amount of acceptance: excessive distensibility in the venous wall, and constitutional weakness in the venous wall.

Because it contains few smooth muscle fibers, the venous wall is highly distensible. This property allows the vein to store large quantities of blood (concept of a venous reservoir). It has been suggested that repeated mechanical pressure by itself could produce abnormalities in the synthesis of collagen or elastin in the venous wall. An abnormal type of collagen has even been identified in cell cultures of fibroblasts from varices. Nevertheless, the link between mechanical and biochemical factors is missing, and increased distensibility appears to be secondary to remodeling. Constitutional weakness in the wall of the vein has also been suggested and points to involvement of hereditary factors. However, this notion applies little to the venous valve.

Ultrasonography studies have examined valvular functioning and have identified the direction and velocity of blood flow.

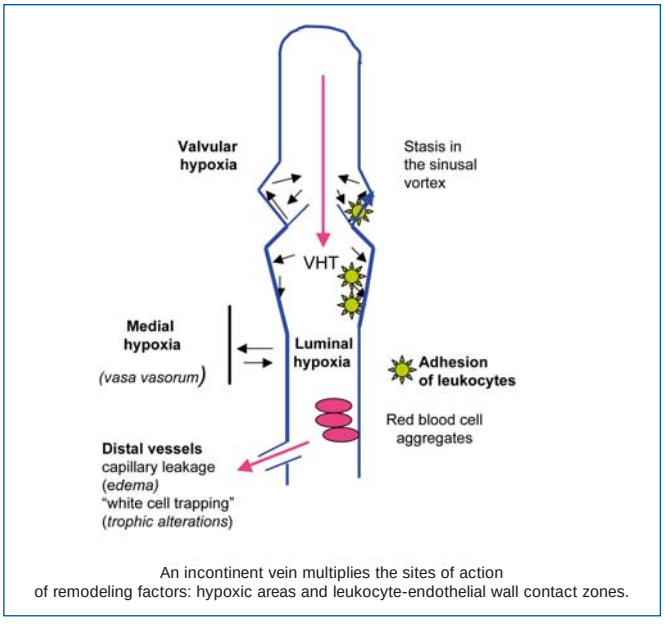


Figure 2. Incontinence of the valvular system produces areas of hypoxia: in the lumen of the blood vessel, by compression of the vasa vasorum, and at the bottom of the sinus. In addition, areas of leukocyte adhesion develop, as a result of lack of shear stress, early onset in the sinus, and along the altered blood vessel wall.

Progressive demonstration of the links between valvular outflow and leukocytes

Hemodynamic measurements in the sinus and during its cycle of action show sinuses as zones of branching flow, where the flow becomes organized into a vortex (*Figure 3*). The major part of the flow remains centripetal, while a small part reverses direction and fills the sinus in a counter-current direction. The residence time of circulating white blood cells therefore increases. Hamer et al have studied this type of outflow in dog veins made transparent by inducing a polystyrene microparticle flow that can be filmed. They described two types of vortex: a superficial vortex and a deep vortex.[10] The superficial vortex is displaced towards the orifice of the sinus, while the particles make parabolic movements, slowly heading to the wall, promoting possible leukocyte adhesion. The vortex will be that much larger when the blood vessel is large. The deep vortex (the counterrotating secondary vortex) is usually empty, but under conditions of abnormal flow it fills in its capacity as a "cell trap." Anoxia develops at the bottom of this vortex. Vortex size is kept small by the pulsatile flow, but increases if there is loss of pulsatility and venous stasis, creating conditions for leukocyte adhesion.[10] In earlier studies, Sewitt observed platelets, red blood cells, and in particular leukocytes at the bottom of valves in deep veins using electron microscopy. According to Sewitt, venous thrombosis in valves in the deep vein system originate at a fibrinous platelet nidus, but he also noted that such a nidus is partially formed in normal persons, all the more so if they are elderly.[11] Lurie defined the venous valve cycle, and noted a separation of flow at the time of an equilibrium phase (leaflets spread apart during systole), with the production of a vortex in the sinus crossed by slow currents (*Figure 3*). The dilated sinus is emptied by pulsatility, which allows reoxygenation of the valve bottom. Such functioning is multifactorial and all rheological factors and stasis alter it. Conversely, movements of the foot promote proper operation of the valvular apparatus (increased velocity, increased luminal pressure of the valve, as well as its potential for closure).[12]

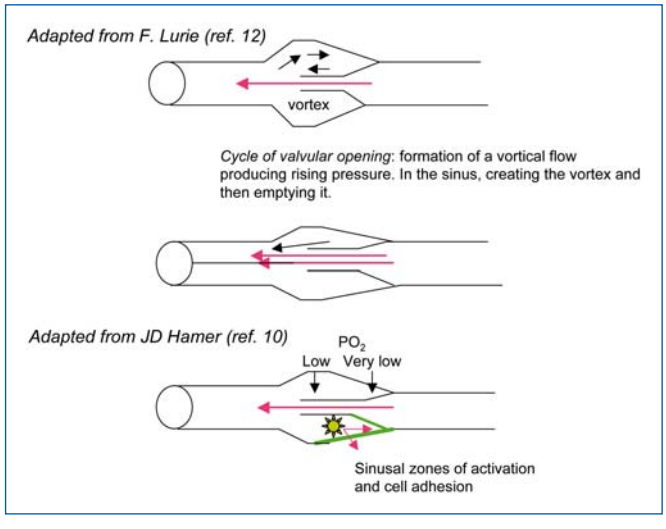


Figure 3. Examination of blood flow through the valvular system shows that vortices form in the sinus also under conditions of valve opening. Measurement of oxygen levels revealed hypoxia at the bottom. Adhesion molecules (VCAM-1, ICAM-1) developed on the anterior side of the cuspid and not below (see text and references).

All these studies have attracted the attention of hemorheologists, and, in particular, the San Diego team of Bergan, Takase, and Schmid-Shönbein, the latter being a founding member of the European Society of Hemorheology. These researchers understood that the conditions for outflow in the valve expose circulating white blood cells to hypoxia and shear stress. Hypoxia activates the endothelial cells, and the lowering of shear stress on the venous wall in contact with zones of slow flow allows leukocyte adhesion. Thus, a new concept to account for damage to the venous valve wall was developed.

Inflammation in the wall of the venous valve

Takase et al studied the course of valvular disease in an animal model by creating an arteriovenous fistula in the rat, according to a technique used by Van Bemmelen et al.[13] After three weeks of elevated pressure, the valve leaflets were damaged, incompetent, retracted, and infiltrated by leukocytes. Identified by specific monoclonal antibodies (immunohistology), these white blood cells were granulocytes, and especially monocytes. In addition, T and B lymphocytes, and cells in apoptosis, were observed.[14] Other experiments by the same authors based on occlusion of the rat mesenteric veins showed that adhesion of white blood cells was greater above rather than below the sinus. The opposite part of the venous wall underwent remodeling. In another study, Takase et al showed that the endothelial cells above the sinus expressed intercellular adhesion molecule-1 (ICAM-1).[15] Thus the concept of the role of leukocytes in producing valvular damage was demonstrated. Moreover, it should be kept in mind that other authors had shown that rats trained to remain on their hind legs (vertical position) for several weeks (the so-called "standing rat" technique) showed venous valve remodeling.[16]

In humans, leukocytes were observed in venous valves in varicose vein disease, in particular monocytes[17] and mast cells.[18] Furthermore, the San Diego team demonstrated that, in venous insufficiency, "plasma inflammation" can be observed by means of markers, and propagates the activation of white blood cells in the circulation.[19]

Development of varicose veins: the essential role of valvular alterations

It is not an alteration in the venous wall that induces damage to the valve but rather the opposite. Once valvular damage is done, it produces venous, and then cutaneous, damage. Nevertheless, varicose vein deformities will themselves promote development of the process, enhancing deterioration of the entire vessel (a vicious circle). Furthermore, progressive alteration of venous wall elasticity and contractility lead to extensive distension of the venous wall, because of the effect of VHT, which then secondarily alters functioning of the valves.

Damage to other valvular systems

The impact of valvular incompetence is variable, as explained by Vin (President of the French Society of Phlebology, personal communication-unpublished results), and its extent is quantified by duplex scanning.[2] If dysplastic alterations develop opposite the ring of a valve located high in the saphenous veins, uncontrolled VHT will exert its effect from the upper to the lower part of the vein, producing segmental remodeling and progressive incompetence of the underlying valves. The valves thus damaged can be terminal valves, or in a collateral thigh vein. Distal, peripheral dilation can also develop, either in the reticular venous tissue dilating the subdermal veins, which then undergo remodeling, or by damage to the perforator veins (40% of cases of primary varicose veins). By a process of aspiration, the overlying saphenous veins become incompetent: the "bobsleigh" theory considers this to occur from the lower to the upper part of the vein.[20] In this context, the ASVAL method (selective ablation of varicose veins under local anesthesia), which is undergoing evaluation, is designed to restore competence to the saphenous veins by phlebectomy of the distal collateral branches.[2]

Cutaneous tissue alterations

Elevated intensity and prolonged duration of VHT in lower limb veins carries the risk of skin disorders, since naive skin is not able to protect itself. An example of this is incompetent perforator venous valves in the juxtamalleolar area, which result in venous ulceration. Similarly, the classical relationship between a leg ulcer and elevated ambulatory venous pressure should be kept in mind. The disorders observed include increased capillary permeability with leakage and edema, capillary changes (Fagrell and Bollinger's microangiopathy), and subsequently skin alterations with alternating inflammatory and atrophic areas. A leg ulcer is the result of these changes, but its course is slow, dissociated, and depends on additional factors. In a first phase, VHT induces mainly edema, with pain, an early sign of venous disease. Hemorheological disorders add to this process (enhanced red blood cell aggregation), due to fluid leakage (contraction of plasma volume), and elevated serum fibrinogen related to inflammation. The mechanisms have been defined by study of skin biopsies and center on the leukocyte/endothelium interaction. The endothelium of microvenules and subdermal plexuses expresses adhesion molecules (ICAM-1, vascular cell adhesion molecule-1 [VCAM-1]).[21,22] Circulating leukocytes are activated and express integrin CD11b. The theory of white blood cell retention and activation proposed by Coleridge-Smith's school (white cell trapping) is now recognized.[23] It sheds light on the pathogenesis of an ulcer, which arises because white blood cells deliver to the epidermis enzymes active on the extracellular matrix,[24] and vascular endothelial growth factor, which is active on capillary permeability.[25]

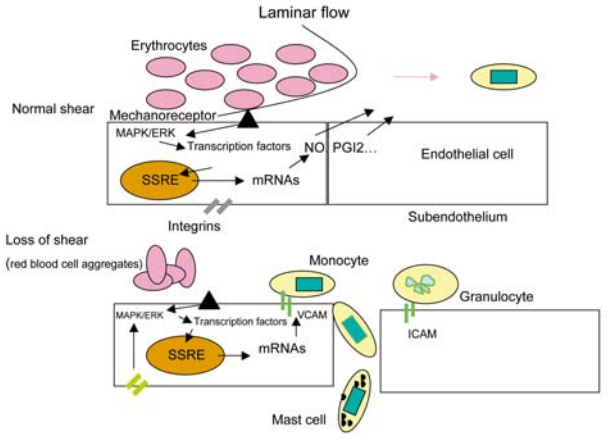
Damage to large veins: formation of a varicose vein by remodeling

A varicose vein develops as the result of degenerative transformation of the layers of the venous wall, which undergo remodeling (which means a "change in shape"). This process is associated with the leukocytes, which, under the influence of VHT, successfully pass into the venous wall, thereby producing hypoxia and alterations in shear stress.

Hypoxia (*Figure 2*) affects the sinus in the venous valves, but is also luminal in the presence of venous stasis,[26] and medial by compression of the vasa vasorum.[27] Hypoxia first affects the sinus, and as seen before is a constant finding in the valvular nidus. The other sites are progressively activated. Hypoxia activates the endothelium, which then expresses adhesion molecules.[28]

Anomalies of shear stress (Figure 4)

Normally, the endothelium lining the venous wall is sheared by laminar flow. Regular, and relatively high pressures keep the adhesive functions of the endothelial tissue dormant and promote homeostasis, in particular by the secretion of nitric oxide (NO).[29] But the circulatory mechanisms form sites where these functions are lost. First and foremost, in the sinus where zones not subject to shear promote contact between leukocytes and endothelium. Then VHT, by virtue of a pressure difference and creation of turbulence, alters laminar flow along the walls of the veins, and forms subvalvular zones of recirculation, which are not subject to shear and also promote transport of cells.



ICAM: inter-cellular adhesion molecule
VCAM: vascular cell adhesion molecule
NO: nitric oxide
PG: prostaglandin
SSRE: shear stress sensitive elements
PGI2: prostacyclin
MAP/ERK: pathway of MAP kinases.

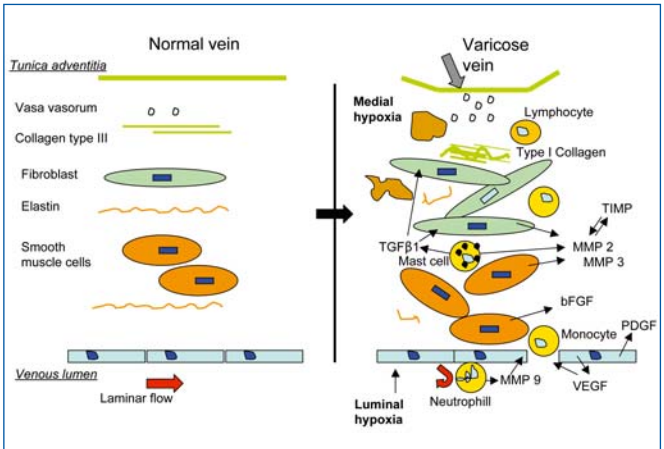
Figure 4. Laminar flow "shearing" of mechanoreceptors of the endothelium in the direction of protection of the blood vessel (10 dynes/cm^2) re-inhibits molecular expression of adhesions, selectins, ICAM-1, and VCAM-1. Under abnormal conditions of blood flow producing a fall in shear stress (< 5 dynes/cm^2), the mechanoreceptors induce the opposite effect. Many genes are sensitive to mechanoreceptors and to stretching of integrins.

Figure 4 depicts the mechanisms of mechanotransduction: from receptors sensitive to pressure variations exerted by circulating blood acting on MAP kinase signaling cascades, and then on transcription factors able to activate genes sensitive to stress, delivering a large number of products, including adhesion molecules.

The front of the shear flow can be altered by red blood cell aggregates, leading to changes in shear stress, thus defining the rheological action.[30] Stretching of integrins, which connect the cell to its subendothelium, has the same action as mechanoreceptors, explaining how stretching and distension of the venous wall impact on venous wall function (stretching). The latter explains the "mechanical" action of pronounced distension acquired after several years of remodeling.

Remodeling, the ultimate result

Figure 5 illustrates the processes that take place in the venous wall. Macroscopically, hypertrophic areas, where ECM components accumulate, alternate with atrophic areas containing few cells and fibers. Macroscopic lesions are characterized by an increase in rigid, type I collagen, and also a decrease in more distensible type III collagen, associated with rupture and rarefied elastin bundles.[31] Intense cellular activity is observed among fibroblasts and smooth muscle cells. The latter, dedifferentiated, acquire secretory properties and migrate towards the thick intimal layer.[32] Thus, the leukocytes are at work, with the neutrophils attached to the outer and inner layers of the endothelium, thus contributing to its high activation. Monocytes, macrophages, and T and B lymphocytes are observed in the tunica intima and media, and especially mast cells, whose abundance greatly increases.[8] Apart from participation in remodeling, mast cells induce extensive activation because they contain high amounts of histamine and bradykinin, the basis for expression of endothelial selectins. Mast cells also play a part in pain, since they can activate the nociceptors of amyelinic C fibers. These changes in the ECM are related to enzyme systems associated with growth factors, which are transported and delivered by the smooth muscle cells and mast cells (*Table I*). Zn-dependent metalloproteinases act at an



bFGF: basal fibroblast growth factor
MMP: matrix metalloproteinase
PDGF: platelet-derived growth factor
TGF: transforming growth factor
TIMP: tissue inhibitor metalloproteinases
VEGF: vascular endothelial growth factor

Figure 5. Interaction between blood cells associated with fibroblasts and smooth muscle cells during remodeling.

NAME	TYPE	PURPOSE	ORIGIN
MMPs *Zn-dependent metalloproteinases*	Protease (collagenase, stromelysin metalloelastase, gelatinase)	Break in the basement membrane Degradation of the ECM	***Mast cell*** (vectors) Fibroblast SMC
MMP 9	Gelatinase B	Early Activates and opens the endothelium	***Neutrophil*** Monocyte Macrophage T Lymphocyte
MMP 2	Gelatinase A	Early Elastin Collagen III Fibronectin	***Fibroblast*** Monocyte Macrophage T Lymphocyte SMC
MMP3	Stromelysin 1	Late (CEAP 4 & 5) Collagen III	***Fibroblast*** SMC T Lymphocyte
TIMPs *Tissue inhibitor metalloproteinases*	Physiological inhibitor of MMPs (by binding of N-terminal domains)	1 to 1 ratio TIMP/MMPs Imbalance due to excess MMPs	***Fibroblast*** SMC
TGFβ1 *Transforming growth factor*	Growth factor	Stimulates fibroblasts	***Mast cell*** (mainly) which transports it
Basal FGF *Fibroblast growth factor*	Growth factor	Stimulates fibroblasts	***Endothelium*** SMC
PDGF *Platelet-derived growth factor*	Growth factor	Stimulates fibroblasts? SMC	***Endothelium***
VEGF *Vascular growth factor*	Angiogenesis	Increases permeability	***Endothelium***

Table I. Cellular factors which participate in remodeling of the blood vessel wall (ECM - extracellular matrix; SMC – smooth muscle cells; MMP - matrix metalloproteinase; TIMP - tissue inhibitor of metalloproteinase).

early stage. MMP 9 arises from granules in neutrophils activated at the paraendothelial level, and observed in varicose venous blood.[33] MMPs 2 and 3 intervene later, are active in the media, to which they are transported by mast cells, and are secreted in situ by fibroblasts and smooth muscle cells. Other types only occur at CEAP stages 5 and 6.[34] The MMPs are in contact with their TIMP inhibitor, whose balance is greatly upset during remodeling.[35] The main growth factor present is TGFβ1. It is transported by the mast cells and strongly activates the fibroblasts to produce fibers.[36] PDGF and basal FGF are produced by the endothelial cells during hypoxia.[26] In summary, the interaction of the cellular mechanisms and factors brought into play in the ECM is complex, variable, and progresses by fits and starts, affecting one venous segment more than another, but reaching macroscopic proportions, which may sometimes be considerable. It should be noted that the same mechanisms intervene as those that interact in the skin. An analogy can be made with atherogenesis in arteries. In summary, the link between a hemodynamic disorder due to dysfunction of venous valves, circulating blood cells, the venous wall, and biochemical processes is established with regard to the etiology of varicose veins, and supports the venous "elasticity" effect of older concepts, which are of course still relevant.[37]

These findings point to how alterations occur in the infiltrated valve, with remodeling of the vein. In contrast to the views of many authors, the primary event no longer lies in the wall of the vein. This does not prevent secondary major mechanical abnormalities in the vessel from worsening and even inducing alterations.

Variability of varices due to many precipitating factors

Varicose vein disease is expressed very differently from one person to another, in terms of familial background, gender, society, and lifestyle. This is not surprising when we consider the large number of factors that predispose to and promote varicose veins.

Risk factors for varices

- *Ethnic group:* the differences observed tend to be related to types of physical activity, which in this context correspond to the role attributed to prolonged VHT.
- *Age:* acts through the duration factor.
- *Female gender*: the influence of hormones on the venous wall is plausible, although difficult to demonstrate, but women with varicose veins have a later menopause. The role of pregnancy is clear, and emphasizes the need for prevention by compression therapy.
- *Height and weight*: height is a demonstrated risk factor, while obesity is not an independent factor. Nevertheless, excess weight increases the risk of leg ulcer.
- *Manual work*: a relationship exists between VHT and uncomfortable physical activity in a prolonged standing position.
- *Genetics:* a family link has been confirmed in several studies, including a well-known investigation by Cornu-Thénard et al,[38] who also reported links to blood group and HLA type.

Hereditary abnormalities in elastin are obviously a cause of varicose veins, as in Marfan disease. There are also abnormal lines of fibroblasts that secrete defective categories of collagen or elastin. Prothrombogenic conditions develop during the course of varicose vein disease, with a propensity to hypofibrinolysis and hypercoagulability.[39,40]

Secondary varices

Congenital valvular aplasia leads to varices, even though the predominant manifestation is edema. Arteriovenous shunts cause varices, differentiating them from development of vasa vasorum. Varices associated with angiodysplasia fall within the scope of Klippel-Trenauney and Parkes-Weber syndromes, with unilateral lower limb hypertrophy. Alternating channels are related to deep vein thrombosis, vascular agenesis, a gravid uterus, and tumors. Lastly, Cockett's syndrome, and venous hyperoutput in athletes, act on venous pressure.

In summary, all these causes, most of which are nevertheless rare, promote VHT, leukocyte adhesion, or remodeling, independently or in combination.

CONCLUSION

The demonstration of a leukocyte/endothelium cellular interaction is another step in elucidating the singular etiology of chronic venous disease. The micronized purified flavonoid fraction (Daflon 500 mg) consisting of 90% diosmin and 10% hesperidin clearly acts on leukocyte adhesion in the arteriovenous fistula model in

the rat.[15] Similar action has been demonstrated in patients.[41] Phlebotropic drugs produce effects that are partly related to leukocyte interactions.[42] Such effects, which are well tolerated, are not associated with a risk of neutropenia, which has been an obstacle for other products. Phlebotropic drugs act on leukocyte "rolling," ie, the recruitment of leukocytes, with no danger to patients.[43]

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Daflon 500 mg and chronic venous insufficiency

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WHAT IS CHRONIC VENOUS INSUFFICIENCY?

The term chronic venous insufficiency (CVI) is defined by Ruckley[1] as "the signs of that category of venous disease in which there are chronic pathologic changes in the skin and subcutaneous tissues of the lower leg. Subjects with truncal varices are not classified as CVI unless they have corona phlebectatica, lipodermatosclerosis, or open ulceration." The term "insufficiency" deserves a clear-cut definition. It usually refers to the failure of an organ or of a given function. So, valvular insufficiency can be denoted as venous valve failure, and venous insufficiency as a venous system incompetence (superficial, deep, or perforator insufficiency for incompetence in, respectively, the superficial, deep or, perforating veins). A given patient may be affected by reflux in one or more of the venous systems.[2] Venous leg ulcer is part of CVI since it affects the skin and is associated with reflux, which may occur in the superficial or deep venous system, or both. A literature review, involving 1153 ulcerated limbs with reflux, found that superficial reflux alone occurred in 45% of limbs, deep reflux alone in 12%, and both forms in 43%.[3]

WHAT IS THE PREVALENCE OF VENOUS LEG ULCERS?

The estimated prevalence in the general population of active or healed venous leg ulcers is approximately 1%.[4] Differences can be observed depending on the type and age of population studied (*Table I*). The prevalence of leg ulcers increases with age.[4,5]

HOW SHOULD ULCERS BE ASSESSED?

Evaluation of healing requires the qualitative and quantitative analysis of chronic ulcers and wounds. The assessment of ulcers has commonly been based on the measurement of wound perimeter or surface area. Measurement of the volume and color of a chronic wound is also an

Keywords:
chronic venous insufficiency, varicose ulcer, micronized purified flavonoid fraction.

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Country (city)	(Author) Year	Population	Prevalence (%) in patients	Prevalence (%) over 50 years of age
USA (Tecumseh)	(Coon) 73	General population	0.2	
Switzerland (Basel)	(Widmer) 78	Chemical workers	1	
Scotland (Edinburgh)	(Dale, Ruckley) 85	General population	0.8	
Scotland (Lothian)	(Callam) 85	General population	0.15	0.52
Brazil	(Maffei) 86	Consultants	3.6	7.7
England (Harrow)	(Cornwall) 86	General population	0.18	0.38
Ireland	(Henry) 86	General population	1.5	
Australia (Perth)	(Baker) 91	General population	0.06	0.33
Sweden (Skaraborg)	(Nelzen) 91	General population	0.3	
Sweden (Malmö)	(Lindholm) 92	General population	0.12	
England (Newcastle)	(Lees) 92	General population	0.19	
Sweden (Gothenberg)	(Anderson) 93	General population	2.3	
France	(Humbert) 96	Consultants	2.7	
Italy (Flebo 2000)	(Servier) 00	Consultants	6	
Italy (San Valentino)	(Belcaro) 02	General population	0.48	

Table I. Prevalence of leg ulcers.

important step in its follow-up over time. Quantitative methods used to assess wound-healing rate are essential for checking treatment response. Numerous techniques are available, ranging from the simple use of tracings to more sophisticated methods requiring the use of cameras, videos, and computers. The parameters most frequently used to measure a wound are the principal axes (length and width), the projected surface area, and the perimeter. Various mathematical calculations have made it possible to establish a relationship between the surface area of a wound, and its perimeter, length, and width. The most commonly employed technique uses an acetate film to obtain a tracing of the wound perimeter. Computer-assisted planimetry is a wound measurement method often used in clinical studies. Stereophotogrammetry measures the contours, surface area, and volume of a wound. It is based on determining the depth of the wound by viewing from two different angles. Ultrasound takes advantage of the difference in path length of an ultrasound wave reflected at the bottom of the wound, compared with the adjacent normal skin. This high-precision and simple method uses profilometric analysis followed by computerized volume assessment. Quantification of a leg ulcer is necessary to ensure an objective assessment. The techniques most widely employed in clinical studies involve the tracing of wound contours using transparent film. More sophisticated techniques that increase the accuracy of wound volume measurements are currently available, but are at present only employed in a research setting.[6]

WHAT ARE THE MECHANISMS OF APPEARANCE OF VENOUS ULCER?

Venous hypertension seems central to the skin changes seen in chronic venous disease. There is evidence for a linear trend towards more severe skin damage with increasing post-exercise venous pressure.[7] Current thinking on the pathophysiological basis of the skin changes in chronic venous disease can perhaps be traced back to the observation that blood returning from feet that have been passively dependent for 40-60 minutes is relatively depleted of leukocytes, especially in patients with chronic venous disease.[8] This suggests that leukocytes accumulate in the lower extremities under conditions of high venous pressure. It is likely that the

accumulation is largely due to leukocyte adhesion to, and migration through, the endothelium of small vessels, especially post-capillary venules. Basic confirmation of what has come to be known as the microvascular "leukocyte trapping" hypothesis has come from immunocytochemical and ultrastructural studies showing elevated numbers of macrophages, T lymphocytes and mast cells in skin biopsies from limbs affected by chronic venous disease.[9] In both acute[10] and chronic[11] experimental rat models of venous hypertension, elevated levels of tissue leukocytes were found in skin samples from affected limbs, but not from sham-operated controls.

HOW DOES DAFLON 500 MG WORK IN ULCER HEALING?

Daflon 500 mg may speed ulcer healing by modulating leukocyte-L-selectin interaction with endothelial selectins responsible for the initial stages of adhesion. By reducing the likelihood of leukocyte adhesion, Daflon 500 mg presumably acts through an anti-inflammatory mechanism.[12] Thus, among the many mechanisms at work in the pathogenesis of venous ulceration, the mechanism involving leukocyte activation and interaction with the endothelium hitherto seems to be the one most responsive to pharmacological treatment. Systemic drugs have been used in addition to standard treatments because of a theoretical ability to modulate one or more of the factors that have been identified in the pathophysiology of venous ulceration. A small number of drugs have been used with varying success. Stanozolol, a fibrinolytic anabolic steroid, was expected to break down pericapillary fibrin cuffs, but did not increase the rate of ulcer healing. Coagulation abnormalities observed in patients with venous disease have been improved by the use of aspirin. In contrast, a thromboxane receptor antagonist (ifetroban) failed to show benefit over compression therapy in ulcer healing. Among phlebotropic drugs, the use of horse chestnut seed extract and of hydroxyrutosides resulted in a reduction in both edema and symptoms of chronic venous insufficiency, but was not superior to compression in advanced chronic venous insufficiency, or in preventing venous ulcer recurrence. This may be because reduction in edema alone is insufficient to treat leg ulceration. The involvement of growth factors and leukocytes in the development of venous ulceration has opened up new areas of investigation.[12]

DAFLON 500 MG AND EVIDENCED-BASED EFFICACY IN ULCERS

In a multicenter (9), randomized, parallel-group, double-blind, placebo-controlled trial of 107 patients with venous leg ulcers,[13] using conventional therapy (standardized local treatment with compression therapy) with either Daflon 500 mg (1 g/day) or placebo (1 g/day) during an 8-week period, complete healing of ulcers <10 cm was statistically higher in the Daflon 500 mg group (32%) compared with placebo (13%) (P=0.028) (*Figure 1*). Time to complete ulcer healing was shorter in the Daflon 500 mg group (P=0.037).

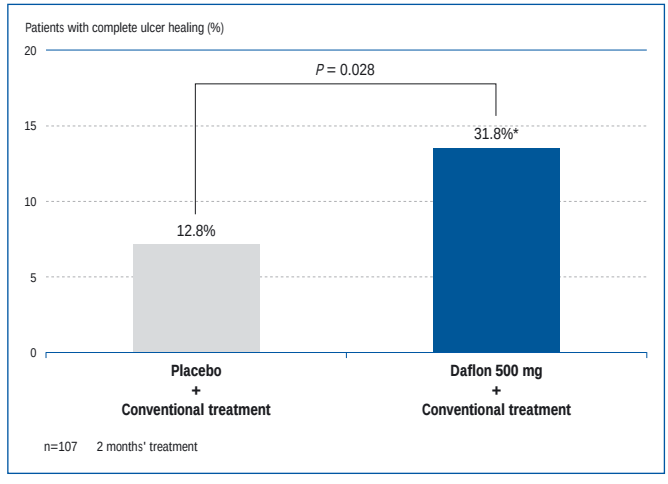

Figure 1. Percentage of patients with complete ulcer healing in Daflon 500 mg group vs control group (from ref 13).

In the study by Glinski[14] (multicenter, randomized, parallel-group, open, controlled trial of 140 patients with either Daflon 500 mg [1 g/day] and conventional therapy, or conventional therapy alone, during a 6-month period), the healing of venous ulcers ⩽10 cm

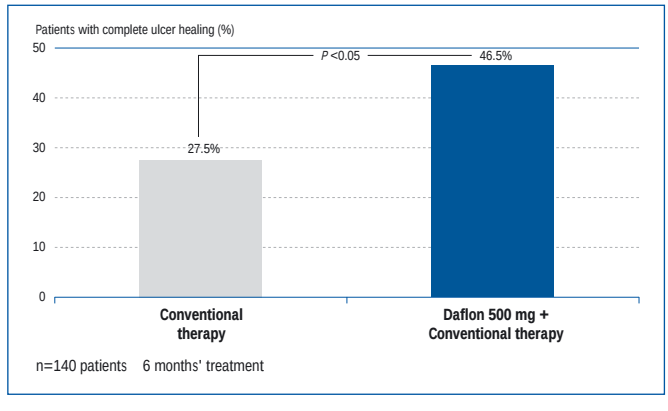

Figure 2. Percentage of patients with complete ulcer healing in Daflon 500 mg group vs control group (from ref 14).

in diameter was accelerated in the Daflon 500 mg group compared with the control group (*Figure 2*).

In the Czech study[15] (multicenter, randomized, parallel-group, open, controlled trial of 150 patients with either Daflon 500 mg [1 g/day] and conventional therapy, or conventional therapy alone, during a 6-month period), Daflon 500 mg, in addition to conventional treatment, significantly reduced ulcer healing time by one month and increased the total number of completely healed leg ulcers (*Figure 3*).

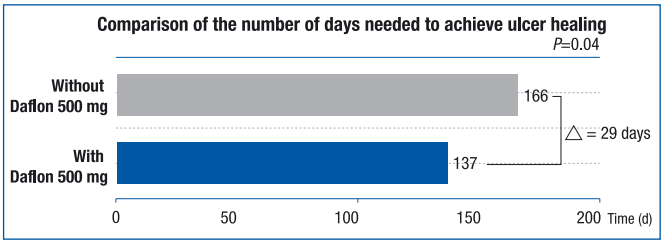

Figure 3. Number of days required to achieve complete ulcer healing in Daflon 500 mg group vs control group (from ref 15).

The results of a meta-analysis[12] of 5 clinical studies using Daflon 500 mg in addition to standard treatment, in the largest ever venous leg ulcer population, confirm the results from other studies that showed venous leg ulcer healing is accelerated by adjunctive therapy (*Figure 4*).

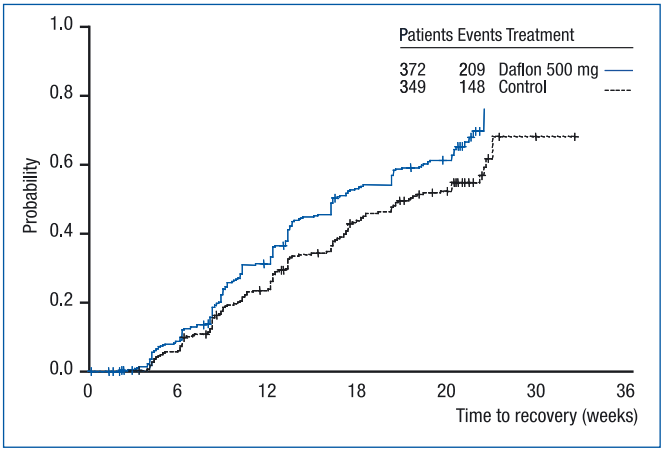

Figure 4. Life-table analysis with cumulative percentage of patients in whom the ulcer healed completely. Comparison in cumulative healing rates between the micronized purified flavonoid fraction group (solid line) and the control group (broken line). Median time to healing: MPFF, 16.14 weeks; control, 21.30 weeks. Hazard ratio, 1.33 (from ref 12).

By adding Daflon 500 mg to conventional therapy, the socioeconomic burden of venous leg ulcers is reduced. Daflon 500 mg reduces the cost of treating venous leg ulcers and improves the cost-effectiveness ratio by 45%.[16]

CONCLUSION

The internationally renowned medical journal, *Drugs*,[17] has devoted a totally independent comprehensive review entirely to Daflon 500 mg. In the opinion of no less than 14 experts, Daflon 500 mg is recognized as "a well established phlebotropic and vasoprotective agent that has been intensively investigated in well designed clinical trials." They conclude that, in the advanced stages, Daflon 500 mg may be used in conjunction with surgery or compression therapy or both.

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Subjective venous symptoms: review and presentation of a pilot study

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SUMMARY

In phlebology practice, the symptoms of heavy legs, feeling of swelling, fatigue, and the sensation of tension in the leg (heavy leg syndrome) are often found without an organic cause. These patients frequently suffer from psychic disturbances accompanied by a reduced quality of life. The discrepancy between symptoms and lack of objective findings leads to an ineffective therapy.
In this article we discuss the problem of leg symptoms without varicose veins and present a survey of heavy leg syndrome and quality of life in phlebology practice.

The feeling of heavy, tired, and occasionally swollen legs, particularly in the ankle region, is frequently a symptom of a chronic venous disease.[1,2] In some patients, however, intensive clinical and instrumental diagnosis (color-coded duplex ultrasonography, photoplethysmography, and venous occlusion plethysmography) reveals neither a venous or arterial nor a lymphological underlying disease. For the patients themselves, however, these complaints often represent a substantial impairment of their general health and quality of life. The disparity between the paucity of objective findings and severe subjective symptoms has resulted in several different names for the disorder:

- hypotonic phlebopathy,
- varicose symptoms without varices,
- functional phlebopathy,
- heavy leg syndrome.

In this article we refer to the disorder as heavy leg syndrome.
The discrepancy between the symptoms and the findings is hardly ever taken seriously from the therapeutic viewpoint and has received little scientific attention. Patients with symptoms but no objective findings are therefore often ignored. This review attempts to show the problem of alleged venous symptoms and, with the aid of a pilot study, to present the actual possibilities for measuring quality of life in people with heavy leg syndrome.

Keywords:
heavy leg syndrome, venous symptoms, quality of life.

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HISTORICAL BACKGROUND

Venous symptoms without varicosis were postulated as an independent clinical picture as long ago as the 1970s by Bassi,[3] who proposed the term functional phlebopathy. Andreozzi et al[4] described a syndrome consisting of heavy legs in an upright position, restless legs, and "evening edema" as hypotonic phlebopathy, and showed its prevalence in the Sicilian population to be 15%. The syndrome affected women twice as often as men. The main symptom was "heavy leg". Cloarec et al[5] likewise reported a prevalence of 15% for the aforementioned functional complaints.

According to the Bonn Vein Study,[2] half of the 3072 subjects reported leg problems, the predominant ones being a feeling of heaviness, tension, and swelling, and pain after prolonged standing. The sex distribution is interesting, however. Sixty-two percent of the women and 49% of the men reported leg symptoms in the last four weeks. However, only 1 man in 6 and 1 woman in 5 had signs of a chronic venous disorder. The Basle Study[6] carried out in workers from the pharmaceutical industry likewise showed that symptoms such as a feeling of swelling and tension, tiredness, and cramps have very low sensitivity and specificity in regard to venous diseases. Leg problems are a common symptom, with numerous possible differential diagnoses (*Table I*). Heavy leg syndrome should be an exclusion diagnosis.[7]

Feeling of heaviness	Edema (cardiac, renal, hepatic, hypoproteinemic, phlebedema, lipedema, lymphedema, angio-edema, ischemia-related edema, edema occurring in increased capillary permeability, drug-induced edema, idiopathic edema), alcohol and drugs, pregnancy
Feeling of tension	Edema, see above; physical activity or sport
Feeling of swelling	Edema, see above
Pain after prolonged standing	Fibromyalgia, discogenic ischialgia, arthrosis, painful legs and restless legs syndrome, chronic pain syndromes of other causes, phlebological and lymphological disease, lipedema
Restless legs	Restless legs syndrome, polyneuropathy, radiculopathy, benign muscle/calf cramps, myogenic hyperactivity, alcohol and drugs, phlebological and lymphological disease, lipedema

Table I. Alleged venous symptoms and common differential diagnoses.

CAUSES

The pathophysiological cause of heavy leg syndrome is unclear. It is assumed that venous hypotonia develops due to structural changes in the connective tissue[8] and smooth muscle cells[9] of the venous wall and to orthostatic loading of the lower extremity as a result of an upright gait. Increased capillary permeability and a change in the renin-angiotensin-aldosterone mechanism[10] may also lead to heavy leg syndrome.

The continuous communication between the brain and the peripheral organs is effected via various nerve and hormone signals. Under conditions of acute or chronic loading, the body uses this communication to initiate appropriate adaptive reactions. Altered adaptive reactions are also described as a cause of heavy leg syndrome in the area of psychosomatic medicine. Depressive states, anxiety states, and hypochondriac states have thus been observed in women with alleged venous leg symptoms.[11]

Blättler et al[12] recorded psychological interviews, all of them with patients with alleged venous symptoms, in phlebology practice. The authors highlighted five principal symptoms:

- being unable to walk away,
- inability to take a step that has long been needed,
- inability to acknowledge the sex-specific attributes of the legs,
- alleged venous symptoms in the presence of a frustrated need for affection,
- obsessive personality with excessive dependence on the opinions of others.

The symptoms are evaluated as representing a conversion neurosis with projection of neurotic conflicts onto the legs.

TREATMENT

One therapeutic approach—though not one that has been confirmed by randomized studies was found by

Partsch et al,[13] who showed that, in 12 was subjects with evening edema, lower leg edema was reduced by wearing knee-high compression stockings. Compression therapy increases the interstitial tissue pressure, decreases the transmural pressure gradient, so that, and edema is resorbed. There is an improvement in the:

- venous macrocirculation,
- cutaneous microcirculation, and
- lymph drainage.

Compression stockings mainly work when the patient is moving. Muscle exercises to increase ankle pump function, of the kind which are recommended for CVI patients,[14] might also represent a treatment option for patients with heavy leg syndrome.
Medication to protect the patient against edema may be another treatment option. For example, an *in-vitro* study[15] performed with venule cells showed that biflavonoids from red vine leaf extract promoted repair of damaged endothelial barriers.

It is known from numerous chronic diseases that quality of life can be significantly improved by the use of supportive psychosocial measures.[15] For doctors with the appropriate background, such an approach could possibly also be very helpful in dealing with patients with heavy leg syndrome who are receptive to the possibility of their symptoms having a psychosomatic origin. Thus, in our experience, empathy and an explanation that the disease is harmless should feature among the initial psychosocial measures to let the patient know that he is being taken seriously as a whole individual. The literature databases (eg, Medline, Med Pilot) do not contain any reports of psychotherapeutic or psychopharmacological treatment in relation to heavy leg syndrome.

PILOT STUDY

This pilot study sought to establish the most common symptoms in heavy leg syndrome and whether there is impairment of general health.

PATIENTS AND METHODS

Inclusion criteria

Presentation in a practice specialized in venous disorders (01/05-06/05): clinical examination and color-coded duplex ultrasonography show no chronic venous insufficiency, no reflux in the subfascial and epifascial venous system, no obstructions of arterial blood flow, no lymphedema (negative for Stemmer's sign); CEAP classification[16]: C (0,1,S), E (p,n), A(n), P(n), feeling of heaviness in the legs (in an upright position, particularly in the afternoon and evening), and patient's written consent.

Exclusion criteria

Reflux in the subfascial and epifascial venous system, phlebothrombosis or post-thrombotic syndrome, peripheral arterial occlusive disease, lymphedema, lipedema, women during pregnancy or the breastfeeding period, acute lumbago, heart failure, renal insufficiency, severe concomitant disease.

Questionnaire

After clinical and instrumental confirmation of the exclusion diagnosis heavy leg syndrome, the patients were interviewed using a three-part questionnaire consisting of:

- a general part covering personal details, the duration of the complaints, and any concomitant diseases and their treatment,
- a symptom questionnaire with a 10-point scale (0: no symptoms, 10: extremely severe symptoms) for the symptoms:
  - feeling of heaviness in the legs,
  - leg problems,
  - swollen legs,
  - feeling of tension in the legs,
  - feeling of tiredness in the legs,
  - feeling of restlessness in the legs,
  - pain in the legs,
  - influence of menstruation on leg complaints,
- standardised SF-12 questionnaire (physical, psychological scale) for general state of health.

STATISTICS

The questionnaires were evaluated after checking for completeness and plausibility with SPSS 11.0 statistics software (www.spss.com) run on the Windows XP operating system. The statistical analysis was carried out mainly with descriptive statistical methods (mean, standard deviation); *P* values <0.05 were regarded as statistically significant.

RESULTS

In the period between 01/05 and 06/05, 21 people (2 men, 19 women) who had been given the exclusion diagnosis heavy leg syndrome were prepared to answer the detailed questionnaire. The mean age of the women was 52.2 years, with an SD of 17.0 years, and the mean age of the men was 25.0 years, with an SD of 5.6 years. The overall mean age was 49.6 years with an SD of 18.1 years (*Table II*). The mean duration of the complaints was 9.3 (± 6.3 years).

The mean body mass index (BMI) was 23.7 kg/m^2 with an SD of 3.0 kg/m^2. The question about whether or not there was known phlebological leg disease in the family was answered in the affirmative by approximately half (57%) of the subjects. One, female patient (5%) mentioned smoking, and two women (10%) reported taking ovulation inhibitors. The most common secondary diagnosis was hypertension (14%).

We then asked about various leg complaints, which the subjects rated on a scale of 0-10. The feeling of heaviness, which was the reason for the phlebological investigation, was reported by all and was given a mean rating of 5.3 (± 2.4) on the 10-point scale. A feeling of swelling, feeling of tiredness, and feeling of tension in the legs were reported very frequently, as were general leg problems (*Table III*). The ratings for restless legs (2.1 ± 2.0) and pain in the legs (2.8 ± 3.3), on the other hand, were relatively low, and these symptoms were reported less often. Six women reported that menstruation had an effect on the leg complaints.

	Male	Female	Total
Sex	2	19	21
Age (years)	25.0 ± 5.6	52.2 ± 17.0	49.6 ± 18.1
Body mass index (kg/m^2)	23.5 ± 0.9	23.7 ± 3.1	23.7 ± 3.0
Venous familial history	1 (50%)	11 (58%)	12 (57%)
Smoking	0	1 (5%)	1 (5%)
Hormonal contraception	0	2 (11%)	2 (10%)
Secondary diagnoses	Hypertension n=3		
	Hypothyroidism n=1		
	Gastritis n=1		
	Lumbago n=1		
Drugs	Antihypertensive n=2		
	Thyroid hormone n=1		

Table II. Patient group (n=21).

Symptom	Scale ratings (0-10)*	Duration (years)*	n (%)
Leg problems	4.8 ± 2.9	9.5 ± 9.0	18 (86%)
Feeling of swelling	4.3 ± 2.6	9.9 ± 7.5	18 (86%)
Feeling of heaviness	5.3 ± 2.4	9.3 ± 6.9	21 (100%)
Feeling of tension	4.3 ± 3.0		17 (81%)
Feeling of tiredness	4.5 ± 3.0		18 (86%)
Restless legs	2.1 ± 2.0		12 (57%)
Leg pain	2.8 ± 3.3		13 (62%)
Leg complaints, menstruation-dependent	1.4 ± 2.8		6 (29%)

**Mean ± standard deviation.*

Table III. Leg complaints: results of the symptom scale (10-point scale; 1: no symptoms, 10: severe symptoms).

The standardized evaluation of the physical summary scale yielded a mean value of 46.48 (± 10.21) in the group investigated; the mean value for the psychological summary scale, on the other hand, was 46.94 (± 8.95). *Table IV* shows the results for the healthy normal German population for the purposes of comparison.

Sum scale	Heavy leg syndrome			Healthy German population (control)		
	Mean	Standard deviation	n	Mean	Standard deviation	n
Psychological	46.95*	8.95	21	52.24	8.1	2805
Physical	46.48	10.21	21	49.03	9.35	2805

**P<0.05 in comparison with the control.*

Table IV. SF-12 summary scales for heavy leg syndrome and the random sample of the healthy German population (not affected by venous disease).[21,24]

On the standardized psychological global scale the psychological scores were significantly higher in the control than patients with heavy leg syndrome ($P<0.05$). The same trend was seen for the physical summary scale, but no statistical difference was reached.

DISCUSSION

The number of patients in this study is very small, 21, and skewed in terms of sex distribution (19 women and 2 men). The investigation should therefore be regarded as a pilot study. It is clear, however, that the principal symptoms of the functional diagnosis heavy leg syndrome are a feeling of heaviness, feeling of swelling, feeling of tension, and feeling of tiredness in the legs. In addition to physical symptoms, with a mean duration of 9.3 (± 6.9) years, there is a psychosocial burden and impaired quality of life. The term quality of life refers to well-being and the ability to function psychologically, physically, socially, and in everyday life, from the point of view of the patient.[17,18]

Standardized, tested, valid methods for the measurement of quality of life have now been available for some time.[19,20] One of the best known includes the SF-36 and SF-12 Health Survey which, despite its notable brevity, fulfils all test-statistical requirements very well. To obtain information on the quality of life of persons with heavy leg syndrome, we employed the SF-12 questionnaire[21] using the interview technique. The SF-12 questionnaire is standardized for the general German population, ie, the data for the different sexes and age groups of the German population are already known.[21-26] In the short, 12-item version of SF-36, the evaluation is made with a physical summary scale (consisting of the subscales physical functional ability, physical role function, pain, and general health perception) and psychological summary scale (consisting of the subscales vitality, social functional ability, emotional role function, and psychological well-being). It should be noted, however, that different test instruments may yield different results (agreement validity).[18]

The pilot study shows that alleged venous symptoms produce a change on the psychological summary scale. However, whether a psychogenic disease leads to the symptoms or whether the leg symptoms produce reactive, psychosomatic symptoms (somatoform disorder) cannot be decided on the basis of the data from the pilot project. The results suggest that patients in the present study have an impaired quality of life due to the heavy leg syndrome they suffer from.

CONCLUSION

Patients with alleged venous symptoms are part of everyday phlebology practice. The exclusion diagnosis heavy leg syndrome should only be made after extensive clinical, instrumental, and quality-of-life investigations. Patients with the above-mentioned symptoms frequently complain of contradictory information and a lack of knowledge of the treatment options on the part of their doctors. Our chief concern should therefore be to provide these patients with effective diagnosis and treatment. Controlled therapeutic studies conducted within a methodologically rigorous framework are desirable.

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Artificial venous valves: an ongoing quest to treat end-stage deep venous insufficiency

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ABSTRACT

End-stage deep venous insufficiency is unrelenting venous hypertension with sequelae, and no standard option is available, or all options have been tried and found wanting. In such cases, there is an opportunity for an artificial venous valve to be used as a native valve. For decades, substitute valves have been studied experimentally, raising hope of bench-to-bedside transfer.
This quest is reviewed with an emphasis on current clinical practice. Venous valves have been made entirely of non-autologous tissues: synthetics, xenografts, or allografts. Many have failed in early experimental evaluation, with some advancing to the clinical arena, but few remain in research and development. Valves constructed from autogenous cells, or from autogenous venous tissue, not originally "de novo" valve tissue, have proven more promising. A variety of techniques have been used clinically, and improved venous hemodynamics and valve competency have been demonstrated. However, the majority of these valve studies await confirmation by other investigators over extended periods.

INTRODUCTION

It is apparent from the current literature that venous ulceration will recur even after the most aggressive treatment of superficial and perforator disease in patients with clinical class $C_{5,6}$ disease.[1] Ulcer recurrence is more common in patients with postthrombotic deep venous insufficiency (~ 70%), but is also seen in patients with primary deep venous insufficiency (~ 30%). The role of proximal iliac vein obstruction may be more prominent than once expected,[2] but surgery to correct deep venous insufficiency (DVI) remains an appropriate option in selected patients. Even in the best hands, and with an architecturally preserved venous valve, about one-third of internal valvuloplasty repairs will fail within 5 years.[3,4] Those requiring valve transposition or transplantation procedures fare less well, with only about 30% to 40% of valves competent at 5 years.[3-5] In the face of unrelenting symptomatic deep venous insufficiency, and the lack of a standard treatment option, there is an opportunity for the use of an artificial venous valve. The quest to address this need has been ongoing for decades, and many avenues have been explored.

Keywords:
prosthetic venous valves, artificial valves, chronic venous insufficiency, venous reflux, venous insufficiency surgery, venous reflux interventions.

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The standard dictionary definition of "artificial" is "not arising from natural growth." Therefore, and for this review, an artificial venous valve is not considered as a "de novo" venous valve. In general, two categories of artificial venous valves have been studied: valves devoid of autogenous components; and valves constructed, at least partially, from autogenous components.

REVIEW OF THE LITERATURE

NONAUTOGENOUS VALVES

Some investigations have never advanced past the point of a promising valve studied for hemodynamic responsiveness. In a lyophilized cadaveric vein, a valve acts mechanically much like a native valve when rehydrated.[6] The cusps withstood greater than 350 mm Hg retrograde pressure without leakage, and the closure time was 0.31± 0.03 seconds. No animal implants or clinical investigations have been reported.

Some valves tested in animal models fared quite poorly, and, therefore, further investigation was deemed unwarranted. Fresh allograft vein segments containing a valve were transplanted into the femoral vein of 14 dogs with only 7% patent at four weeks.[7] A human umbilical vein fitted over an aluminum mandrel, sculptured into a bicuspid valve and then glutaraldehyde-fixed, was implanted as a xenograft. All ten canine transplants failed in three days.[8] A liquid pellethane bicuspid valve was poured and fashioned using the same aluminum mandrel as that used for the umbilical vein experiment. All 10 canine implants thrombosed in 8 days.[8]

Animal studies, or occasionally even unrelated clinical studies, raised hope. Platinum or pyrite-carbon–covered, titanium, center-hinged bileaflet valves implanted in the dog femoral vein had 100% patency and competency at three months.[9] Unfortunately, extensive neointimal overgrowth resulted in valve failure within 2 years.[10] These results hold some promise that modifications might be able to extend valve life into a useful clinical range.

Decellularization of allograft veins containing valves could provide a transplant devoid of potentially immunogenic donor cells. A cryopreserved decellularized allograft, used as an arteriovenous fistula (AVF) for dialysis access, incited little antigenic response, with good overall function.[11] When implanted into the right ventricular outflow tract, a relatively high flow situation, pulmonary valve allografts functioned well for at least 6 months in a sheep model.[12] Implantation of pulmonary valve allografts as an adjunct to the Ross procedure did not induce an antibody response, as determined by panel reactive antibody (PRA) testing.[12] However, decellularized vein–containing valve allografts, implanted as venous valves in recipient sheep, and unaided by supportive anticoagulation, all failed in six weeks.[13] Although this animal study was unsuccessful, clinical experience, with the same material as an AVF or cardiac valve, suggests that further study might be rewarding.

There are valve substitutes free of autogenous tissue that have advanced to clinical trial. A single allograft valve utilizing standard allogenic cross-matching, and cryopreservation for storage, has reached this level of investigation. As a preamble to the clinical trial, dog erythrocyte antigen–matched and cryopreserved veins containing valve allografts were transplanted into recipient dogs with experimental hind limb venous insufficiency. Following ligation of a post-implant high-flow dAVF at 3 to 6 weeks, all four transplants remained patent and competent for three more weeks, at which time sacrifice demonstrated acceptable histologic findings.[14] The inner surface had an endothelial-like cell covering, and cusp sinuses were free of thrombus. A multicenter feasibility study (*Figure 1*) unfortunately suggested that a low-grade rejection phenomenon was damaging the allogenic femoral vein valves, with primary patency rate of 67% and primary competency rate of only 56%.[15] A two-year clinical study reported a disappointing 27% patency and competency rate.[16] The cryopreserved valve allograft failed in early and midterm clinical trial, and is not considered a suitable valve substitute for treating DVI.

Another clinical investigation utilized a cryopreserved allograft pulmonary valve monocusp implanted surgically into the common femoral vein in patients with longstanding, active venous ulcerations (> 3 years).[17] It was difficult to determine if the patients had an autogenous alternative, but the technique is unique. Fourteen of 40 (33%) implants were incompetent at follow-up, the length of which was not clearly stated. If the valve remained competent, the clinical results were excellent (24/27 or 89%), while recurrent reflux led to recurrent ulceration or non-healing. Mention of an immunogenic reaction, especially without blood type–specific matching, was considered a problem. No further report has been forthcoming.

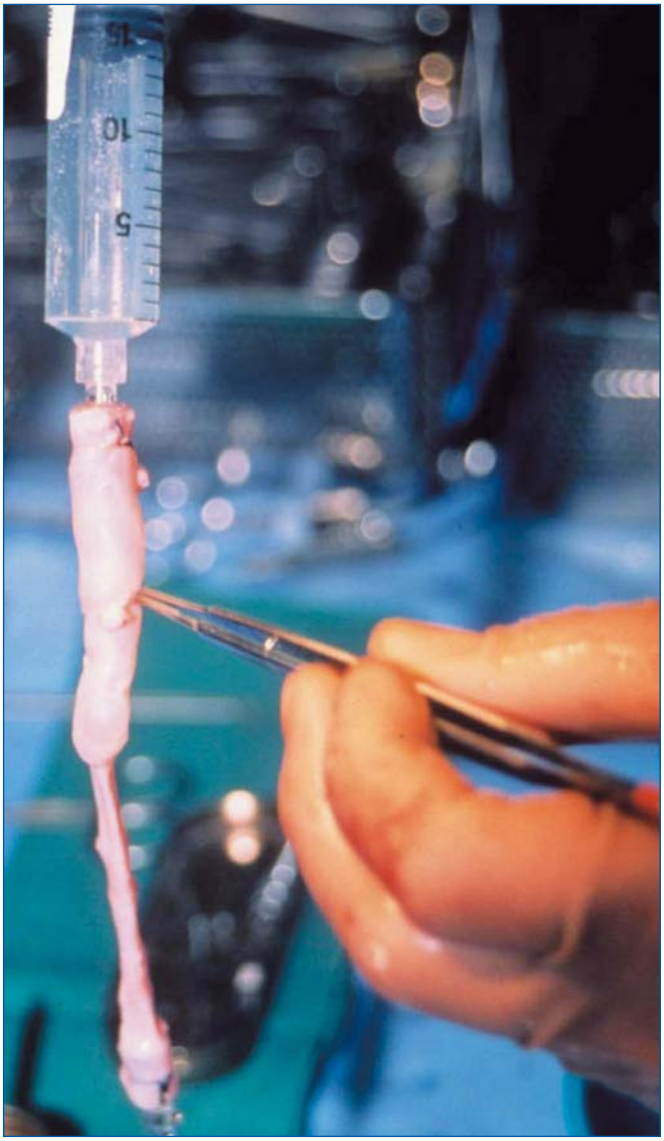

Figure 1. Photograph showing valve competence prior to implant of a cryopreserved vein-containing valve.

Cryopreserved femoral valved vein (cryovalve) is available from CryoLife (CryoLife, Inc. Kennesaw, Ga). During testing, the valve remains competent to at least 125 mm Hg of retrograde pressure. Data suggest that primary valvuloplasty may be required post-thaw to ensure initial competence.[16] As noted previously; this valve fails quickly over time, but what if one could temper the chronic rejection that seems to damage the valve over time?[15,16] Immunosuppressive agents would have to be well tolerated and not risk systemic infection. The suggested mechanism of rejection is the cytotoxic T cell response to foreign endothelium,[18] which could be modified with agents such as aziathioprine or cyclosporin A. No clinical trials have tested this hypothesis.

Glutaraldehyde-preserved vein-containing valve allografts, with adjuvant distal AVF support, remained patent (80%), but rarely competent (25%), in a 7-week canine study.[19] Glutaraldehyde-preserved bovine cardiac valves function well as human heart valves, and there is one report of a successful open surgical implantation of a glutaraldehyde-preserved pericardial allograft mono-cusp valve designed to treat a patient with DVI.[20] This tissue is no longer available from the supplier, so the authors have changed their line of investigation.[17] The technology existed to construct glutaraldehyde-preserved bovine venous valves for clinical use, and therefore this became an area for investigation. Early hemodynamic testing of bovine jugular vein valves proved very promising, and the vein diameter was of appropriate size for human use.[21] The possibility of valve transplantation by a percutaneous route was demonstrated experimentally and reported in the literature (*Figure 2*).[22] Subsequently, in a swine model, a glutaraldehyde-preserved bovine vein-containing valve was implanted via a percutaneous route. In the three

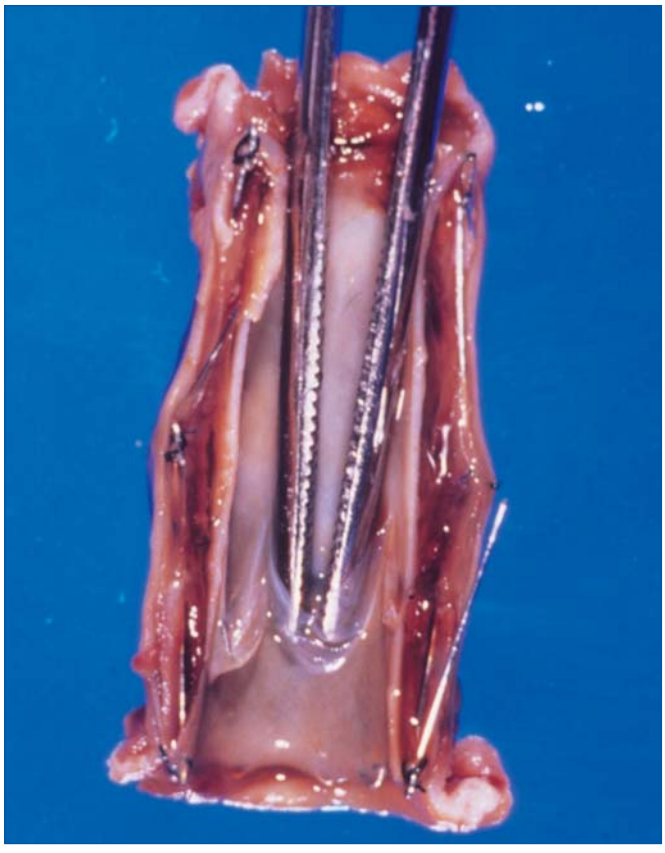

Figure 2. Photograph of a vein-containing valve that has been attached to a Z–stent and explanted after percutaneous implantation into a canine model. Note the normal appearance of the valve, highlighted by the instrument, with some narrowing at the proximal end of the stent.

surviving animals, the valves were patent and competent.[23] Further experimentation in an even larger animal study suggested that this approach was possible, but there was still some concern with valve competence, since while 5 of 5 valves at 4 weeks were patent, only 3 were competent.[24] Additional unpublished data supported the concept that a clinical feasibility trial was appropriate. A report from the Jobst Institute confirmed that two percutaneous placements of this device were accomplished as a phase 1 trial.[25] Recruitment was difficult due to the stringent criteria to insure that only end-stage patients were being treated. At approximately 1.3 years of follow-up, both stent valves were patent, but one was found to be incompetent at 14 months. These and other early results were somewhat discouraging, and pointed to a need to redesign. The new design likely failed to solve clinical concerns since the parent company no longer exists.

The most recent venture into the use of a nonautogenous valve for clinical use is a bioprosthetic valve made of porcine small intestinal submucosa (SIS). A bioprosthetic, bicuspid stent-based xenograft valve was developed and deployed percutaneously in the external jugular vein of a sheep model.[26] SIS is essentially a collagen skeleton with growth factors, which was stretched over a square metal frame with a slit cut to form the valve opening. The valve was found to be resistant to thrombosis, and becomes repopulated with endothelial cells from the recipient.[26,27] An 88% patency and competency rate was reported, but tilting led to valve malfunction or occlusion in 3 animals.[26] Three patients were treated, thus demonstrating the feasibility of the approach.[28] A design change enabled automatic centering of the valve, and 6 of 8 valves were competent at 5 weeks in an animal study.[29] The company sponsoring the project (Cook, Inc., Bloomington, Ind) is continuing research and development, with early clinical studies performed outside the United States. A third design change is planned to improve venous valve hemodynamics and prevent cusp thickening.

AUTOGENOUS VALVES

Repopulating a decellularized valved vein allograft with donor smooth muscle and endothelial cells would make a transplant much like an autogenous valve, but with an allograft infrastructure. This hybrid is difficult to categorize, but, I believe, fits the autogenous category best for the purposes of this review. In a sheep model, such a seeded allograft was transplanted into the external jugular vein of the cell donor. Devoid of long-term anticoagulation, 9 of 12 seeded allografts were patent and competent at 12 weeks. One transplant had occluded, and two valves were frozen by neointimal ingrowth.[13] These allografts did perform much better than unseeded allografts, which universally failed, but not as well as 8 autografts, which were all patent and competent. This is promising experimental work.

Intussusception of an autogenous vein forms a bicuspid valve by placing two sutures 180 degrees from each other to hold the intussusceptum in place.[30-32] The tissue is autogenous, but the valve is artificially constructed. In canine studies performed without chronic anticoagulation, short-term patency was excellent, with valve competence demonstrated at physiologic pressures. The valve was, of course, thicker than a native valve by virtue of its method of construction (*Figure 3*).[30] When transplanted into the femoral vein of a canine DVI model, the 90% venous refill time was modestly improved, but not the venous filling time, suggesting a less rapidly responsive valve when compared to a native valve.[30] The British experience with this type of valve was evaluated by the Harvey strip test and descending venography, and long-term competence (1-112 days) was demonstrated in animals.[31] All 41 valves were immediately competent by the strip test, 38 by descending venography, and 24 of 27 fully competent to a vertical pressure gradient of up to 250 cm H_2O in this animal study.[31] A modification to allow thinner valve cusps showed that the valve opened rapidly with minimal retrograde pressure, closed at a pressure of 3 to 5 cm of water, and could withstand physiologic hydrostatic pressure without reflux.[32] In the absence of

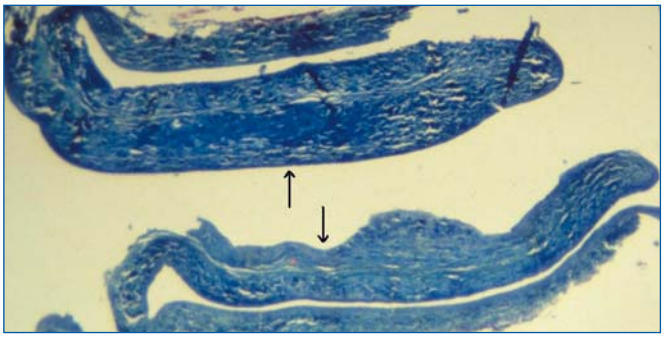

Figure 3. Photograph of an intussusception-type venous valve showing the double thickness of the valve construct, which may help to explain the slower response of the valve during hemodynamic study.

prolonged anticoagulation, a thin layer of thrombus formed along the thinned cusp walls, resulting in valve incompetence. Overall, with some modifications, this could function as a substitute valve, but animal studies have raised concerns as to optimal function and a higher-than-normal risk of thrombosis. Although an invaginated valve has been used in the saphenous system to prevent reflux,[33] this valve design has not yet been investigated in the deep venous system of patients.

There are clinical reports of attempts to use autogenous venous tissue to fashion intraluminal venous valve cusps. It is my belief that this avenue of study initially resulted from the pressing need for a valve during surgery, when no other option was available.

Raju and Hardy report a small series of *de novo* valve reconstruction procedures.[34] Using autogenous vein from various locations, and after trimming adventitia and part of the media, semilunar cusps were cut to shape and sutured into the recipient vein. The non-endothelial surface was directed toward the lumen to decrease the risk of thrombosis.[34] All 7 valves were patent at 15 to 24 months of follow-up, primary healing of venous ulcers was recorded in 6 patients, with one requiring a skin graft to complete the healing process. No recurrences were noted.

Plagnol et al invaginated a stump of the great saphenous vein into the femoral vein to make a bicuspid valve, and 19 of 20 clinical reconstructions were patent and competent at a mean of ten months.[35] Reflux was noted in one case because of insufficient valve length. I have some concerns regarding invagination of an adventitial surface into the venous lumen, but these are not substantiated in this report.

Maleti made bicuspid or monocusp venous valves (*Figure 4*) by dissecting an inner layer from the thickened post-phlebitic vein wall to form the cusp(s). The initial 7 cases were sufficiently successful to warrant further study.[36] At the 2005 American Venous Forum, Lugle and Maleti reported the construction of 18 venous valves in 16 patients with recurrent or non-healing venous ulcers.[37] Six months of chronic anticoagulation was standard. At an average of 22 months, 83% of the valves remained primarily patent, with improved duplex and air plethysmographic findings. Early thrombosis below the valve was observed in two patients, and one patient experienced a late occlusion after beginning oral contraceptives. Corcos et al report one case in which the "intimal flap" method of constructing a venous valve was successful in healing a venous ulcer, and in improving venous hemodynamics.[38]

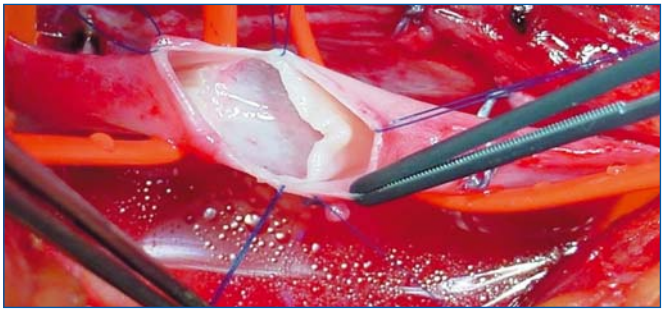

Figure 4. Photograph of a Maleti-type monocusp venous valve constructed by dissecting the inner wall of a post-phlebitic vein away from the outer wall to form a venous cusp. This photograph was generously provided by Dr. Oscar Maleti with permission to publish.

The early and midterm results are certainly promising for all the reported autogenous vein methods of new valve construction, but few methods have been substantiated by other investigators.

CONCLUSIONS

Valve cusps made of autogenous vein are currently the only artificial venous valves available with at least preliminary data to support their use in cases of chronic deep venous insufficiency, for which there are no standard options. Non-autogenous, off-the-shelf venous valve substitutes are in research and development, or have hitherto failed clinical evaluation. With modifications, some of the latter do hold promise for the future.

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Book review

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NEW ENGLAND JOURNAL OF MEDICINE

Mechanisms of Disease: Chronic Venous Disease

J. Bergan, G.W. Schmid-Schonbein, P. Coleridge-Smith, A.N. Nicolaïdes, M.R. Boisseau, and B. Eklof
N Engl J Med. 2006;355:488-498.
(2006 Massachusetts Medical Society
ISSN-0028-4793
Web site: www.nejm.org)

MECHANISMS OF DISEASE: CHRONIC VENOUS DISEASE

A commentary by Michèle Cazaubon

We are pleased to see publication of an article on venous disease in one of the most prestigious reference medical journals. It is an article designed to improve our understanding of the mechanisms that lead to chronic venous disease, and its excellent quality is to be expected considering the authors.

Problem position: An epidemiological approach was required to correctly position the problem. The Edinburgh study[1] was used as the reference, the rationale being the good methodology of this study in over 1,556 subjects, 18 to 64 years of age, and, importantly, chosen from the general population (and not from a hospital cohort or private series of patients). Consequently, this may be one of the reasons for a marked predominance of male subjects in the prevalence of varicose veins (40% in men versus 16% in women), which is a well-known result of this study (the only one to find such results). The economic impact of chronic venous disease (CVD) is associated mainly with that of venous ulcers, and even though its prevalence does not exceed 1% of the population, it has a major impact on the health care budget (1% to 3% of total expenditure).

Among symptoms classically attributed to CVD, are aching, heaviness, a sensation of swelling, cramps, itching, tingling, and restless legs syndrome.[2]

The pathophysiological approach considers the precise contribution of venous hypertension and its causes, and in particular the authors emphasize the failure of the musculo-venous pump mechanism in obese subjects, or subjects with a sedentary life style.
Recent data on “remodeling” of venous valves are well explained by the authors based on angioscopic studies using a fiberoptic catheter. Anatomical changes in these valves (stretching, thinning, twisting of valvular cusps) and histological findings (infiltration of valves by macrophages and monocytes with the release of adhesion molecules [ICAM-1]) are discussed.
The vein wall also undergoes remodeling due to the action of growth factors released by macrophages and monocytes, with a succession of hypertrophic and atrophic zones in a given vein, associated with anomalies of collagen production, in particular reduced synthesis of collagen type III, the primary component in venous wall distensibility. The different growth factors also participate in these processes, which contrast synthesis and degradation of structures in the vein wall.

Phlebolymphology. 2007;14(2):86-89.

In hemodynamic terms, the authors reiterate the role of increased venous pressure and the well-known role of shear forces, better defined by the term "shear stress", a recognized factor. An interesting finding was that a vein can well tolerate high pressures for a limited period of time. If the pressure is prolonged, however, valve remodeling begins, with gradual stretching of the valves and the occurrence of reflux.

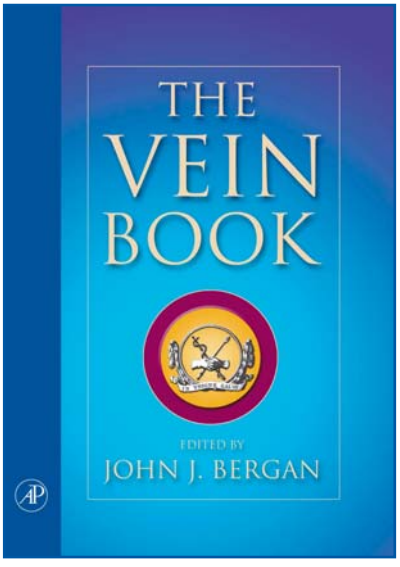
Alterations caused by shear stress partly explain what triggers an inflammatory reaction in the venous valve and vein wall.

Skin changes are clearly related to venous hypertension, and the authors review published studies, which have demonstrated the concomitant development of skin changes and venous pressure following exertion. Currently, the theory of cuffs of fibrin around dermal capillaries impeding diffusion of oxygen has been abandoned in favor of the theory of chronic inflammation, with the well-known studies of Coleridge-Smith on trapping of white blood cells, and more recent studies on white blood cell adhesion, even though the plasma factor responsible for such adhesion has not yet been discovered.

The authors conclude with a few implications for treatment, in particular regarding the possible use of cellular and molecular therapies in the future. They add that early pharmacological treatment to inhibit inflammation may offer the greatest opportunity to prevent venous hypertension, reflux, and inflammation. This could alleviate symptoms of chronic venous disease and reduce the risk of complications. The greatest strength of this article is the addition of striking artwork to the most recent theories "of the proponents of basic sciences," which can be used for continuing medical education. The article also provides an update on unresolved problems of the progressive features of chronic venous disease.
Lastly, I would advise everyone who eagerly wishes to read the entire article to start by memorizing the general aspects of chronic venous disease of the lower limbs. An excellent anatomical and physiological review also includes fine artwork, and an overview of recent findings in the field of venous valve mechanisms.[3]

Adapted from a review published in French *in Angéiologie.* 2005;58(3):62-63 with the kind permission of Dr Michèle CAZAUBON.

1. This fact could have been better explained in this article, which is intended for readers who are not necessarily familiar with venous diseases.
2. In the quoted article by Criqui et al, the restless legs syndrome is clearly called into question regarding its role in the symptoms of venous disease (*Am J Epidemiol.* 2003;158:448-456, also in *Angéiologie,* 2005).
3. M. Perrin. *Affections veineuses chroniques des membres inférieurs*. General aspects. Anatomical and Physiological review. EMC (Encylopedia of Medicine and Surgery), in French. Surgical Techniques, Vascular Surgery, Elsevier 2006.



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The Vein Book
Bergan J-J, ed (Elsevier Academic Press; 2007: 617 pp.
ISBN-13:978-0-12-369515-4
Web site: www.books.elsevier.com)

THE VEIN BOOK

A review by Michel Perrin

The Vein Book deserves its title, as every topic concerning this field is covered in its 617 pages and 65 chapters. Editor-in-Chief J-J Bergan has brought in 89 contributing authors to achieve this challenging task. Most of them are well known in the venous cosmos, but interestingly they come from different disciplines, and include angiologists, epidemiologists, basic research scientists, internists, phlebologists, researchers, and surgeons, and as they practice in different countries the final result is a worldwide view of the specialty.
The book is divided into 4 parts: Basic Considerations (Associate Editor L. Pascarella), Primary Superficial Venous Insufficiency (Associate Editor MP. Goldman), Venous Thromboembolism (Associate Editor AJ. Comerota), and Chronic Venous Insufficiency (Associate Editors P. Neglen and S. Raju).
Starting with an historical introduction illustrated by beautiful drawings, some of them unpublished, the basic considerations deal with embryology, anatomy, epidemiology, physiology, pathophysiology, investigation, and classification.

The second part, whose 202 pages make it the longest, is devoted to superficial venous disorders. Clinical examination, ultrasound investigation, quality of life, treatments, and their results are successively set out. Telangiectasias, reticular and varicose veins are covered, and all intervention treatments are depicted: sclerotherapy (liquid, foam), conventional surgery, phlebectomy (ambulatory, powered), laser and VNUS® Closure®. Some special topics are dealt with: small saphenous vein reflux, recurrent varicose veins, and pelvic congestion syndrome. It is regrettable that only the mechanism of compression action is described, that its precise indication in chronic venous disease is not given, and that venocative drugs are not mentioned at all.

The third part is devoted to every aspect of venous thromboembolism, including the etiology of thrombosis, its basic mechanisms, acquired and congenital hypercoagulable syndromes, thrombotic risk factors, prophylaxis and diagnosis of thrombosis. All treatment options are reported in detail, including the most recent and sometimes controversial techniques. From conventional heparin treatment to thrombolytic therapy, including thrombectomy (mechanical or percutaneous) and cava filters (temporary or permanent). Two chapters cover upper limb thrombosis. Conservative Europeans and others should be surprised by the interventional approach recommended here.

The last part is entitled chronic venous insufficiency (CVI). According to the CEAP classification, the term chronic venous insufficiency should only be used to describe C3-C6 patients, but that does not mean that in patients with edema or skin changes the etiology is not primary varices. This point is underlined in the first chapter whose title is the primary cause of CVI. It again seems that advanced CEAP describes the patient more precisely than the basic CEAP, which only reports the upper clinical class and can be confusing, or at

least imprecise. Detailed reports are given on the indications and results of superficial venous surgery, subfascial endoscopic perforator surgery, and ultrasound sclerotherapy of perforating veins. The following chapters focus on deep venous obstruction (diagnosis and treatment) and reflux (valve repair and prosthetic venous valves). Again, conservationists should consider these controversial new procedures warily, as there is no randomized controlled study comparing them with compression, but most patients treated by venous reconstructive surgery were not improved by conservative treatment.

More than one thousand references are quoted in the different chapters and the design of the Vein Book is outstanding, including the printing, figures, and tables.

If you're seeking a professional gift for someone interested in venous disorders, I suggest you need look no further than the Vein Book.

Book review or Commentary on major articles

Your comments on new books or on major articles are encouraged and can be sent to the editorial department of *Phlebolymphology*.*

Book or article reviews should briefly present the topic of the document and its purpose, the target readership (GPs, specialists, Fellows, etc.), a short description of its content, and which points are of special interest, the strengths and weaknesses of the document.
All texts should be submitted in English. The required length of articles is 500 words, or two standard typed pages. References, if cited, should in no case exceed 5. No abstract or illustrations should be included.

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Congress and conference calendar

XVIITH CONGRESS OF THE EUROPEAN CHAPTER OF THE INTERNATIONAL UNION OF ANGIOLOGY (EUROCHAP) – A SOCIETY FOR VASCULAR MEDICINE AND SURGERY AND VASCULAR INTERVENTIONS IN CONJUCTION WITH THE XVIITH CONGRESS OF THE MEDITERRANEAN LEAGUE OF ANGIOLOGY AND VASCULAR SURGERY (MLAVS)

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This congress will be held in Marseille (France) from May 10 to 12, 2007.

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VITH NORTH SEA MEETING ON VENOUS DISEASES: EVIDENCE BASED STRATEGIES IN PHLEBOLOGY IN VERY YOUNG AND VERY OLD PATIENTS

This congress will be held in Antwerp (Belgium) from May 11 to 12, 2007.

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XXXIIIRD CONGRESS OF EUROPEAN GROUP OF LYMPHOLOGY

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VTH INTERNATIONAL VEIN CONGRESS

This congress will be held in Miami (Florida, USA) from May 16 to 17, 2007.

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LVITH EUROPEAN SOCIETY FOR CARDIOVASCULAR SURGERY (ESCVS) INTERNATIONAL CONGRESS

This congress will be held in Venice (Italy) from May 17 to 20, 2007.

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XXXVITH MEETING OF THE EUROPEAN SOCIETY FOR PHLEBECTOMY

This congress will be held in Nice (France) on May 19, 2007.

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SPRING MEETING OF THE SWISS SOCIETY OF PHLEBOLOGY (THE ROLE AND THE POSSIBILITIES FOR DEEP VENOUS RECONSTRUCTIVE SURGERY IN PATIENTS WITH SEVERE VENOUS INSUFFICIENCY)

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VIIITH MEETING OF THE EUROPEAN VENOUS FORUM

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VTH INTERNATIONAL CONGRESS OF PHLEBOLOGY / MEDITERRANEAN SOCIETY OF PHLEBOLOGY AND HELLENIC SOCIETY OF DERMATOLOGIC SURGERY

This congress will be held in Corfu from July 1 to 4, 2007

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XXXVIITH BRAZILIAN CONGRESS OF ANGIOLOGY

This congress will be held in Goiânia (Brazil) from September 4 to 8, 2007

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XXIST ANNUAL MEETING, THE EUROPEAN SOCIETY FOR VASCULAR SURGERY

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XVITH ARGENTINA CONGRESS OF CARDIOVASCULAR SURGERY

This congress will be held in Buenos Aires (Argentina) from October 3 to 5, 2007.

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THE ARCTIC FIORDS CONFERENCE AND WORKSHOPS ON CHRONIC VENOUS DISEASE (UNDER THE AUSPICES OF THE EUROPEAN VENOUS FORUM)

This congress will be held in Hurtigruten (Norway) from October 2 to 6, 2007.

• *For further information, please contact:*

Organizing committee: Bo Eklöf, Olle Nelzén, Andrew Nicolaides, Dag Sörlie

Organizing secretariat:
Anne Taft
Beaumont Associates
PO Box 172
Greenford
Middx, UB6 9ZN, UK

Tel/Fax: +44 20 8575 7044

E-mail: evenousforum@aol.com /
Taftbeaumont@aol.com
Web site: www.europeanvenousforum.org

IVTH CONGRESS OF NORTH AFRICAN & MIDDLE EAST CHAPTER OF INTERNATIONAL UNION OF ANGIOLOGY (IUA) – IIIRD ANNUAL CONGRESS OF THE VASCULAR SOCIETY OF EGYPT

This congress will be held in Cairo (Egypt) from November 8 to 11, 2007.

• *For further information, please contact:*

President: Prof Salvatore Novo

Organizing secretariat:
Misr 2000 Conferences and exhibitions
2, El Gabal el Akhdar Bldgs
Nasr Road
Nasr City
11471 Cairo, Egypt

Tel: +202 458 17 57 / +202 674 50 13 / +2010 163 4354
Fax: +202 685 25 49

E-mail: misr_2000@hotmail.com
Web site: www.misr2000online.com

XXIST ANNUAL CONGRESS OF ACP

This congress will be held in Tucson (USA) from November 8 to 11, 2007.

• *For further information, please contact:*

Organizing secretariat:
Starr Pass Marriott Resort
Tucson
Arizona, USA

Tel: +1 510 834 6500
Fax: +1 510 832 7300

E-mail: ACP@amsinc.org
Web site: www.phlebology.org

XVITH WORLD MEETING OF THE UNION INTERNATIONALE DE PHLEBOLOGIE (UIP)

This congress will be held in the principality of Monaco from August 31 to September 4, 2009.

• *For further information, please contact:*

Chairman of scientific committee:
Prof Eberhardt Rabe
Chairman of organizing committee:
Dr Jean-Jérôme Guex

Organizing secretariat:
Publi Créations – Partner of AIM
27, boulevard d'Italie
98000 Monaco

Tel: +377 9797 3555
Fax: +377 9797 3550

E-mail: uip2009@publicreations.com
Web site: www.aim-internationalgroup.com/2009/uip

XXIVTH WORLD CONGRESS OF THE INTERNATIONAL UNION OF ANGIOLOGY (IUA)

This congress will be held in Buenos Aires (Argentina) from April 21 to 25, 2010.

• *For further information, please contact:*

President: Roberto Simkin

Organizing secretariat:
Ana Juan Congresos
Malasia 884 (C1426BNB)
Buenos Aires, Argentina

Tel: +54 11 4777 9449
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Web site: www.iua2010.com.ar

LETTER TO THE EDITOR

Letters that raise new or controversial issues of interest to readers, or posing a question or challenge to an article published in Phlebolymphology, will be considered for publication. The Editor may send the letter to the authors of the original paper so their comments may be published simultaneously.

More information on Venous or Lymphatic Diseases ?

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CEAP classification
Chronic venous disease
Chronic venous insufficiency
Deep venous surgery
Deep venous thrombosis
Edema
Hemorrhoidal disease
Investigation in venous and lymphatic disease
Lymphedema
Pelvic varicose veins and congestion syndrome
Phlebotonic drug
Postthrombotic syndrome
Venous and lymphatic pathophysiology
Thromboembolic disease
Venous malformations
Varicose vein (surgery)
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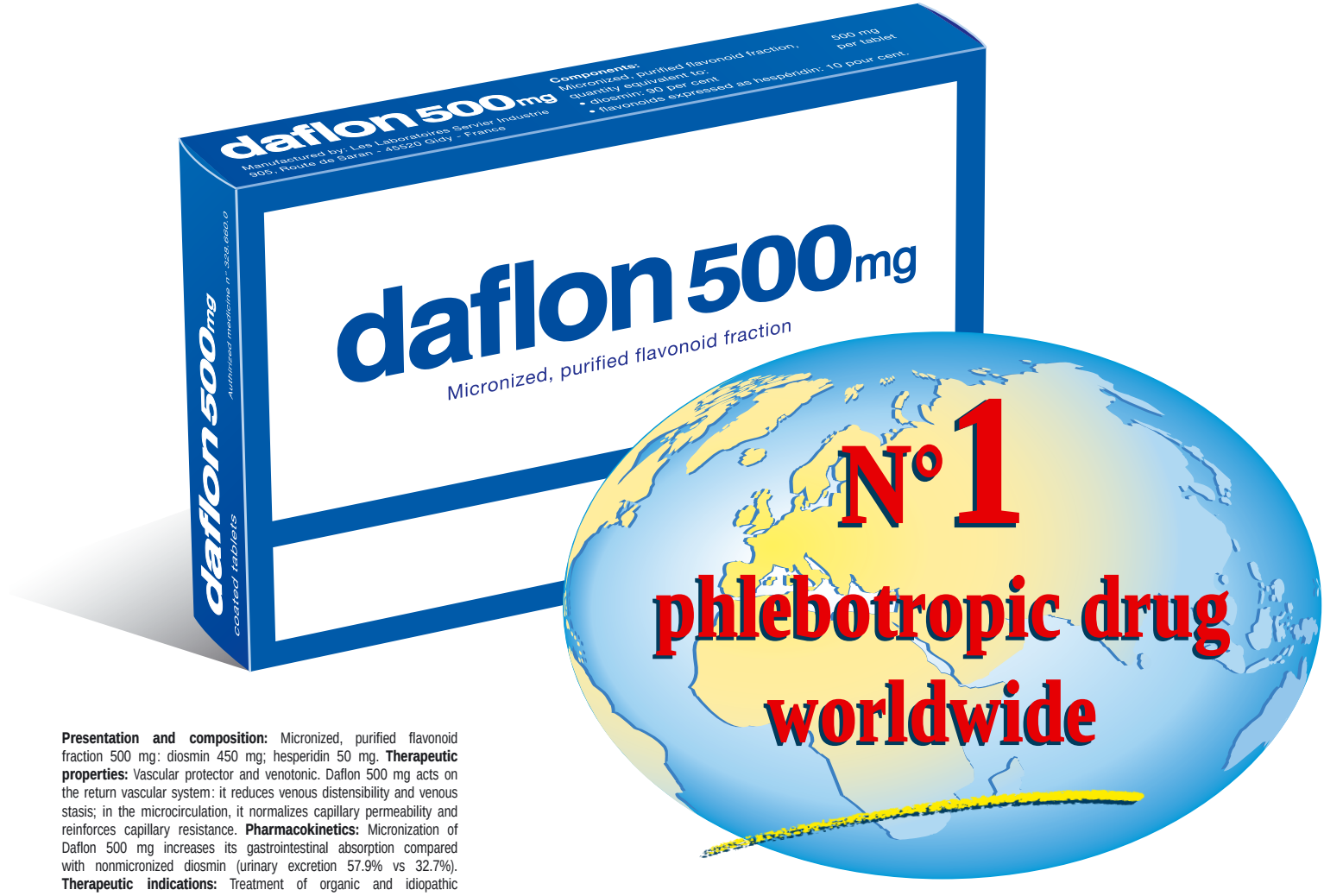

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Chronic venous insufficiency

2 tablets daily

Hemorrhoidal disease

up to 6 tablets daily

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