New Targets for Pharmacological Treatment in Primary Chronic Venous Disease

A. N. Nicolaides, Cyprus

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Primary chronic venous disease: a painful disease process linked to leukocyte-endothelium interaction

by A. N. Nicolaides, Cyprus

CHRONIC VENOUS DISEASE, WITH ITS DIVERSITY OF SYMPTOMS and signs, is primarily the result of venous hypertension. In the majority of cases, venous hypertension occurs because of reflux through incompetent venous valves. In a minority, it occurs because of obstruction or even more rarely because of obstruction and reflux.

Primary damage to valves has been linked to infiltration of valve leaflets and the venous wall by monocytes and macrophages. These findings suggest that inflammatory processes are involved during structural remodeling in venous valves and during the development of varicose veins. This could partly explain why chronic venous disease is painful right from the beginning of the process associated with changes in the venous wall. It could be said that chronic venous disease is joining the ranks of inflammatory diseases. It is now believed that genetic risk factors, hormonal impregnation, prolonged hydrostatic load, and abnormal fluid shear stress may serve as mechanisms that lead to a cascade associated with an aseptic inflammation (see Bergan; this volume).

Activated endothelium, leukocytes, mast cells, macrophages, and fibroblasts target the extracellular matrix as well as parenchymal cells and produce a spectrum of inflammatory mediators and metabolites, cell membrane adhesion molecules, prothrombotic receptors, growth factors, and chemotactic agents. The mechanisms that could bring about hypertrophic changes in varicose veins are related to proteinases from inflammatory cells such as mast cells or other sources, that can activate matrix metalloproteinases (MMPs) and cause extracellular matrix degradation (see Buján et al; this volume).

The inflammatory cascade in chronic venous insufficiency serves on the one hand as a tissue repair mechanism but the resulting valvular incompetence and its sequelae may favor further inflammation, which leads to varicosities and venous stasis and ultimately the occurrence of ulcers.

Axial reflux in the superficial and deep venous system is the major underlying dysfunction in chronic venous ulceration. There is an increased prevalence of leg ulceration with increasing ambulatory venous pressure as observed in a sample of patients with chronic venous disease. Among the many proposed mechanisms linking venous hypertension with skin changes, “leukocyte trapping” is currently the most believable. This theory suggests that leukocytes accumulate in the lower extremity under conditions of high venous pressure and that the accumulation is largely due to leukocyte adhesion to the endothelium and migration through small vessels, especially postcapillary venules. Basic confirmation of this hypothesis has come from immunochemical and ultrastructural studies showing elevated numbers of macrophages, T lymphocytes, and mast cells in skin biopsies from chronic venous disease limbs (see Coleridge Smith; this volume).

The molecular mechanisms involved in leukocyte adhesion and activation in chronic venous disease patients are associated with the expression of several types of membrane adhesion molecules on the leukocyte surface (L-selectin) and on endothelial cells (E-selectin). These adhe-
sion molecules have been shown to increase significantly in response to venous hypertension, and were found to be higher in patients with chronic venous disease. In addition, chronic venous disease patients have a tendency for systemically elevated leukocyte adhesion.

The proportion of patients presenting with any venous symptom increases significantly with clinical class of the clinical, etiological, anatomical, pathophysiological (CEAP) classification in some studies, while the correlation is weak in others. Possible reasons why a clear correlation between individual symptoms and disease severity may not always be found include the finding that patients with more severe chronic venous disease have peripheral neuropathy affecting sensory nerve fibers which may result in reduced perception of symptoms (see Allegra; this volume). The interaction between leukocytes and endothelium is a possible mechanism for symptom appearance (see Boisseau; this volume).

Symptoms and, in particular, pain, can be evaluated with self-evaluation rating scales (see Allaert; this volume), but the use of comprehensive quality-of-life instruments has shown greater consistency than the simple reporting of individual symptoms (see Cazaubon; this volume). Chronic venous disease is associated with reduced quality of life, particularly when symptoms are present (see Perrin; this volume).

Most studies have shown that the prevalence of chronic venous disease increases with age and is higher in women than in men. Little has been studied about the prevalence of symptoms (see Carpentier, this volume). Grading of chronic venous disease has been standardized by introduction of the CEAP classification system, which is continuously evolving (see Eklöf; this volume). Unified definitions are needed for clinical studies (see Ruckley; this volume).

Rapid advances and better understanding of the pathophysiological mechanisms involved has allowed the identification of targets for pharmacological intervention. Daflon 500 mg has been shown to attenuate various elements of the inflammatory cascade, particularly the leukocyte-endothelium interactions that are important in many aspects of the disease (see Pitsch; this volume).

The question may thus be asked, what are the cellular mechanisms that produce an “anti-inflammatory state” in the circulation? One possible answer is to hypothesize that maximizing tissue and vascular integrity and minimizing cell activation in the circulation will achieve this anti-inflammatory state. With better understanding of the mechanisms at work in the progression of chronic venous disease and better knowledge about the human genome, we are in a position to examine these requirements systematically, a task that will inevitably lead to improved treatments.

REFERENCES

Keywords: chronic venous disease; reflux; venous hypertension; quality of life; leukocyte
L'hypertension veineuse est la principale cause de la maladie veineuse chronique (MVC), dans la diversité de ses signes et symptômes. Le reflux dans les valves veineuses incompétentes provoque, dans la majorité des cas, l'hypertension veineuse. L'obstruction ou plus rarement l'obstruction et le reflux en sont moins souvent la cause.

Les lésions valvulaires primitives sont liées à une infiltration des feuilles des valves et de la paroi veineuse par les monocytes et les macrophages. Ces observations suggèrent que des processus inflammatoires sont impliqués lors du remodelage structurel des valves veineuses et du développement des varices. La composante algique dès le début de la maladie, associée à des changements de la paroi veineuse, pourrait en partie être expliquée par ces résultats. La MVC pourrait alors rejoindre le rang des maladies inflammatoires. Les facteurs de risque génétiques, l'imprégnation hormonale, une charge hydrostatique prolongée et une contrainte de cisaillement liquide anormale peuvent servir de mécanisme conduisant à une cascade associée à une inflammation aseptique (voir l'article de Bergan).

Les fibroblastes, macrophages, mastocytes, leucocytes et endothélium activés ont pour cible la matrice extracellulaire ainsi que les cellules parenchymateuses et produisent un ensemble de médiateurs inflammatoires et de métabolites, molécules d'adhésion membranaire des cellules, récepteurs prothrombotiques, facteurs de croissance et produits chimiotactiques. Les mécanismes conduisant aux changements hypertrophiques des varices sont liés aux protéinases issues des cellules inflammatoires telles que les mastocytes ou autres, qui peuvent activer les métalloprotéinasases de la matrice et causer une dégradation de la matrice extracellulaire (voir l'article de Buján et al.).

La cascade inflammatoire de l'insuffisance veineuse chronique sert d'une part comme mécanisme de réparation tissulaire mais l'incompétence valvulaire qui en résulte et ses séquelles peuvent favoriser une inflammation ultérieure, conduisant à des varicosités et à une stase veineuse et finalement à l'apparition des ulcères.

Le disfonctionnement sous-jacent le plus important de l'ulcère veineux chronique consiste en un reflux axial dans le système veineux profond et superficiel. Un échantillon de patients atteints de maladie veineuse chronique a présenté une prévalence accrue d'ulcères de jambes accompagnée d'une pression veineuse augmentée. La « capture des leucocytes » est le mécanisme actuellement le plus probable parmi tous ceux qui lient l'hypertension veineuse aux changements cutanés. Cette théorie suggère que les leucocytes s'accumulent dans les membres inférieurs en cas de pression veineuse élevée et que l'accumulation serait due en grande partie à l'adhésion des leucocytes à l'endothélium et à la migration à travers les petits vaisseaux, en particulier des veinules postcapillaires. La confirmation initiale de cette hypothèse est issue d'études immunocytochimiques et ultrastructurales montrant un nombre élevé de macrophages, de lymphocytes T et de mastocytes dans des biopsies cutanées de membres atteints de MVC (voir l'article de Coleridge Smith).

Les mécanismes moléculaires impliqués dans l'activation et l'adhésion leucocytaires chez les patients atteints de MVC sont associés à l'expression de plusieurs types de molécules d'adhésion membranaire sur la surface du leucocyte (L-sélectine) et sur les cellules endothéliales...
(E-sélectine). Ces molécules d’adhésion augmentent de façon significative en réponse à une hypertension veineuse, et semblent être plus élevées chez les patients atteints de MVC. De plus, les patients atteints de MVC présentent généralement une adhésion leucocytaire élevée.

Dans certaines études, et pas dans d’autres, le nombre de patients ayant des symptômes veineux augmente de façon significative avec la classe clinique de la classification CEAP (clinique, étiologique, anatomique et physiopathologique). Les patients ayant une MVC plus sévère présentent une neuropathie périphérique affectant les fibres nerveuses sensorielles conduisant éventuellement à une diminution de la perception des symptômes, c’est pourquoi on ne retrouve pas toujours de liens évidents entre les symptômes individuels et la sévérité de la maladie (voir l’article d’Allegra). Un mécanisme possible pour l’apparition des symptômes pourrait être une interaction entre les leucocytes et l’endothélium (voir l’article de Boisseau).

Les symptômes, et en particulier la douleur, peuvent être évalués avec l’échelle d’auto-évaluation (voir l’article d’Allaert), mais l’utilisation d’instruments complets de qualité de vie (QDV) s’est montrée plus cohérente que la notification des symptômes individuels (voir l’article de Cazaubon). Surtout en présence de symptômes, la MVC s’associe à une QDV réduite (voir l’article de Perrin).

Dans la plupart des études, la prévalence de la MVC augmente avec l’âge et est plus élevée chez la femme que chez l’homme. La prévalence des symptômes a été très peu étudiée (voir l’article de Carpentier). La classification de la MVC a été standardisée grâce au système de classification CEAP qui évolue en permanence (voir l’article d’Eklöf). Des définitions unifiées sont nécessaires pour les études cliniques (voir l’article de Ruckley).

Les progrès rapides et une meilleure compréhension des mécanismes physiopathologiques impliqués ont permis l’identification de cibles pour un traitement pharmacologique. Daflon 500 mg permet d’atténuer l’activité des différents composants de la cascade inflammatoire, en particulier les interactions endothélium-leucocytes qui sont importantes dans de nombreux aspects de la maladie (voir l’article de Pitsch).

Quels sont les mécanismes cellulaires qui produisent un « état antiinflammatoire » dans la circulation ? Il est possible d’émettre l’hypothèse qu’en maximisant l’intégrité tissulaire et vasculaire et en minimisant l’activation cellulaire dans la circulation nous réaliserons un état antiinflammatoire. Une meilleure compréhension des mécanismes mis en œuvre dans la progression de la MVC et une meilleure connaissance du génome humain nous permettront d’examiner systématiquement ces conditions, travail qui conduira inévitablement à l’amélioration des traitements.
Leukocytes and venous valve damage in chronic venous disease

by J. Bergan, USA

It is an unfortunate fact that the research interest and public funding attracted by chronic venous disease (CVD) has been in inverse proportion to its prevalence and socioeconomic burden—not to mention its capacity to impair the quality of patients’ lives, mildly in most cases, but moderately in many, and severely in the case of the significant number with ulceration. The purpose of this article is to show that this state of affairs is unwarranted, not simply on the common sense and humanitarian counts of cost benefit and alleviation of suffering, but also in terms of fundamental research. Recent studies in venous disease have addressed many of the same problems, many of the same molecules, and many of the same micromechanisms as are featured in high-profile subjects such as angiogenesis and atherogenesis. Cross-fertilization of ideas with these disciplines has been substantial. It has illuminated our understanding of venous disease to the extent that it may now be useful to review current knowledge in terms of what we know and still do not know, with particular regard to the roles of the key players in the recent observations, namely the leukocyte, its products, and biomechanical forces.

What we know

* Epidemiology
The statistics are well documented and always bear brief restating. In the United States, for example, an estimated 25 million people have varicose veins, while between 2 and 6 million have more advanced forms of CVD, such as edema and skin changes, while half a million have debilitating venous ulcers.1 In 1994, the prevalence in the developed world was estimated at between 1% and 2%, with venous ulceration being present in 20% of CVD patients in the United Kingdom, at the then annual cost of between €3000 euros and €5300,2 working out to an annual total of between €300 million and €1 billion.

Risk factors comprise the mechanical (essentially any impediment to venous return, which includes raised intra-abdominal pressure, particularly

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**Keywords:** leukocytes; chronic venous disease; inflammation; venous hypertension; macrophages

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**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>CVD</td>
<td>chronic venous disease</td>
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<tr>
<td>ERK1/2</td>
<td>extracellular signal-regulated kinase 1/2</td>
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<tr>
<td>ICAM-1</td>
<td>intercellular adhesion molecule 1</td>
</tr>
<tr>
<td>PDGF</td>
<td>platelet-derived growth factor</td>
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<tr>
<td>TGF</td>
<td>transforming growth factor</td>
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<tr>
<td>VACM-1</td>
<td>vascular cell adhesion molecule</td>
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<td>VEGF</td>
<td>vascular endothelial growth factor</td>
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obesity, but also pregnancy and constipation), the hormonal (in particular progesterone, the principal hormone of pregnancy), and the occupational (prolonged standing in women). There is therefore a distinct female preponderance, with prevalence ranging from 25% to 33% in women versus 10% to 20% in men.2 There is also evidence of a familial predisposition. Unfortunately, none of these factors offer specific grounds for therapeutic recommendations, apart from the general benefits of exercise and weight control: it is not unusual for a patient with varicose veins to be a nonsedentary male with a normal body mass index.

The mechanism of venous pressure in healthy subjects and patients with venous reflux was established in the mid-1960s by Arnoldi,8,9 who described the muscle pump and the consequences of retrograde flow on venous pressure after exercise. In the normal subject, pressure in both the superficial and deep venous systems rises when the lower leg muscles contract. When they relax, pressure in both venous compartments falls below that in resting muscle, thanks to the valves that prevent gravitational flow in the venous system. During contraction, pressure throughout the deep compartment, in muscles but also veins, exceeds that in the superficial compartment. During diastole, pressure in the deep veins falls below than in the superficial veins. In patients with venous reflux, early filling of the venous pool occurs in the lower extremity after emptying by muscle contraction, causing a steady and sustained build-up of pressure in the superficial system.10

Intraluminal capillary pressure mirrors the venous hypertension in the superficial system and is responsible for the classic cutaneous microangiopathy of the garter area in CVD.11 Raised ambulatory pressures extend into the dermal and epidermal capillaries where they are largely responsible, via a cascade of effects that are beginning to be understood at the molecular level, for the microangiopathy that results in ulceration.12 The capillaries become dilated, tortuous, and surrounded by a halo of edema fluid that has been termed a fibrin cuff. In 1982, it was assumed, on intuitive grounds similar to those that drove the venous stasis hypothesis, that this might act as a barrier between capillary and tissue, resulting in oxygen deprivation.13 However, studies a decade later using oxygen-15 positron emission tomography and xenon diffusion (xenon being similar in size and characteristics to molecular oxygen) found that the fibrin cuff did not significantly impede oxygen diffusion.14 The cuff has since proved a much more complex structure than expected, containing type IV collagen, laminin, fibronec tin, tenascin, and T lymphocytes in addition to fibrin.

Venous hypertension

In 1930, Eugene Landis (1901-1987) published the results of the microcapillary studies he had started as a student and conducted at his own expense throughout. He used a microinjection method to cannulate the arteriolar limb of capillaries in human fingernail beds to measure capillary blood pressure.4 The average normal ranges he reported (32 mm Hg in the arteriolar limb, 22 mm Hg in the midcapillary bed, and 12 mm Hg on the venous side) were subsequently confirmed using laser Doppler methods, and they were used to document venous hypertension in CVD. It has been the common link in all subsequent etiological theories.

The effect of Landis’ data was to displace the earlier long-held view that it was the pooling of stagnant blood within dilated veins in the skin that caused anoxia and cell death leading to ulceration.5 The assumption had been that such blood was poorly oxygenated, prompting the concept of venous stasis as the sole cause of the signs and symptoms of CVD. However, subsequent direct needle electrode measurements of skin oxygen tension produced the counterintuitive result that oxygen levels were in fact only minimally reduced.5 In fact, venous blood returning from a varicose extremity has a greater oxygen content than normal.5

Venous hypertension has therefore come to occupy the place previously held by venous stasis in discussions of CVD, with the crucial difference being that it is viewed as the predominant but not the sole cause. We now know that CVD is nothing if not multifactorial.

Venous valve failure

It has long been known that valve incompetence is a cardinal feature of CVD. Our own group’s particular interest in the valve as a distal but fundamental ingredient in venous hypertension was sparked by angioscopy, which became available in the 1980s. The angioscope is a miniature fiberoptic endoscope that can be threaded into the saphenous vein where it provides an elegant view of the internal architecture. As expected, patients with preoperative evidence of reflux on duplex ultrasonography showed numerous valvar abnormalities. Most obviously, patients had fewer valves than controls, confirming the report of this deficit by Cotton in 1961.15

As for the lesions themselves, Hoshino et al classified them into 3 types ranging from stretched commissures to perforations and valve splitting.16 Our own observations point to an increase in the commissural space as the earliest detectable change.
This allows reflux along the vein border and appears to be the initiating step in varicose reflux. It is followed by thinning, elongation, stretching, splitting, and tearing, with the degenerative process culminating in thickening, contraction, and possibly adhesion between valves—a picture that has been confirmed by other endoscopists. However, it was the histopathology behind these naked-eye changes and its relationship with findings in the vein wall which triggered much of the research work in recent years.

**Cellular infiltration**

Microscopy using a CD68 monoclonal antibody stain showed monocyte infiltration of the altered venous valves (Figure 1). This was consistent with the observation by other groups of leukocyte infiltration into varicose veins, associated with the release of multiple vasoactive substances including histamine, tryptase, prostaglandins, leukotrienes, and cytokines. Inflation was greater on the cranial (proximal) than on the caudal (distal) surfaces of the valve leaflets and vein wall, suggesting a relationship with raised venous pressure. No case of infiltration was found in any control.

In an attempt to account for this infiltration, we developed an initial model of venous hypertension in rat mesentery, using a pipette to occlude a 50-µm vein. Videomicroscopy revealed early evidence of inflammation, such as progressive leukocyte rolling, adhesion, and subsequent migration, associated with microhemorrhages on the high-pressure side of the postcapillary venule. Parenchymal cell death was detected by propodiom iodide labeling. Not only did this occur soon after establishing venous hypertension, but it continued to progress after occlusion was released. Thus hypertension triggered a mechanism which then became autonomous.

In a rat model developed by another group, venous hypertension was induced by ligating the inferior vena cava, both common iliac veins, and both common femoral veins, thereby elevating hind-limb venous pressures compared with the fore limb (controls). Tissue leukocytes measured 1 week later using the standard myeloperoxidase assay were significantly higher in hypertensive hind limbs than in fore limbs or sham-operated hind limbs. The study confirmed that venous hypertension alone was sufficient to induce the leukocyte trapping reported a decade earlier in the dependent legs of patients with CVD, when leukocyte depletion had been noted in blood returning from feet that had been passively dependent for 40 to 60 minutes. The answer to the question: where have the leukocytes vanished to? was onto, and into, peripheral microvascular endothelium.

These animal models, together with other observations, indicated that leukocyte-endothelium interaction and inflammatory infiltration induced by venous hypertension could be involved in initiating or compounding valve and vein wall damage in CVD. The inappropriate activation of leukocytes and their conversion to macrophages is depicted in a schematic valve cusp in Figure 2.

**Leukocyte activation and trophic changes**

Leukocytes mediate tissue damage in many conditions. On activation, they release cytoplasmic granules containing proteolytic enzymes. A nonmitochondrial respiratory burst also enables them to release free radicals, including the superoxide radical. The leukocyte trapping documented in dependent hypertensive limbs therefore has potentially sinister connotations. In 1999, Coleridge Smith made it the cornerstone of a unifying theory accounting for the skin and subcutaneous tissue damage that leads to venous ulceration. He subsequently eliminated oxygen diffusion block from the theory in the light of evidence that neutrophil degranulation occurred in blood samples from both patients and controls after only brief periods of venous hypertension.

According to this theory, which is consistent with numerous observations in both venous disease and vascular research generally, the sequence of events leading to lipodermatosclerosis involves factors both biomechanical and cellular. It begins with microcirculatory dilatation induced by the obligatory venous hypertension. Shear rates then fall in skin capillaries, encouraging the slowing and adhesion of leukocytes. Monitoring of leukocyte-endothelium interaction has shown that adhesion increases after only 30 minutes of experimental venous hypertension. This is associated with neutrophil degranulation and extrusion of proteolytic enzymes which then become autonomous. The inappropriate activation of leukocytes and their conversion to macrophages is depicted in a schematic valve cusp in Figure 2.

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**Abbreviations:** ICAM, intercellular adhesion molecule; IL, interleukin; TNF, tumor necrosis factor.


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**Figure 2.** Schematic illustration of key events that may lead to valve damage in primary venous disease. Inflammatory gene expression (such as leukocyte membrane adhesion molecule expression, cytokines) on endothelium may be induced by a shift in venous hydrostatic pressure and fluid shear stress. This supports leukocyte rolling, adhesion, and migration together with free radical formation, apoptosis, and tissue necrosis. In the process, macrophages become the instruments of tissue damage.
Leukocytes and venous valve damage in CVD – Bergan

Leukocytes and the presence of soluble endothelial molecules in lower extremity venous blood (Figure 3). The sequence is physiological, not pathological. It is the normal response to increased venous pressure. As such, it is found in both controls and patients, the only difference being that it is always more pronounced in patients, given that they have months or years of venous hypertension behind them. At the molecular level, leukocyte activation induces the plasma membrane to express adhesion glycoproteins, which draw the leukocytes first onto the endothelium and secondarily onto interstitial connective tissue structures and cells. The L-selectin on the leukocyte surface binds to the E-selectin on the endothelial surface to initiate rolling; shed L-selectin molecules are found in the plasma following this reaction. Activated leukocytes and endothelial cells then produce toxic free radicals leading to lipid peroxidation and eventual cellular apoptosis with necrosis of interstitial cells as well as destruction of connective tissue components.

As evidence for the elements of this theory, we have shown that expression of the immunoglobulin intercellular adhesion molecule 1 (ICAM-1) is upregulated on valve endothelium, more markedly on the proximal or cranial surface than on the caudal surface. It is similarly increased in the vasa vasorum within the media and adventitia layers of the vein wall.

Others have made similar observations in the clinical situation. Ciuffetti et al measured circulating ICAM-1, vascular cell adhesion molecule 1 (VCAM-1), and E-selectin, all of which mediate leukocyte-endothelium adhesion, in saphenous blood samples from 20 patients with CVD (10 with varicose veins and 10 with deep venous insufficiency) and 10 controls, before and immediately after walking, and on recovery. Leukocyte counts were significantly decreased, and ICAM-1 and VCAM-1 increased at both postexercise time points only in the deep venous insufficiency groups ($P<0.01$). Such persistence of high circulating adhesion molecules into the recovery period is entirely consistent with the unifying theory of CVD pathology.

Figure 3. Early cellular events leading to the skin changes of chronic venous insufficiency may begin with venous hypertension inducing low shear stress that favors leukocyte adhesion and spreading on the endothelium. Degranulation occurs as cytoplasmic granules containing proteolytic enzymes are released. Subsequent tissue damage may induce a secondary stimulation of leukocytes and endothelial cells in the lipodermatosclerotic skin.

Figure 4. Summary of contrasting effects of steady, laminar shear stress (upper panel) and turbulent or reversing shear stress (lower panel) on vessel walls.

◆ Biomechanical factors
The prime and central biomechanical factor in CVD is, of course, elevated venous pressure. But there is increasing evidence that at the local level fluid shear stress is a major mechanism in the control of inflammatory reactions in endothelial cells and circulating leukocytes (Figure 4). In the normal circulation, leukocytes rarely show pseudopod formation. Instantaneous pseudopod retraction is observed in vitro in leukocytes subjected to fluid shear stress; on removal of the stress, pseudopod projection returns and the cell spreads. In rat mesentry microvessels after occlusion, ie, at high pressure, circulating leukocytes project pseudopods when attached to the endothelium; as soon as flow is restored, the pseudopods on adhering leukocytes retract, and the cells begin to roll and detach from the endothelium. Any marked departure from normal fluid shear stress promotes the expression of inflammatory gene products. Mechanical distension of vein wall or valve cusp has an identical effect. Responses mirror the quality and quantity of the stress, being sensitive to stress history (along the spectrum of acute to chronic); so long as the stress persists, the responses are capable of sustaining the inflammatory state, and hence the conditions favoring valve failure. The process may be further enhanced in the presence of humoral inflammatory mediators, which serve to suppress the anti-inflammatory reaction of normal physiological fluid shear stresses.

Biomechanical factors are likely to be particularly important for the perforator check valves that normally control the flow of venous blood from the superficial to the deep compartment. They have been much less studied than their saphenous counterparts. Under physiological conditions, the valves are subject to intermittent bursts of venous hypertension with every muscular contraction, as opposed to the more chronic pressure on the saphenous valves. This clearly predisposes to local leukocyte activation and subsequent valve damage. In addition, the presence of superficial reflux, the perforators have to cope with increased volumes of blood as superficial venous blood recycles through the deep system into the superficial system and then back into the deep system. Increases in volume expand the vein, in both length and diameter, as seen most obviously in the venous system. There are therefore 2 probable explanations for perforator valve failure: leukocyte-induced valve damage, on the one hand, and valve inability to cope with the increased prograde flow. Unfortunately, perforator valve failure transmits the venous hypertensive wave from muscle contraction directly to skin and subcutaneous tissue, leading to the classic demarcated hypervascularization and lipodermatosclerosis observed in perforator outflow areas.

◆ Trophic/hemodynamic mismatch and the importance of reflux
Venous hypertension involves reflux through incompetent valves, and partial or total obstruction. Reflux is present in virtually every case. Valve incompetence is present in all cases, due to structural changes in 70% to 80%, and to deep vein thrombosis or trauma in the remainder, with congenital abnormality accounting for 1% to 3%. Appearance of the postthrombotic vein is not a reliable guide to its pathophysiological effect. In a 1991 study of venous obstruction, Raju and Fredericks found no obvious correlation between the site or extent of an obstruction and its hemodynamic severity. Extensive proximal lesions could be hemodynamically mild, while phlebography gave a poor idea of collateral formation. Ulceration did not differ significantly between patients assigned to 4 grades of venous obstruction, neither did objective measures of ambulatory venous pressure. The authors concluded that skin ulceration in venous obstruction was related to associated reflux rather than to the hemodynamic severity of the obstruction itself. Corroborative evidence was the correlation between improvement in venous reflux, measured by the Valsalva maneuver, and venous ulcer healing. Even in patients with the severest obstruction, saphenectomy, which traditionally was not advised, actually improved the grade of obstruction by eliminating reflux flow. Hypertensive reflux was therefore the classic culprit, for the constellation of events reviewed above.

◆ Trophic changes
Dermal fibrosis is a characteristic trophic feature in CVD. Assay of punch biopsy specimens has shown significant elevation of the well-documented fibrogenic cytokine, transforming growth factor β1 (TGF-β1), in lower calf skin from CVD patients versus not only controls, but versus lower thigh skin from the same patient. In addition, dermal fibroblasts from seemingly healthy areas of skin in patients with varicose veins have shown altered collagen synthesis.

◆ Targeted pharmacological intervention
The practical purpose of elucidating the molecular steps involved in the development of valve lesions is to intervene with a targeted treatment. The sequence of leukocyte adhesion, endothelial interaction, activation, and migration, and its association with valvular damage focused attention on molecules with known activity in this regard. Flavonoids currently possess the most appropriate profile, since they have a variety of benefits in vein tissue, including oxygen free radical scavenging and inhibition of adhesion molecule response to cytokine stimulation. At the same time, they inhibit the activation of enzymes involved in converting polyunsaturated fatty acids such as phospholipase A, cyclooxygenase, and lipooxygenase. Intervention with a micronized purified flavonoid fraction containing 95% diosmin and 5% hesperidin decreased leukocyte interaction with venule endothelium. What we do not know

◆ Venous hypertension/valvular incompetence: chicken or egg
The term venous hypertension is loosely used to denote not simply elevated pressure in the superficial veins of the leg, but also the clinical syndrome and...
the constellation and cascade of pathophysiological events and mechanisms with which that raised pressure is associated. But in the majority of cases (a history of thrombosis or other identifiable obstruction), the extent to which the elevated pressure is primary, “essential” or “idiopathic,” and not itself secondary to another cause, remains unknown.

When hypertension is known to be primary because induced experimentally, it is clearly a direct and sufficient cause of valve failure. Thus, after Van Bemmelen et al induced venous hypertension by creating arteriovenous fistulas in Wistar rats (femoral venous pressure jumped from 11 mm Hg to 94 mm Hg), healthy valves were stretched immediately and became incompetent 2 days later. Structural changes occurred within 2 months. Cusp elongation, separation, and leakage developed along the entire valvular free border and by 4 months valve areas had become difficult to recognize because commissures were lost and bulging of the valve sinus disappeared.40 In this case, primary hypertension was indisputably the cause of valve failure. But the relevance of this study to the majority of cases of clinical CVD is uncertain. The reverse experiment—destruction of the venous valves—would have given the same result in favor of valve incompetence as the primary cause.

The origin of valve failure in the clinical situation remains undetermined. Whether it is secondary to, responsible for, or coincident with venous hypertension remains unknown. Both may share an origin in an as-yet unidentified common venous defect. Our own impression is that the valve damage we have documented is acquired rather than essential, and that it is caused by factors, notably leukocyte activation, triggered by venous hypertension. An alternative view, based on the fact that a primary absence of valves is a rare but well-documented cause of CVD, is that CVD may simply be a question of quantity, namely overload of a congenital lack of saphenous valves. Thus, patients with symptomatic CVD (n=51) undergoing saphenectomy were found to have fewer valves (P<0.0001) than controls consisting of patients without CVD undergoing in situ greater saphenous vein bypass under angioscopic surveillance (n=26) (as described by Cotton and mentioned above). However, the 2 groups were not comparable in 2 major risk factors for CVD, age and sex distribution.

**Lipodermatosclerosis**
The precise mechanism by which chronic, sterile, inflammatory lipodermatosclerosis eventually progresses to skin ulceration is not known, but it is accompanied by enhanced leukocyte infiltration and possibly secondary leukocyte stimulation in the dermotosclerotic skin. Sustained low-grade endothelial injury over months and years is presumed responsible for the chronic skin changes. Tissue response to the chronic inflammatory process, including endothelial inflammatory gene expression, may induce macrophage and T-lymphocyte infiltration. Vascular proliferation may be authentic or artefactual, due to the elongation and distension of vessels reappearing within a single area on microscop-
shear stress modulate gene expression in endothelial cells. Driving the attempt to identify a mechano-receptor molecule, complex, or network is the concern to identify a target for drug intervention at the venous hypertension–leukocyte interface.

**Conclusion**

Venous hypertension in conjunction with valvar incompetence and reflux is the common and central factor accounting for the signs and symptoms of CVD. It exerts its mechanical effects at local level via a mechanoreceptor transduction system that awaits identification but results in leukocyte trapping, leukocyte-endothelium interaction, and migration, perhaps initiating or compounding damage to valves and vein wall. Much has now been learned about the molecular mechanisms involved in this chain of events and it is hoped that this knowledge will identify targets for yet more effective pharmacological intervention, whether prophylactically or therapeutically.

**REFERENCES**


**NEW TARGETS FOR PHARMACOLOGICAL TREATMENT IN PRIMARY CHRONIC VENOUS DISEASE**

Leukocytes and venous valve damage in CVD – Bergan

Leucocytes et lésion valvulaire veineuse dans la maladie veineuse chronique

Les signes et les symptômes de la maladie veineuse chronique (MVC) sont l’expression conjointe d’une incompetence valvulaire veineuse et d’une hypertension veineuse. Des lésions valvulaires ont été observées par angioscopie au cours de la chirurgie variqueuse. Les segments de veine saphène issus de patients atteints de MVC sont caractérisés par un nombre réduit de valvules par rapport aux témoins, avec présence fréquente d’un remodelage, d’une cicatrisation et même d’un effacement importants. Une infiltration de la paroi veineuse et valvulaire par des monocytes et des macrophages tissulaires a été mise en évidence au moyen d’anticorps monoclonaux. Cette infiltration est plus importante à la partie proximale du sinus valvulaire et de la paroi veineuse que sur la surface distale de la valvule, témoignant de l’action de forces liquidiennes de cisaillement induites par la pression veineuse. La présence d’une inflammation a également pu être mise en évidence au niveau de ces trois sites, comme en témoigne une réponse positive de l’endothélium pour la présence de molécules d’adhésion, à type de molécule d’adhésion intercellulaire 1 (ICAM-1). Ces résultats suggèrent l’implication d’un mécanisme inflammatoire dans le remodelage structural de la valvule veineuse.
Leukocytes and varicose vein etiology

by J. Buján, G. Pascual, and J. M. Bellón, Spain

The vein wall is a highly dynamic structure with 2 well-differentiated sides that guarantee its correct functioning: the luminal and adventitial sides. The luminal side of the vein wall, where the presence of valves indicates that the complex interaction between blood and wall takes on a particularly dynamic and metabolic dimension, is lined with an endothelium whose characteristics differ from the well-known properties of the arterial or microvascular endothelium. The adventitial side, the site of mechanical support and nutrient intake for the entire wall, also plays an active role in fighting against the forces of gravity. This complex role of the vein wall is, nevertheless, discrete and any decrease in its efficiency runs a slow course; hence its ambiguous assignment to the group of “chronic diseases.”

Our interest lies in the role that certain endogenous or environmental factors have in the development of CVI. Among the intrinsic factors, aging is being ascribed an ever more relevant role. Some of the genetic features of the aging process, such as the loss of function of telomerases and their involvement in maintaining the cell population or changes in the expression (dysregulation) of other genes, lead to qualitative and quantitative changes in cellular and extracellular proteinomics that enter into the realm of consequences more than cause.

The participation of white blood cells (WBC) in the development of venous disease is well-established,1-3 and aggregated WBC are known to be the most common cause of venous stasis. Stasis of blood
flow, whether at the luminal level due to valve failure or at the adventitial microvascularization level, triggers the activation of leukocytes as part of an inflammatory process aimed at functional recovery and tissue repair. Hence, what in principle is a protective mechanism can turn hostile to the detriment of the blood vessels.

Little is known about how CVI leads to the local tissue destruction seen so commonly in clinical practice. Increased evidence points to a central role for abnormal leukocyte–endothelial cell interactions in the pathogenesis of this condition. Some theories have suggested that leukocytes are sequestered in the legs of patients with CVI. This sequestration leads to the activation of white cells, which results in the generation of free radicals, proteases, histamine, neutrophil chemoattractants, and complement. The actions of these substances destroy the endothelial layer of the vessel and their basement membranes, increasing vascular permeability and disturbing microcirculatory flow. Other authors propose other factors that might activate leukocytes and cause them to act inappropriately in the venous system. Some factors present in the plasma of patients can activate unstimulated leukocytes. Such a factor could be any of a variety of stimuli, including bacteria, fungi, and their products. Endothelial cells also need to be activated so that leukocytes can migrate into the tissue through the endothelium. Scarce cytokine expression has been observed in some investigations, even though a considerable number of monocytes have been noted to adhere to the endothelium and migrate into tissue, suggesting that factors other than inflammatory mediators (high pressure, low shear stress) may activate the endothelium.

Little is known about the role of inflammatory cells in the biochemical and histological changes observed in varicose disease. Increased numbers of macrophages/monocytes and mast cells have been observed in varicose veins, suggesting that vein damage in refluxing saphenous veins is associated with a leukocyte infiltrate. Mononuclear cells such as neutrophils normally circulate in a quiescent state but when activated are capable of adhering to the endothelium and entering tissues releasing a variety of noxious substances known for their ability to cause tissue damage. Active proteases can either be secreted directly by inflammatory cells, including elastase and cathepsin G produced by polymorphonuclear leukocytes, chymase and trypsin by mast cells, and granymes by lymphocytes, or can be generated from circulating zymogens by activation in close contact with the cells.

The aim of the present study was to establish the influence age has on the changes that occur in the vein wall and to characterize leukocyte infiltration in the wall, exploring its association with the varicose condition.

**Patients and methods**

Forty vein specimens were obtained during surgery from patients undergoing bypass surgery (controls) or surgery for varicose veins. All 40 subjects gave their informed consent to participate in this study. The vein specimens were first visually checked for the presence of damaged areas and then divided according to subject age to establish the following study groups:

- **Group I control (n=20)**
  This group was comprised of 10 vein specimens harvested from patients under 50 years (mean age 39.4±6.8; range 26-46 years) and a further 10 specimens from patients of 50 years or over (mean age 71.5±10.6; range 57-89 years). These segments of saphenous vein were obtained from patients with no history of venous insufficiency or proven reflux during aortoconoray bypass surgery.

- **Group II varicose veins (n=20)**
  This group was comprised of 10 vein specimens harvested from patients under 50 years (mean age 39.4±6.8; range 26-46 years) and a further 10 specimens from patients of 50 years or over (mean age 71.5±10.6; range 57-89 years). This time, the portions of saphenous vein were obtained during vein stripping from patients with primary venous insufficiency and clinically confirmed reflux.

- **Inflammatory cells**
  The detection and quantification of inflammatory cells was undertaken using immunohistochemical techniques. For the identification of CD4/CD8 and CD68 cells, tissue samples were fixed in 10% formaldehyde, embedded in paraffin, and cut into 5-mm slices using a microtome (Microm, Barcelona, Spain). The sections were then deparaffinated, hydrated, and equilibrated in phosphate-buffered saline (PBS) buffer (pH 7.4). Pretreatment of tissue by heat-induced epitope retrieval was required. This involved immersing the tissue in 10 mM citrate buffer pH 6.0 and microwave boiling for 2 minutes. Acetone-fixed frozen sections were used to identify CD19-positive cells and neutrophil collagenase (matrix metalloproteinase [MMP] 8).

  We used as primary antibodies a mouse monoclonal anti-human CD68 (1:50) (DakoCytomation, Glostrup, Denmark) to identify macrophages/monocytes, mouse monoclonal anti-human CD4 (1:10) (Neomarkers, Fremont, Calif) and CD8 antibodies (1:50) (DakoCytomation, Glostrup, Denmark) to identify T cells, a mouse monoclonal anti-human CD19 antibody (1:100) (Neomarkers, Fremont, Calif) to identify B cells, and a mouse monoclonal anti-human MMP8 (1:200) (Chemicon, Temecula, Calif) to identify neutrophils. The antigen-antibody reaction was detected by the alkaline phosphatase–labeled avidin–biotin procedure. The chromogenic substrate contained alpha-naphthol and fast red. Nuclei were counterstained with Carazzi hematoxylin. After the immunohistochemical procedure, the tissue sections were examined under a light microscope (Zeiss, Jena, Germany). The number of infiltrated cells were counted under the microscope (×200) in 4 areas of 0.5 mm² per patient (40 high-power fields per group). All values were expressed as means±SE. Data were compared using the Student t test. The level of significance was set at P<0.05.
RESULTS

Inflammatory cells

In general, we observed increased numbers of CD4+ cells, B cells (CD19+), and monocytes/macrophages (CD68+) in the varicose veins with respect to the normal patients. No differences were observed in CD8 and neutrophils compared with control veins. In addition, we examined the distribution of these cells as an indication of the inflammatory environment in aging and CVI.

In the control vein specimens, CD4+ cells were scarce, appearing mainly in the adventitial layer in segments obtained from the young subjects (Figure 1a) and more toward the media and infiltrating the valves in control specimens from older subjects. Varicose veins showed significantly increased numbers of CD4+ cells compared with controls (Figure 1c) (P<0.005). In specimens from the older subject group, CD4+ became infiltrated in the subendothelium and valves (Figure 1b) while in the varicose vein/young specimens, these cells were mainly observed in the adventitial and medial layers. Varicose veins showed significantly increased CD4+ cells compared with the normal veins, in the younger population (Figure 1d). These results appear to indicate that the presence of CD4+ cells is related to the varicose condition.

Immunolabeling for CD8 cells was scarce both in the vein wall of healthy and varicose specimens and appeared in the adventitial and medial layers (Figure 2a and b). Differences between the groups were not found (Figure 2c and d). Only vein specimens from one subject, in which areas of hemorrhage and inflammation were observed, showed significantly higher numbers of CD8+ cells. This subject was therefore excluded from the study.

B cells were identified by the CD19 antibody. The distribution of CD19+ cells was conditioned by age. In the wall of specimens from young subjects, B cells mostly appeared in the endothelium (Figure 3a), whereas in vein specimens from the older subjects (Figure 3b), CD19+ cells were mainly confined to the adventitial layer, regardless of the varicose or healthy condition. B-cell numbers were significantly higher in varicose veins compared with healthy veins (Figure 3c) (P<0.005). When stratified by age, this difference was only maintained for the group of older subjects (Figure 3d) (P<0.01).

Figure 1. Immunohistochemical detection of CD4+ cells (**) in the control veins (a) and varicose veins of an older patient (b). Quantification of the stained cells in the different groups excluding the age factor (c) showing significant differences (**P<0.005) between varicose and normal veins due to the disease process. Quantification and statistical analysis including the age of the patients (d). Note that this factor did not affect the number of CD4+ cells (**P<0.05).

Abbreviation: C, control; L, lumen; V, varicose vein.

Figure 2. Image of the immunohistochemical detection of the number of CD8+ cells (**) in the vein walls of healthy specimens (a) and varicose specimens (b). Quantification of CD8-labeled cells in the different groups excluding the age factor (c) showing no significant differences between the varicose and normal veins. Differences were also not significant when the different age-groups were compared (d).

Figure 3: Immunohistochemical detection of CD19+ cells (**) in control (a) and varicose veins (b). Quantification of positive cells in both groups excluding the age factor (c) showing significant differences (**P<0.005) attributed to the disease process. When stratified by age (d), differences between control and varicose veins were only maintained in the older study population (**P<0.01).

Abbreviations: C, control; L, lumen; V, varicose vein.
Leukocytes and varicose vein etiology – New Targets for Pharmacological Treatment in Primary Chronic Venous Disease

In control specimens, CD68+ cells were observed in the lower layers of the tunica media (Figure 4a), while in the varicose vein specimens, these cells infiltrated the upper areas of the media. Higher numbers of CD68+ cells (macrophages/monocytes) were recorded in the varicose group (Figure 4c) (*P<0.05). In specimens from young persons, the odd CD68+ cell appeared throughout the vessel wall with the exception of the intimal layer of the vein. In the specimens from elderly subjects, these cells were observed in the upper media layer, endothelium, and valves.

The most notable changes in the distribution of CD68+ cells in varicose vein specimens were the presence of monocytes/macrophages at the valves and nearby endothelium (Figure 4b). In addition, significantly higher numbers of these cells were detected in the older varicose veins (*P<0.05).

When stratified by age, higher numbers of CD68+ cells were detected in both healthy and varicose specimens from the older subject group (Figure 4d). Among the specimens from older subjects, significantly more CD68+ cells were detected in the varicose veins than in the controls (*P<0.01) (Figure 4d). Hence, overall there were clear differences attributable to age and the varicose condition in the distribution patterns and the numbers of CD68+ cells. These cells were also found to be associated with valve failure.

MMP8 is a type II collagenase secreted by neutrophils. The expression of this enzyme was not observed in the control vein specimens from the younger group (Figure 5a). In healthy specimens from the older subjects, MMP8 labeling appeared in areas of the tunica media and adventitia corresponding to degranulated neutrophils (Figure 5b). In specimens from young subjects with varicose veins, small numbers of nondegranulated cells could be seen, in all the layers of the vein wall. In the varicose vein specimens from older subjects, MMP8+ cells were found in the valves (Figure 5d), intima, adventitia (Figure 5c), and vasa vasonum of the vein wall, many of which were already degranulated. Hence, the most outstanding finding related to this enzyme was neutrophilic degranulation related to age regardless of the healthy or varicose condition of the veins.

Discussion

In previous papers, aging was established as an important factor responsible for changes in the vein wall, and these changes were similar to those produced at the different stages of CVI. In this study, we tried to separate the effects of these 2 overlapping processes particularly those related to the inflammation process contributing to the general mechanism of aging (physiological) or the inflammatory response to disease (venous insufficiency).

The basal state of vein wall is characterized by a special property of microcirculation venules, where the wall shear stress is low and endothelial cells can recruit inflammatory cells. In young people, white blood cells are rarely seen in the adventitial microvessels. During aging, we observed the movement of white blood cells from the adventitia to the medial layer and the upper part of the vein wall, along with the presence of white blood cells at the level of the valves, especially CD4+ and CD68+. These types of inflammatory macrophages/monocytes play a key role in tissue remodeling due to their ability to release MMPs, growth factors, and proinflammatory cytokines. In addition, some authors advocate that macrophages/monocytes can enhance cell adhesion
molecule expression by the vascular endothelium and induce changes in the smooth muscle phenotype. It would be interesting to determine whether the presence of these cells was a consequence or cause of vein wall remodeling during aging. Whatever the case, the discrete presence of these cells from the microvessels toward the vein interior would be consistent with the immunohistochemical changes in collagen and MMPs in the aging vein wall and with the reduction in elastin components and increased elastase activity previously described by us. The presence of these inflammatory cells in the medial layer of the wall could be the triggering factor for remodeling of the wall, perhaps as the consequence of a discrete but sustained chronic inflammatory process.

When we evaluated the appearance of white blood cells in varicose processes, we found a general significant increase in all the cells examined (except CD8 and neutrophils) with respect to control, healthy veins, once again supporting the participation of inflammatory cells in the changes that affect the insufficient vein wall. Nevertheless, the distribution of these cells in the vein wall and the effects of age also need to be established.

In young CVI patients, CD4+ T lymphocytes were detected mainly in the adventitial area as occurred in the control group, only these appeared in significantly greater numbers. In the vein specimens from older subjects, a change was observed in the distribution of these cells, which accumulated at the level of the valves and in adjacent endothelial and subendothelial areas. Our findings differ in part from those of other authors, who described no significant increase in the number of T lymphocytes in varicose veins. The increased number and more importantly the distribution of CD4+ cells confirm the changes that occur at the valve and luminal surface of the insufficient vein in older patients.

CD4+ lymphocytes, depending on the types of cytokine they produce, can be of the Th1 or Th2 type. Th1 lymphocytes secrete interleukin (IL) 2 and interferon gamma, which induce the inflammatory response through 2 mechanisms: facilitating the cell immune reaction and stimulating B cells. Th2 lymphocytes produce IL-4, IL-5, IL-9, IL-10, and IL-13. This array of cytokines is, in part, responsible for activating B cells. The increased numbers of the CD19+ population in the varicose condition could be correlated with the change from an inflammatory status provoked by the CD4+ cells. Other authors find no changes in B lymphocytes (CD20+/CD30+), although we observed the expression of the CD19+ epitope in all B cells except plasma cells, indicating the wide distribution range of this cell type.

It is well known that macrophages/monocytes accumulate at varicose veins valves, and they are more commonly observed adhering to the valve and to the vein wall above the valve complex, suggesting a role in the genesis of primary vein dysfunction. These findings confirm those of other studies in which macrophages/monocytes and mast cells were differently distributed throughout the vessel wall, showing a significant increase in the varicose vein wall, compared with controls. Takase et al observed CD68+ macrophages on the endothelium, subendothelium, and all other areas of the insufficient vein wall. We propose that the presence of these cells on the luminal surface and in particular on the valves is a good indication of valve dysfunction, a rationale supported by its significant increase with age. The set of varicose vein specimens from the older subjects showed a greater accumulation of macrophages both in the areas of the vein wall and along the valves. The disease thus enhances this difference.

The increase in CD68+ cells has been correlated with the overexpression of transforming growth factor β (TGF-β) and that of inducible nitric oxide synthase (iNOS) with the extent of damage. These findings are in agreement with previous results from our laboratory. Thus, we detected increased TGF-β levels in the veins of CVI patients, which, added to the augmented CD68+ cells detected here, would support Jacob’s findings.

The deposition of these cells in the valve area in CVI allows us to establish an infiltration gradient during the aging and disease process, which is probably related to the changes in pressure and shear stress at the level of the valves proposed by Takase et al.

Finally, we examined the part played by neutrophils in these processes. In the literature regarding the genesis of CVI, authors such as Sayer report no difference in the behavior of these cells in the vein wall, although others have described differences in the peripheral circulation. According to some authors, in the disease state, neutrophils in the blood are activated through the mediation of enzymes secreted upon the degranulation of neutrophils. Our findings are not completely in line with this theory concerning neutrophil activation (as measured by their degranulation), since we observed neutrophil degranulation in both control and varicose vein specimens from older subjects, suggesting an indirect measure of vein wall ischemia. This factor would support the chronicity of the process.

In summary, the findings of our study indicate a clear increase in the inflammatory environment provoked by aging, which starts with the vasa soro and goes on to markedly affect the valves in the vein wall. In our young patients with CVI, most damage appears in the luminal area and this damage then becomes more generalized in aged patients with CVI, particularly at the level of the valves.

It may therefore be concluded that inflammatory cells play a pivotal role both in the aging process and the varicose process. The distribution of these cells is a good indicator of the state of the vein wall and also allows us to infer that dysfunction of the microvascular endothelium is the primary effect related to age, while valve dysfunction is most marked in venous insufficiency. Although the disease and aging processes run a parallel, overlapping course, the aging process may be accelerated in CVI coinciding with the remodeling of the vein wall affecting both its cellular component and its extracellular component, as observed in our previous work.
Leukocytes and varicose vein etiology – the pathogenesis of vascular disease.

Leukocytes and capillaries in chronic venous disease

by P. Coleridge Smith,
United Kingdom

Patients with chronic venous disease suffer persistently raised pressures in their deep and superficial veins in the lower limb. Leukocytes become “trapped” in the circulation of the leg during periods of venous hypertension produced by sitting or standing. Studies of the plasma levels of neutrophil granule enzymes show that these are increased during periods of venous hypertension, suggesting that this causes activation of the neutrophils. Investigation of the leukocyte surface ligands CD11b and CD62L shows that the more activated neutrophils and monocytes are sequestered during venous hypertension. Measurement of plasma levels of the soluble parts of the endothelial adhesion molecules vascular cell adhesion molecule (VCAM), intercellular adhesion molecule (ICAM), and endothelial leukocyte adhesion molecule (ELAM) show that these are all elevated in patients with chronic venous disease compared with controls. Following 30 minutes of venous hypertension produced by standing, these levels are further increased. These data suggest that venous hypertension causes neutrophil and monocyte activation, which in turn causes injury to the endothelium. Chronic injury to the endothelium leads to a chronic inflammatory condition of the skin that we know clinically as lipodermatosclerosis. This is mediated by perivascular inflammatory cells, principally macrophages, in the skin microcirculation. These stimulate fibroblasts in the skin leading to tissue remodeling and the laying down of fibrous tissue. Vascular endothelial growth factor (VEGF) stimulates proliferation of capillaries within the skin. Skin in this state has the potential to ulcerate in response to minor injury.

Keywords: venous hypertension; adhesion molecule; injury; leukocyte; endothelium; trapping; activation

SELECTED ABBREVIATIONS AND ACRONYMS

CEAP: clinical, etiological, anatomical, pathophysiological (classification)
CVI: chronic venous insufficiency
ELAM: endothelial leukocyte adhesion molecule
ICAM: intercellular adhesion molecule
IL: interleukin
MPFF: micronized purified flavonoid fraction
TGF-β: transforming growth factor β
TNF-α: tumor necrosis factor α
VCAM: vascular cell adhesion molecule
VEGF: vascular endothelial growth factor

The clearance of $^{133}$Xe from the skin as an assessment of the efficiency of the microcirculation in handling a molecule of similar size to oxygen had been measured. This gas has a molecular weight four times that of oxygen, so its diffusion rate would be half that of oxygen, assuming similar solubility for oxygen and xenon in body fluids (water). Measurements were made in the liposclerotic skin of patients with venous disease, and compared with control subjects under conditions of reactive hyperemia after 5 minutes of cuff-occlusion of the arterial supply to the leg. No difference in xenon clearance was found between patients with venous disease and control subjects. These findings lead to the conclusion that in patients with chronic venous insufficiency (CVI) skin changes are not principally attributable to failure of skin oxygenation.

**The “white cell trapping” hypothesis**

The search for alternative mechanisms of skin damage in venous disease has resulted in investigation of the blood itself. Thomas investigated a series of patients and control subjects who were subjected to experimental venous hypertension by sitting with the legs dependent for a period of 60 minutes. Blood samples were taken from the great saphenous vein at the ankle. After 60 minutes, patients with venous disease were “trapping” 30% of the white cells and control subjects were trapping 7%.

White cell margination is a normal event in the peripheral vascular resistance despite their small numbers in the circulation compared with red cells. In myocardial infarction, they cause capillary occlusion, which can be prevented in experimental animals by first rendering the animal leukopenic. White blood cells are substantially larger than red cells to deform on entering a capillary bed, and are responsible for about half the peripheral vascular resistance. If some of the capillaries were occluded, this might result in heterogeneous perfusion and therefore tissue hypoxia and ischemia. Thomas investigated a series of patients with venous disease, and compared with control subjects. Increased levels of CD11b were observed in that limb. Subsequently, expression of the surface neutrophil ligand CD11b has been investigated as a marker of neutrophil activation. The experiment was repeated as before on control subjects. Blood was taken from a dorsal foot vein. CD11b expression was assessed by fluorescent-labeled monoclonal antibody used to label neutrophils in whole blood that were counted using flow cytometry. During the period of ambulatory venous hypertension in control subjects, no rise in CD11b expression was seen in that limb. Subsequently, expression of the surface neutrophil ligand CD11b has been investigated as a marker of neutrophil activation. The experiment was repeated as before on control subjects. Blood was taken from a dorsal foot vein. CD11b expression was assessed by fluorescent-labeled monoclonal antibody used to label neutrophils in whole blood that were counted using flow cytometry. During the period of ambulatory venous hypertension in control subjects, no rise in CD11b expression was seen in that limb. Following return to the supine position, when neutrophils might be expected to leave the lower limb, according to the studies of Thomas, increased levels of CD11b were observed. This indicates that neutrophils were unregulated by their period of adhesion to normal endothelium. An increased white cell–red cell ratio was also observed during this phase confirming white cell egress from the lower limb.
A similar study has also been conducted in patients with venous disease, including only subjects with uncomplicated varicose veins and one with skin changes (lipodermatosclerosis) attributable to venous disease. The adhesion of neutrophils and monocytes to endothelium was investigated. This is a two stage process. Initially, these cells roll along the endothelium, binding in a loose manner using a ligand on the leukocytes known as CD62L or L-selectin.

When binding occurs, a fragment of L-selectin is released into the plasma (soluble L-selectin) and can be detected by an enzyme-linked immunosorbent assay (ELISA). It was found that the concentration of soluble L-selectin rose during venous hypertension, confirming that endothelium-leukocyte binding had occurred. There was no major difference in magnitude between the two groups of patients. Subsequently, firm binding of neutrophils and monocytes occurs using CD11b/CD18 ligands which link to endothelial intercellular adhesion molecule (ICAM). This is reflected in the peripheral blood by a fall in the cells expressing most CD11b. Just such a fall was seen in the blood taken from the leg in both groups of patients. On return to the supine position, I had expected to see an egress of leukocytes expressing more CD11b in these patients, but this was not observed, in contrast to the studies in control subjects. In the timescale of this experiment (up to 10 minutes following venous hypertension), the more activated neutrophils and monocytes remained bound to the endothelium of the lower limb.

Plasma lactoferrin and elastase have been assessed in groups of patients with active venous disease. Blood was taken from the arm veins of patients (not the lower limb veins) with varicose veins, liposclerotic skin change, and active venous ulceration. In all samples, the levels of lactoferrin and elastase were higher in the patients than the age- and sex-matched control groups (Figures 2 and 3).

Figure 2. Results of plasma neutrophil elastase measurements in patients and control subjects. Error bars show the median and interquartile range of data. Statistical analysis was tested by the Mann-Whitney U test.

Abbreviations: LDS, lipodermatosclerosis; VV, varicose vein.


Figure 3. Results of plasma neutrophil lactoferrin (Lf) measurements in patients and control subjects. Error bars show the median and interquartile range of data.

Abbreviations: LDS, lipodermatosclerosis; VV, varicose vein.

Histological studies have been used to investigate the events in the skin in chronic venous disease. A quantitative histological study has been reported in which 3 groups of patients were studied. The first were patients with no evidence of skin changes as a consequence of their venous disease. The next group exhibited lipodermatosclerosis without a history of ulceration. The third group had healed ulcers with residual lipodermatosclerosis. Patients with normal skin had a low number of white blood cells visible (4 per mm²) in the upper 0.5 mm of the skin. There were 8 times as many in patients with liposclerotic skin and 40 times as many in patients with healed venous ulcers. Subsequently, an immunohistological study was undertaken to determine the types of white cell present in this infiltrate. The majority of cells are macrophages with a T-lymphocyte component, but no excess of neutrophils compared with control sections taken from normal limbs. So this infiltrate is a reflection of a chronic inflammatory process.

**The endothelium**

The microcirculation of the skin has been investigated by histology and by capillary microscopy. Both methods demonstrate capillary proliferation in patients with CVI—vastly more capillaries are visible by both techniques. However, capillary microscopy shows that these probably arise from a single capillary loop and appear like a glomerulus, rather than an increase in the numbers of capillaries. Recently, quantitative measurement of the capillary convolution in patients from each of the clinical, etiological, anatomical, pathophysiological (CEAP) clinical classes has been published. Recent immunohistochemical investigations have shown that the pericapillary cuff contains far more than fibrin. The capillary endothelium is perturbed, expressing increased amounts of factor VIII–related antigen, and adhesion molecules, especially ICAM-1. Endothelial leukocyte adhesion molecule 1 (ELAM-1) may be slightly upregulated but vascular cell adhesion molecule (VCAM) appears to be normal in patients without venous ulceration. Perturbed endothelium is more likely to attract the adhesion of leukocytes. The presence of the pericapillary fibrin cuff has been confirmed, but it also contains collagen IV, laminin, fibronectin, and tenascin. A marked degree of leukocyte infiltration has been measured in patients with venous disease. These cells are macrophages and T lymphocytes. The cytokines involved include interleukin (IL) 1α and 1β. Tumor necrosis factor α (TNF-α) was not detected in these histological sections. The presence of the perivascular “fibrin cuff” (with other components) is a reflection of the inflammatory process and is seen in other chronic inflammatory conditions. In patients with venous disease, increased plasma D-dimer levels have been observed suggesting enhanced deposition of fibrin. The perturbed state of the endothelium allows the passage of large molecules though the endothelium permitting their perivascular accumulation and ex-
Leukocytes and capillaries in chronic venous disease – Coleridge Smith

New Targets for Pharmacological Treatment in Primary Chronic Venous Disease

Leukocytes and capillaries in chronic venous disease. P=0.001, Wilcoxon

Positive TGF-β and von Willebrand factor. Patients with chronic venous disease (a group with uncomplicated varicose veins and a group with skin changes) were again studied and compared with normal controls. The concentration of soluble VCAM was elevated in both patient groups compared with control subjects, and was highest in the group with skin changes (Figure 6). Histological search for angiogenic factors

The vascular proliferation seen in the skin of patients with venous disease has been known for many years but has not been explained. In recent years, many angiogenic factors have been recognized which stimulate the growth of blood vessels. Immunohistochemistry was used to evaluate the presence of a number of such factors in the skin of patients with venous disease. Skin biopsies were taken at the time of surgery for varicose veins from the legs of patients with and without skin changes as well as from breast skin in patients without clinical evidence of venous disease, for use as a control. There was an increase in platelet-derived growth factor, subtype BB (PDGF-BB), in patients with venous disease. This was found in the capillary wall in vessels of the dermal papillae. There was also considerable upregulation of the production of vascular endothelial growth factor (VEGF) in the epidermis of patients with venous disease, most marked in those with skin changes. It seems likely that VEGF may account for at least some of the vascular proliferation seen in the skin of patients with venous disease. This growth factor is also responsible for increased vascular permeability to large molecules, a feature of the skin microangiopathy that has been reported from capillary microscopy studies. The mechanism of stimulation of epidermal VEGF production is unclear at present.

Skin fibrosis in venous disease

The role of transforming growth factor β1 (TGF-β1) in the skin damage of CVI has been studied in considerable detail by Pappas et al using immunohistochemical examination, electron microscopy, and examination of TGF-β1 gene expression. This investigation indicated that activated leukocytes traverse perivascular cuffs and release active TGF-β1. Positive TGF-β1 staining of dermal fibroblasts was observed and suggests that fibroblasts are the targets of activated interstitial leukocytes. A potential mechanism for quick access and release is storage of TGF-β1 in the extracellular matrix. TGF-β1 was exclusively elevated in areas of clinically active disease, indicating a localized response to injury. These data suggest that alterations in tissue remodeling occur in patients with CVI and that dermal tissue fibrosis in CVI is regulated by TGF-β1.

The fibrosis seen in the skin of patients with lipodermatosclerosis has also been investigated by other authors. This study shows that enhanced cell proliferation and an increase in the number of procollagen mRNA-expressing fibroblasts contribute to the development of lipodermatosclerosis (Figure 7). The fibrotic changes that result may not only be mediated by inflammatory cell–derived factors but also by additional profibrotic agents released in the skin as a consequence of chronic venous hypertension.

![Figure 6. Plasma vascular cell adhesion molecule 1 (VCAM-1) levels in normal controls and patients with chronic venous disease (with and without skin changes), before and after venous hypertension produced by sitting with the lower limbs dependent for 30 minutes. Descriptors: medians and interquartile ranges. Statistics: Wilcoxon and Mann-Whitney U test for unpaired data.](image)

![Figure 7. Increased procollagen type I–expressing cells in skin with lipodermatosclerosis (LDS). The number of positive dermal cells, as demonstrated by in situ hybridization, was assessed in skin sections from the control patients (n=12), from patients with chronic venous insufficiency but no clinical evidence of LDS (clinical, etiological, anatomical, pathophysiological [CEAP] class 2-3, n=10), and from patients with LDS (CEAP class 4, n=12). Data represent mean and SEM. Modified from reference 42: Deigiorgio-Miller AM, Treharne LJ, et al. Procollagen type I gene expression and cell proliferation are increased in lipodermatosclerosis. Br J Dermatol. 2005;152:242-249. Copyright © 2005, Blackwell Publishing.](image)
Figure 8. Diagrammatic summary of findings from many investigations in skin capillaries in patients with chronic venous disease. The capillaries comprise endothelial cells showing activation. The vessels are surrounded by an inflammatory cuff with a cellular infiltrate that includes macrophages. These and other cell types release a range of cytokines that, among other things, produce vascular proliferation and skin fibrosis. 

**Abbreviations:** MMP, matrix metalloproteinase; TGF-β1, transforming growth factor β1; VEGF, vascular endothelial growth factor.

Some authors have studied the distribution of growth substances and connective tissue proteins in skin biopsies using immunohistochemical staining. In particular, they studied the pericapillary cuffs, which were once thought to inhibit oxygen transfer to the tissues. The cuffs were positive for actin, type IV collagen, factor XIIIa, and α₂-macroglobulin and there was increased TGF-β1. They observed that TGF-β1 immunoreactivity was present within the fibrin cuffs, but not in the provisional matrix in the ulcer bed around the cuffs. These observations suggest that growth factors critical in wound healing, such as TGF-β1, are present within venous ulcers, but are abnormally distributed. Their distribution within fibrin cuffs and colocalization with extravasated plasma proteins, particularly α₂-macroglobulin, which is a recognized scavenger molecule for TGF-β and other growth factors, provides evidence for a possible “trapping” of growth factors in venous ulcers. This proposal has been advanced as a cause for failure of venous leg ulcers to heal.

**Interpretation of data from existing studies**

Endothelial adhesion is a normal physiological activity of neutrophils and monocytes. During venous hypertension, the fall in blood flow to the lower limb and increase in diameter of capillaries results in a fall in the shear rate in cutaneous capillaries. This favors leukocyte adhesion, which may be observed, even in control subjects, but is of greater magnitude in patients with venous disease, presumably due to the modifications that take place in the endothelium in chronic venous disease.

It has been found that leukocyte-endothelium interaction occurs during short-term venous hypertension (within 30 minutes) and that during this period neutrophil degranulation may be detected, releasing primary and secondary granule enzymes into the region of the endothelium. At the same time, an increase in von Willebrand factor and soluble endothelial adhesion molecules can be found in the leg blood. These arguments apply to control subjects as well as to patients, although the magnitude of change is always greater in the patients rather than the control subjects. The research shows that when the venous system becomes deranged, endothelial injury may be the result. Activated leukocytes leave the lower limbs of control subjects following venous hypertension. In patients with venous disease, these cells appear to remain in the lower limb, perhaps attached to the abnormal endothelium. The chronic changes seen in liposclerotic skin may be the response to sustained, low-grade injury to the endothelium by neutrophils and monocytes over many months or years. The perivascular infiltration of vessels in the papillary dermis by macrophages and T lymphocytes may simply be a tissue response to the chronic inflammatory processes referred to above (Figure 8). Endothelial activation is seen during this phase with increased expression of endothelial adhesion molecules. This would favor the adhesion of further leukocytes encouraging this process to continue.

The chronic inflammatory process results in the release of cytokines that encourage vascular proliferation. VEGF has been shown to be involved in this process. Whether this is simply an associated phenomenon or crucial to subsequent ulceration remains unclear at present. Extensive skin fibrosis that is part of the clinical syndrome of lipodermatosclerosis is a feature of chronic venous disease. The macrophages present in the perivascular inflammatory process release TGF-β and this in turn stimulates fibroblasts to synthesize more collagen and connective tissue proteins.
The progression from chronic skin damage to actual ulceration remains difficult to understand. A possible explanation is that an initiating stimulus causes massive activation of the perivascular macrophages resulting in extensive tissue and blood vessel destruction. This might occur spontaneously or minor trauma to the region may set in motion the series of events that leads to ulcer formation.

The data collected in the studies of neutrophil, monocyte, and endothelial cell activity have so far failed to identify major differences between those patients who develop skin changes and are at risk of ulceration and those who do not. Inflammatory mechanisms are very complex and identifying those that predispose to the development of skin changes and ulceration will be a complex task.

Implications for pharmacological treatment in venous disease

Although bandaging and stockings have been used effectively in the treatment of CVI for many years, modern pharmacological science may provide assistance in healing venous ulcers and perhaps some insight into the mechanisms of the disease.

Pentoxifylline has been used for the treatment of claudication for a number of years, with moderate success. Its mechanism of action is probably through an effect on inhibition of cytokine-mediated neutrophil activation. Its efficacy in healing venous leg ulcers has been reported in a recent meta-analysis. Nine trials involving 572 adults were included. Pentoxifylline plus compression is more effective than placebo plus compression (relative risk of healing with pentoxifylline 1.30; 95% confidence interval, 1.10-1.54). This drug could be considered for use in patients with venous leg ulceration when used in combination with compression.

Prostaglandin E2 has a number of profound effects on the microcirculation, including reduction in white cell activation, platelet aggregation inhibition, small vessel vasodilatation, and reduction in wall vessel cholesterol levels. Recently, the results of a randomized, placebo-controlled, single-blind study in 87 patients with venous leg ulcers were reported. Patients were treated with compression bandaging and conventional wound management. They also received treatment for 20 days with an infusion of prostaglandin E2 analogue (Prostavasin) or placebo. After 4 months, all ulcers were healed in the active treatment group but only 32 of 38 in the placebo group. This is a potentially useful drug but the limitation of giving intravenous infusions restricts it applicability.

Laurent investigated micronized purified flavonoid fraction (MPFF) and showed that this drug reduced the symptoms of venous disease (aching, itching, feeling of swelling) and also reduced ankle edema. More recently, MPFF has been studied for its effects on venous leg ulcer healing. A meta-analysis has been published in which 5 prospective, randomized, controlled studies involving 723 patients with venous ulcers were included. Patients were treated with compression bandaging and local wound care in all cases. In 2 studies, MPFF was compared with placebo and in 3 studies MPFF was compared with standard treatment alone. At 6 months, the chance of healing ulcer was 32% better in patients treated with adjunctive MPFF than in those managed by conventional therapy alone. The main benefit of MPFF was present in the subgroup of ulcers between 5 and 10 cm² in area and those present for 6 to 12 months’ duration.

MPFF may therefore be a useful drug to combine with compression management in countries where it is licensed.

Conclusions

The precise mechanisms through which venous hypertension causes ulceration still remain unclear. There is clear evidence of leukocyte activation in venous disease and many inflammatory mechanisms are upregulated in the skin. So far, it has been impossible to say which is the main cause of the problem and which are simply a response to the inflammatory process. Drugs that mitigate leukocyte activation appear to benefit ulcer healing. A better understanding of the initiating processes may lead to improvements in the management of patients with venous ulceration.

REFERENCES

Leukocytes and capillaries in chronic venous disease

New Targets for Pharmacological Treatment


Leucocytes and capillaries dans la maladie veineuse chronique

Les patients présentant une maladie veineuse chronique souffrent de façon permanente de pressions élevées au niveau des veines superficielles et profundes des membres inférieurs. Les leucocytes sont « bloqués » dans la circulation des jambes au cours des périodes d’hypertension veineuse et cette augmentation pourrait être à l’origine de l’activation des neutrophiles. L’étude des ligands de surface des leucocytes CD11b et CD62L indique que les neutrophiles et les monocytes les plus activés sont séquestrés pendant l’hypertension veineuse. La mesure des concentrations plasmatiques de la partie soluble des molécules d’adhésion endothéliale VCAM (molécule d’adhésion cellulaire vasculaire), ICAM (molécule d’adhésion intercellulaire) et ELAM (molécule d’adhésion leucocytaire endothéliale) montre qu’elles sont toutes élevées chez les patients présentant une maladie veineuse chronique comparés aux témoins. Après 30 minutes d’hypertension veineuse induite par l’orthostatisme, toutes ces concentrations sont encore plus élevées. Ces données suggèrent que l’hypertension veineuse produit une activation des neutrophiles et des monocytes, ce qui en retour provoque des lésions endothéliales. Les lésions chroniques de l’endothélium provoquent un état inflammatoire chronique de la peau et stimulent la prolifération des capillaires cutanés. Les fibroblastes cutanés sont ainsi stimulés et entraînent un remodelage tissulaire et un affaissement du tissu fibreux. Le VGEF (vasculaire endothelial growth factor) stimule la prolifération des capillaires cutanés. Ainsi remaniée, la peau peut s’ulcérer à partir de lésions insignifiantes.
According to the literature, chronic venous disease includes patients who present with so-called symptoms and/or signs of venous disease that characterize each class of chronic venous disease in the clinical, etiological, anatomical, and pathophysiological (CEAP) classification system, from class C0 to class C6. The symptoms traditionally ascribed to chronic venous disease include aching, heaviness, a feeling of swelling, cramps, itching, tingling, and restless legs. The C0s clinical class of the CEAP classification takes into account those patients who present with chronic venous disease–related symptoms but without visible signs. The grading of chronic venous disease has been facilitated and standardized by the introduction of the CEAP, making comparison between studies much easier. Unfortunately, little is still known about the prevalence of symptoms in chronic venous disease and even less on the prevalence of patients in class C0s despite the introduction of this patient profile into the CEAP classification.

Among epidemiological surveys that have been performed since the advent of the CEAP, at least 6 have used this classification. The percentage of symptomatic patients with chronic venous disease varied between 25% and 84%, depending on the population studied, the severity of the disease, and the mean age of patients (Table I, next page).

Since 1989, an Italian team has been interested in this type of patients presenting with venous symptoms but without venous signs. They set up an epidemiological survey in Acireale, a city of 40000 inhabitants in Italy, with participants taken from electoral lists and found that the prevalence of C0s patients was 15.90% in the general population and that it was higher in women. This C0s Acireale population was characterized by functional abnormalities detected on plethysmography and duplex scanning. The authors named this particular condition functional phlebopathy.

In a recent epidemiological survey of 2408 adults of the general population of San Diego, Calif, the prevalence of C0s patients was 15% but they did not present with either functional anomalies on duplex ultrasonography or visible clinical signs of chronic venous disease, so the authors concluded that symptoms are not specific for the condition.

Previously, Cloarec et al defined a prevaricose syndrome encompassing intermediate phases between a normal venous system and overt varicose disease. Careful investigation for reflux in symptomatic but apparently healthy subjects revealed a hypotonic vein wall, altered venous reactivity, hyperdistensibility, and wall thickening. Cloarec et al argued that subjects at risk required routine screening and prophylactic intervention to avoid progression to an objective disease.

In addition to prevaricose syndrome, studies by Andreozzi and Cloarec thus identified a group of patients with the symptoms of chronic venous dis-
ease (peripheral edema, and heavy, restless, and painful legs), but with no specific risk factors, no evidence of reflux, and no progression to varicose disease.

The clinical description of this condition is of a symptomatic patient with disorders not directly related to failure of the superficial and/or deep venous system but related to extrinsic causes that modify and alter the mechanisms of venous flow. Functional phlebopathy may be due to extravenous impairment of the push-and-pull mechanisms of venous flow. The push mechanism consists of compression of the venous plexus in the sole of the foot, the calf muscle pump, and the pulsation of the contiguous arterial system. Pull is exerted by the diaphragm and negative mediastinal pressure.

Multiple extravenous factors can impair these mechanisms: sedentary lifestyle, obesity, respiratory and cardiac disease, work in the standing position, repeated pregnancy (inferior vena cava compression, altered endocrine environment, inadequate diaphragmatic excursion), peripheral arterial disease (where low perfusion pressure is combined with low or absent pulsatility), lower-limb disease (nerve root pathology, foot arch deformities), and altered plantar support area. All these mechanisms corresponding to altered vis a tergo and vis a fronte can cause the onset of chronic venous disease with initial functional symptoms provided that there is a family history of varicose veins or a thrombophilic status. Another typology of patients, described by us, present symptoms of chronic venous disease without specific macrocirculatory modifications.

In 1997, we published our 10-year data on 300 controls and 820 patients with sporadic diffuse and/or regional edema, heavy restless legs, lipodermatosclerosis (cellulite), permanent objective acral hypothermia, subjective diffuse hypothermia, an allergic diathesis, and low-normal systolic blood pressure (100±5 mm Hg; World Health Organization range, 90 to 130 mm Hg). The women in this population reported menstrual abnormalities (frequency, quantity, and duration) and benign breast disease. Our study identified constitutional functional venopathy (CFV) defined by symptoms of venolymphatic hypertension (heavy restless legs, tension, cramps, pain), decreased venous tone, cellulitis, and permanent acral hypothermia, and by the absence of reflux or any evidence of structural macrovascular pathology on clinical examination or standard methods of investigation.

### Table I. Summary of epidemiological surveys using the clinical, etiological, anatomical, pathophysiological (CEAP) classification.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CVF</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone</td>
<td>14±10&lt;sup&gt;†&lt;/sup&gt;</td>
<td>26±8</td>
</tr>
<tr>
<td>(normal value 3.30 ng/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17ß-estradiol</td>
<td>170±50</td>
<td>140±60</td>
</tr>
<tr>
<td>(normal range 6-200 pg/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactin</td>
<td>23±8&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>14±6</td>
</tr>
<tr>
<td>(normal range 2-25 ng/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dedhydroepiandrosterone</td>
<td>Normal value</td>
<td>Normal value</td>
</tr>
<tr>
<td>(normal range 1.2-3.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>Normal value</td>
<td>Normal value</td>
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<tr>
<td>(normal range 0.1-1.1)</td>
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</table>

<sup>‡</sup><sub>P<0.5</sub>  
<sup>†</sup><sub>P<0.05</sub>

Table II. Endocrine changes in women with constitutional functional venopathy (CFV) compared with controls.
**Endocrine changes in CFV**

Investigations included endocrine screening (testosterone, dihydroepiandrosterone, 17β-estradiol, progesterone, and prolactin on day 21 of the menstrual cycle) (Table II). In women, endocrine changes account for many dysfunctional complaints typical of the childbearing years, including idiopathic cyclic edema, menstrual migraine, and premenstrual mastodynia. In women with functional phlebopathy, they also account for diffuse edema, specific adipose tissue distribution, a menstrual symptom pattern, and cellulite.

The trend of the hormones involved in many dysfunctional conditions of the fertile age (idiopathic cyclic edema, menstrual migraine, premenstrual mastodynia) accounts for diffuse edema, the peculiar disposition of the adipose tissue, menstrual alterations, and edematofibrosclerotic lipodystrophy (cellulite).

**Microangiopathy in CFV**

Traditional nailfold capillaroscopy (wild capillaroscopy, magnification ×10; parameters: loop count, morphology, distribution, dimension) was performed (Table III). The data were analyzed using the Student t test.

Seventy-eight consecutive patients underwent dynamic capillaroscopy (capillary red blood cell velocity, relative microhematocrit), microlymphography (microlymphatic loop count, microlymphatic diameter, endolymphatic pressure). Results are summarized in Table IV. Laser Doppler (resting flux, venoarterial reflex) and venous duplex scanning (femoral and popliteal venous diameter ratios between the supine and upright positions) were also undertaken (Tables V and VI).

The demonstration of venular and endolymphatic hypertension is consistent with the presence of postural edema and could be considered as the microvascular pathogenesis of cellulite.

**Hypotheses on the pathophysiology of CFV**

The signs differentiating CFV from the prevaricose patients described by Cloarec et al.²¹,²² and the Acireale project²³ are vein wall hypotonicity without reflux, venular hypertension, altered hormone levels, and cellulite (Table VII); however, the many patients in these 2 studies who showed no changes in vein wall tone or reflux, and who did not progress to overt disease, are likely to have had the CFV that we have described, confirming early studies by Merlen.²⁴,²⁵ CFV is a syndrome midway between an endocrine disorder and the stasis microangiopathy possibly responsible for cellulite. In terms of the CEAP classification, it may be difficult to differentiate from the prevaricose syndrome (Cso-, Epo-, Ao-; Pox; unclassified; clinical score, 1-2; anatomical score, 0; disability score, 1). However, diagnosis is important for 2 reasons: (i) CFV is common, accounting for 30% of the outpatients at San Giovanni Hospital, Rome (Figure 1, next page); and (ii) the CFV entity is more than a cosmetic complaint of cellulite and correct diagnosis avoids inappropriate therapy, whether with compression (which is poorly tolerated) or, worse, surgery. Patients can instead be offered effective venotonic agents (flavonoids and dihydroergotamine), lifestyle advice (high-protein diet, avoidance of sport involving high sustained mediastinal and/or abdominal pressure), and physiotherapy (heat therapy in iodinated salt water, manual lymph drainage, etc).
The syndrome we have described above and termed CFV or constitutional phlebostasis according to the Latin or Greek root chosen can be defined as follows: a familial, constitutional, and functional syndrome, characterized by clinical signs of venous hypertension (dull legs, cramps, tension, restless legs), decreased venous tone, without reflex, independent of organic macrovascular pathology highlighted with clinical examination and usual diagnostic tools, cellulite, and permanent acral hypothermia. The importance of recognizing this complex syndrome, halfway between an endocrine disturbance and stasis microangiopathy, perhaps responsible for lipodermatosclerosis or cellulite, is due to (i) the underestimated suffering of the patients, often interpreted as a simple cosmetic problem of cellulite; (ii) a subsequent incorrect therapeutic approach using compression therapy hardly tolerated by these patients or, even worse, surgical operations; (iii) high prevalence of this syndrome; (iv) good response to flavonoids and phlebotonic drugs; (v) changes in lifestyle habits that may improve the condition (practice of nonviolent sporting activities, hyperproteinic diet, thermal therapy with waters rich in salt/iodine, manual lymphatic drainage). Another group of patients has the so-called “restless legs syndrome” showing symptomatology similar to chronic venous disease without signs and demonstrated progression to chronic venous disease.19

Conclusions and comment

According to the studies reported above, we can define 6 kinds of patients:

❖ Patients with symptoms of chronic venous disease without signs; the plethysmography shows reduced venous compliance, and perhaps should be considered as a prevaricose syndrome.11,12

❖ Patients with symptoms of chronic venous disease with no progression to true chronic venous disease, evaluated with plethysmography and duplex scanning.9

❖ Patients with symptoms of chronic venous disease with progression to chronic venous disease, evaluated with duplex scanning and plethysmography.13,14

❖ Patients with symptoms of chronic venous disease and alteration of vis a tergo and vis a fronte; they occasionally progress to chronic venous disease on condition that a family history of varicose veins13 or a thrombophilic status is present.

❖ Patients with symptoms of chronic venous disease due to abnormalities in neurotransmitters that help regulate muscle movements or due to abnormalities in the part of the central nervous system that controls automatic movements (restless legs syndrome)14; they occasionally progress to chronic venous disease.

In conclusion, the symptoms reported in C0s of the CEAP classification (aching, heaviness, a feeling of swelling, cramps, itching, tingling, and restless legs) are not specific to chronic venous disease. Consequently, we could propose removing C0s from the CEAP classification together with C1s since, up till now, there has been no scientific evidence that reticular veins and telangiectases are signs of progression toward chronic venous disease: we have to start from C2s, which should include C0s and C1s. Another solution, perhaps the most appropriate, could be to include in the C0 stage “symptoms which arise in the orthostatic position and disappear in the lying position,” and to include in the C3 stage “gravitational or orthostatic edema which disappears in the lying position.” By so doing, both symptoms and edema would be definitely attributed to venous pathology.

In the future, research should clarify how predisposing causes or so-called risk factors for chronic venous disease can result in symptomatic disease using familial vertical studies or by means of the evaluation of enzymatic modifications of the venous wall or the microcirculatory system, such as hemosiderin in chronic venous insufficiency.20

Furthermore, the different groups of patients should be evaluated by means of homogeneous, reliable, and reproducible instrumental examinations for defining initial chronic venous disease.□

REFERENCES


**Patients présentant des symptômes de maladie veineuse chronique sans signe clinique : prévalence et hypothèses**

La maladie veineuse chronique regroupe des patients présentant des symptômes et/ou des signes de maladie veineuse qui caractérisent chacune de ses classes cliniques dans la classification CEAP (clinique, étiologique, anatomique et physiopathologique) de la classe C0 à la classe C6. Parmi les symptômes habituellement attribués à la maladie veineuse chronique on trouve une douleur, une pesanteur, une sensation d’œdème, des crampes, des démangeaisons, des fourmillements et un syndrome des jambes sans repos. Le niveau C0s de la classification CEAP prend en compte ces patients qui présentent des symptômes de maladie veineuse chronique sans signe clinique visible. Malgré la connaissance du profil de ces patients dans une classification reconnue dans le monde entier, leur prévalence n’a pas été clairement évaluée dans des études épidémiologiques. En Italie, plusieurs groupes de chercheurs se sont intéressés au sujet depuis les années 80 et ont tenté d’en expliquer la physiopathologie. Il semble que les facteurs de risque et les modifications hémodynamiques du flux veineux avec apparition de signes de reflux en soient à l’origine. Ces patients ont donc été considérés comme présentant un syndrome prévariqueux avec des perturbations fonctionnelles dans lesquelles une stase microcirculatoire et des troubles hormonaux peuvent coexister.
How are leukocytes involved in the symptoms of chronic venous disease?

by M. R. Boisseau, France

**New Targets for Pharmacological Treatment in Primary Chronic Venous Disease**

**Michel René BOISSEAU, MD**

Department of Pharmacology, Université Victor Segalen, Bordeaux, FRANCE

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**Selected abbreviations and acronyms**

ASIC acid-sensitive ion channel  
CEAP clinical, etiological, anatomical, pathophysiological (classification)  
CGRP calcitonin gene-related peptide  
CVD chronic venous disease  
ERK1/2 extracellular signal-regulated kinase 1/2  
GM-CSF granulocyte macrophage colony-stimulating factor  
ICAM intercellular adhesion molecule  
LDS lipodermatosclerosis  
LFA-1 leukocyte function associated antigen 1  
MMP matrix metalloproteinase  
MPFF micronized purified flavonoid fraction  
NGF nerve growth factor  
NOS nitric oxide synthase  
PECAM platelet endothelial cell adhesion molecule  
PGE$_2$ prostaglandin E$_2$  
RELIEF Reflux assessment and quality of life improvement with micronized flavonoids (study)  
TGF-β transforming growth factor β  
TNF-α tumor necrosis factor α  
TTX2 tetrodotoxin 2  
VCAM vascular cell adhesion molecule  
VEGF vascular endothelial growth factor  
VLA-4 very late antigen 4  
VR1 vanilloid receptor 1

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**Keywords:** chronic venous disease; cramp; edema; heaviness; leg; leukocytes; mast cell

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**Medicographia. 2006;28:128-136.** (see French abstract on page 136)

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**Address for correspondence:** Professor M. R. Boisseau, Département de Pharmacologie, Université Victor Segalen Bordeaux 2, 146 rue Léo Saignat, 33076 Bordeaux, France  
(e-mail: m.r.boisseau@wanadoo.fr)
Studies vary in the stages at which they place these symptoms in the natural history of CVD in large patient groups and unselected subjects. Some have found an increase with age and disease severity, in particular between stages C4 (skin and subcutaneous changes) to C6 (active venous ulcer) of the clinical, etiological, anatomical, pathological (CEAP) classification, meaning that the symptoms reflect the increased and dysregulated venous pressure; others have found wide variation and even no symptoms at all.

Thus, pain can be absent in 45% of a varicose vein population and in 45% of subjects with reflux on Doppler lower limb venography. It is independent of varicose vein volume. It may be greater from small veins or in the early CEAP stages (C0s, C1s). Variability also reflects the type of study. Cross-sectional population studies have found pain in the presence of varicose veins much less frequently. Thus, pain was present in only 45% of subjects without varicose veins in the Edinburgh Vein Study and in 15% of men without reflux in another study of the same type. In contrast, in subjects with a CVD-related lower limb complaint, the frequency increases considerably, eg, 80% in the Reflux Assessment of Lower Limb complaint, the frequency increases considerably, eg, 80% in the Reflux Assessment of Lower Limb

Leukocytes and venous symptoms – Boisseau
The main terminal cell is the polymorphonuclear neutrophil (neutrophil). Its short life, although variable, often does not exceed a few days or a few hours. Neutrophils terminate in tissue zones into which they have been drawn by chemotaxis to exert their macrophage activity, mainly against microorganisms. The circulating lymphocyte count follows a circadian rhythm, being very low in the fasting state (prompting mistaken diagnoses of neutropenia), and high after food and exercise.

Neutrophils can be viewed as circulating in a variety of pools:

- Monocytes are macrophages that scavenge for large, often parasitic or lipid particles; they are multipotential, capable of synthesizing cytokines, prostaglandins, and growth factors, and readily penetrating tissue after adhering to the vessel wall with the aid of vascular cell adhesion molecule 1 (VCAM-1).
- Eosinophils and basophils, although similar to mast cells, are readily differentiated among the smaller leukocyte families on blood smears.
- Mast cell precursors and bone marrow stem cells circulate in small numbers and cannot be identified using routine staining techniques; mast cells are found only in tissue, whether mucous membrane (typically nose and gut, in the case of thymus-dependent mast cells) or connective tissue (artery and vein wall, in which case their distinguishing features include large metachromatic granules and the c-kit gene encoding a tyrosine kinase receptor [KIT]).

Although margination is common to all leukocytes (Tables I and II), it is particularly striking in neutrophils. Variation in the circulating neutrophil count both over 24 hours and between counts prompted the hypothesis of 2 pools, one circulating and the other marginal. In normal subjects, the circulating pool is thought to be stable, with variation relating to the marginal pool. Yet at the slightest infectious alert, the circulating pool can swell considerably in a matter of hours, due to intense bone marrow productivity under the influence of increased granulocyte macrophage colony-stimulating factor (GM-CSF) production by cytokines. The marginal pool probably consists of leukocytes adhering to the vessel wall, whose numbers increase at the expense of the circulating pool. This reserve pool is located in the venous circulation, mainly in splanchnic and lower limb veins.

Peripheral leukocyte distribution remains complex and poorly understood. Of the various mechanisms proposed, one invokes “passive” postural changes in blood volume: in the vascular compartments in which blood volume is decreased, leukocyte volume is thought to undergo a proportionate decrease. In a remarkable 1998 study, Edwards et al used isotopic labeling to show that leukocyte counts in distal lower limb veins depended on blood volume, and were greater in the supine than in the dependent-legs sitting position; meanwhile marginal leukocyte counts remained constant. Other expanding sectors of the vascular compartment, eg, splanchnic vessels, also probably retain more leukocytes.

Another active mechanism more closely associated with margination could be involved: the leukocyte rolling reported in 1973 by Born and Atherton. In those sectors of the circulation in which slow blood flow exerts low shear stress, leukocytes circulate in contact with the wall at greatly reduced speed: the lower the shear stress, the lower the speed. The vessels where this occurs are mainly venules and, in the microcirculation, postcapillary venules. It also occurs over the margins of atheromatous plaques in arteries, perivalvular areas in veins, and indeed in any slow-flow zone, such as kinks in the walls of veins in the process of remodeling. Although leukocytes may initiate margination by extruding pseudopodia (Figure 1), the main mechanism is rolling, based on endothelial selectin expression, which itself is triggered by falling shear stress, hypoxia, histamine-generating inflammation, and leukocyte activation. Primed monocytes and neutrophils secrete matrix metalloproteinase 9 (MMP-9) and oxygen species on contact with the vessel wall. Leukocytes are thus recruited and made available to the vessel wall, where they may accumulate in considerable numbers, threatening the wall itself and adjacent tissue. Binding between leukocyte and endothelium remains reversible at this stage, however, with rolling leukocytes still able to return to the bloodstream. Only leukocytes that have gone beyond the rolling phase adhere firmly to the wall and are able to migrate through it.

In summary, the leukocyte-blood cycle identifies 2 groups of cells particularly suited to playing a highly active role at vessel wall level: neutrophils on the one hand, and mast cells on the other, both with substantial metabolic and enzymatic potential.

![Figure 1. Leukocyte margination, adhesion, and migration.](image)

**Abbreviations:** VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

*Reversible by restoring flow.*

†Lay et al.*
However, all blood cells can enter into contact with the wall, including mediator-transporting monocytes, interferon γ-producing T lymphocytes, and erythrocytes whose ability to suffuse from microvessels in skin lesions is responsible for iron pigment deposition. Given that many leukocyte mediators are algogenic, we now need to examine the conditions governing their release in CVD.

**Leukocyte fate in CVD**

Leukocytes leave the circulation because of inflammation (an incipient focus in the vascular intima or media), preinflammatory endothelial cell activation (hypoxia in the vessel lumen or wall), or altered hemodynamics (decreasing or abnormal shear stress). All such conditions may obtain in the damaged veins of CVD, either in the microcirculation or in the larger (varicose) sector.

**White cell trapping**

Moyes et al in 1987 and Thomas et al in 1988 measured leukocyte counts in subjects with CVD and controls using a catheter introduced into the long saphenous vein at the ankle.22,23 Same-patient counts were lower in the standing than in the supine position, with leukocytes being trapped in the superficial tissue drained by the diseased veins. In control subjects, on the other hand, leukocyte trapping disappeared on standing when leukocytes simply returned to the systemic circulation. These data demonstrated the relationship between leukocyte trapping and the venous hypertension responsible for the reduction in capillary perfusion pressure and hence the reduced capillary flow rate in the superficial cutaneous microcirculation. Trapping is independent of blood mass in the large veins (80% of the blood in the limb) and is broadly equivalent to the venule blood mass (5% to 15%). In the natural history of CVD, trapping is intensified by endothelial activation, which ensures that over and above rolling and accumulation, leukocytes adhere firmly to the venule wall in the cutaneous microcirculation.

**Circulating leukocytes in varicose veins**

Endothelial cell activation in varicose veins subject to high venous pressure has been extensively documented for several years.19 Significant increases in VCAM were first observed in varicose vein blood from subjects with lipodermatosclerosis.20 This corroborates the finding of intercellular adhesion molecule (ICAM), VCAM, leukocyte function associated antigen 1 (LFA-1), and very late antigen 4 (VLA-4) in pericellular biopsy material.21 At the ulcer stage of CVD, T lymphocyte cluster of differentiation (CD) 3 markers are decreased in circulating blood, while monocyte CD14 markers are increased, pointing to the possible contribution of these cells to trophic changes.22 In the nonulcer situation, simple prolonged standing increases ICAM, VCAM, L-selectin, and MMP-9 levels in varicose blood and even VCAM levels in brachial vein blood.23 Venous hypertension also increases circulating elastase and lactoferrin levels.24 Thus, in CVD, in response to venous hypertension stress, endothelium overexpresses surface ligands for all the leukocyte families: neutrophils, monocytes, lymphocytes, and mast cells. Complementary neutrophil activation also occurs (L-selectin shedding, MMP-9, and the release of lactoferrin and elastase), and does so within the lumen, as opposed to the activation of other cells by contact with the vein wall, thought to be triggered mainly by hypoxia25 (which demonstrably increases during induced stasis26). Another more localized mechanism involves vessel wall adhesion molecules, prompted by changes in shear stress at specific points in the venous circulation, eg, perivalvular areas14 or at kinks in varicose veins.26

**Leukocytes in the varicose vein wall**

Neutrophils have never been demonstrated in varicose vein wall. However, peroperative or punch biopsy has shown mast cells in the media,22 associated with macrophage clusters and T lymphocytes.23 The same cells have recently been found in venous valves.24 Thus, leukocyte behavior in CVD, whether in blood, in contact with the vessel wall, or within the wall itself, shows that these cells are activated by the hemodynamic changes and hypoxia induced by venous hypertension to seek out adhesion ligands on the wall, obstruct the lumen (making a substantial contribution in this regard, especially in cutaneous microvessels), and—in the case of mast cells and mast cell–macrophages—penetrate into vascular tissue. To what extent are these activities painful or a prelude to edema? The answer lies in the effect of leukocyte products on the microstructures responsible for pain and capillary permeability.

**Leukocyte products and edema**

Detailed studies show that leukocytes are involved in the development of edema. Key experiments by Messmer’s group in Munich showed that firm leukocyte adhesion to vein wall in a hamster microcirculatory model is followed by the leakage of fluorescent markers through intercellular gaps in the endothelium.20 Permeability was subsequently shown to be shear-dependent: shear stress downregulates occludin mRNA, thereby decreasing its levels at the endothelial cell junction, and upregulates the levels of vascular endothelial growth factor (VEGF). These effects combine to increase particle transit. VEGF increases permeability via a mechanism involving the extracellular signal-regulated kinase 1/2 (ERK1/2) regulation factor pathway in association with nitric oxide synthase (NOS).21 However, leukocyte adhesion remains the main mechanism increasing permeability,22 including in vitro,23 where the profusion of leukocytes concerned suggests they are neutrophils.

Thus, by lowering the flow rate, decreased shear stress in the microvessels activates the pathways required for downregulation of junctional proteins, while leukocytes (mainly neutrophils) play a key role by adhering to endothelial cell junctions. Platelet endothelial cell adhesion molecule (PECAM) and
New Targets for Pharmacological Treatment in Primary Chronic Venous Disease

Leukocyte products and pain

Given the frequent accumulation of leukocytes in CVD and their active contribution to endothelial activation and mediator release, the mechanism of their relationship to pain fibers deserves detailed examination.

Neurological recruitment of chemoreception mediators

The abundant biochemical mediators in leukocytes (Table III) are presumed responsible for stimulating the nerve extremities in CVD (Figure 2b). Mediators occur in vein and venule wall, the vicinity of nociceptors, and interstitial inflammation. Such inflammation may reverse to a degree or gradually develop into the trophic changes of CVD. At any event, there are cellular interactions between endothelium, leukocytes, and neurons. C fiber activation involves opening tetrodotoxin 2 (TTX2) depolarization channels and vanilloid receptor 1 (VR-1) ion channels, and drawing in ambient Ca++ under the effect of multiple phosphorylating mediators such as protein kinase A or C. Endothelial cells produce prostaglandins, leukotrienes, and cytokines, while neutrophils produce leukotrienes. Mast cells appear to play a major role in generating pain. Their large granules contain bradykinin, which is particularly active and augmented by the presence of prostaglandin E2 (PGE2). Equally active are histamine and serotonin, which work in combination.

Leukocytes and venous symptoms – Boisseau

Platelet activating factor (PAF) also contribute to a complex mechanism that combines mechanical forces with molecular biology. It has also been found that the venous hypertension that distends veins probably does not distend microvenules but rather slows their blood flow, thus prompting the leukocyte adhesion and biochemical events responsible for fluid leakage. Specific situations, such as capillary hypertension due to abnormal arteriolar perfusion and direct action by inflammatory mediators, also increase permeability. Neutrophils retain a recognized role in the development of CVD edema.

Neurological substrate of venous pain

Venous nerve fibers have their cell bodies in the spinal ganglia (Figure 2a). The sympathetic sensory afferents that track along peripheral nerves comprise a cluster of highly myelinated Aβ fibers, responsible for touch (Meissner’s and Ruffini’s corpuscles, hair bulbs), and much less myelinated Aδ fibers or unmyelinated C fibers that run in a sleeve around the microvenules and supply the intima and media throughout the endothelium of larger veins. The terminal boutons of Aδ and C fibers are believed to act as nociceptors primarily sensitive to chemical mediators, ie, as chemoreceptors. These fibers have well-defined features: C fibers are plentiful in skin (600 per cm²), but nociceptors in veins and venules are few. Thus, veins account for only 1% of the C fibers carried by the saphenous nerve. Venous nociceptors are largely insensitive to distension, meaning that venous dilatation is to an extent painless. Nociceptors are multimodal, responding with the same intensity to different stimuli. Response is somewhat delayed, being relayed at only 0.4 to 2 m/s, but sustained.

Neurological recruitment of chemoreception mediators

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Figure 2. Perivascular cell interactions.

Abbreviations: ASIC, acid-sensing ion channel; ATP, adenosine triphosphate; BK, bradykinin; CGRP, calcitonin gene-related peptide; COX, cyclooxygenase; EC, endothelial cascade; ERK, extracellular signal-regulated kinase; GDNF, glial-derived neurotrophic factor; IL, interleukin; MMP-9, matrix metalloproteinase 9; NGF, nerve growth factor; P2X, membrane-bound purinergic receptors; PG, prostaglandin; PK, protein kinase; RET, receptor-type tyrosine kinase protooncogene; TGF, transforming growth factor; TNF, tumor necrosis factor; Trk, tyrosine receptor kinase; TTX, tetrodotoxin; VCAM, vascular cell adhesion molecule; VR, vanilloid receptor.

Leukocytes and venous symptoms – Boisseau
with these mediators, together with prostaglandin and PAF produced by the endothelium. Under their combined effect, peptidergic C fibers secrete substance P, calcitonin gene-related peptide (CGRP), and neurokinin, giving rise to perivenous neurogenic inflammation. Substance P increases leukocyte adhesion and activates leukocytes and platelets. Inflammatory tissue is also maintained by the arrival of macrophages and monocytes secreting tumor necrosis factor α (TNF-α) and interleukin (IL) cytokines (IL-1, IL-6, and IL-8). Under modulation from mast cells (transforming growth factor [TGF-β1]) and inflammation, fibroblasts secrete nerve growth factor (NGF) which binds to its tyrosine receptor kinase A (TrkA) receptor and stimulates peptidergic fiber secretion. Inflammatory tissue releases H+ ions which act on the acid-sensitive ion channel (ASIC) receptor, and also adenosine triphosphate which acts on ligand-gated purinergic P2X3 nociceptors to produce the adenosine that will activate the P2Y2 receptor in situ. All these actions, which we have listed in snapshot fashion, develop gradually or in a succession of waves to result in the recruitment of “silent” nociceptors. The sensations overlap with, and extend, those relayed by their Aδ fiber counterparts because they are slower and longer-lasting. Thus, a truly painful sensation relayed by large myelinated touch fibers will be followed by the more diffuse and sustained pain produced by cell-derived mediators acting on C fibers. Norepinephrine is absent from these processes. In addition, substance P and CGRP are involved in vasomotor regulation and can modify blood flow. Their action does not necessarily produce pain under normal circumstances, especially in striated muscle, but definitely does so in areas of perivenular inflammation.

Activated nociceptors vary in sensitivity. They can be sensitized and display a depressed pain threshold, but subsequently they may also lose their sensitivity, due to decreased cell reactivity (reversibility, compression, treatments) or degeneration (peripheral neuropathy). As we shall see, subject intentionality — or readiness to feel pain — is a critical determinant of such sensations.

**Leukocyte involvement in the clinical stages of CVD**

Having understood the potential role of blood cells in vein-related pain, we can now attempt to characterize their involvement in the different stages of the CEAP (while never forgetting the subjective component), as a prelude to determining an appropriate therapeutic response.

◆ **Stages C3 to C6**

Cell counts within the walls of the steadily remodeled veins and microcirculation continue to increase through these stages.

◆ **Varicose veins**

In addition to the trophic changes associated with varicose veins, multiple mast cells have been reported in the vein wall, together with macrophages and T lymphocytes. Mast cells appear to concentrate at perivalvular sites, from which neutrophils are absent, since they act mainly in the lumen. Hypoxia and abnormal shearing are believed to activate endothelial tissue in conjunction with neutrophils, resulting in the migration of a cluster of cells, mainly mast cells, which are themselves sensitive to hypoxia. Migrating cells and remodeling inflammation form the biological basis of pain (Figure 3, next page). Venous pain has been correlated to CEAP stages C3 to C6 but varies widely in study populations. There is currently no evidence that neutrophils or mast cells are directly responsible for triggering pain. No relationship has been found between patient-reported pain and inflammatory marker

| Table III. Leukocyte mediators and reactive products. |
|-----------------|-----------------|-----------------|
| **Neutrophil** | Respiratory burst; Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase: O₂⁻ (superoxide anion, H₂O₂) Nitric oxide (NO) synthase—derived products: NO and NOO⁻ Antimicrobials: myeloperoxidase, lysozyme, cathepsin G Proteinases: collagenase, elastase, cathepsin G Hydrolases: β-glucuronidase, phospholipase A₂ (leukotrienes and prostaglandins), collag enases B and D |
| **Monocyte** | Oxygen free radicals Prostaglandins and leukotrienes Cytokines Neutral proteinases (elastase) Hydrolases (cathepsin B, D, and L) Growth factors |
| **T lymphocyte** | Interferon γ |
| **Eosinophil** | Cationic proteins Neurotoxins Peroxidases Lysoosomal enzymes Cytokines (interleukins 1, 3, 5, granulocyte macrophage colony stimulating factor [GM-CSF]) |
| **Basophil** | IgE Fc receptor Heparin Histamine Serotonin Leukotrienes Prostaglandins |
| **Mast cell** | Histamine Prostaglandins (PGD2); interleukins 1, 4, 5, 6; GM-CSF Leukotrienes (LT): LTC4 IgE Fc receptor Sensitive to C3a, C5a Neutral proteases, tryptase Tumor necrosis factor Induces secretion of peptidergic C-fibers |
Leukocytes and venous symptoms

Blood levels (von Willebrand factor, ICAM-1, VCAM-1, selectins, interleukins, or TNF-α). However, VEGF levels correlated with CEAP stage and the sensation of swelling in another study. There appears to have been no attempt to examine the relationship between mast cell markers (methylhistamine, tryptase, CGRP levels) and venous pain, in contrast to other pain syndromes. Inflammation appears to be the primary event in the natural history of CVD lesions, aided by the recruitment of blood cells.

**Cutaneous microvessels**

Punch biopsy shows leukocyte infiltration in patients with lipodermatosclerosis or trophic skin changes, while cutaneous histochemistry shows perivascular clumps of macrophages and T lymphocytes. Neutrophils are absent in these biopsies, just as they are from the distended convoluted capillaries typical of CVD. The relationship between ulcer and leukocyte deposition is now well established. Leukocytes may play a role in pain in patients with trophic changes by virtue of their contribution to inflammation and edema. Pain is also influenced by peripheral neuropathy and variations in nociceptor status.

**Stages C0s and C1s**

The hypothesis of leukocyte nociceptor stimulation is justified by leukocyte involvement at the onset of CVD. The postulated sequence of events begins with orthostatic hypoxia and abnormal shearing, which cause neutrophils to accumulate on endothelial surfaces, as shown by the varicose blood levels of MMP-9, elastase and lactoferrin, L-selectin shedding, and priming (surface integrin expression). Hemodynamic pressure represents a direct mechanoreceptor stimulus to C fibers. Reversibility is brought about by neutrophil de-adhesion (return to rapid rolling). These events are preparatory to mast cell migration; distorted valvular flow facilitates adhesion and transmigration of mast cells and macrophages. Yet neutrophils remain independent of the presence of mast cells in the perivascular environment, at least in the animal model.

**Readiness to feel pain (subject intentionality)**

Pain is by definition subjective. An identical painful stimulus may not cause an identical pain, even for the same individual. Subjects have the ability to determine the pain threshold, raising it (in which case they may feel no pain) or lowering it (in which case they may report severe and sustained pain). CVD pain is a typical and by no means exclusive example. The sensations transmitted by C fibers are visceral, meaning that they are sustained, diffuse, and a cause of anxiety. Clinicians must give pain its due. “No pain is benign.” According to expert working parties, all pain must be attended to, especially if there is objective evidence of impairment of quality of life without mental pathology overlay.

**Leukocyte-targeted treatment of CVD symptoms**

Can venous pain be treated by targeting leukocytes? Many studies have been prompted by the ability to block leukocyte adhesion to the vessel wall. In ischemic arterial disease, there are drugs that act directly on neutrophils and lower endothelial cell activation (allopurinol, iloprost). For a more targeted attack, monoclonal antibodies against adhesion molecules (anti-VCAM or anti-ICAM) are highly active in animal models. However, in humans, all such treatments have proved disappointing or ineffective, and even dangerous in that they induce neutropenia, in particular postoperatively in the case of allopurinol. Other side effects have also restricted their use.

Venotonics have no such drawbacks. They have proved active at the leukocyte level, in particular as antioxidants. Micronized purified flavonoid fraction (MPFF; Daflon® 500 mg, Servier, France) has protective endothelial effects while partially inhibiting leukocyte adhesion by reducing adhesion molecule expression. Flavonoids also act on mast cells. Recently, in an animal model of venous hypertension created using an arteriovenous fistula for 3 weeks, MPFF dose-dependently inhibited both superficial venous valve infiltration by granulocytes, monocytes, and T lymphocytes, and decreased endothelial cell overexpression of adhesion molecules P selectin and ICAM-1. This anti-inflammatory effect complements the numerous other protective effects of MPFF whether at macro- or microcirculatory level.

Although venotonics appear to act mainly on circulating leukocytes in CVD, they do not critically decrease their numbers, in contrast to monoclonal antibodies. This may be because they help to recover margined leukocytes. In an in vitro study of rolling with endothelial cells in culture, venotonics prompted a return to the fast rolling described by Ley. This effect reduces the leukocyte risk factor without the threat of absolute neutropenia.
Conclusion

Leukocytes play a well-established role in the development of varicose veins (vein wall remodeling) and trophic changes (microvascular activity). Recent studies of their relationships—or, more precisely, the relationships of their algogenic mediator contents—with nociceptors relaying venous pain show that they play an important role in this regard.

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**QUELLE EST L’IMPlication DES LEUCOCyTES DANS LES SYMPTÔMES DE LA MALADIE VEINEUSE CHRONIQUE ?**

L'étude des douleurs au cours de la maladie veineuse chronique (MVC) montre que leur intensité varie non seulement avec les stades CEAP mais aussi avec l’état de conscience qu’en ont les patients, la douleur étant subjective par définition. L’hyperpression veineuse, à l’origine des lésions variqueuses et cutanées de l’affection, pourrait aussi mettre en jeu différents mécanismes algiques d’évolution et d’intensité variable. Ces mécanismes impliqueraient plus particulièrement les leucocytes, cellules variables en nature, potentiellement et en cycles de vie sanguine. Le phénomène de margination leucocytaire rendu possible par la capacité de roulement (« rolling ») des leucocytes, aboutit à l’accumulation de grandes masses de neutrophiles sur les parois vasculaires. Au cours de la MVC, l’hypoxie et la stase (l’hyperpression veineuse entraînant des changements de contrainte de cisaillement au niveau de la paroi), activent les leucocytes marginés. Cette activation des leucocytes s’exprime par l’élimination de la L-sélectine de la surface leucocytaire, l’expression d’intégrines, de métalloprotéinase 9, d’élastase, de lactoferrine et de radicaux libres. En regard, l’endothélium exprime des molécules d’adhérence permettant le roulement lent sur l’E-sélectine puis l’adhésion-migration leucocytaire à l’intérieur des structures tissulaires. Le phénomène d’adhésion leucocytaire est réversible mais peut conduire à la rétention des leucocytes dans les veines superficielles cutanées. Au niveau de la paroi des veines et autour de leurs valves, ces processus conduiraient à la migration de mastocytes, de monocytes-macrophages et de lymphocytes T à l’intérieur des structures, aboutissant à leur remodelage. Toutes ces cellules blanches sont riches en médiateurs algiques. Les fibres neuro-ronales sensitives C et Aδ, enroulées autour des veines cutanées et également présentes dans l’intima et la media des veines, représentent les nocicepteurs sensibles aux médiateurs leucocytaire (bradykinine des mastocytes) à l’origine des douleurs de type visceral. L’inflammation neuronale, puis liée au remodelage pariétal accentue les symptômes. Cependant, aucune preuve directe de relation liant les douleurs avec les marqueurs sanguins des mastocytes n’a été établie à ce jour. L’augmentation de la perméabilité capillaire conduisant à l’éthème est liée à l’adhésion leucocytaire. Au cours de l’évolution de l’affection veineuse chronique, de C5 à C6 de la classification CEAP, les douleurs s’accidentent mais avec une perception variable selon les sujets, à l’image des autres syndromes algiques. Aux stades précoces de la maladie (C0s et C1s de la CEAP) la participation algique des leucocytes est liée aux polymédullaires. Sur le plan thérapeutique, le repos postural et les veinotoniques, seuls ou associés à la contention, ont une action de délogement et de freinage leucocytaire. La fraction flavonoïque purifiée microsérie (FFPM, Daflox 500 mg, Servier, France) développe une action sur l’endothélium vasculaire (protection contre l’hypoxie, diminution de l’expression des molécules adhésives) et sur les leucocytes circulants (activation et rôle dans la perméabilité capillaire). Les veinotoniques, au contraire d’autres actions thérapeutiques antileucocytaire, ne font pas courir de risque de neutropénie.
Pain is the commonest presenting complaint in medicine. Chronic venous disease (CVD) is no exception, in any country; 40% to 65% of patients with CVD complain of pain. The consensus over pain as a core symptom of CVD contrasts with the debate over other symptoms, such as restless legs, night cramps, or paresthesia. At the onset of CVD, pain with or without a feeling of heaviness is often the main or even sole complaint in women and, increasingly, in men. Its cause lies in the development of structural and functional venous abnormalities that cause hypoxia and the release of metabolic products that stimulate nociceptors via mechanisms that await full elucidation.

Not all lower limb pain heralds CVD. Only a careful history followed by clinical and, often, ultrasound examination will establish the diagnosis to the exclusion of the many alternatives. The task is then to evaluate the pain using the most reliable and reproducible method possible to monitor its response to intervention. A number of duly validated tools are available for this purpose, whether for therapeutic trials or individual patient follow-up. Optimal use of these tools by angiologists and phlebologists presupposes familiarity with their advantages and limitations.

This is the purpose of the present article, which also aims to assess the contribution of composite severity and quality-of-life scores. Although major, this contribution must not be allowed to overshadow the role of dedicated pain instruments, in particular in therapeutic trials.

Defining and evaluating chronic pain

In 1999, a task force convened by the former French National Agency for Accreditation and Evaluation in Public Health (ANAES, since replaced by the French National Authority for Health [HAS]) produced a thorough analysis of chronic pain evaluation and follow-up in ambulatory adults. Much of the present section draws on this guideline or refers directly or indirectly to it. After reviewing all pre-existing definitions, the guideline offered a definition of chronic pain that combines the definition of pain by the International Association for the Study of Pain (IASP) and World Health Organization (WHO) (“an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage, persisting for more than 3 to 6 months and/or that adversely affects the function or well-being of the patient, attributable to any nonmalignant etiology”), which made no mention of the time dimension, with that of chronic pain by the American Society of Anesthesiologists (“chronic pain is defined as persistent or episodic pain of a duration or intensity that adversely affects the function of well-being of the patient, attributable to any nonmalignant etiology”), which failed to specify a duration: “Chronic pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage, persisting for more than 3 to 6 months and/or that adversely affects the function or well-being of the patient, attributable to any nonmalignant etiology.”

Keywords: pain; venous disease; scale; questionnaire; visual analogue scale; quality of life; venotonic

Address for correspondence: Professor F. Allaert, CHU du Bocage, DIM, BP 1542, 21034 Dijon cedex, France (e-mail: contact@cenbiotech.com)
The minimum duration of 3 to 6 months is an addition by the task force, but not a mandatory requirement, since pain qualifies as chronic as soon as it impairs function or well-being. However, it is an important reminder that patients included in therapeutic trials must have experienced stable or increasing pain over several weeks at least, since this confirms the existence of established pathophysiology that is unlikely to undergo spontaneous remission. Unless this precaution is taken, differences between test treatment and comparator, whether reference therapy or placebo, risk being nullified. This could account for the numerous failures to demonstrate the efficacy of venotonics in clinical trials.

**Pain evaluation tools**

If we define a validated measurement tool as an instrument shown in published studies to meet the 3 criteria of validity, accuracy, and sensitivity to change, several such tools are available for evaluating not only the intensity of pain, but also its psychological, social, behavioral, and cognitive dimensions.

**Tools for measuring pain intensity**

In the absence of a validated instrument for the investigator rating of pain in the ambulatory setting, pain must be measured using self-rating scales duly explained to the patient. Physicians tend to underestimate pain intensity reported by patients as high and to overestimate pain. Pain must be measured using self-rating scales duly explained to the patient.

Physicians tend to underestimate pain intensity reported by patients as high and to overestimate that of pain reported as low. Analgesic consumption by patients as high and to overestimate pain must be measured using self-rating scales duly explained to the patient.

In the absence of a validated instrument for the in-patient or from bottom to top, from one end marked “no pain” to the other marked “maximum pain imaginable” at 100 or preferably 10, Jensen et al having shown that scales numbered from 0 to 100 provide no additional information. Numerical scales offer an alternative method of follow-up for patients who have problems with a VAS, except that the option cannot be made available within the same clinical trial.

A further option is the simple verbal rating scale, generally broken down into 5 or 7 descriptors: mild, moderate, severe, etc. A major disadvantage is that there is not necessarily a linear relationship between descriptors, eg, pain which is patient-rated under descriptor 6 as “very severe” may not be twice as intense as that rated under the descriptor 3 as “moderate.” The resulting data can only be viewed as semi-quantitative at best, thereby methodologically undermining the sadly common practice of performing calculations and comparisons of the mean on such data.

Few studies have sought to compare the appropriateness of choosing one scale rather than another but the VAS is generally preferred for its greater sensitivity to change, at least with respect to simple verbal rating scales.

**Other pain evaluation tools**

Far more complex scales have been devised to rate the overall impact of pain. One of the most widely referenced is the McGill Pain Questionnaire (MPQ) (adapted into French as the Saint-Antoine pain questionnaire). These duly validated questionnaires have been used in many studies but are impractical in routine care. The short versions are better suited to daily practice but lack proper validation for use in therapeutic trials.

In addition, the ANAES task force recommended 2 of the many multidimensional pain rating scales: the Brief Pain Inventory and Multidimensional Pain Inventory (also the Dallas Pain Questionnaire, which is heavily skewed toward back pain and thus not really appropriate for CVD). These questionnaires explore the various dimensions of pain, in particular its impact on activities of daily living, social repercussions, and psychological distress, thus making them very similar to quality-of-life questionnaires such as those specifically developed and duly validated for CVD.

**Contribution of pain rating tools to the evaluation of venotonic treatments**

Given the development of composite severity and quality-of-life scores, it is reasonable to ask how useful dedicated pain rating tools can continue to be. Such tools can appear narrowly focused, especially when compared with relatively longstanding instruments such as the Chronic Venous Insufficiency Questionnaire (CIVIQ, 1996) or more recent counterparts such as the severity score developed in con-
junction with the clinical etiological anatomical pathophysiological (CEAP) classification or the quality-of-life score — each of which we can view as a reference instrument given that they represent the 2 current trends in the quantitative approach to CVD.

The American Venous Forum Ad Hoc Committee on Venous Outcomes Assessment drew up a venous severity scoring system to ensure that clinical trials recruited patients with disease of similar severity, hence facilitating comparison of treatment response.30 Each of the 10 items is rated on a semi-quantitative scale (0, absent; 1, mild; 2, moderate; 3, severe), equivalent in the case of pain (item 1) to a simple verbal scale — each of which we can view as a reference instrument given that they represent the 2 current trends in the quantitative approach to CVD.

Pain scales in venous disease — Allaert

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Absent=0</th>
<th>Mild=1</th>
<th>Moderate=2</th>
<th>Severe=3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>None</td>
<td>Occasional, not restricting activity or requiring analgesics</td>
<td>Daily, moderate activity limitation, occasional analgesics</td>
<td>Daily, severe limiting activities or requiring regular use of analgesics</td>
</tr>
<tr>
<td>Varicose veins†</td>
<td>None</td>
<td>Few, scattered: branch varicose veins</td>
<td>Multiple: great saphenous varicose veins confined to calf or thigh</td>
<td>Extensive: thigh and calf or great saphenous distribution</td>
</tr>
<tr>
<td>Venous edema‡</td>
<td>None</td>
<td>Evening ankle edema only</td>
<td>Afternoon edema, above ankle</td>
<td>Morning edema above ankle and requiring activity change, elevation</td>
</tr>
<tr>
<td>Skin pigmentation‡</td>
<td>None or focal, low intensity (tan)</td>
<td>Diffuse, but limited in area and old (brown)</td>
<td>Diffuse over most of gaiter distribution (lower third) or recent pigmentation (purple)</td>
<td>Wider distribution (above lower third) and recent pigmentation</td>
</tr>
<tr>
<td>Inflammation</td>
<td>None</td>
<td>Mild cellulite, limited to marginal area around ulcer</td>
<td>Moderate cellulite, involves most of gaiter area (lower third)</td>
<td>Severe cellulite (lower third and above) or significant venous eczea</td>
</tr>
<tr>
<td>Induration</td>
<td>None</td>
<td>Focal, circummalleolar (&lt;5 cm)</td>
<td>Medial or lateral, less than lower third of leg</td>
<td>Entire lower third of leg or more</td>
</tr>
<tr>
<td>No. of active ulcers</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>&gt;2</td>
</tr>
<tr>
<td>Active ulceration, duration</td>
<td>None</td>
<td>&lt;3 mo</td>
<td>&gt;3 mo, &lt;1 y</td>
<td>Not healed &gt;1y</td>
</tr>
<tr>
<td>Active ulcer, size§</td>
<td>None</td>
<td>&lt;2 cm diameter</td>
<td>2 to 6 cm diameter</td>
<td>&gt;6 cm diameter</td>
</tr>
<tr>
<td>Compressive therapy§</td>
<td>Not used or not compliant</td>
<td>Intermittent use of stockings most days</td>
<td>Wears elastic stockings most days</td>
<td>Full compliance: stockings + elevation</td>
</tr>
</tbody>
</table>

* Varicose veins must be >4 mm diameter to qualify so that differentiation is ensured between C1 and C2 venous pathology.
† Presumes venous origin by characteristics (eg, brawny [not pitting or spongy] edema), with significant effect of standing/limb elevation and/or other clinical evidence of venous etiology (ie, varicose veins, history of deep venous thrombosis). Edema must be regular finding (eg, daily occurrence), Occasional or mild edema does not qualify.
‡ Focal pigmentation over varicose veins does not qualify.
§ Largest dimension/diameter of largest ulcer.
¶ Sliding scale to adjust for background differences in use of compressive therapy.

A 25-item quality-of-life score and 10-item symptom score were developed on the basis of the Venous Insufficiency Epidemiological and Economic Study (VEINES).28 Although the test characteristics are highly satisfactory from the psychometric standpoint, clinical correlations are more open to question, with particular respect to early CEAP classes. When using the quality-of-life score to compare patients with varicose veins versus those without, the developers found significant impairment of quality of life only in patients with concomitant venous edema and/or ulcers.29 Quality-of-life and symptom scores decrease significantly with CEAP class but the differences in resulting values, even when significant, appear minor, especially between low CEAP classes.30 This applies irrespective of country or clinical improvement, with the score showing differences of no more than 2 points in mean values of around 50. As with the severity score, this raises the question of the sample size required in therapeutic trials to demonstrate such low-grade differences, in particular in early CEAP disease.
DIFFÉRENTES ÉCHELLES DE DOULEUR ET QUESTIONNAIRES POSIBLES POUR ÉVALUER LA DOULEUR DANS LA MALADIE VEINEUX IN PRIMAIRE

Conclusion

Dedicated pain rating scales and/or questionnaires remain extremely valuable in early CVD both for the routine management of individual patients and therapeutic trials of venotronics. In more advanced disease, their reproducibility and rapidity of execution account for their continuing utility but composite scores probably provide a more accurate reflection of the overall impact of CVD.

Réflexions méthodologiques sur la place des échelles de douleur dans l'évaluation des désordres veineux

La douleur ou la sensation de lourdeur douloureuse constituent le motif principal de consultation des patients présentant des troubles veineux. L’évaluation de la douleur peut être réalisée de manière simple et rapide par des échelles et des questionnaires validés permettant de quantifier la douleur et son retentissement physique et social. Parmi ces outils les plus utilisés sont les échelles visuelles analogiques, les échelles numériques, les échelles verbales simples et les questionnaires de douleur comme le McGill Pain Questionnaire. Cet article rappelle les caractéristiques de ces outils et analyse leur intérêt au regard des différents scores de sévérité et de qualité de vie qui apparaissent en grand nombre actuellement. Cette analyse montre qu’aux stades précoces de l’évolution de la maladie, les échelles d’évaluation de l’intensité de la douleur et/ou les questionnaires d’évaluation de la douleur gardent un intérêt majeur tant pour le suivi de la prise en charge des patients en pratique quotidienne que pour les essais thérapeutiques visant à évaluer l’effet des traitements veino-tiques. Aux stades plus avancés, leur intérêt reste encore important en raison de leur rapidité de réalisation et de leur reproductibilité mais les scores composés permettent sans doute de mieux appréhender le retentissement de la maladie veineuse dans sa globalité.

REFERENCES

Validated quality-of-life scales for measuring treatment response in chronic venous disease

by M. Cazaubon, France

As budgetary constraints tighten and patients become better informed about their rights and the benefits they can expect from the various treatments offered for chronic venous disease, quality-of-life scales are taking on an increasingly important role. Several validated questionnaires are in international use in different language versions. Generic questionnaires include the 36-item Short Form Health Survey and the Nottingham Health Profile; specific questionnaires include the Chronic Venous Insufficiency Questionnaire, the Aberdeen Varicose Vein Symptom Severity Score, and the Venous Insufficiency Epidemiological and Economic Study Quality of Life questionnaire. Therapeutic trials should ideally combine a generic with a specific questionnaire, while bearing in mind that such instruments are not for the sole use of clinical researchers and epidemiologists, but should be incorporated into daily practice.

Medicographia. 2006;28:141-145. (see French abstract on page 145)

Keywords: quality of life; varicose veins; chronic venous disease; ulcer; surgery; validation; medical economics; generic scale; specific scale

Chronic venous disease (CVD) is common in the industrialized world, affecting to various degrees 1 in 2 women and 1 in 3 men. Given its prevalence and the high cost of caring for its complications, CVD represents a major public health burden, accounting for estimated €10 million annually per million inhabitants in France and almost 2% of health expenditure in Europe. Cost-benefit considerations make it essential to evaluate the efficacy of the treatments on offer. Next to changes in clinical severity and disability scores based on the clinical, etiological, anatomical, pathophysiological (CEAP) classification of venous disease, the best method of determining the cost-effectiveness of treatment is to measure its impact on quality of life.

Quality-of-life scales can be generic or specific. Generic scales provide data on health and quality of life irrespective of specific disease and even in the absence of disease. Specific scales supply disease-specific data. Both are based on patient questionnaires. The combination of a specific with a generic questionnaire provides a sensitive method of assessing small changes in health status in response to a study treatment and of comparing one disease with another.

Criteria of a good quality-of-life scale for assessing CVD treatments

For a quality-of-life scale to become accepted and implemented, it must meet several criteria based on internal consistency (interitem correlation) and sensitivity to small changes in health status. Patients must find the questions readily understandable, since it is they who must complete the questionnaires (physicians underestimate not only the intensity of patients’ symptoms but also the impact of venous disease on the quality of patients’ lives). Questionnaires also require validation, usually against a gold standard such as the 36-item Short Form Health Survey (SF-36).

Selected abbreviations and acronyms

AVVSSS Aberdeen Varicose Vein Symptom Severity Score
CEAP clinical etiological anatomical pathophysiological (classification)
CIVIQ Chronic Venous Insufficiency Questionnaire
CVD chronic venous disease
FLQA Freiburger Questionnaire of Quality of Life in Venous Disease (Augustin Questionnaire)
NHP Nottingham Health Profile
RELIEF Reflux Assessment and quality of life improvement with micronized flavonoids
SF-36 36-item Short Form Health Survey
VEINES-QOL Venous Insufficiency Epidemiological and Economic Study Quality of Life instrument
WHOQOL World Health Organization Quality Of Life instrument
In therapeutic trials, multidimensional health profiles such as the SF-36 supply data on changes in overall quality of life but also in the various domains tested, some of which may show improvement and others deterioration, resulting, for example, from side effects. Generic questionnaires of this kind can also be used to compare different populations or diseases and can thus prove more relevant to public health decision-makers. Specific questionnaires, on the other hand, are more sensitive to minimal change and can thus better assess treatment efficacy. For these reasons, the two types of questionnaire are best combined. The ideal therapeutic trial should also be randomized, comparing a treated group with an untreated or placebo group. A few such studies have been performed with venotonics and compression therapy for venous ulcers. However, they are less feasible when it comes to varicose vein surgery or sclerotherapy.

**Generic questionnaires for evaluating CVD treatments**

The SF-36 is the most used questionnaire of its kind in all areas of health worldwide. It includes 8 health concepts giving 2 component scores, one physical and the other mental (Figure 1). Simplified versions (SF-12 and SF-8), including in French, can be directly accessed at www.sf36.com. As the SF-36 has proved valid and reliable in groups of patients with varicose veins, vascular surgeons have applied it in practice and observed the following results:

- Overall scores in candidates for stripping are not significantly poorer than in the general population.
- In the first postoperative month, an increase in the Pain item adds to the cost of surgery, encouraging the development of mini-invasive methods of vein obliteration.
- By month 6, virtually all SF-36 items show significant improvement (*P*<0.01).

Other major generic questionnaires include the Nottingham Health Profile (NHP) and the World Health Organization Quality of Life (WHOQOL) instrument. The NHP is insufficiently sensitive in mild CVD but can be used to assess the impact of venous ulcer treatments. Tight compression improves all areas tested by the NHP: physical activity, social activity, pain, and mental state. The NHP has been found more sensitive than the SF-36. The 100-question WHOQOL instrument covers 5 domains and has been validated in peripheral arterial disease. It proved sensitive to treatment-induced change, but has yet to be used in venous disease.

**Specific questionnaires for evaluating CVD treatments**

To compensate for the insensitivity of generic questionnaires, improve understanding of the natural history of CVD, and assess treatment response, a number of disease-specific quality-of-life scales have been developed, some of which have implemented Steiner and Norman’s recommendations for constructing questionnaires. Below we discuss only those that have been properly validated.

The Chronic Venous Insufficiency Questionnaire (CIVIQ) developed by Launois et al is widely used, in particular to evaluate venotonic treatments. The 20-item scale covers 4 dimensions: pain, a physical component, a psychological component, and a social component. It was validated at international level in the 22-country Reflux assessment and quality of life improvement with micronized Flavonoids (RELIEF) study where it proved reliable in measuring quality of life in CVD with or without reflux. The RELIEF study found that flavonoids improved quality of life over the 6 study months while also improving the signs and symptoms of CVD.

The Aberdeen Varicose Vein Symptom Severity Score (AVVSSS) is a dedicated and validated quality-of-life scale comprising 13 questions on the signs and symptoms of varicose veins and a diagram of the lower limbs on which patients indicate the distribution of their veins. The scale is scored from 0 (best) to 100 (worst), in contrast to the SF-36. It has...
proved useful in assessing the efficacy of surgical resection in the 2-year follow-up of patients with varicose veins. A prospective study by the same team in 203 unselected patients identified the factors predicting poorer poststripping outcome: high AVVSSS at inclusion, surgery for recurrent varicose veins, high CEAP class (C4 to C6), prior thromboembolism, coexisting peripheral arterial disease, and surgeon qualification.

A study combining a generic and a specific questionnaire, the SF-36 and AVVSSS, found that patients whose varicose veins recurred after surgery had significantly poorer symptom scores and were less satisfied than patients with primary disease. The Venous Insufficiency Epidemiological and Economic Study Quality of Life (VEINES-QOL) instrument was developed for a prospective international cohort study of the epidemiology and clinical care of CVD. Its 25 items measure 10 venous symptoms, scored using gradations similar to those of the SF-36. It has been validated in UK English, French, and French-Canadian, but not in US English. VEINES-QOL scores, like those of the SF-36, decrease significantly with increasing CEAP class. Its developers also showed that the CEAP classification predicted VEINES-QOL scores but not SF-36 scores, thus demonstrating the greater specificity of the VEINES-QOL instrument over its generic counterpart, and its utility in treatment follow-up.

The prevalence of venous ulceration is high, approximately 1% of the population, and the incidence has shown no sign of decreasing over the last 25 years, representing a major drain on health resources, both now and in the future. Generic questionnaires such as the SF-36 demonstrate the impact of this trophic condition in all the physical and mental domains but are too insensitive for use in evaluating treatment response. Hence, the utility of specific questionnaires. The Charing Cross Venous Ulcer Questionnaire comprising 8 groups of ulcer-related questions is a specific quality-of-life instrument that was validated against the SF-36. Its authors believe that the combination of this specific questionnaire with the SF-36 provides a suitable instrument for monitoring the disease course and assessing treatment effect, especially as scores undergo a marked improvement with ulcer healing.

The CIVIQ has also been used in conjunction with the SF-36 in a quality-of-life study in 200 patients undergoing venous ulcer therapy randomized to 2 groups, one treated by 4-layer compression, the other receiving conventional therapy. Quality of life—notably physical activity and social function—improved markedly with 4-layer compression, as did the overall score. Unsurprisingly, quality of life was a direct reflection of ulcer healing. Other quality-of-life scales are regularly advocated to evaluate ulcer treatment in particular but have yet to be validated at international level.

Surgery (saphenofemoral junction ligation and stripping of the long saphenous vein) is generally accepted to carry the least risk of recurrence. However, new endovascular methods are being introduced, such as endovenous laser and radiofrequency ablation.

Lurie et al used the CIVIQ to compare results in patients randomized to conventional versus endovascular therapy. Initially, radiofrequency was associated with significantly better overall and pain scores. The magnitude of the difference then declined steadily between 1 week and 4 months (end of study). In the most severe form of CVD with suprainguinal venous obstruction, stenting may relieve symptoms and enhance quality of life, as shown by Raju et al using the CIVIQ.

The specific 83-item Freiburger Questionnaire of Quality of Life in Venous Disease (FLQA, or Augustin Questionnaire) incorporates 7 dimensions: physical complaints, everyday life, social life, emotional status, therapy, satisfaction, and occupation. It has demonstrated internal consistency and convergent validity with the NHP. It has not been validated against the SF-36 and is available to date only in German. These restrictions aside, it appears sensitive, giving scores that match both CVD severity and treatment response, although the treatments were not detailed in the original publication. The developers recently validated the FLQA for evaluating quality of life in lymphedema and intend applying it to the assessment of treatment efficacy.

As for compression, the French Phlebology Society 2002 consensus conference recommended incorporating quality-of-life studies in any therapeutic trial of compression in CVD. Neither the SF-36 nor NHP have ever been used for this purpose. However, the CIVIQ detected a significant response to low-grade ankle compression of 10 mm Hg to 15 mm Hg in patients with early CVD (C1 to C3) in a controlled, randomized, and double-blind multicenter study versus socks having zero compression effect.

Future prospects

The long and nonexhaustive list of quality-of-life scales (Table I) reflects the complexity and variability of the clinical signs and symptoms of CVD. However, not all these scales have won general specialist acceptance. The CEAP classification has greatly

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Target</th>
<th>Generic/Specific</th>
<th>Language</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHP</td>
<td>Venous ulcers</td>
<td>Generic</td>
<td>English (UK)</td>
</tr>
<tr>
<td>SF-36</td>
<td>All</td>
<td>Generic</td>
<td>All</td>
</tr>
<tr>
<td>WHOQOL</td>
<td>Peripheral arterial disease</td>
<td>Generic</td>
<td>English (UK)</td>
</tr>
<tr>
<td>AVVSSS</td>
<td>Varicose vein and ulcer surgery</td>
<td>Specific</td>
<td>English (UK)</td>
</tr>
<tr>
<td>CIVIQ</td>
<td>Venotonics and surgery</td>
<td>Specific</td>
<td>All</td>
</tr>
<tr>
<td>FLQA</td>
<td>Varicose veins, lymphedema, treatment response</td>
<td>Specific</td>
<td>German</td>
</tr>
<tr>
<td>VEINES-QOL</td>
<td>Chronic venous disease and postthrombotic syndrome</td>
<td>Specific</td>
<td>French, French-Canadian, UK English, but not US English</td>
</tr>
</tbody>
</table>

Table 1. Selected validated questionnaires in peripheral vascular disease.

Abbreviations: AVVSSS, Aberdeen Varicose Vein Symptom Severity Score; CIVIQ, Chronic Venous Insufficiency Questionnaire; FLQA, Freiburger Questionnaire of Quality of Life in Venous Disease (Augustin Questionnaire); NHP, Nottingham Health Profile; SF-36, 36-item Short Form Health Survey; VEINES-QOL, Venous Insufficiency Epidemiological and Economic Study Quality of Life instrument; WHOQOL, World Health Organization Quality of Life instrument.

QOL scales for measuring treatment response in CVD – Cazaubon
aided adoption of a shared terminology. The venous severity scoring system proposed by the American Venous Forum Ad Hoc Committee on Venous Outcomes Assessment could likewise serve to validate a specific CVD questionnaire that is accepted by phlebologists as being sufficiently reliable and sensitive for monitoring disease course and treatment response. Combination of the SF-36 and a universally validated specific questionnaire constructed by phlebologists would be useful in the daily practice not only of general physicians, but also of health economists and epidemiologists. Whether phlebologists will be confirmed, or at least guided, in their treatment choices by such a combination remains to be seen—this has not yet proved the case in other areas.

REFERENCES

En cette période de nécessité d’économies médicales, associées à une meilleure information des patients sur leurs droits et les bénéfices qu’ils peuvent attendre des différentes thérapeutiques proposées dans les affections veineuses chroniques, les échelles de qualité de vie prennent une place de plus en plus importante. Il existe des questionnaires validés, utilisables dans leurs différentes traductions. Parmi les questionnaires génériques, on peut citer le SF-36 (36-item Short Form Health Survey) ou le Nottingham Health Profile et parmi les questionnaires spécifiques, le CIVIQ (Chronic Venous Insufficiency Questionnaire), le questionnaire d’Aberdeen ou le VEINES-QOL (Venous Insufficiency Epidemiological and Economic Study Quality of Life Instrument). L’étude thérapeutique idéale associe un questionnaire générique et un questionnaire spécifique. Ces instruments ne sont pas réservés aux seuls chercheurs, cliniciens et épidémiologistes mais doivent s’insérer dans notre pratique quotidienne.
The impact on quality of life of symptoms related to chronic venous disorders

by M. Perrin, France

Quality of life (QOL) in patients with chronic venous disorders has been shown to be globally impaired. The detrimental impact that chronic venous disorders and their associated symptoms may have on patients’ daily activities and the evaluation of symptomatic treatments with scientifically rigorous measures of QOL, have become important issues. We performed a complementary analysis of the Reflux assEssment and quaLity of lIfe improvEment with micronized purifed Flavonoid fraction (RELIEF) study whose objective was twofold: first, to assess the impact of demographics and clinical data on the QOL of patients with chronic venous disorders, and, second, to identify the factors with a central role in improvement in patient QOL during the course of 6 months’ treatment with Daflon 500 mg. Patients for this analysis (in clinical class C0s to C4 of the clinical, etiological, anatomical, pathophysiological [CEAP] classification) were taken from the RELIEF study database. Quantification of QOL used the Global Index Score (GIS) of the ChronIc Venous dIsorders quality of life Questionnaire (CIVIQ) and was performed during the washout period (D-15), at baseline (D0), day 60 (D60), day 120 (D120), and day 180 (D180), according to the presence of symptoms, reflux, and the “C” of the CEAP. In the 3948 observations included, age, female gender, body mass index, ankle circumference, presence of reflux, and assignment to a severe CEAP clinical class had a slight impact on QOL with a minor GIS change. In contrast, symptoms and particularly heaviness and pain were found to seriously affect patient QOL. During the course of 6 months’ treatment with Daflon 500 mg, GIS changes between D0 and D180 were significant in the different patient subgroups (with reflux, without reflux, whatever the CEAP C class, symptomatic or not symptomatic; P < 0.001 in all subgroups). Throughout the period of treatment with Daflon 500 mg, the difference between the QOL of patients “with” and those “without” reflux, and in the different subgroups of “C” patients remained stable, while patients with symptoms had a greater GIS increase than patients without symptoms (ΔGIS [D180-D0] = 17.70 versus 6.38; P < 0.001). The significant increase in GIS seen during treatment with Daflon 500 mg in all patient subgroups means that such treatment substantially improves QOL. In patients with chronic venous disorders whatever the severity of the condition. On the other hand, QOL is greatly improved in symptomatic patients while it remains low in asymptomatic patients. Daflon 500 mg treatment improves patient QOL even in the absence of severe signs, and this improvement is believed to result from the alleviation of symptoms as evidenced through the previous RELIEF study in patients in C0s to C4. In conclusion, symptoms have the most negative influence on patient QOL even in the absence of reflux or signs. To the extent that Daflon 500 mg improves venous symptoms, prescription of this treatment may be recommended to improve QOL.

Keywords: quality of life; chronic venous disorders; symptoms; CEAP classification; venous reflux; multivariate analysis; venotropic drug

Address for correspondence: Dr Michel Perrin, 26 Chemin de Decines, 69680 Chassieu, France (e-mail: m.perrin chir.vasc@wanadoo.fr)
may have on daily activities. It is also important that symptomatic treatments are evaluated with scientifically rigorous measures of QOL.

Many researchers have estimated that chronic venous disorders deserved specific scales for different reasons. First, chronic venous disorders are often painful and may result in physical or psychological impairment (physical handicap regarding standing, crouching abilities, etc.). In addition, this disorder affects legs and may deeply affect women in their social life (cosmetic prejudice of varicose veins). Second, the negative impact that chronic venous disorders may have on patients’ daily life is usually underestimated using only physician-based assessments of the disease. Third, chronic venous disorders are frequent. In Europe, epidemiological studies indicate that 1 out of 2 adults complains at least of symptoms and/or of signs of chronic venous disorders. In addition, the population age pyramid in industrial nations is leading to an increase in the frequency of patients with these disorders. Four, chronic venous disorders have a considerable socioeconomic impact: estimations of the overall annual costs vary from US $720 million to US $1 billion in Western European countries, representing 1% to 2% of the total health care budget.

Disease-specific instruments are usually sensitive to key dimensions of QOL that are specifically impaired by the disease and that are not captured by generic scales. The Chronic Venous Disorders quality of life Questionnaire (CIVIQ) has been constructed and validated in different languages to specifically assess the QOL of patients with symptoms and signs related to chronic venous disorders.

**Aim of the study**

The aim of our study was twofold. Firstly, it was designed to assess the impact of demographic data, clinical data, signs, and symptoms on the QOL of patients with chronic venous disorders. This was done by establishing which of these parameters were statistically significant in terms of the QOL, and then by measuring the effect on QOL of each parameter in isolation.

Secondly, it aimed to identify the factors with a central role in QOL improvement in patients with chronic venous disorders during the course of a 6-month period of treatment with Daflon 500 mg.

### Methods

Patients were taken from the database of the Reflux assistance and quality of life improvement with micronized purified Flavonoid fraction (RELIEF) study. In this study, outpatients consulting for lower limb problems, diagnosed as C0s to C4 in the clinical class of the CEAP classification, aged over 15 years, male or female, of any race, whether wearing compression stockings or not, were enrolled in the study. Reflux in the superficial venous system was detected by means of a pocket Doppler. When reflux was present on Doppler examination, a complementary photoplethysmography was performed. The symptoms sensation of swelling, cramps, and leg heaviness were measured using a 4-point scale (0=absent to 3=severe), and pain was assessed using a 10-cm visual analogue scale (VAS). Edema was estimated by the leg circumference measurement (using the Leg-O-Meter®).

For the assessment of QOL, the Global Index Score (GIS) (ranking from 0 = worst quality of life to 100 = excellent quality of life) of the CIVIQ questionnaire serves as a standard scale. During the 6-month-period of Daflon 500 mg treatment, patient QOL was assessed during the washout period (D-15), at baseline (D0), then at month 2 (D60), month 4 (D120), and month 6 (D180). This was done according to the presence or absence of symptoms, the presence or absence of reflux, and according to the different clinical class “C” of the CEAP, with the basic CEAP classification being used.

### Statistical analysis

For establishing whether demographic data, clinical data, signs, and symptoms had a significant impact on the QOL, a univariate analysis was performed. Use of a multivariate linear regression model then allowed assessment of the specific contribution of each factor to the level of QOL. Regarding the second step of the present analysis (identification of the factors with a central role in the QOL improvement in patients with the disease during the course of a 6-month period of Daflon 500 mg treatment), the mean change in GIS from D-15 to D180 was analyzed using a mixed-effects model.

### Results

The database included 3948 observations for which the clinical and QOL data were completed. Patients were mostly Caucasian (77.9%), female (81.1%), with mean age 45.5±12.3 years, mean body mass index (BMI) 26.1±6.47, mean duration of chronic venous disorders 12.4±9.8 years. Venous reflux was found in 46.6% and CEAP distribution C0s-C1 in 21.1%, C2 in 40.5%, and C3-C4 in 36%.

| Relationship between symptoms and other clinical parameters: results at baseline |

Of all the symptoms investigated (heaviness, feeling of swelling, night cramps, and pain in the legs), leg heaviness and pain were the symptoms most

### SELECTED ABBREVIATIONS AND ACRONYMS

- **BMI**: body mass index
- **CEAP**: Clinical, etiological, anatomical, pathological (classification)
- **CIVIQ**: Chronic Venous disorders quality of life Questionnaire
- **GIS**: Global Index Score
- **QOL**: quality of life
- **RELIEF**: Reflux assistance and quality of life improvement with micronized purified Flavonoid fraction
- **VAS**: visual analogue score

**Visual analogue score**

**Flavonoid fraction**

**Assessment and quality of life improvement with micronized purified Flavonoid fraction**

**Improvemen with micronized purified Flavonoid fraction**

**New Targets for Pharmacological Treatment in Primary Chronic Venous Disease**

**MedicoGraphia, Vol. 28, No. 2, 2006**
Impact of symptoms of CVD on quality of life – presence or absence of venous reflux.

Table II. Relationship between symptoms related to chronic venous disorders and the clinical C class of the clinical, etiological, anatomical, pathophysiological (CEAP) classification.

<table>
<thead>
<tr>
<th>Table I. Relationship between symptoms related to chronic venous disorders and the clinical C class of the clinical, etiological, anatomical, pathophysiological (CEAP) classification.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with the symptom (%) in: C0s</td>
</tr>
<tr>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>Heaviness</td>
</tr>
<tr>
<td>Feeling of swelling</td>
</tr>
<tr>
<td>Cramps</td>
</tr>
<tr>
<td>Pain</td>
</tr>
</tbody>
</table>

Severity of the symptoms “sensation of swelling,” “heaviness,” and “cramps” was significantly more pronounced in patients with reflux (Table II). Similarly, severity of pain, as measured on the VAS, was significantly higher among patients with reflux compared with patients without reflux (P=0.0002) (Table III).

On the other hand, in patients without a given symptom independently of the others, the absence of the symptom “feeling of swelling” was significantly more common in patients without reflux (P<0.0001). This was not the case for “absence of heaviness” and “absence of cramps,” which were independent of the presence or absence of reflux (P=NS) (Table IV).

The GIS of QOL as measured on the CIVIQ was approximately 95% of patients complained of these symptoms from the onset of the disease. The frequency of other symptoms, “sensation of swelling” and “cramps,” was significantly enhanced in higher CEAP classes (P<0.0001). The difference between C0s-C2 and C3-C4 was substantial, especially for the symptom “sensation of swelling” (Table I).

was a difference of about 10 points between these 2 CEAP subsets (C0-C2 and C3-C4) (P<0.0001), indicating a sharp deterioration in QOL with increasing CEAP classes (Figure 1). It is not known if this is in fact related or not to the marked presence of some symptoms (such as “sensation of swelling” and “cramps”) in the higher C CEAP classes, as shown in Table I.

The QOL evaluation in symptomatic versus asymptomatic patients was not feasible considering the very small sample of asymptomatic patients. Regarding the QOL evaluation according to the presence or the absence of venous reflux, 4.5 GIS points on average were lost when reflux was present compared with no reflux. The difference was significant (P<0.0001) (Figure 2). Once again, there is no indication as to whether this significant difference in the QOL between the 2 groups of reflux is related or not to the accentuated presence and severity of symptoms in patients with reflux (see Tables II and III).

Impact of demographics and clinical parameters on the quality of life of patients with chronic venous disorders (univariate and multivariate models)

Results of univariate analyses are shown in Table V. The second column of the Table shows that all parameters have a significant impact on the QOL, except the ethnic origin of patients. After adjustment for all parameters (column 3), BMI and “duration of chronic venous disorders” (expressed as the time from first symptoms and/or signs of the disease) no longer had a significant impact. Reflux and C class had lower significance compared with the other parameters.

Since univariate analyses did not demonstrate a significant impact of ethnic background on QOL as demonstrated above, this parameter was excluded from the multivariate model, together with “BMI” and “disease duration” parameters, which did not significantly contribute to the model, after adjust-
NEW TARGETS FOR PHARMACOLOGICAL TREATMENT IN PRIMARY CHRONIC VENOUS DISEASE

Change in QOL in patients with chronic venous disorders during the course of 6 months treatment with Daflon 500 mg, 2 tablets a day

At baseline, asymptomatic patients were found to have a far better GIS than symptomatic patients (82.03 versus 63.38; \( P < 0.001 \)) (Figure 3, next page), as did patients in C0s and C1-C2 compared with C3-C4 (70.06 and 68.06, respectively, versus 59.13; \( P < 0.001 \)) (Figure 4), and patients without reflux compared with those with reflux (66.74 versus 62.17; \( P < 0.001 \)) (Figure 5).

During the course of a 6-month period of treatment with Daflon 500 mg, only patients with symptoms had greater improvement in their QOL than patients without symptoms (\( \Delta \text{GIS} [D180-D0]=17.70 \) for symptomatic patients versus 6.38 for asymptomatic patients; \( P < 0.001 \)). Regarding the other sets of patients, GIS changes over treatment were comparable across the different subgroups of CEAP and reflux, since the difference in GIS points between D180 and D0 were not significant whatever the patient profile at baseline: with or without reflux, or whatever the CEAP C class.

Table V. Results of univariate analyses on the impact of demographics and clinical parameters on the quality of life of patients in C0s to C4 of the clinical, etiological, anatomical, pathophysiological (CEAP) classification of the Reflux assessment and quality of life improvement with micronized purified Flavonoid fraction (RELIEF) study.

<table>
<thead>
<tr>
<th>Variable/ significance</th>
<th>Unadjusted regression</th>
<th>Adjusted regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnic origin</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.0001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Gender</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>&lt;0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>Time from first disorders</td>
<td>&lt;0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>Reflux</td>
<td>&lt;0.0001</td>
<td>0.0007</td>
</tr>
<tr>
<td>CEAP C class</td>
<td>&lt;0.0001</td>
<td>0.0009</td>
</tr>
<tr>
<td>Heaviness</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Feeling of swelling</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cramps</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pain</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table VI. Final model of multivariate analysis after adjustment for confounding variables.

<table>
<thead>
<tr>
<th>Independent factor</th>
<th>Attributable difference in GIS</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (every additional year)</td>
<td>-0.12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender (female compared with male)</td>
<td>-4.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (every kg/m²)</td>
<td>-0.08</td>
<td>0.037</td>
</tr>
<tr>
<td>Ankle perimeter (every additional cm)</td>
<td>-0.17</td>
<td>0.0042</td>
</tr>
<tr>
<td>Reflux (presence compared with absence)</td>
<td>-1.80</td>
<td>0.0008</td>
</tr>
<tr>
<td>CEAP (assignment to C4 compared with assignment to C0)</td>
<td>-0.56</td>
<td>0.0016</td>
</tr>
<tr>
<td>Sensation of swelling (severe/absent)</td>
<td>-7.85</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heaviness (severe/absent)</td>
<td>-14.40</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nocturnal cramps (severe/absent)</td>
<td>-7.13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pain (every additional cm on VAS)</td>
<td>-2.31</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\( P^* \) is the difference between groups.
**Discussion**

This study demonstrated that symptoms usually attributed to chronic venous disorders are the factors with the most negative influence on patient QOL. After adjustment for confounding variables, BMI and duration of chronic venous disorders did not significantly influence patient QOL. The low number of obese patients enrolled in this survey may explain the absence of influence of BMI on QOL, while the lack of an association between duration of the disease and worse QOL might be due to the well-known fact that patients progressively become accustomed to their symptoms.

One limitation of our study was the use of pocket Doppler and the protocol for detection of reflux that allowed detection of incompetent superficial veins only (isolated or combined with deep reflux), which means that isolated deep reflux was not identified. We found a relationship between impaired QOL and the presence of reflux and between QOL and higher CEAP C class. Despite a great limitation of this study regarding the detection of reflux, we compared our results with those of the recent San Diego epidemiological survey which assessed QOL (using the 36-item Short Form Health Survey [SF-36]) of patients with various signs of chronic venous disorders.

A positive correlation was found in our study and the San Diego study for QOL and reflux as well as QOL and signs. Functional anomalies assessed with duplex ultrasonography had an impact on the QOL scores in the San Diego survey and also in our study. Symptoms were not considered in the San Diego study, but signs (defined as “visual categories of chronic venous disorders”: spider veins, varicose veins, and trophic changes) were found to have a strong linear effect on the physical component scores of the SF-36 compared to a greater extent than reflux. This was similar in our study despite the fact that the impact of reflux and signs on the QOL were not so marked.

We found that symptoms are not only independent predictors of poorer QOL but also impair QOL to a greater extent than telangiectases or varicose veins. Multivariate analyses confirmed that there is a positive correlation between symptom severity and poorer QOL. In the Venous Insufficiency Epidemiological and Economic Study (VEINES), reflux was not assessed in contrast to symptoms and signs and QOL scores using the specific-disease scale VEINES-QOL. The low QOL scores at C0 and C1 in this study were attributed to a probable high prevalence of symptoms in the C0 and C1 class. Nevertheless, the lowest mean QOL scores were found...
in C5 to C6, which meant that QOL scores tend to worsen with increasing CEAP C class as in our study. But since C5 to C6 patients were not included in our study, this does not allow full comparison.

Another aspect of our analysis addresses the relationships between symptoms and CEAP class, and symptoms and presence or absence of reflux. We found an increasing presence of the symptoms “feeling of swelling” and “cramps” with increasing CEAP. The Middlesex study partly analyzed this aspect of the disease. In this study, patients with C2 to C5 signs were considered for inclusion. Symptoms were recorded on a VAS and were correlated with C of the CEAP. Duplex scanning was used to assess the extent of venous disease. Symptoms appeared unrelated to the veins affected by chronic venous disorders. The greatest symptom scores were observed in the lowest CEAP classes (here in the C2 and C3 groups), but sensation of swelling was highest in C3 and cramps highest in C4. These results do not differ from ours.

The relationship between symptoms and reflux was investigated in the participants of the Edinburgh study. Unlike in our study, the authors found symptoms and reflux to be weakly associated but both symptoms and refluxing venous systems were evaluated separately unlike in the RELIEF study. However, there were so many differences between the Edinburgh study enrollment cohort and that of RELIEF, that a comparison is not possible.

Despite the various methods of assessment of QOL and reflux used in the studies discussed above, together with the different types of patients included, which made comparison difficult, we found some common trends: symptoms usually attributed to chronic venous disorders have a negative influence on the patient QOL (VEINES study), a relationship exists between impaired QOL and the presence of reflux (San Diego study), and between QOL and increased CEAP C class (VEINES Study). Regarding the relationships between symptoms and CEAP class, we found a positive correlation for sensation of swelling and cramps that was highest in C3 and C4 as in the Middlesex study. The correlation between symptoms and the presence of reflux remains contradictory according to the studies considered. The QOL results after treatment with Daflon 500 mg and their interpretation is another aspect of this analysis. The significant difference in GIS at baseline between patients “with” and those “without” reflux, and between the C0s and C1-C2 patients and the C1-C2 and the C3-C4 patients confirms what has been stated above: that QOL worsens with the presence of reflux, and with higher CEAP C class. The fact that this difference remains stable throughout the 6-month period of Daflon 500 mg treatment could be interpreted as the inability of this treatment to compensate for the organic disorders that occurs with increasing severity of the disease. This points to the need for early treatment or intervention for better relief and QOL of patients.

The significant increase in GIS seen during the period of Daflon 500 mg treatment in all patient subgroups means that this treatment substantially improves the QOL of patients with chronic venous disorders whatever the severity of the condition. On the other hand, QOL is greatly improved in symptomatic patients while it remains weak in asymptomatic patients. Such improvement thus probably results mainly from the alleviation of symptoms as evidenced in previous analysis of the RELIEF Study, in which improvement between D180 versus D0 in pain, heaviness, swelling, and cramps was significant (P<0.001 for all symptoms) throughout the 6 months of Daflon 500 mg treatment.

In conclusion, this study has evidenced the negative influence that symptoms may have on the QOL of patients with chronic venous disorders. This suggests that a treatment reducing symptoms might improve the QOL of these patients, provided they are symptomatic, even in the absence of detectable reflux or sign. The dramatic improvement in QOL observed in patients treated with Daflon 500 mg can be interpreted as a result of symptom alleviation.

To the extent that Daflon 500 mg improves venous symptoms, as shown through the RELIEF study (among others) in patients in C0s to C4, prescription of this treatment may be recommended for improving QOL.

REFERENCES
2. Garde C, Perrin M, Chérier P, et al. First meeting of review and validation of the Leg-O-Meter, an improved tape measure dedicated to the veins affected by chronic venous disorders. The greatest symptom scores were highest in C3 and cramps highest in C4. These results do not differ from ours.

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**NEW TARGETS FOR PHARMACOLOGICAL TREATMENT IN PRIMARY CHRONIC VENOUS DISEASE**

Impact des symptômes sur la qualité de vie chez les patients qui présentent une affection veineuse chronique

La qualité de vie (QDV) des patients qui présentent une affection veineuse chronique est globalement dégradée. L’analyse du retentissement des affections veineuses chroniques et des symptômes qui les accompagnent sur l’activité quotidienne des patients qui en sont affectés, et l’impact des traitements à visée symptomatique par la mesure scientifique et rigoureuse de la QDV sont devenus des outils d’appréciation importants. Nous avons procédé à une analyse complémentaire de l’étude Reflux assessment and quality of life improvement with micronized flavonoid fraction (RELIEF) (Évaluation du reflux et de la qualité de vie par un traitement à la fraction flavanique purifiée micronisée). Le but de ce travail était double : premièrement évaluer l’impact des données démographiques et cliniques sur la QDV des patients qui présentaient une affection veineuse chronique, deuxièmement identifier les facteurs-clés jouant un rôle majeur dans l’amélioration de la QDV lors d’un traitement de 6 mois par Daflon 500 mg. L’analyse a été réalisée à partir de la base de données de l’étude RELIEF où avaient été inclus malades C0 à C4 suivant la classification CEAP (clinique, étiologique, anatomique, physiopathologique). L’évaluation de la QDV a été réalisée en utilisant le GIS (Global Index Score) c’est-à-dire l’index de score global du questionnaire CIVIQ (Chronique Veineux disorder Quality of life questionnaire). Ce score a été apprécié pendant la période précédant la prise de médicament (J-15), juste avant le traitement (J0) puis à 60 (J60), 120 (J120) et 180 jours (J180) du traitement ; ont été évalués les symptômes, le reflux et le C de la classification CEAP. 3498 patients ont été inclus. Il est apparu que l’âge, le sexe, l’indice de masse corporelle, le périmètre de cheville, la présence d’un reflux, la classe clinique n’avaient qu’un impact modéré sur la QDV appréciée par le calcul du GIS. À l’inverse, les symptômes dans leur globalité, la douleur et la sensation de jambe lourde avaient un impact négatif important sur la QDV. Lors des 6 mois de traitement par Daflon 500 mg, le GIS était significativement amélioré dans tous les sous-groupes de patients (avec ou sans reflux, quelle que soit la classe clinique, patient symptomatique ou non). Durant ce traitement par Daflon 500 mg, la différence à l’intérieur des 2 premiers sous-groupes qui viennent d’être définis restait stable pendant toute la durée du traitement, alors que les patients symptomatiques avaient une amélioration plus importante de leur GIS lorsqu’ils étaient comparés aux patients asymptomatiques. En d’autres termes on notait globalement une augmentation significative du GIS dans tous les sous-groupes lors du traitement par Daflon 500 mg, ce qui signifie que cette thérapeutique améliore de façon importante les patients qui présentent une affection veineuse chronique quelle que soit la sévérité de leur pathologie. Dans le détail, il convient de relever que le GIS est plus amélioré chez les patients symptomatiques même en l’absence de signe sévère, il est donc probable que cette action favorable résulte de l’amélioration de la symptomatologie chez les patients classés C0-C4 comme l’avait démontré l’étude RELIEF. En conclusion, ce sont les symptômes qui ont l’impact le plus défavorable sur la QDV même en l’absence de signe ou de reflux. Dans la mesure où Daflon 500 mg améliore la symptomatologie veineuse, on peut recommander sa prescription pour optimiser la QDV chez les patients qui présentent une affection veineuse chronique. 

*Perrin*
Is systematic detection of venous reflux mandatory in practice?

1. Z. Pécsvárady, Hungary

Chronic venous insufficiency (CVI) is a progressive disease classified by the clinical, etiological, anatomical, pathophysiological (CEAP) classification. One of the major determinants of CVI is venous reflux caused by insufficient venous valves of the superficial veins, the deep veins, or the perforator system. In clinical practice, one of the major questions is: to how many veins involved from the perforator and deep system? There are simple and expensive tools available for the diagnosis of CVI such as the percussion (Schwartz test); the Valsalva maneuver; continuous wave Doppler; duplex sonography; photo, air, and strain-gauge plethysmography; simple or magnetic resonance venography; ambulatory venous pressure (AVP) measurement; and intravascular ultrasound (IVUS). The percussion test is easy to use, and no device is necessary. It is useful but is just a screening test for the superficial venous system in clinical practice. In the Valsalva maneuver, the sudden increase in intra-abdominal pressure can cause reflux especially in the proximal veins, which we can measure either with continuous wave Doppler or duplex sonography. The lack of a standardized mode to raise intra-abdominal pressure and the difference in reflux when the patient is in the horizontal position are limitations of this method. The manual squeeze test with Doppler (or duplex sonography) control can identify the reflux segmentally. A more standardized method is when pneumatic cuffs are used to empty veins below the transducer. It is nowadays the gold standard for clinical practice. These tests can measure the reflux in individual veins. It is also possible, and, indeed, necessary to measure “total leg” reflux. The most useful measurement obtained with air plethysmography is the venous filling index (VFI). Photoplethysmography can measure the venous reflux time, which is shorter in the case of reflux. It is very useful for testing superficial vein insufficiency. Unfortunately, using a tourniquet to block the superficial venous reflux can not provide accurate enough data from deep venous insufficiency. Strain gauge plethysmography, venography, or magnetic resonance venography are useful for monitoring control of pelvic outflow or obstruction. As the time of reflux is not enough to determine the degree of CVI, some also calculate values (eg, reflux time, venous filling index, volume of reflux, total limb reflux volume) but this is mainly for research purposes. AVP is not used regularly now as it is an invasive procedure. IVUS could be a useful tool for the future monitoring of valve competence. The most popular tool is duplex sonography, which can show the anatomical situation (size, diameter of the vessel, location of occlusion, condition of the veins and valves) and measure dysfunction (eg, reflux) of the venous system. Unfortunately, none of these tests show a perfect correlation with the severity of CVI alone. The most effective means of classifying patients for the different tests is by dividing them according to CEAP (CEAP 1-3/4-6) and age (young/old), as advised by an expert panel. Young patients in CEAP class 1 to 3 are more likely to have superficial vein insufficiency only, which is amenable to vascular surgery or other interventions. In clinical practice, the most common investigations for identifying CVI are continuous wave Doppler, duplex sonography, and photoplethysmography together with clinical examination. Similar tests are necessary for older patients in CEAP classes 4 to 6, who are less likely to be suitable for deep venous reconstruction because of their general health. Young patients in CEAP grade 4 to 6 are the best candidates for extended interventions using all the available methods mentioned in order to determine the deep and superficial vein disturbances before providing the right conservative and reconstructive treatment. This classification is simple, but has proved to be a useful and cost-effective diagnostic tool for the different CVI patients.

FURTHER READING

Is systematic detection of venous reflux mandatory in practice?
The debate on this issue is not a new one. In 1986, Browse asked a very similar question: Is the vascular laboratory necessary in the management of venous disease? And his answer was: "...if we interpret the word mandatory in a literal sense, then we can answer this question either way: no, because we have enough with the clinical evidence; or else yes because that is not enough and we have to look for some kind of aid to establish the diagnosis." It is an accepted fact that chronic venous insufficiency (CVI) is generated by, and develops from, venous hypertension (VHT) secondary to pathological venous reflux (PVR), and that this may present on its own or in association with the superficial venous system (SVS), deep venous system (DVS), or perforating veins (PV). And it is also accepted without too much dispute that the serious complications of this condition—C4 to C6 of the clinical, etiological, anatomical, pathophysiological (CEAP) classification—are basically the consequence of the PVR of the DVS and the perforating veins. Nonetheless, a considerable amount of controversy still surrounds 2 issues: which hemodynamic variable can most reliably be related to PVR and which is the most suitable hemodynamic study to assess it? Those authors arguing in favor of not performing an obligatory PVR study in CVI maintain that, in varicose veins, the application of the classic and relatively simple clinical tests for the SVS, such as the Trendelenburg and Perthes maneuvers, are sufficient to establish the points of PVR. In my opinion, the argument to counter this statement is that PVR in perforating veins has been observed in association, in no fewer than 75% of limbs with varicose veins in the SVS and that, in our experience (based on the clinical-operative correlation), the clinical examination derived from these tests has only been able to identify between 45% and 55% of these cases. Other authors maintain that, for the identification of PVR in the perforating veins, the duplex examination is superior to phlebography. A duplex examination (an extremely reliable and precise test in expert hands) provides real-time 2-dimensional measurements of venous hemodynamics that has been correlated with the PVR. Having reached this point, however, there is a second controversy with respect to which hemodynamic variable allows differentiation between PVR and physiological values. In the Edinburgh study, one of the goals of which is to assess the prevalence of PVR in the general population using duplex, the finding was positive in 18% of the individuals without clinical manifestations examined. Variables such as peak reflux velocity or reflux time have been called into question by authors who maintain that these examinations are performed in static conditions of standing and therefore do not consider the hemodynamics of the soleus-gemellar and plantar muscle pumps, a fundamental aspect at the level of PVR studies in the popliteal vein. Nonetheless, there is limited experience in the development of new tests such as the dynamic reflux index. Another question that must be asked in the context of this debate is whether information obtained on PVR by duplex will change the therapeutic strategy. Although some authors hold that duplex investigation should only be indicated in strategic surgical proposals for relapsed and recurrent varicose veins, a study published in 2001 revealed that 65% of vascular surgeons in the United Kingdom used some kind of hemodynamic test when examining varicose veins (83% of them opted for duplex as the first-choice study) and that this implied a change of surgical strategy in 24% of the limbs examined, in comparison with that established previously on the basis of clinical tests. Given the clinical and hemodynamic complexity of CVI, establishing the existence of PVR and its location as reliably as possible is, in my opinion, mandatory. Even though in our experience this goal is not achieved in a large percentage of patients who only have symptoms in the absence of clinical signs, the duplex study must be indicated on the basis of rigorous diagnostic criteria. In advanced stages of the illness (grades C4-C6), I understand that there are sufficient arguments for duplex to be obligatory in the discussion of therapeutic strategies. Finally, there still remains in this context a question insufficiently resolved, ie, which hemodynamic parameter of the duplex study most reliably establishes the existence of PVR?

REFERENCES

Is systematic detection of venous reflux mandatory in practice?

MEDICOPHARIA, VOL 28, No. 2, 2006

CONTROVERSIAL QUESTION

Chronic venous insufficiency (CVI) of the lower limbs remains a serious medical, social, and economic problem among the developed countries. The symptoms and signs characteristic of primary CVI result from venous hypertension and are due to functional and structural disorders of the veins. The secondary abnormalities of the venous wall and its valves result from thrombosis, recanalization, or the disturbances of blood flow. The retrograde flow related to valve incompetence can be detected during activity of the muscle pump or breathing. That leads to CVI symptoms such as heaviness, tiredness, cramps, or swelling. Simultaneously, dilatation of superficial veins lead to their varicosity, skin changes, and ulceration. Deterioration of venous sufficiency is usually related to the progression of venous reflux. The final target of impaired venous hypertension is blood capillary circulation marked with skin changes, eczema, and ulceration. The clinical picture of CVI and objective pathophysiological investigations are essential in decision making regarding the therapeutic options. In the era of the development of various technical and pharmacological possibilities, the elective treatment of CVI still remains unsatisfactory, especially when long-term results are assessed. The initial evaluation of patients with CVI consists of determining the presence or absence of reflux, venous flow obstruction, or both pathologies. In the past, the phlebogram was used to visualize the venous bed and to localize a pathological direction of blood flow from deep to superficial veins or vice versa. These investigations were essential for describing different types of venous reflux. Currently, the most commonly used methods for the detection and measurement of venous reflux are continuous wave Doppler and photoplethysmography. Venous disease investigation requires a great deal of experience and is more demanding than diagnosis in arterial disease. It is much more operator-dependent. Duplex ultrasound techniques detect reflux in each vein segment, whereas photoplethysmography measures overall venous function: venous outflow and total venous reflux (valvular incompetence and muscle pump sufficiency). It is now considered as a gold standard in planning the therapeutic options.

FURTHER READING

Venous reflux is the bidirectional flow of blood in the veins due to valvular incompetence. It may be detected by noninvasive ultrasound duplex scan with color flow of the lower limb. The principal importance of venous reflux is its role in the pathogenesis of chronic venous insufficiency of the lower limb (CVIL). Some studies suggest that up to 90% of CVIL is associated with its presence. CVIL is a common disease, and surveys suggest a point prevalence of 5% to 10% in the general population. It is chronic, and, if untreated, progresses to debilitating venous leg ulcers. In India, most patients are in their productive years with stage 3 of the CEAP (clinical, etiological, anatomical, and pathophysiological) CVIL classification, which includes pedal edema, and about 30% have venous reflux. For these reasons CVIL qualifies as a public health problem and warrants early detection and treatment. In this context, the main argument for making systematic venous reflux assessment mandatory in practice is that CVIL can be present without its classic symptoms (lower limb pain, swelling, cramps, or heaviness) especially in the very early stages. The detection of venous reflux in such patients would allow its early diagnosis and treatment, thus preventing progression. In addition, the detection of reflux is noninvasive and may be a useful guide to the specific line of management. On the other hand, the argument against making systematic venous reflux assessment mandatory is that the symptoms of CVIL are nonspecific, and a large proportion of patients with such complaints do not have CVIL, there being a weak correlation between symptoms and severity of disease. It would therefore be a waste of scarce resources to routinely assess reflux in all patients. At present in India, systematic detection of venous reflux for the diagnosis of CVIL is not considered mandatory in general practice. Typically, the general practitioner or the primary care provider is the patient’s first point of contact, but patients sometimes consult an internist, dermatologist, general surgeon, or vascular surgeon. A reasonable and practical approach would be for the first-contact care provider to begin with conservative treatment aimed at reducing venous reflux in patients who present with symptoms of CVIL. Such treatment could include muscular exercise to activate the calf muscle pump, ankle flexion, avoidance of high heels and prolonged standing, leg elevation above the level of the heart for as much time as possible, and use of elastic compression stockings. Micronized purified flavonoid fraction (MPFF) may be prescribed. It has been shown to oppose the microcirculatory effects of reduced venous tone, elevated inflammatory mediators, increased capillary fragility and permeability, and decreased lymphatic flow that underlie the pathogenesis of CVIL. In randomized and other studies, MPFF effectively suppresses symptoms and facilitates the healing of leg ulcers due to CVIL. If, on follow-up, symptoms of CVIL are not relieved with conservative treatment, or there are skin changes suggestive of the later stages of CVIL, then it should be mandatory for the first-contact care provider to refer the patient to a vascular surgeon for full evaluation, which will include the assessment of venous reflux, and specific treatment.

REFERENCES
**U. Bengisun, Turkey**

Chronic venous disease (CVD) of the lower extremities is a major socioeconomic burden with high health care expenditure in many countries. The spectrum of clinical manifestations of CVD ranges from telangiectasias to varicose veins and severe venous skin changes (i.e., lipodermatosclerosis and venous ulcer). Epidemiological studies have demonstrated that the prevalence of varicose veins, as the most common clinical form of CVD, is around 25% to 33% in women and 10% to 20% in men. Although the pathogenesis of CVD is not fully or clearly understood, sustained venous hypertension is the result of symptoms or signs of varicose veins which are due to valvular incompetence and venous obstruction. The presence of reflux alone is found in 80% of patients with CVD while obstruction alone is detected in only 2%. The combination of reflux and obstruction is seen in about 17%. Because of primary valvular incompetence or postthrombotic damage, superficial veins are affected in 90% of lower extremities with CVD, the deep veins in only 30%, and perforating veins in 20%. In contrast to a wide variety of lower limb symptoms including aching, heaviness, pruritis, swelling, and restless legs, many patients with CVD are asymptomatic. Additionally, many studies have shown that such symptoms are present in about half the adult population and increase significantly with age. Symptoms of venous disease alone are usually not characteristic. There is no good correlation across clinical symptoms, varicose vein patterns, and severity of venous reflux. Moreover, venous aching or swelling may not be associated with apparent varicose veins during examination. Interestingly, similar patients who have minimal or no varicosities can show major venous reflux by duplex scanning. Therefore, symptomatic patients should be assessed with great care starting with history taking and physical examination in search of the characteristic features of alternative ischemic, arthritic, or neuralgic causes of pain. This will lead to appropriate diagnostic investigations and treatment modalities. The agreement between symptoms and signs in patients with varicose veins is so poor that it may be of little value in determining whether symptoms are of venous origin or whether treatment will relieve them. Although there is no consensus about the relationship between clinical symptoms and CVD, the most common underlying cause of varicose veins is venous reflux. The majority of patients (70%-80%) with varicose veins have great saphenous vein incompetence while 15% to 20% of patients have lesser saphenous vein incompetence and the remaining 10% have incompetence in the nonsaphenous veins. The distribution and extent of reflux is associated with the severity of the disease such as skin changes and increases with the extent of reflux and obstruction. It has been reported that primary valvular incompetence is significantly more common than secondary (postthrombotic) disease. Also, it is very important to differentiate between primary CVD and secondary CVD. After clinical assessment including history taking and physical examination of the patient, the next step is the application of various diagnostic tests in order to better assess the pathophysiology, severity, distribution, and extent of underlying abnormalities. These tests reveal the presence or absence of reflux, obstruction, or both. In this way, we can diagnose and classify precisely (using the clinical, etiological, anatomical, pathophysiological [CEAP] classification) the underlying venous problem, which offers guidance on the correct treatment. The diagnostic evaluation of the patient with CVD can be organized into one or more of three levels of testing, depending on the severity of the disease, which was suggested very clearly at the consensus meeting on investigations on chronic venous insufficiency. Hand-held Doppler, which could be applied after the first clinical assessment, can provide some information about the presence of reflux at the saphenofemoral junction, saphenopopliteal junction, saphenous veins, and obstruction at the proximal deep veins. However, this method can still have some drawbacks. A major drawback of hand-held Doppler examinations is the inability to be certain about which veins are being examined. Complicated anatomy including duplicated, tributary, and collateral veins is usually the major cause of errors. Also, the detection of refluxing veins, severity of reflux, and the site and diameter of incompetent perforating veins cannot be fully determined. Currently, duplex ultrasound is the gold standard for determining underlying venous abnormalities. Color flow duplex provides more precise mapping of the refluxing veins and helps identification of the possible causes. Moreover, duplex scanning can reveal asymptomatic hidden reflux and studies have shown that this may be as high as 39%. The author believes that the first step for an appropriate and successful therapeutic approach is the correct diagnosis of venous disease. Systematic reflux detection should be mandatory in patients with varicose veins, which can appear unexpectedly and be complex. Therefore, patients’ complaints should be noted and taken very seriously in conjunction with noninvasive venous investigation and the CEAP classification. The proper treatment method should be chosen in this way. This will prevent potential mistreatment and unnecessary expenditure. It also increases the correlation between treatment and reduction in symptoms and signs of venous disease.

**REFERENCES**

The symptoms of chronic venous disease (CVD) are not always specific. They include principally pain, leg heaviness, paresthesia, restless legs, and nocturnal cramps. They are encountered in all stages of CVD from class C0 symptomatic to class C6 (active ulcer). Although the patient history leads to an initial screening, the clinical examination remains vital for the evaluation of CVD. This permits a selection of the C (clinical) items of the clinical, etiological, anatomical, pathophysiological (CEAP) classification. However, it has to be complemented by non-invasive investigations, Doppler and especially echo-Doppler, to specify the items E, A, and P items. Duplex ultrasound scanning is being increasingly used to investigate venous disease, and recourse to phlebography or varicography has become very rare. B-mode allows visualization of the venous system, particularly the infrafascial segments that are not easy to evaluate clinically, and to exactly orientate the Doppler beam which “listens” to the blood circulation, gives information about venous hemodynamics, and the presence or absence of reflux. The detection of venous reflux is indisputable testimony to the presence of CVD. At the earliest stages of venous disease, some patients may complain of symptoms only without having any visible or detectable signs of CVD (Cos). In these cases, Doppler ultrasound is still indicated, because it can detect a silent anomaly of the superficial or deep venous network. A normal result means the patient can be reassured about the lack of significant venous pathology. To take into account these patients, the letter “n” was recently added to the E, A, and P items of the CEAP classification (ie, “no” etiological, “no” anatomical, and “no” pathophysiological anomaly detected). However, various lower limb symptoms may be present without signs of CVD. The search for other causes of lower limb symptoms, such as those arising from locomotor, neurological, or psychological disorders, should be undertaken. The systematic use of Doppler ultrasound to evaluate venous pathology is still, unfortunately, controversial. The reason for this is essentially cost-related, hence the lack of duplex availability. In our clinic, a Doppler ultrasound is performed in each patient suffering from potential venous symptoms whatever the complaint may be. This investigation allows the etiology of CVD to be established and the most appropriate treatment to be selected.

Telangiectasias
A normal echo-Doppler can reassure an anxious patient with a family history of varicose veins or cosmetic problems (C1a). “Fan-like” telangiectasias are often related to reflux of variable degree of a feeding vein, which can be detected by echo-Doppler and treated accordingly. Telangiectasias may also be an indicator of underlying changes in the deep and/or superficial venous systems. Their importance must not be underestimated in a symptomatic patient (C1s) and an echo-Doppler must be undertaken before any surgery or extensive sclerotherapy.

Varicose veins
In asymptomatic (C2a) or symptomatic (C2s) varicose veins, the duplex provides detailed information on the patency of the saphenous trunks, perforating veins, and deep veins, and the function of their valves. It establishes the etiology of varicose veins (primary varicose veins are due to superficial or perforating venous insufficiency, while secondary varicose veins are due to a post-thrombotic syndrome) and is essential in the choice of optimal treatment. It is particularly useful to establish the anatomy of the varicose veins before surgery or echosclerosis.

Edema
The echo-Doppler helps to specify the etiology of edema (C3). Causes of edema are multiple and may be associated. An alteration of the deep and/or superficial venous system as seen by ultrasound confirms venous involvement in the edema. The echo-Doppler also allows the detection of extrinsic venous compression. A normal result should lead to the search for another etiology. A clinical examination is sufficient to diagnose lymphedema or lipedema.

Trophic lesions
When cutaneous trophic lesions of variable degree (C4, C5, and C6) are present, the echo-Doppler has become irreplaceable in deep and perforating venous evaluation. In active leg ulcer, Doppler ultrasound must also be used to evaluate the quality of peripheral arterial perfusion with measurement of peripheral blood pressure. The importance of phlebography is tending to decrease. However, in recurrent ulceration, phlebography or varicography may be necessary in complex situations if the echo-Doppler is not able to furnish sufficient information, particularly in the popliteal fossae. Ultrasound investigations are widely used and recourse to other techniques has become rare. Magnetic resonance imaging remains the investigation of choice of venous malformations. Venous plethysmography is used to evaluate the quality of the venous muscular pump and to estimate the preoperative results that can be expected from varicose vein surgery. Other techniques such as phlebodynamometry, volumetry, transcutaneous oximetry, capillaroscopy, and thermography remain of academic interest and are only rarely indicated in practice.

CONTROVERSIAL QUESTION

Is systematic detection of venous reflux mandatory in practice?
Is systematic detection of venous reflux mandatory in practice?

**Retrospectively, flow in the lower limb veins occurs physiologically just before valve closure and pathologically as a result of valve absence or incompetence from recanalization, dilatation, or denervation. The spectrum of symptoms attributed to it in the literature is wide and nonspecific. The clinical manifestations of venous disease can result from acute deep venous obstruction/thrombosis or may be secondary to valvular incompetence and venous insufficiency. Thus, the patient's symptoms cannot give us enough information to make an accurate diagnosis. Furthermore, at present, various procedures have been performed for the treatment of venous reflux disease, including selective stripping, high ligation of the saphenous vein, sclerotherapy, and endoscopic perforator surgery. Adequate preoperative evaluation is therefore of paramount importance in the process of decision-making as to whether or not to operate on patients with venous reflux and which surgical strategy would be the most appropriate. Previously, not much attention has been paid to the influence of preoperative examinations on the treatment plan for patients with mild chronic venous insufficiency. Investigation incorporating noninvasive diagnostic techniques may include the diagnosis, treatment, and natural history of acute deep venous obstruction/thrombosis and chronic venous insufficiency, assessment prior to and following venous reconstruction, and the basic science aspects of acute and chronic venous disease. According to the results of recent studies, routine systematic detection reduces the incidence of incorrectly planned surgical treatment. In accordance with the CEAP (clinical, etiological, anatomical, pathological) classification, the aim of the diagnostic process in CVI is to obtain differentiated information on the causes and expression of the pathological picture in order to be able to implement effective treatment. The basic diagnostic procedures comprise documentation of the patient's medical history, clinical examination, and Doppler ultrasonography. In the further diagnostic process, duplex ultrasonography is very much in the foreground, having replaced phlebography in routine investigations. For quantitative functional diagnosis, use can be made of plethysmographic methods like photo-plethysmography, air-cuff plethysmography, and venous occlusion plethysmography. In addition to this, the venous pressure can be measured directly in the foot region. Doppler ultrasonography as a rule allows the localization of insufficient vein segments in the epifascial, transfascial, and subfascial venous systems, but it is not suitable for exact morphological diagnosis. What is more, erroneous evaluations are possible in anatomically difficult regions such as the popliteal fossa. It should be noted that while the absence of reflux in the inguinal or popliteal fossa region can be taken as relatively reliable evidence for excluding valvular insufficiency in that area, in the opposite case, ie, if a reflux phenomenon is observed, it is extremely difficult to assign it to the particular vein segment. Color-coded duplex ultrasonography is currently regarded as the true gold standard of modern phlebological diagnosis. In most phlebological investigations, duplex ultrasonography is more sensitive than clinical examination, Doppler ultrasonography, or photoplethysmography. In the evaluation of reflux in the superficial and deep venous system, duplex ultrasonography is largely similar to phlebography. Occlusions or rarefaction of the venous system in the postthrombotic syndrome can be evaluated morphologically, as well as valvular insufficiency in the superficial and deep venous system with a diagnosis of reflux. In general, retrograde flow lasting more than 0.5 to 1 second is regarded as pathological. The reflux can be triggered by the Valsalva maneuver or by proximal compression or distal decompression of the vein. Exact quantification of the reflux velocity and reflux length is difficult, because neither the Valsalva maneuver nor manual compression can be standardized. For scientific investigations, a pneumatic pressure cuff, which can be inflated and quickly deflated, has proved useful. A disadvantage of duplex ultrasonography is the difficulty in documenting its results, which do not afford sufficient insight into the complex pathological relationships to anyone who has not carried out the examination personally. For the representation of complex pathological alterations, for example, in angiodyplasias or in the presence of a pronounced postthrombotic syndrome, phlebography is therefore preferred as an invasive imaging method. Strain-gauge plethysmography also allows an evaluation of the function of the deep venous system in the same way as venous occlusion plethysmography. For this purpose, the patient is instructed to lie down and an inflatable cuff is placed around his or her thigh. During a phase of obstruction of the venous return, the volume increase in the lower leg region is determined, and after release of compression the venous outflow is measured from the initial volume decrease. In the past, the method was used predominantly to screen patients for thrombosis. This indication has now been replaced by duplex ultrasonography. With the aid of the parameters measured, ie, “venous capacity” and “venous outflow,” the permeability of the deep venous system can be evaluated, eg, in the course following deep leg vein thrombosis or where there is a suspicion of venous outflow disturbance. Air-cuff plethysmography was promoted in 1988 by Christopoulos and Nicolides. With this technique, an air-filled cuff placed on the lower leg between the ankle and the knee is connected to a pressure monitor and a computer, and various function parameters are determined in the course of a complex examination program involving...**
compressive maneuvers and movement exercises, as well as a change from the recumbent to the standing position. The most important of these measurements are the venous filling index as a parameter for venous reflux and the ejection fraction as a measure of muscle pump function. All in all, quantifying venous function measurements makes an important contribution to the evaluation of venous function disturbances, but they are unable to establish a reliable diagnosis of the venous disease that is present. Accordingly, they are used as auxiliary methods, in combination with Doppler or duplex ultrasonography and with the clinical picture, to supplement the evaluation of the global functional impairment of the venous system.

Prof Wang continued

Venous stasis is a common condition in which the flow of blood from the legs to the heart is abnormal. When everything is working normally, a series of one-way gates (valves) makes sure that the blood can only move in one direction. However, when the valves are damaged, the “muscle pump” does not work. This condition is called venous reflux. Many studies have confirmed that a significant degree of reflux is associated with a higher venous pressure. Anatomically, venous reflux can be in one or more of the following 3 sites: (i) superficial venous system (SVR); (ii) deep venous system (DVR); (iii) perforating veins (PVR). Hemodynamically, venous reflux can be of 2 types: (i) axial venous reflux, which is continuous reverse blood flow from the groin region to below knee; (ii) segmental venous reflux, which involves reverse blood flow in a specific vein segment, usually in a deep vein at its junction with an incompetent superficial vein (eg, common femoral vein and great saphenous vein). Reflux in the deep venous system was proved to have a significant role in the progression of chronic venous insufficiency (CVI) and ulcer formation, particularly significant axial reflux.

Role of ultrasound in the assessment of CVI
CVI is responsible for significant morbidity and health expenditure. Doppler ultrasound provides a noninvasive method for identifying structural and functional abnormalities associated with CVI; this information allows treatment options to be considered. Ultrasound allows clear identification of specific venous segments and provides information on the patency of these segments, the presence or absence of reflux, perforator veins, collateral channels, occluded deep vein segment, or patterns of recurrence after surgery.

Colored duplex guides in choosing the treatment approach
The precise anatomical and functional diagnostic ability of color duplex examination is of great importance not only as a diagnostic tool, but also in choosing the treatment approach. It also helps to determine the best operative strategy. In patients with concomitant deep and superficial venous reflux, saphenous vein ablation results in resolution of deep reflux in about a third of patients. Superficial femoral vein reflux is seldom corrected in limbs with axial reflux compared with those limbs with segmental reflux. In a study to define the role of superficial venous surgery in patients with combined superficial and segmental deep venous reflux as documented with duplex study, it was found that in patients with combined SVR and segmental DVR, superficial venous surgery alone corrects DVR in almost 50% of limbs and is associated with ulcer healing in 77% of limbs at 12 months. These findings suggest an extended role for superficial venous surgery in the management of patients with complicated venous disease.

Systematic detection of venous reflux is mandatory in practice, to define the proper approach for initial treatment, to follow up the patient with medical conservative treatment, and to pick up cases with deteriorating superficial or deep venous function to guide in changing the mode of treatment before complications of CVI appear. It is also useful for the early detection and management of recurrence after surgery.
DAFLON 500 MG: PROTECTIVE AND EFFECTIVE RIGHT FROM THE ONSET OF CHRONIC VENOUS DISEASE

by F. Pitsch, France

It is generally agreed that primary venous insufficiency is characterized by reflux through incompetent venous valves. Abnormally elevated venous pressure, also called venous hypertension, links all theories regarding pathogenesis of chronic venous disease (CVD). The definition of CVD in this review includes all symptoms, pain in the legs, heaviness, sensation of swelling, and muscle cramps as described in the clinical section of clinical, etiological, anatomical, pathophysiological (CEAP) classification.1

Venous hypertension: the clinical hallmark of CVD

Primary venous insufficiency is associated with venous hypertension largely through reflux in failed venous valves. This reflux may be in superficial axial veins, deep veins, or perforating veins that connect the superficial to the deep veins. Superficial reflux is part of the cause of a progressive and sustained increase in calf vein pressure. The other aspect is reflux through incompetent perforating veins during muscular contraction.2

The causes of such valve failure is unproven and under investigation.3 One theory is that valvaral insufficiency is caused by vein wall dilation.4 Another is that primary cusp degeneration or valve remodeling occurs.5 For many years, a third theory, first coined by Fegan, is that abnormal hemodynamics or turbulent flow is responsible for valve changes.6 Examination of surgical specimens suggest that the two main theories can overlap.7 Some think that 3 factors combine to produce venous reflux through failed valves. One is dilation of the valvular annulus and the second is atrophy of the valve cusps, the third being a hemodynamic disorder that leads to mechanical injury of the annulus and valve cusps.8

Chronic venous disease (CVD) of the lower limbs is characterized by symptoms and/or signs as a result of abnormalities in the veins. This is a progressive disease that may lead to complications. Symptoms are present throughout the disease progression. One of several theories put forward as a possible cause of CVD progression is that primary valcular dysfunction is acquired. This view is supported by findings such as activated leukocytes, which have been shown to migrate into the endothelium of proximal surfaces of the vein valves and promote remodeling of the valves with consequent valcular insufficiency. A pharmacological model of chronic elevation of venous pressure has been shown to be associated with an inflammatory reaction in venous valves, a process that may lead to their dysfunction, reflux, and upstream elevation of venous pressure. It has been evidenced that these effects were mitigated by the anti-inflammatory action of Daflon 500 mg in a dose-dependent manner. Up to now, Daflon 500 mg has shown the greatest potential for accomplishing blockade of the inflammatory cascade and the promise of better tissue protection. Activated leukocytes, endothelium, mast cells, macrophages, and fibroblasts target the extracellular matrix as well as parenchymal cells and produce a spectrum of inflammatory mediators that serve as a tissue repair mechanism, but, with resulting valcular incompetence, may favor further inflammation which greatly contributes to the etiology of varicose veins as well as to the skin changes and ultimately ulceration seen in CVD. Work on animal and human models has shown that Daflon 500 mg modulates leukocyte adhesion, and prevents endothelial damage in both veins and capillaries. Such treatment is useful first line for edema as well as in the associated symptoms of CVD. It continues to be effective in all subsequent stages of the disease, including leg ulceration. The results of a recent meta-analysis confirm that venous leg ulcer healing is accelerated by adding Daflon 500 mg to conventional treatment. Larger ulcers and long-lasting ulcers were found to benefit most from such treatment. These ulcers tend to heal more slowly, and an adjuncive treatment may be of advantage in such circumstances. Better understanding of the etiology of venous disorders will lead to better knowledge of pharmacological targets and to better tissue protection, allowing early protection against progression of CVD as well as alleviation of the considerable suffering of patients in the long term.

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Keywords: chronic venous disease; chronic venous insufficiency; venotropic drugs; leukocytes; venous endothelium; inflammation; remodeling; venous valve; venous ulcer; symptoms

Address for correspondence: Mme Françoise Pitsch, Servier International, 192 avenue Charles de Gaulle, 92578 Neuilly-sur-Seine, France (e-mail: francoise.pitsch@fr.netgrs.com)
This explanation is reinforced by a description of embryological development of vein valve endothelium and vein wall. Bicuspid venous valves are a condensation of the endothelium from the venous wall in fetal life.

**Venous valve failure: leukocytes have a central role**

The theory holding that valve failure is an acquired phenomenon is supported by recent fundamental research findings. These latter studies revealed that just as leukocyte trapping and activation takes place to produce skin damage in chronic venous insufficiency, so leukocytes can attack vein valves and the vein wall in the macrocirculation. Just as leukocytes can attack and destroy skin and subcutaneous tissue, it seems possible that activated leukocytes can migrate into the endothelial of the proximal surfaces of the vein valves as well as proximal vein walls and promote destruction of supporting structures and remodeling of the valves with consequent valvular insufficiency. Immunohistochemical studies using monoclonal antibody specific for monocytes and macrophages have demonstrated monocyte/macrophage infiltration into the valve leaflets and venous wall of patients with varicose veins (CEAP class 2). Monoclonal antibody studies have found leukocyte infiltration to be greater in the base of the valve leaflets and in the proximal venous wall (Figure 1). Venous valves have been found to be prominent in regions of low shear stress with venous eddies and recirculation. It may be that these phenomena explain how the leukocytes are preferentially deposited in these regions.

**Figure 1. Leukocyte-endothelium interactions on a venous valve.**

Abbreviations: ICAM-1, intercellular adhesion molecule 1; IL, interleukin; TNF, tumor necrosis factor.

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**Daflon 500 mg: a protective effect against valve damage**

Daflon 500 mg mitigates the effects of chronic inflammation. It has been shown to inhibit leukocyte adhesion and migration and decrease protein leakage. In a model by Takase et al of venous occlusion and reperfusion, the subsequent elevation of venular blood pressure exacerbated the inflammatory cascade and tissue injury. On the upstream side of the occlusion where venous pressure is elevated, the number of rolling, adherent, and migrating leukocytes increased as did the number of apoptotic cells in the parenchyma. In Daflon 500 mg-treated animals, the cardinal markers of inflammation were decreased in a dose-dependent manner. Injured processes were significantly inhibited by Daflon 500 mg as well as the neutrophil expression of CD62L. A 1-week period of treatment with Daflon 500 mg served to significantly reduce parenchymal cell death as well as leukocyte rolling, adhesion to postcapillary venules, and migration into the tissue both during occlusion and reperfusion. Taken together, these results on the microcirculation in these animal models suggests that Daflon 500 mg might be useful clinically to decrease the effects of CVD.

In a rat model of venous hypertension caused by a femoral arterial venous fistula, femoral venous pressure, valve morphology, femoral venous reflux, and selected molecular inflammatory markers as examined by immunohistochemistry were studied. In this model, Daflon 500 mg reduced reflux through veins that were subjected to profound venous hypertension. In the same model, several indicators of the ensuing inflammatory reaction (adhesion molecule expression, leukocyte infiltration) were reduced by Daflon 500 mg. These and the level of apoptosis were influenced in a dose-dependent fashion, and revealed the ability of Daflon 500 mg to suppress damage to the valve structures. This suggests that Daflon 500 mg may have a protective effect on the venous valves in chronic conditions.

It is now acknowledged that the inflammatory cascade with resulting valvular incompetence may favor further inflammation, which leads to varicosities and venous stasis and ultimately the occurrence of ulcers. Through these experiments conducted at both the micro- and macrocirculatory level, Daflon 500 mg has shown its ability to block the inflammatory process.

**Vein wall changes: one of the multifaceted aspects of inflammation in CVD**

Ultimately, macrophages become the instrument of tissue damage that softens the venous wall and favors valve destruction. Venous valve failure and subsequent reflux causing venous hypertension displacally may contribute to the sustained and chronic hypertension that is responsible for leukocyte activation on the endothelium and leukocyte destruc-

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*Also registered as Alvenor®, Ardium®, Arvenum 500®, Capiven®, Detralex®, Elatec®, Fiebroprin®, Variton®, Venitol®, Vaitec®*
cell infiltration into the venous wall may have a role in the development of varicose veins. Increased expression of intercellular adhesion molecule 1 (ICAM-1) and presence of CD-68 on the endothelial surface of venous walls in patients with venous insufficiency has been proven and may be related.\textsuperscript{17,18} These findings suggest a continuing inflammatory reaction that is related to venous wall remodeling.\textsuperscript{19,20} The actual factors that activate leukocytes to inappropriate activity have not yet been identified. Certainly, cell activation increases with the severity of venous disease.\textsuperscript{4}

On the other hand, endothelial cells must be activated to allow leukocytes to migrate through the cells into the tissue.\textsuperscript{17} It is believed that endothelial stretching may induce activation of the endothelium, since, as blood flow itself is affected, fluid shear stress may also change. Fluid shear stress is a key regulatory component of endothelial cells and a reduction in shear rates leads to enhanced adhesion of leukocytes on the endothelium.\textsuperscript{2}

Hypoxia has always been thought to be part of the process of destruction of mammal strength and venous valves. That theory has been reactivated recently by Michiels.\textsuperscript{21} The Bochum study demonstrated over its 20-year progress that reflux precedes varicose veins.\textsuperscript{22} Also, angiographic observations by Van Cleef has demonstrated venous valve lesions in young individuals. It is felt that these early lesions could not be explained by venous wall disease.\textsuperscript{23,24} Many believe that genetic defects are the cause of varicose veins in most families.\textsuperscript{25,26} In line with the observations about a genetic influence, it has been found that a deficiency in collagen type III has been demonstrated in cultured venous smooth muscle cells from patients with varicose veins.\textsuperscript{27} This defect was generalized in different tissues in the same patients. There is also a genetic influence on the alteration of remodeling in venous valves.

**Daflon 500 mg: is it protective against the enzymatic degradation of the venous wall?**

It has been hypothesized that a key event in the inflammatory cascade is the enzymatic degradation by metalloproteinases (MMP) of the valve leaflets and venous wall.\textsuperscript{28,29} The previous rat femoral fistula model with venous hypertension was set up in order to examine the MMP in veins exposed to elevated pressures up to 6 weeks. Zymography shows increased activity of pro–MMP-2 at 3 and 6 weeks. MMP-2 and MMP-9 activity was predominantly observed on day 7 and 21 after creation of the fistula. The degree of extracellular matrix remodeling correlates with the morphological finding of macroscopic lesions. This suggests that MMP-2 and MMP-9 activation is present in veins already days after exposure to elevated blood pressure and coincides with periods of early alterations of the valve morphology and early forms of reflux (unpublished results). Pharmacological intervention with Daflon 500 mg aimed at blocking MMP activation may have promise in delaying or even preventing venous wall degradation.

**Daflon 500 mg: effective right from the early symptoms of CVD**

Although symptoms are acknowledged to occur, little is known about the cause of such symptoms. Some believe capillary leakage that results in tissue edema may be painful because of pressure exerted on nerve endings.\textsuperscript{29} During the period of macroscopic changes, veins are subjected to stretching and remodeling that most probably affects C nociceptors in the venous wall, providing an explanation for the pain that is present right from the onset. C fibers are nonmyelin nerve endings located inside the vein wall and are in connection with C nociceptors that are sensitive to chemical stimuli.\textsuperscript{29} It is believed that pain from CVD may come from such fibers. Inflammatory mediators released after endothelial activation may be the cause of stimulation of C nociceptors. Platelet-activating factor, prostaglandins, leukotrienes, bradykinin, histamine, and serotonin are able to lower the threshold of activation of C nociceptors. It is thought that pain related to CVD might mirror the endothelial activation with the cascade of inflammatory mediators released early in the disease process.

Despite the fact that mechanisms causing symptoms are not understood or have not been elucidated, it is widely reported that symptoms appear at the onset of venous insufficiency even before reflux and the appearance of varicose veins. The CEAP classification contains a C0 clinical class to include those patients with venous symptoms but without obvious venous insufficiency. In recent international studies of CVD patients, using overall symptom severity scores, assessed by a validated, disease-specific questionnaire\textsuperscript{30} or in which the presence of symptoms was simply reported,\textsuperscript{31} a significant correlation between CEAP clinical class and venous symptoms was shown.

In one double-blind, placebo-controlled, randomized study\textsuperscript{32} including 40 patients with CVD, several symptoms were considered, classified into “functional” symptoms (functional discomfort, leg heaviness, pain, fatigue when standing, night cramps, paresthesia, burning sensation, itching) and “objective” symptoms (sensation of edema in the evening, redness and cyanosis, sensation of heat, and sensation of skin induration). Each parameter was quantified by the patient on a 4-point scale according to the intensity and repercussion on daily activities. Global scores were calculated for functional and “objective” symptoms. In the Daflon 500 mg group, the results demonstrated after a 2-month period of treatment significantly better improvement in global ($P<0.001$ for “functional” score and $P=0.034$ for “objective” symptom score) and separated symptom scores ($P$ different depending on the symptom, from $P=0.001$ for functional discomfort to $P=0.033$ for sensation of burning). In this trial, the presence of venous disease and treatment effi-
cacy were confirmed by testing parameters using strain gauge plethysmography and edema measurement.

Another double-blind, placebo-controlled, randomized study33 included 160 symptomatic patients with CVD related to postthrombotic syndrome (24 patients), primary varicose veins (59 patients), or others (77 patients). Patients were equally distributed into 2 groups and treated either with placebo or with Daflon 500 mg, 2 tablets daily for 8 weeks. Evaluation of venous symptoms was the primary end point of the study. Each symptom (functional discomfort, heaviness, pain, night cramps, sensation of swelling, paresthesia, redness and/or cyanosis, sensation of heat and/or burning) was rated 0 (no symptom), 1 (moderate symptom without repercussion on daily activities), 2 (appreciable symptom but allowing daily activities), or 3 (severe symptom, causing discomfort or hampering daily activities). At the end of the study and compared with the placebo group, the changes in the symptoms were significantly better in the Daflon 500 mg group (Table I) (from P<0.001 for functional discomfort, sensation of heaviness, and sensation of swelling; up to P=0.027 for pain; the only symptom without significant improvement was redness/cyanosis). These changes were significant after 4 weeks of treatment for the functional discomfort, sensation of heaviness, nocturnal cramps, and sensation of swelling. Improvement in other objective parameters of edema and trophic skin changes paralleled the improvement in symptoms.

The Reflux assEssment and quaLity of lIfe im-...
present the initial inflammatory signal that results in leukocyte recruitment and migration into the dermis.

A cascade of pathological events occurs during leukocyte migration into the dermis and the end product of these is dermal fibrosis. One of the pathological events is an increase in transforming growth factor \( \beta_1 \) (TGF-\( \beta_1 \)), which is either released by macrophages and mast cells or autoinduced by dermal fibroblasts. An increase in TGF-\( \beta_1 \) causes an imbalance in tissue remodeling resulting in increased collagen synthesis and affecting matrix MMPs as well as tissue inhibitors of MMPs (TIMPs). It is hypothesized that an imbalance in MMPs and their regulation may cause, or contribute to, venous ulcer formation.

There is some evidence that the severity of venous reflux may be related to the risk of ulceration in patients with CVD. Some believe that there is a linear relationship between the severity of skin changes such as ulceration and ambulatory venous pressure (AVP). Sustained venous hypertension may indeed be linked to skin changes in the Basle study long term (11-year follow-up of individuals revealed the fact that 50% of individuals developed chronic venous insufficiency complications if they entered the study with severe varicose veins; 20% of these developed ulceration. This is in contrast to 0.8% for the development of ulceration in the individuals who entered the study period with mild chronic venous insufficiency). It is recognized that 57% to 80% of individuals with leg ulcer have severe venous disease.

**Daflon 500 mg accelerates leg ulcer healing**

In three randomized, controlled, multicenter trials, 2 tablets of Daflon 500 mg daily plus standard venous leg ulcer management was compared with standard venous leg ulcer management alone (n=140 and 150, respectively) or in addition to placebo (n=107). The group receiving Daflon 500 mg had a significantly higher ulcer healing rate than the other group (Table II). In the study by Glinski et al., the time to achieve complete healing was significantly shorter in the Daflon 500 mg group (137 days compared with 166 days in the control group \( P=0.042 \)), and a significantly larger number of patients had complete ulcer healing during the study with Daflon 500 mg (64.6%) in comparison with the control group (41.2%; \( P=0.04 \)).

A meta-analysis of randomized prospective studies using Daflon 500 mg in addition to conventional treatment confirmed the previous results. Five prospective, randomized, controlled studies in which 723 patients with venous ulcers were treated between 1996 and 2001 were included in the analysis. Conventional treatment (compression and local care) in addition to Daflon 500 mg was compared with conventional treatment plus placebo in 2 studies (n=309), or with conventional treatment alone in 3 studies (n=414). The primary end point was complete ulcer healing at 6 months. The results were expressed as reduction in the relative risk (RRR) of healing which should be positive to indicate a benefit of adjunctive Daflon 500 mg over conventional therapy alone. At 2 months, results were statistically significant and the chance of ulcer healing was 44% better in patients treated with adjunctive Daflon 500 mg than in those managed by conventional therapy alone (RRR=44%; confidence interval [CI], 7%-94%, \( P=0.015 \) (Figure 3).

**Table II. Published studies demonstrating efficacy of Daflon 500 mg in ulcer healing**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Number of patients</th>
<th>Trial design*</th>
<th>Period (months)</th>
<th>Control ulcer size (cm)</th>
<th>Daflon 500 mg Control</th>
<th>Daflon 500 mg Control</th>
<th>Time to complete ulcer healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guilhot</td>
<td>107</td>
<td>Placebo</td>
<td>2</td>
<td>≤10</td>
<td>31.8</td>
<td>12.8†</td>
<td>0.028</td>
<td>Shorter time 0.037</td>
</tr>
<tr>
<td>Glinski</td>
<td>140</td>
<td>Open</td>
<td>6</td>
<td>&lt;3; 3-6; &gt;6</td>
<td>46.5</td>
<td>27.5</td>
<td>&lt;0.05</td>
<td>-</td>
</tr>
<tr>
<td>Roztocil</td>
<td>150</td>
<td>Open</td>
<td>6</td>
<td>≥2; ≤10</td>
<td>64.6</td>
<td>41.2†</td>
<td>0.004</td>
<td>137 days 166 days† 0.04</td>
</tr>
</tbody>
</table>

* Micronized purified flavonoid fraction 500 mg, 2 tablets daily, in association with standard therapy.
† Control group: placebo + standard therapy.
‡ Control group: standard therapy alone.

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**Figure 3.** Increasing chance (expressed as reduction in the relative risk) of ulcer healing at 2 months in randomized controlled trials (RCT) comparing Daflon 500 mg with control.

Abbreviations: CI, confidence interval; E, expected number of healed patients; N, total number of patients; O, observed number of healed patients; V, variance.

This difference was present at month 6 (RRR=32%; CI, 3%-70%; P=0.0035), and was associated with a shorter time to healing (16 weeks vs 21 weeks; P=0.0034) (Figure 4).

The benefit of Daflon 500 mg was found in the subgroup of ulcers between 5 and 10 cm² in area (RRR=40%; CI, 6%-87%), as in patients with ulcers of 6 to 12 months’ duration (RRR=44%; CI, 6%-97%). These results confirm that venous ulcer healing is accelerated by Daflon 500 mg treatment. Daflon 500 mg might be a useful adjunct to conventional therapy in large and long-standing ulcers which might be expected to heal slowly.

Conclusion

While molecular mechanisms of CVD are becoming understood, many questions remain unanswered as to why progression from symptoms to reflux to varicose veins and eventually to ulcer does not progress at the same rate or in all patients. Despite this, the role of activated leukocytes in the cascade of inflammation that results in valvular incompetence and thus may greatly contribute to the etiology of varicose veins as well as to the skin changes and ultimately ulceration is now better known. Daflon 500 mg has evidenced its ability to delay and even block the inflammatory reaction at both levels: macro- and microcirculation. The clinical consequences of such findings may be important. This opens new prospects for further studies confirming the ability of their compound to better protect patients against the progression of this chronic state.

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La maladie veineuse chronique (MVC) englobe l’ensemble des troubles cliniques (symptômes ou/et signes) attribués aux veines des membres inférieurs qui évoluent sur un mode chronique. C’est une maladie qui peut aboutir à des complications très sévères. Les symptômes peuvent être présents à tous les stades de la maladie. Les mécanismes qui président à la progression de cette maladie sont loin d’être élucidés et nombre de théories ont été avancées. Les études récentes suggèrent que l’atteinte primaire des valves veineuses pourrait être un phénomène acquis et ne résulterait pas seulement d’une prédisposition génétique. En effet, on a récemment montré que ce sont les leucocytes qui sont au cœur du problème. Une fois activés, les leucocytes migrent massivement vers la surface proximale des valves veineuses, adhèrent à l’endothélium, puis s’infiltrent dans les tissus sous-jacents conduisant à la destruction progressive de l’appareil valvulaire. La mise au point de modèles expérimentaux d’hyperpression veineuse chez l’animal a permis de mieux comprendre comment ces phénomènes sont générés: les perturbations de l’hémodynamique veineuse sont associées à une réaction inflammatoire au niveau des valves, entrainant une incompétence de ces dernières puis un reflux. Ces événements engendrent une hyperpression veineuse à l’origine des manifestations cliniques de la maladie. Parmi les veinotoniques disponibles, Daflon 500 mg est le seul à avoir démontré une action protectrice sur la valve veineuse se traduisant par une diminution du reflux veineux sur un modèle animal. Les phénomènes inflammatoires qui président au remodelage des valves et parois veineuses et conduisent à l’incompétence valvulaire et à l’apparition des varices font intervenir de nombreux acteurs tels que l’interaction endothélium/leucocyte induisant une activation leucocytaire, les mastocytes, les macrophages ou les fibroblastes. Les médiateurs de l’inflammation induisent une cytotoxicité des cellules endothéliales et un endommagement du tissu et des structures sous-jacents. C’est en limitant, voire bloquant, l’interaction endothélium/leucocyte et l’activation leucocytaire à l’origine de l’inflammation que Daflon 500 mg protège les tissus contre l’action des médiateurs, comme prouvé sur des modèles animaux. De la même façon, Daflon 500 mg protège la microcirculation des médiateurs inflammatoires en bloquant l’interaction endothélium/leucocyte au niveau des capillaires. Ce mode d’action contribue à expliquer l’action anti-oedémateuse de Daflon 500 mg et sa capacité à accélérer la cicatrisation des ulcères veineux. L’efficacité de Daflon 500 mg à tous les stades de la maladie veineuse chronique a été démontrée, en particulier sur les symptômes, l’œdème veineux et la cicatrisation de l’ulcère. Une méta-analyse des études de Daflon 500 mg dans la cicatrisation de l’ulcère a confirmé qu’un traitement associant Daflon 500 mg à une compression accélérerait la guérison. L’association de Daflon 500 mg à un traitement standard était d’autant plus bénéfique que les ulcères étaient plus larges (>5 cm²) et plus anciens (>6 mois). Daflon 500 mg, grâce à son mode d’action unique, est le traitement de première intention des symptômes et de l’œdème d’origine veineuse quel que soit le stade de la maladie. Dans l’ulcère veineux de jambe, Daflon 500 mg peut être associé à un traitement standard pour accélérer la cicatrisation.
PREVALENCE, RISK FACTORS, AND CLINICAL SIGNIFICANCE OF VENOUS SYMPTOMS

Interview with P. H. Carpentier, France

What is the significance of symptoms in chronic venous disorders?

Chronic venous disorders (CVD) constitute an important cause of discomfort and disability that is widespread in industrialized countries, and venous symptoms are the principal reason for seeking medical help in patients with this condition. However, the medical literature regarding venous symptoms is scarce and shows several apparent contradictions that may seem disconcerting. Here, I would like to bring together the documented facts regarding these venous symptoms in order to clarify their medical significance.

Characterizing venous symptoms is not straightforward and this difficulty leads to a substantial part of the misunderstanding. They are reported in the clinical, etiological, anatomical, pathophysiological (CEAP) classification as “lower extremity aching, pain, and skin irritation” and most usually described as sensations of heaviness or swelling in the legs influenced by the standing position. Indeed, it is difficult for the patient to find the right words for a satisfactory description of the kind of perceptions he or she feels, and in addition to heaviness and swelling, other descriptions such as sensations of tension, aching, congestive pain, and “tired legs” are encountered.

In contrast to the type of symptoms, the location of these symptoms is consistently reported as the lower leg, and the associated circumstances are more reproducible and include the influence of:

- the standing position, which is often considered as a trigger, and associated with a usual increase in symptoms during the course of the day;
- immobility, especially when combined with the orthostatic position such as in standing still and the prolonged sitting position;
- environmental temperature, with a worsening of symptoms by warmth and frequent relief by exposure to cold.

Other associated symptoms are sometimes found in addition, and include:

- itching restricted to the ankle area or the lower leg;
- phlebalgia, ie, pain restricted to the very site of a superficial, most often varicose vein, exacerbated by palpation;
- “impatient legs,” a distinct kind of discomfort requiring the patient to move his or her legs, with no uncontrolled movements such as in the classic restless legs syndrome, but often considered as a minor form of it;
- sensation of heat;
- and cramps.

How reliable is the correlation between symptoms and venous disorders?

Since the Basel study, “venous symptoms” have been considered in the medical literature as rather unspecific and only weakly related to CVD. Actually, in their pioneering work, Widmer et al showed that approximately two thirds of subjects with varicose veins, but also one third of those without varicose veins, complained of leg symptoms. Two comments have to be made on this traditional view. First, this view does not take into account patients with venous symptoms only (C0s) and no demonstrable venous dysfunction; however, the introduction of a descriptor Pn in the CEAP classification recently produced a shift in this point of view, since patients with C0sEpA0Pn are now included in the group of subjects with CVD. Second, most publications describe the symptoms only according to their type and do not from 30% to 55%, with a clear predominance in women. Besides female sex, varicose veins and trophic skin changes are the most important risk factors for venous symptoms, but the strongest association is found with the presence of pitting edema. Prolonged sitting or standing position at work is also a significant risk factor. There is a crucial need for further clinical studies on these symptoms, using careful characterization based upon a comprehensive description of signs and symptoms.

Keywords: Epidemiology; chronic venous disorders; venous insufficiency; varicose veins; leg symptoms; venous symptoms

Address for correspondence: Professor Patrick H. Carpentier, Centre de Recherche Universitaire de La Léchère, F-73260 Aigueblanche, France (e-mail: Patrick.Carpentier@ujf-grenoble.fr)
take into consideration other features such as location and associated circumstances. In the Edinburgh Vein Study, Bradbury et al. analyzed the relationship between the presence of varicose veins and the prevalence of leg symptoms taken one by one. They found a significant but weak relationship for itching in both sexes, for heaviness or tension and for aching in women only, and concluded that most lower-limb symptoms probably have a nonvenous cause, even in the presence of varicose veins. However, they only took into account the type of symptom and not the associated circumstances; no analysis testing the association of symptoms was reported.

In a second paper, they documented a significant relationship between venous reflux and certain symptoms only (heaviness/tension and itching for isolated superficial reflux in women; feeling of swelling, cramps and itching in men, aching and cramps in women with combined superficial and deep vein reflux). Again, only the type of symptom as the description proffered by the patient was taken into account, which could explain the apparent inconsistency of the results, when comparing the results obtained in men and women, and people with only superficial and those with combined superficial and deep venous reflux.

However, in a third analysis of the same study, Ruckley et al. found a significant correlation between the severity grades of CVD (assessed according to the Widmer classification) and the prevalence of heaviness/tension, feeling of swelling, aching, and itching.

We also found such a correlation between the severity of CVD (CEAP “C” classes) and the prevalence of venous symptoms in both a population-based study and in a clinic-based patient series, and a correlation between the severity of the symptoms and the CEAP “C” classes was also shown by Kahn et al.

Indeed, in a recent study comparing symptoms in the lower limbs reported by patients with documented chronic venous disease with those of patients with rheumatological, arterial, or neurological problems affecting the lower limbs, we found that a combination of a few features of venous symptoms as described above was able to produce a diagnostic score with a potentially high discriminating value for CVD (Table I). Whether this score is efficient enough for a practical use remains to be assessed in a “real life” clinical setting, but this study already shows that characterizing venous symptoms for studies involving group comparisons is feasible.

### Table I. Diagnostic scoring system for venous symptoms. The number of the criteria validated (0 to 4) among those listed increases with the likelihood of a venous origin of symptoms which is only 6% when the score is 0 or 1, and 95% when the score is 3 or 4.

<table>
<thead>
<tr>
<th>Type</th>
<th>Prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling of heaviness or of swelling</td>
<td>Any kind</td>
</tr>
<tr>
<td>Associated with a sensation of itching, and/or restless legs, and/or pain in the place of superficial visible veins</td>
<td>Any kind</td>
</tr>
<tr>
<td>Worsened by warmth and/or improved by cold</td>
<td>Any kind</td>
</tr>
<tr>
<td>Improved or at least not worsened by walking</td>
<td>Any kind</td>
</tr>
</tbody>
</table>

We can conclude that despite some discrepancies in the literature, characterization of venous symptoms is possible, but we really need more studies using a comprehensive approach not only of the type, but also of the other characteristics of the symptoms in different clinical settings, in different countries, languages, and cultures before universally acceptable criteria can be defined.

### Tell us about the actual prevalence of venous symptoms and the risk factors for venous disease

The prevalence of venous symptoms can only be derived from population-based studies, but most studies of this nature were restricted to varicose veins and to skin trophic changes, and scarce data are available regarding venous symptoms in the general population. These data, obtained from 5 different European countries, is summarized in Table II. It shows that a large proportion of adults (30% to 55%) complain about such discomfort, with a substantially higher proportion of women than men.

Regarding the risk factors, besides female sex, the most prominent risk factors were the other venous disorders as discussed above: presence of varicose veins, presence of trophic skin changes, venous reflux, a history of venous thromboembolism, and the severity of the CVD as explained by the C class of CEAP. However, the strongest association was found with the presence of edema: in our epidemiological study, only one patient out of 33 with pitting edema of venous origin did not complain of venous symptoms, and in a European multicenter series of venous patients, an analysis of correspondence of every sign or symptom of CVD also showed a strong link between symptoms and edema.

Prolonged standing or sitting position was also found to be a significant risk factor for venous symptoms, both in occupational surveys, and in our epidemiological study in the general population.

Testing the influence of other factors such as age, overweight, and estrogen treatment gives conflicting results, and no clear evidence can be drawn from the study of the literature on this question. Although they are the most common cause for seeking medical help in pa-
tients with CVD and are linked to im-
paired quality of life, and despite the fact 
that they are amenable to effective med-
ical therapy, venous symptoms remain 
poorly studied. However, the available 
data already quite clearly show that their 
prevalence is high in the general popu-
lation, that they are linked to demonstrable 
venous dysfunction in most but not in 
all patients, and that it is possible to char-
acterize them from the point of view of 
signs and symptoms. The most obvious 
conclusion of this interview is that there 
is a crucial need for further clinical stud-
ies on these symptoms, using careful 
characterization based upon a compre-
hensive description of clinical signs and 
symptoms.

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The clinical, etiological, anatomical, pathophysiological (CEAP) classification has made important strides toward international consensus in standardizing descriptions of venous conditions and grading venous disorders. However, it has, to some extent, put the cart before the horse because basic definitions and terminology have yet to be agreed.

The possibility of unifying the definitions and terminology of venous disease is an attractive challenge. Inappropriate or ambiguous terms need to be set aside in favor of terms with explicit and precise meanings. The aim is to arrive at an agreed lexicon of acute and chronic venous conditions. The purpose of this article is not to pronounce on what the correct terminology should be but rather to point out some of the areas in which our current terminology does not serve us well and to suggest the principles upon which more appropriate definitions should be based.

We are in an era of medical rationalization and consolidation. Consequently we are forced to better define and standardize the tools of our trade. One basic tool is terminology. Important among the forces driving us to revise medical terminology are the relatively recent emphasis on evidence-based medicine, quality assurance, and the setting of international standards in medical care. A less obvious but probably more compelling driving force is economics. It is difficult to place a value on a product or a service if there is no agreement on how it should be named and defined.

It was fitting, in the early days of acquisition of knowledge of venous disease, that anatomical features, physiological and chemical processes, diseases, and techniques were identified by the names of their discoverers, for whom affection and respect is still harbored. Gradually, eponymous nomenclature has given way to more appropriate descriptive terms.

This would be an important step forward were it not for duplication and different understanding as to what is meant by many of our current medical terms. In today’s world, there is a universal and, in this author’s view, an often counterproductive obsession with change. However, we might sidestep that issue by suggesting that what is required is rationalization and clarity rather than change for the sake of change.

Most clinicians are no doubt perfectly comfortable with the terminology that they employ within their own clinical practices and institutions. Difficulties arise when the scientific net is cast wider, particularly when attempting to compare data in studies of epidemiology, clinical trials, clinical registers, and quality assurance.

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The current appreciation of the importance of evidence-based medicine and of quality assurance has made it necessary for us to standardize the way we describe conditions. Such initiatives as the clinical, etiological, anatomical, pathophysiological (CEAP) classification have made important strides in the classification of venous conditions. However, at a more basic level, there is no consensus on terminology. There is a need to move away not merely from eponymous nomenclature but also from terms that lack specificity and mean different things in different parts of the world. We need, for example, to distinguish between venous conditions, disorders, anomalies, and diseases. Among the terms that merit review are: chronic venous disease, chronic venous insufficiency, postthrombotic syndrome, postphlebitic syndrome, lipodermatosclerosis, and primary and secondary varicose veins. There are doubtless many others. The purpose of this article is to highlight the problem and to suggest principles upon which agreement on terminology might be reached.

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Keywords: venous disease; classification, nomenclature; varicose veins; venous thrombosis; postthrombotic syndrome; lipodermatosclerosis

Address for correspondence: Professor C. V. Ruckley, 1 Mayfield Terrace, Edinburgh EH9 1RU, United Kingdom (e-mail: ruckley@msn.com)
Conditions, disorders, and diseases

Let us start with the collective terms. All chronic venous conditions are not necessarily diseases. Epidemiological studies confirm that venous abnormalities are so common and so closely related to advancing age as almost to be considered the norm. Conversely, symptoms conventionally attributed to venous disease commonly occur in individuals in whom there is no apparent venous pathology. In recognition of this fact, some authors when writing about the characteristics of venous conditions encountered in epidemiological studies have preferred the term disorder (Table I), in order to include conditions that neither give rise to specific symptoms nor have a significant deleterious effect on the well-being of the individual.

The authors of the CEAP classification prefer the term “chronic venous disorders” as encompassing “the full spectrum of morphologic and functional abnormalities of the venous system, from telangiectasia to venous ulcers.”

It can be argued that the term disorder is not entirely appropriate, since it is defined as disarray, disturbance, or deviation from health, whereas conditions that we may wish to include in our classification can simply be asymptomatic abnormalities of morphology, anatomical variants or conspicuous configurations of a nonpathological venous system which do not create illness or disability. Examples of abnormalities that do not significantly impair physiological function would be some varieties of congenital venous anomalies, telangiectasias, and reticular veins. If a classification includes these conditions, it is not strictly a classification of disease or disorder.

Given that classifications normally progress from the general to the particular, condition is the least specific term, disorder conveys an abnormal arrangement but not necessarily a pathological one, while disease indicates a clinically significant pathological change. Chronic venous conditions may therefore be a more suitable option for a nonspecific title to head a general phlebological classification.

Chronic venous disease

The term chronic venous disease has been equated implicitly or explicitly in many publications with those types of venous diseases associated with chronic ambulatory venous hypertension (CAVH), ie, varicose veins, chronic venous insufficiency, postthrombotic syndrome (PTS), and chronic venous leg ulcer. However, a number of chronic venous diseases are not necessarily associated with venous hypertension including certain venous anomalies, neoplasms, telangiectasias, and aneurysms. Perhaps classifications should more explicitly identify, or relate to, the mechanisms by which venous conditions arise.

Venous anomaly

The word anomaly is used rather differently in medical than in nonmedical contexts. In English-language medical publications and routine medical usage, the word anomaly is not used to indicate a disease or disorder, but rather it refers to a deviation from anatomical normality. Thus it is seldom used in clinical practice except when referring to congenital anomalies, in other words, developmental vascular malformations. Indeed, these 2 terms appear to be used interchangeably. Anomaly would thus encompass conditions ranging through simple vessel duplication to complex arteriovenous-lymphatic malformations. With the introduction of the Hamburg system, the classification of these conditions has improved considerably. Perhaps the collective terminology could also be unified?

Chronic venous insufficiency

Many authors endow this term with mechanical or functional connotations, applying it specifically to patients shown to have venous valvular incompetence (reflux). According to this approach, it must therefore include patients with primary uncomplicated varicose veins, however trivial.

In publications of epidemiological studies from Edinburgh, we have followed the lead of Widmer and others who have used this term in a more general sense as meaning a clinical syndrome manifesting as the sequelae, in the skin and subcutaneous tissues, of CAVH. The patient, to qualify for this label, must have evidence of venous hemodynamic dysfunction coupled with the stigmata of CAVH, ie, lipodermatosclerosis.

The authors of the CEAP classification have adopted a similar approach: “The term chronic venous insufficiency implies a functional abnormality of the venous system and is usually reserved for more advanced disease, including edema (C3), skin changes (C4), or venous ulcers (C5-6).”

Both approaches can be criticized. Many patients with incompetent (insufficient) valves and chronic varicose veins, with or without skin changes, have evidence of previous deep venous thrombosis (DVT) on duplex scanning or phlebography. The hemodynamic dysfunction will therefore in many cases include an obstructive component as well as valvular insufficiency. If used simply to describe hemodynamic dysfunction, the term chronic venous insufficiency implies a level of pathological precision that is not justified. Reflux is a more specific term.

In routine clinical practice, relatively few patients presenting with lipodermatosclerosis or chronic leg ulcer will receive a sufficiently detailed laboratory assessment to allow quantitative attribution...
of their hemodynamic dysfunction to valvular incompetence versus obstruction. On the other hand, the use of the term chronic venous insufficiency to describe a clinical syndrome comprising unspecified venous dysfunction with lipodermatosclerosis also fails the test of descriptive accuracy and clarity. It says nothing that relates to skin complications. We need to decide which of these meanings we wish to endorse or to whether to coin new and more germane terminology.

**Postthrombotic or postphlebitic syndrome**

In general clinical usage, one finds that these terms are often applied loosely and inappropriately, particularly in patients who have not been proven ever to have suffered from DVT. However, in this author’s view, they are terms that deserve high marks as aptly embodying the principles we seek, that is, they provide certain information explicitly and succinctly. In three words they tell us a great deal, ie, that the patient suffers from an array of symptoms and signs that have followed an acute episode of thrombosis. Admittedly, postthrombotic syndrome (PTS) could describe an arterial condition whereas postphlebitic syndrome (PPS) leaves no doubt that we are talking about veins, and on that criterion the latter scores the higher marks. But to further muddy the waters, phlebitis, at least in UK practice, is only used in the context of superficial phlebitis.

The pattern of symptoms and signs in this syndrome will depend on to what extent they are caused by valve reflux or obstruction. They may range from venous claudication to chronic leg ulcer. Furthermore, the onset of certain manifestations of PTS/PPS such as venous claudication, cyanosis, swelling, discomfort, and tiredness may commence at the time of the DVT or may only emerge in the form of lipodermatosclerosis many years later. The former pattern blurs the distinction between the acute and chronic features of DVT, while the latter is a slowly emerging chronic condition — two very different clinical scenarios.

It is an important principle that patients should not be labeled as having PTS or PPS unless they have been shown by objective means to have sustained valvular or obstructive damage due to previous DVT. The practical difficulty of doing this in many cases is a testimony of our frequent failure to investigate suspected DVT effectively in its acute stage or later.

Once it has been objectively established that a patient has deep vein damage and has had proven DVT, it is reasonable to attribute an array of signs and symptoms to that cause. This might include chronic swelling, the tired, heavy aching leg, venous claudication, and lipodermatosclerosis including ulceration.

**Lipodermatosclerosis**

Lipodermatosclerosis is a term that can be commended as compressing a great deal of information into the minimum number of words, in this case, a single neologism. The term was coined by Browse in 1983. It embodies a sclerosing condition affecting the skin and subcutaneous tissues. However, it is not always clear how much pathology lipodermatosclerosis encompasses. It refers to an inflammatory process secondary to ambulatory venous hypertension, which is usually chronic but in its early stages often takes the form of an aggressive acute inflammatory reaction affecting the skin and subcutaneous tissues. In this form, it may be difficult to distinguish from other acute inflammatory conditions such as cellulitis or superficial thrombophlebitis.

In Browse’s view, lipodermatosclerosis encompassed in its acute stage erythema, pain, tenderness, and heat. In its chronic stage, he lists induration, contraction of the skin and subcutaneous tissues, pigmentation, scarring from healed ulceration, and subcutaneous calcification. It leads to the “champagne bottle leg,” stiffness of the ankle joint, and shortening of the Achilles tendon. In describing lipodermatosclerosis, Browse et al considered it a preulcer condition. Without treatment, the natural history of the condition is that lipodermatosclerosis will inevitably progress to ulceration. It would therefore seem logical to include ulceration as an intrinsic part of the pathological process of lipodermatosclerosis.

The definition of lipodermatosclerosis provided with the CEAP classification is as follows: “Localized chronic inflammation and fibrosis of skin and subcutaneous tissues of lower leg, sometimes associated with scarring or contracture of Achilles tendon.” Lipodermatosclerosis is sometimes preceded by diffuse inflammatory edema of the skin, which may be painful and which often is referred to as hypodermatitis. It must be differentiated from lymphangitis, erysipelas, or cellulitis by their characteristically different local signs and systemic features. Lipodermatosclerosis is a sign of severe chronic venous disease.

The 2004 revision of the CEAP classification, C4 is divided into 2 categories “to better define the differing severity of venous disease”:

- C0 No visible or palpable signs of venous disease
- C1 Telangiectasies or reticular veins
- C2 Varicose veins; distinguished from reticular veins by a diameter of 3 mm or more
- C3 Edema
- C4a Pigmentation or eczema
- C4b Lipodermatosclerosis or atrophie blanche
- C5 Healed venous ulcer
- C6 Active venous ulcer

I have quoted these publications in detail to illustrate a practical difficulty. By separating pigmentation, eczema, and healed ulceration from lipodermatosclerosis, CEAP has altered the original definition of the condition. Lipodermatosclerosis was coined as a collective term for the manifestations of the inflammatory process induced by CAVH. It can therefore be argued that it should comprise all the clinical manifestations by which we recognize that process, namely pigmentation, induration, swelling, inflammation, dermatitis (eczema), scarring, contracture, subcutaneous calcification,
atrophie blanche, and ulceration, whether healed or unhealed. Evidently a collective term such as lipodermatosclerotic causes difficulty when included in a classification whose other categories comprise readily identifiable unambiguous individual conditions.

**Primary and secondary varicose veins**

These terms should not cause any confusion but in practice they often do. For example, it is not uncommon to see varicose veins that have received no previous treatment or the veins of newly referred patients referred to as primary varicose veins while the term secondary is sometimes used as synonym with recurrent. They are strictly pathological terms. Primary varicose veins are the inherited variety or those that have developed without any obvious causative disease process. Secondary varicose veins are the consequence of a preexisting disease process such as thrombosis, trauma, arteriovenous fistula, or other causes of venous obstruction.

The reader will no doubt be able to identify further examples of descriptive terms which merit review. It is time we put venous definitions and terminology under the spotlight, in the hope that comprehension of scientific data may be accompanied by an equivalent measure of comprehension as to exactly what conditions we are talking about.

**REFERENCES**


**VERS UNE MEILLEURE DÉFINITION DE LA MALADIE VEINEUSE CHRONIQUE**

L’évaluation actuelle de l’importance de la médecine basée sur les preuves et de l’assurance qualité nous a poussés à standardiser la façon dont nous définissons nos pathologies. Des initiatives comme la classification CEAP (Clinique, Étiologique, Anatomique et Physiopathologique) ont permis de faire un grand pas dans la classification de la pathologie veineuse. Cependant à un niveau plus basique, il n’y a aucun consensus sur la terminologie. Il faut s’écarter, pas seulement de la nomenclature patronymique mais aussi des termes qui manquent de spécificité et qui veulent dire des choses différentes dans différentes parties du monde. Par exemple nous avons besoin de distinguer pathologies, troubles, anomalies et maladies veineuses. Parmi les termes qui nécessitent d’être étudiés on trouve : maladie veineuse chronique, insuffisance veineuse chronique, syndrome postthrombotique, syndrome postphlébitique, hypodermite scléreuse et varices primaire et secondaire. Et il y en a sans doute beaucoup d’autres. Le but de cet article est de souligner le problème et de suggérer les principes grâce auxquels on peut aboutir à un accord sur la terminologie.
Revision of the CEAP Classification
10 Years After Its Introduction in 1994

by B. Eklöf, Sweden

In issue 79 of Medicographia, there was an excellent review on “Venous disorders and evidence-based medicine” where several experts discussed the clinical, etiological, anatomical, pathophysiological (CEAP) classification of chronic venous disorders (CVD). Ramelet stated that evidence-based medicine has had little impact on CVD studies to date, where one of the probable reasons was the absence of a consensus classification, an omission that the CEAP system should succeed in rectifying, especially after further revision of classes C1 to C4.

Classification of diseases is a basic instrument for uniform diagnosis and meaningful communication about the disease. In CVD, reliance has for too long been placed on the clinical appearance of the superficial effects of CVD, such as spider veins, varicose veins, swelling, skin changes, and ulcerations without requiring accurate objective testing of the venous system to substantiate the diagnosis. This practice has caused errors of diagnosis and has been largely responsible for the poor correlation of results between treatment methods. There have been several classifications in the past that have added to our understanding of CVD but all lack the completeness and objectivity needed for scientific accuracy.

The Tower of Babel was created by the followers of Noah to reach heaven, but the Lord punished the arrogant people by splitting their common language and spreading them from Babylon all over the world. The American Venous Forum (AVF) has tried to tear down this Tower of Babel and create the clinical, etiological, anatomical, pathophysiological (CEAP) classification as a common language for chronic venous disorders (CVD) which previously suffered from a lack of precision in description. This deficiency led to conflicting reports in studies of CVD, at a time when new modalities were being offered to improve treatment for simple as well as more complicated venous diseases. It was believed that these conflicts could be resolved by precise diagnosis and classification of the underlying venous problem. At the 6th annual meeting of the AVF on Maui in 1994, an international ad hoc committee chaired by Andrew Nicolaides with representatives from Australia, Europe, and the United States developed the first CEAP consensus document. The classification was based on clinical manifestations (C), etiological factors (E), anatomical distribution (A), and the underlying pathophysiological findings (P). The CEAP consensus was published in 26 journals and books, and translated into 9 languages. Today, most published papers on CVD use all or portions of the CEAP. The diagnosis and treatment of CVD is developing rapidly and the need for a revision was obvious. In 2002, an ad hoc committee of the AVF was appointed to review the classification and make recommendations for change by 2004, 10 years after its introduction. An international ad hoc committee was also established to assure continued utilization. The committees held four meetings revising the document, which was published in Journal of Vascular Surgery in December 2004. The recommended changes include: (i) refinements of several definitions used in describing the CEAP; (ii) refinement of the C classes of the CEAP; (iii) addition of the descriptor n (no venous abnormality identified); (iv) incorporation of the date of classification and the level of investigation; (v) description of the basic CEAP introduced as a simpler alternative to the full (advanced) CEAP classification.

Keywords: chronic venous disorders; previous classifications for chronic venous disorders; CEAP classification; revision of CEAP classification

Address for correspondence: Bo Eklöf, Batteritorget 8, SE-25270 Helsingborg, Sweden (e-mail: mobokot@telia.com)
pression therapy. Could surgery or sclerotherapy be helpful? He recommended a classification based on involvement of superficial, perforator, and deep veins using objective measures such as foot volumetry and ambulatory venous pressure to discriminate between “betterable” (besserbare) and “not betterable” (nicht besserbare) patients.

Sytchev published a classification very similar to the present CEAP classification in 1985 (see Table I). The same year, Pierchalla and Tronnier suggested differentiating between primary and secondary (postthrombotic) disease, and between superficial, perforator, and deep venous disease using objective measures.

In 1988, Porter et al published reporting standards for venous disease developed by an ad hoc committee for the Society for Vascular Surgery (SVS) and the North American Chapter of the International Society for Cardiovascular Surgery (ISCVS). This was similar to the Widmer classification with the addition of etiology and anatomical distribution. This was what provided the impetus for the CEAP classification that followed later.


Etiology

- Primary venous dilatation
- Secondary (postthrombotic) occlusion and recanalization
- Congenital dysplasias

Central hemodynamics

A. Compensation
B. Decompensation
- “underloaded”
- “overloaded”

In April 2002, an ad hoc committee on the CEAP was appointed by the AVF to review the classification logically follows. It is important to stress that CEAP is a descriptive classification. Venous Severity Scoring (VSS) was developed to allow longitudinal outcomes assessment, but it became apparent that the CEAP itself required updating and modification. In April 2002, an ad hoc committee on the CEAP was appointed by the AVF to review the classification.

**Table I. Sytchev’s classification of varicose veins.**

<table>
<thead>
<tr>
<th>Stages of regional circulatory-trophic disorders:</th>
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<tbody>
<tr>
<td>I. Compensation</td>
</tr>
<tr>
<td>II. Decompensation (cyanosis, edema, cruralgia)</td>
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<table>
<thead>
<tr>
<th>Degrees</th>
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<tbody>
<tr>
<td>1. By the end of the day</td>
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<tr>
<td>2. By midday</td>
</tr>
<tr>
<td>3. At the beginning of the day</td>
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<tr>
<th>Phases</th>
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<tbody>
<tr>
<td>a. Functional trophic disorders (hyper-, hypo-, and anhidrosis of the skin)</td>
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<tr>
<td>b. Pre-ulcer condition of tissues</td>
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<tr>
<td>c. Trophic ulcers</td>
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<tr>
<th>Etiology</th>
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<tr>
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<tr>
<th>Central hemodynamics</th>
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<tbody>
<tr>
<td>A. Compensation</td>
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</tr>
<tr>
<td>- “underloaded”</td>
</tr>
<tr>
<td>- “overloaded”</td>
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</table>

**Revision of the CEAP classification**

At the 5th annual meeting of the American Venous Forum (AVF) in 1993, John Porter suggested using the same approach as the tumor node metastasis (TNM) classification for cancer in developing a classification system for venous diseases. Following a year of intense discussions, a consensus conference was held at the 6th annual meeting of the AVF in February 1994, on the island of Maui, Hawaii, at which an international ad hoc committee, chaired by Andrew Nicolaides, and with representatives from Australia, Europe, as well as the United States, developed the first CEAP consensus document. It contained two parts, a classification of CVD and a scoring system of the severity of CVD. The classification was based on clinical manifestations (C), etiological factors (E), anatomical distribution of disease (A), and the underlying pathophysiological findings (P), thus the name CEAP. The severity scoring system was based on 3 elements: the number of anatomical segments affected, grading of symptoms and signs, and disability. The CEAP consensus statement was published in 26 journals and books in 9 languages, truly a universal document for CVD.

It was endorsed by the Joint Councils of the SVS and the North American Chapter of the ISCVS, and its basic elements were incorporated into venous reporting standards. Today, most published clinical papers on CVD use all or portions of the CEAP classification.

**Revision of the CEAP**

The diagnosis and treatment of CVD is developing rapidly and the need for an update of the classification logically follows. It is important to stress that CEAP is a descriptive classification. Venous Severity Scoring (VSS) was developed to allow longitudinal outcomes assessment, but it became apparent that the CEAP itself required updating and modification. In April 2002, an ad hoc committee on the CEAP was appointed by the AVF to review the classification.
The term “CEAP” refers to the clinical, anatomical, pathophysiological classification of chronic venous diseases. This classification system is used to describe the severity of chronic venous disorders (CVD) and includes the following components:

- **Clinical** (C): represents the anatomical location of the disease.
- **Etiological** (E): describes the cause of the disease.
- **Anatomical** (A): refers to the anatomical location of the disease.
- **Pathophysiological** (P): describes the pathophysiological changes associated with the disease.

### Refinement of the CEAP Classification

The CEAP classification has been refined to improve its accuracy and applicability. Some of the changes include:

- **Refinement of C classes in CEAP**

  The essential change here is the division of class C4 into two subgroups that reflect different severities of disease. This allows for a more precise description of the disease severity.

- **Refinement of E. A. and P in CEAP**

  To improve the assignment of designations under E, A, and P, a new descriptor n is now recommended for use where no venous abnormality is identified. This n can be added to E (En, no venous etiology identified), A (An, no venous location identified), and P (Pn, no venous pathophysiology identified). Observer variability in assigning designations may have been contributed to by the lack of a normal option. Further definition of the A and P has been afforded by the new venous severity scoring system, which was developed by the ad hoc Committee on Outcomes of the AVF to compliment CEAP.

The revised CEAP classification aims to provide a more accurate and comprehensive description of chronic venous disorders, facilitating better diagnosis and treatment.

### Table II: Members of the American Venous Forum ad hoc committee on revision of the clinical, etiological, anatomical, pathophysiological (CEAP) classification.

<table>
<thead>
<tr>
<th>Name</th>
<th>Country</th>
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</thead>
<tbody>
<tr>
<td>Bo Eklöf, chair</td>
<td>Gregory Moneta</td>
</tr>
<tr>
<td>John Bergan</td>
<td>Frank Padberg</td>
</tr>
<tr>
<td>Peter Gloviczki</td>
<td>Robert Rutherford</td>
</tr>
<tr>
<td>Robert Kistner</td>
<td>Thomas Wakefield</td>
</tr>
<tr>
<td>Mark Meissner, secretary</td>
<td></td>
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</tbody>
</table>

### Table III: The International ad hoc committee on revision of the clinical, etiological, anatomical, pathophysiological (CEAP) classification.

<table>
<thead>
<tr>
<th>Name</th>
<th>Country</th>
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</thead>
<tbody>
<tr>
<td>Claudio Allegri, Italy</td>
<td>Peter Neglen, USA</td>
</tr>
<tr>
<td>Pier Luigi Antignani, Italy</td>
<td>Andrew Nicolaidis, Cyprus</td>
</tr>
<tr>
<td>Patrick Carpentier, France*</td>
<td>Hugo Partsch, Austria</td>
</tr>
<tr>
<td>Philip Coleridge Smith, United Kingdom*</td>
<td>Michel Perrin, France*</td>
</tr>
<tr>
<td>André Cornu-Thenard, France</td>
<td>Eberhard Rabe, Germany</td>
</tr>
<tr>
<td>Ermenegildo Enrici, Argentina</td>
<td>Seshadri Raju, USA</td>
</tr>
<tr>
<td>Jean Jerome Guex, France</td>
<td>Vaughan Ruckley, United Kingdom*</td>
</tr>
<tr>
<td>Shinichi Hoshiba, Japan</td>
<td>Ulrich Schultz-Ehrenburg, Germany</td>
</tr>
<tr>
<td>Arkadiusz Jarek, Poland</td>
<td>Jean Francois Uhl, France</td>
</tr>
<tr>
<td>Nicolas Labropoulos, USA</td>
<td>Martin Veller, South Africa</td>
</tr>
<tr>
<td>Fedor Lubie, USA</td>
<td>Yuqi Wang, China</td>
</tr>
<tr>
<td>Mark Malouf, Australia*</td>
<td>Zhong Gao Wang, China</td>
</tr>
<tr>
<td>Nick Morrison, USA</td>
<td>Kenneth Myers, Australia*</td>
</tr>
</tbody>
</table>

*Editorial committee

**Date of classification**

CEAP is not a static classification; the patient can be reclassified at any future point in time. Classification starts with the initial visit, but can be better defined after further investigations. A final classification may not be complete until after surgery and histopathological assessment. We therefore recommend that any CEAP classification be followed by the date, eg, C4b,S,Ep,As,p,Pr (2003-08-21).

| C0 | No visible or palpable signs of venous disease |
| C1 | Telangiectasia or reticular veins |
| C2 | Varicose veins—distinguished from reticular veins by a diameter of 3 mm or more |
| C3 | Edema |
| C4 | Changes in the skin and subcutaneous tissue secondary to chronic venous disorders (now divided into two subclasses to better define the differing severity of venous disease): |
| C4a | Pigmentation and/or eczema |
| C4b | Lipodermatosclerosis and/or atrophie blanche |
| C5 | Healed venous ulcer |
| C6 | Active venous ulcer |

Table IV. Recommended definitions applying to the clinical “C” class of the clinical, etiological, anatomical, pathophysiological (CEAP) classification.


| Telangiectasia—a confluence of dilated intradermal venules of less than 1 mm in caliber. Synonyms include spider veins, hyphen webs, and thread veins. |
| Reticular veins—dilated bluish subdermal veins usually from 1 mm in diameter to less than 3 mm in diameter. They are usually tortuous. This excludes normal visible veins in people with thin, transparent skin. Synonyms include blue veins, subdermal varices, and venulectasies. |
| Varicose veins—subcutaneous dilated veins equal to or more than 3 mm in diameter measured in the upright position. These may involve saphenous veins, saphenous tributaries, or nonsaphenous superficial leg veins. Varicose veins are usually tortuous, but tubular saphenous veins with demonstrated reflux may be classified as varicose veins. Synonyms include varix, varices, and varicosities. |
| Corona phlebectatica—a fan-shaped pattern of numerous small intradermal veins on the medial or lateral aspects of the ankle and foot. This is commonly thought to be an early sign of advanced venous disease. Synonyms include malleolar flare and ankle flare. |
| Edema—a perceptible increase in volume of fluid in the skin and subcutaneous tissue, characteristically indented with pressure. Venous edema usually occurs in the ankle region, but it may extend to the leg and foot. |
| Pigmentation—a brownish darkening of the skin resulting from extravasated blood, which usually occurs in the ankle region but may extend to the leg and foot. |
| Eczema—an erythematous dermatitis, which may progress to a blistering, weeping or scaling eruption of the skin of the leg. It is most often located near varicose veins but may be located anywhere in the leg. Eczema is usually seen in uncontrolled chronic venous disease (CVD) but may reflect sensitization to local therapy. |
| Lipodermatosclerosis (LDS)—localized chronic inflammation and fibrosis of the skin and subcutaneous tissues of the lower leg, sometimes associated with scarring or contracture of the Achilles tendon. LDS is sometimes preceded by diffuse inflammatory edema of the skin which may be painful and which is often referred to as hypodermitis. This condition must be distinguished from lymphangitis, erysipelas, or cellulitis by their characteristically different local signs and systemic features. LDS is a sign of severe CVD. |
| Atrophie blanche or white atrophy—localized, often circular whitish and atrophic skin areas surrounded by dilated capillaries and sometimes hyperpigmentation. This finding is a sign of severe CVD and is not to be confused with healed ulcer scars. Scars of healed ulceration may also have atrophic skin with pigimentary changes but are distinguishable by history of ulceration and appearance from atrophic blanche and are excluded from this definition. |
| Venous ulcer—full-thickness defect of the skin most frequently in the ankle region that fails to heal spontaneously and is sustained by CVD. |

Table V. Refinement of the clinical “C” classes in the clinical, etiological, anatomical, pathophysiological (CEAP) classification.


**Level of investigation**

A precise diagnosis is the basis for correct classification of the venous problem. The diagnostic evaluation of the patient with CVD can be logically organized into one or more of three levels of testing, depending on the severity of the disease:

- **Level I:** the office visit with history and clinical examination, which may include use of a hand-held Doppler.
- **Level II:** the noninvasive vascular laboratory, which now routinely includes duplex color scanning, with some plethysmographic method added as desired.
- **Level III:** invasive investigations or more complex imaging studies including ascending and descending venography, venous pressure measurements, computed tomography scan, venous helical scan, or magnetic resonance imaging.

It is recommend that the level of investigation (L) should also be added to the classification, eg, C2,Ab,S,Ep,As,p,Pr (2003-08-21,L II).

**The basic CEAP**

A new “basic CEAP” is offered here. Use of all components of CEAP is still encouraged. Unfortunately, many use the C classification only, which is only a modest advance beyond the previous classifications based solely on the clinical appearance. Venous disease is complex, but can be described by the use of well-defined categorical descriptions. For the practicing physician, CEAP can be a valuable instrument for correct diagnosis to guide treatment and assess prognosis. In modern phlebological practice, the vast majority of patients will have a duplex scan of the venous system of the leg, which will largely define the E, A, and P categories.

Nevertheless, it is recognized that the merits of using the full (advanced) CEAP classification sys-
tem hold primarily for the researcher and for standardized reporting in scientific journals. It allows grouping of patients so that the same types of patients can be analyzed together and such subgroup analysis allows their treatments to be more accurately assessed. Furthermore, reports using CEAP can be compared with one another with much greater certainty. This more complex classification, for example, also allows any of the 18 named venous segments to be identified as the location of venous pathology. Take a patient with pain, varicose veins, and lipodermatosclerosis where duplex scan confirms primary reflux of the GSV and incompetent perforators in the calf. The classification here would be C2,4b,S, Ep, As,p, Pr2,3,18.

While the detailed elaboration of venous disease in this form may seem unnecessarily complex, even intimidating, to some clinicians, it provides universal understandable descriptions that may be essential to investigators in the field. To serve the needs of both, the full CEAP classification (Table VI), as modified above, is retained as “advanced CEAP” and the following simplified form is offered as “basic CEAP.”

In essence, the basic CEAP applies two simplifications. First, in the basic CEAP, the single highest descriptor can be used for clinical classification. For example, a patient with varicose veins, swelling, and lipodermatosclerosis would be C4b. The more comprehensive clinical description, in the “advanced” CEAP, would be C2,3,4b. Second, in the basic CEAP, where duplex scan is performed, E, A, and P should also be classified using the multiple descriptors recommended, but the complexity of applying these to the 18 possible anatomical segments is avoided in favor of applying the simple s, p, and d descriptors to denote the superficial, perforator, and deep systems. Thus, using the basic CEAP, the same patient cited in a previous example (painful varicosities plus lipodermatosclerosis and duplex scan—determined reflux involving the superficial and perforator systems) would be classified as C4b,S, Ep, As,p Pr (rather than C2,4b,S, Ep, As,p, Pr2,3,18).

Revision of CEAP—an ongoing process

With improvement in diagnostics and treatment, there will be continued demands to adapt the CEAP classification to better serve future developments. There are several conditions that are not included in the CEAP classification but which can influence the management of patients:

<table>
<thead>
<tr>
<th>Clinical classification</th>
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<tbody>
<tr>
<td>C0: no visible or palpable signs of venous disease</td>
</tr>
<tr>
<td>C1: telangiectasies or reticular veins</td>
</tr>
<tr>
<td>C2: varicose veins</td>
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<tr>
<td>C3: edema</td>
</tr>
<tr>
<td>C4a: pigmentation and/or eczema</td>
</tr>
<tr>
<td>C4b: lipodermatosclerosis and/or atrophie blanche</td>
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<tr>
<td>C5: healed venous ulcer</td>
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<td>C6: active venous ulcer</td>
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<table>
<thead>
<tr>
<th>Etiological classification</th>
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</thead>
<tbody>
<tr>
<td>Ec: congenital</td>
</tr>
<tr>
<td>Ep: primary</td>
</tr>
<tr>
<td>Es: secondary (postthrombotic)</td>
</tr>
<tr>
<td>En: no venous etiology identified</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anatomical classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>As: superficial veins</td>
</tr>
<tr>
<td>Ap: perforator veins</td>
</tr>
<tr>
<td>Ad: deep veins</td>
</tr>
<tr>
<td>An: no venous location identified</td>
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<th>Pathophysiological classification</th>
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<tbody>
<tr>
<td><strong>Basic CEAP:</strong></td>
</tr>
<tr>
<td>Pr: reflux</td>
</tr>
<tr>
<td>Po: obstruction</td>
</tr>
<tr>
<td>Pr:o: reflux and obstruction</td>
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<tr>
<td>Pr:n: no venous pathophysiology identifiable</td>
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<th>Advanced CEAP:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same as Basic CEAP with the addition that any of 18 named venous segments can be utilized as locators for venous pathology:</td>
</tr>
<tr>
<td><strong>Superficial veins:</strong></td>
</tr>
<tr>
<td>1. telangiectasies/reticular veins</td>
</tr>
<tr>
<td>2. Great saphenous vein (GSV) above knee</td>
</tr>
<tr>
<td>3. GSV below knee</td>
</tr>
<tr>
<td>4. Small saphenous vein</td>
</tr>
<tr>
<td>5. Nonsaphenous veins</td>
</tr>
<tr>
<td><strong>Deep veins:</strong></td>
</tr>
<tr>
<td>6. Inferior vena cava</td>
</tr>
<tr>
<td>7. Common iliac vein</td>
</tr>
<tr>
<td>8. Internal iliac vein</td>
</tr>
<tr>
<td>9. External iliac vein</td>
</tr>
<tr>
<td>10. Pelvic: gonadal, broad ligament veins, other</td>
</tr>
<tr>
<td>11. Common femoral vein</td>
</tr>
<tr>
<td>12. Deep femoral vein</td>
</tr>
<tr>
<td>13. Femoral vein</td>
</tr>
<tr>
<td>14. Popliteal vein</td>
</tr>
<tr>
<td>15. Crural: anterior tibial, posterior tibial, peroneal veins (all paired)</td>
</tr>
<tr>
<td>16. Muscular; gastrocnemial, soleal veins, other</td>
</tr>
<tr>
<td><strong>Perforating veins:</strong></td>
</tr>
<tr>
<td>17. Thigh</td>
</tr>
<tr>
<td>18. Calf</td>
</tr>
</tbody>
</table>

Example: A patient presents with painful swelling of the leg and varicose veins, lipodermatosclerosis, and active ulceration. Duplex scanning on May 17, 2004 showed axial reflux of GSV above and below the knee, incompetent calf perforators and axial reflux in the femoral and popliteal veins. No signs of postthrombotic obstruction.

Revision of the CEAP classification – Eklöf

Table VI. Revision of the clinical, etiological, anatomical, pathophysiological (CEAP) classification.

Combined arterial/venous etiology.
Postthrombotic lymphedema.
Ankle ankylosis with atrophy of the calf.
Venous aneurysms.
Venous neuprophty.
Corona phlebectatica.
Pelvic congestion syndrome.
Morbid obesity.

The role of corona phlebectatica was discussed during the meetings and the Atlantic Ocean was a clear divider. In parts of Europe, corona phlebectatica has been used as an early indicator of advanced CVD. Its scientific significance is now under investigation particularly in France. There is a need to incorporate appropriate new features without too frequent disturbances of the stability of the classification. As one of the committee members (F. Paberg) stated in our deliberations:

REFERENCES

It is critically important that recommendations for change in the CEAP standard be supported by solid research. While there is precious little that we are recommending which meets this standard, we can certainly emphasize it for the future. If we are to progress we should focus on levels of evidence for changes rather than levels of investigation. While a substantial portion of our effort will be developed from consensus opinion, we should still strive to achieve an evidence-based format.


Révision de la classification CEAP 10 ans après son avenêm en 1994

La Tour de Babel a été construite par les descendants de Noé pour atteindre le ciel, mais le Seigneur a puni le peuple arrogant en brouillant leur langue commune et en les dispersant de Babylone sur toute la surface de la terre. Le Forum Vieux Américain (FVA) a essayé de détruire cette Tour de Babel et de créer la classification CEAP comme langue commune de la maladie veineuse chronique (MVC) qui a jadis souffert d’un manque de précision dans la description. Cette carence a conduit à des résultats discordants dans les études sur la MVC, à un moment où l’on proposait de nouvelles modalités pour améliorer le traitement des maladies veineuses les plus simples comme les plus compliquées. On croyait que ces discordances pourraient être résolues par un diagnostic précis et une classification du problème veineux sous-jacent. Un Comité international ad hoc présidé par Andreu Nicolaides et composé de représentants d’Australie, d’Europe et des États Unis a élaboré le premier document de consensus de la CEAP au 6e congrès annuel du FVA à Maui en 1994. La classification était fondée sur les manifestations cliniques (C), les facteurs étiologiques (E), la distribution anatomique (A) et la physiopathologie sous-jacente (P). Le document de consensus de la CEAP a été publié dans 26 journaux et livres et traduit en 9 langues. La plupart des articles publiés aujourd’hui sur la MVC utilise tout ou partie de la CEAP. Le diagnostic et le traitement de la MVC se développent rapidement et le besoin d’une révision était évident. Un comité ad hoc du FVA a été nommé en 2002 pour revoir la classification et faire des recommandations pour un changement en 2004, 10 ans après ses débuts. On a aussi mis en place un comité international pour permettre de poursuivre son utilisation. Le comité a tenu quatre réunions pour revoir le document qui a été publié dans la revue Journal of Vascular Surgery en décembre 2004. Voici les changements préconisés : (i) mise au point de plusieurs définitions utilisées dans la description de la CEAP ; (ii) mise au point de la classe C de la CEAP ; (iii) addition du descriptor n (absence d’anomalie veineuse) ; (iv) ajout de la date de classification et du niveau d’investigation ; (v) description de la CEAP de base comme alternative plus simple à la classification CEAP complète (avancée).

UPDATING THE CEAP CLASSIFICATION 10 YEARS AFTER ITS INVENTION IN 1994

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Man of letters, poet, and scholar, Dom Pedro d’Alcantara (1825-1891), or Pedro II, second emperor of Brazil, managed to create, thanks to his intellect and turn of mind, close links between the Brazilian and French cultures. Throughout his reign, he never missed an opportunity to promote Franco-Brazilian exchanges. In Brazil today, the 19th century is considered as the time when French culture flourished. For Brazilian intellectuals, Paris had an overwhelming attraction as a cultural capital. In the field of education, the French influence was extremely important. In 1838, the Imperial College of Pedro II, just inaugurated, became the center for the study of French history in Brazil. Up until 1862, teaching was directly influenced by French historians. The use of textbooks based on French authors, in particular those concerning the baccalaureate, guided the organization of studies including those dealing with the history of Brazil. In 1871, Pedro II undertook his first voyage to Europe. After visiting various countries in Europe and the Near East, he...
Emperor Dom Pedro II of Brazil (1825-1891), son of Pedro I and the Empress Leopoldina. Throughout his reign, he showed great interest in French culture and made several trips to France, where he mixed with the likes of Louis Pasteur and Victor Hugo, who described Dom Pedro as the “new Marcus Aurelius.” He abdicated in 1889, when the Brazilian Republic was proclaimed. He died in Paris. © Roger Viollet.

arrived in Paris on the 15th of December. He took up residence in the Grand-Hôtel, near the Opera, where numerous personalities paid their respects including the writer Ernest Renan, with whom he liked to discuss ancient cultures, religions, and the sacred texts. He then left for the French Riviera and Marseilles where he met Frédéric Mistral, a Provençal poet who spoke Occitan, and who recounted their discussions in the Arman Prouvençau. Meanwhile, Le Petit Marseillais, a daily newspaper, devoted a series of articles to Brazil and the visit of Pedro II to Provence. During a second voyage in 1876, Pedro II visited Victor Hugo, attended meetings of the academy of science, and frequented Pasteur’s laboratory, the Sorbonne, the Collège de France, and the Sainte-Geneviève Library. In 1889, Dom Pedro abdicated and the Brazilian republic was declared. The ideas of the French philosopher Auguste Comte had a great influence on the constitution of the “United States of Brazil” in 1891, and on the country’s motto that became “order and progress.” Pedro II later settled in Cannes and attended the meetings of the scientific and literary society, of which he became honorary president. In March 1890, the society organized a major conference on Brazil. Thus, close scientific and literary relations had already been established between France and Brazil. The medical history that binds our two countries is a faithful reflection of this.

As Sigerist noted in his book entitled A History of Medicine, “it would be a mistake to claim that medical history is a concern of historians and philologists alone and of no interest to physicians. Medical history is medicine also.” Thanks to Alphonse Pavie, an ordinary doctor, medical treatment in the Minas Gerais region of Brazil was able to evolve. The name Pavie probably does not mean much to the reader, yet this Frenchman who hailed from Amiens deserves to be recognized. He is quite simply one of the pioneers of modern medicine in Brazil. Circumstances dictated, in a rather unusual manner, that in the first decade of the twentieth century a small town in the Jequitinhonha valley had access to medical treatment of the same scientific level as that then available in Europe. In the little town of Joâo Baptist, today Itamarandiba, Pavie practiced medicine comparable to the way it was practiced in France. At the time, he was working with the best doctors of Juiz De Fora and Belo Horizonte, the two medical centers in the state. Itamarandiba is 450 km from Belo Horizonte, at the extreme northeast of the great hinterland of Minas Gerais.

As Auguste Comte (1798-1857), French philosopher who, thanks to mathematics, introduced positivism to Brazil. The scientific and political watchword of the philosopher: “Order and Progress” is inscribed on the Brazilian flag. Photograph courtesy of the Musée Auguste Comte.

Brazilian flag bearing the motto Ordem e Progresso (Order and Progress). Flag provided by: www.worldatlas.com, with permission.

Alphonse Pavie, from Amiens to Brazil
Alphonse Marie Edmund Pavie was born in Amiens on 16th August, 1868, of parents of aristocratic origin. The family owes its name to a feat of arms performed by an ancestor, a French soldier called Pompéran, who distinguished himself during the battle of Pavia, in 1525, by saving the life of François I. This was during the war against Charles V, king of Spain and Holy Roman Emperor. Pavie’s schooling began with Archbishop Mallet at Mont-de-Marsan (to the south of Bordeaux), where he was sent in 1870 when Amiens was invaded during the war between France and Prussia. Later, he studied at the Collège de la Providence in Amiens. Aged 16,
he began to attend surgical operations in the Amiens Hôtel-Dieu Hospital. In 1888, he enrolled in the Paris Medical Faculty, where his teachers included Chauffard, Labbé, Peyrot, Reclus, and Richelot. In 1892, during his last year of medicine, he fell in love with an actress. He abandoned his studies and, using the fortune he had inherited from his father two years earlier, he accompanied her on a tour of several countries on the American continent. In Rio de Janeiro, his money ran out, at the same time as his relationship with the actress ended. In order not to compromise his family’s honor, he changed his name to Alfonso Ulrik, and took the decision never to return to France. This penitence was imposed by his noble blood and rigid education.

Minas Gerais, one of the sources of modern Brazilian medicine

In 1894, Pavie traveled to the interior of Minas Gerais in Brazil to work on the construction of the Bahia-Minas railway line. After construction ended in 1898, he then stayed another year in Téofilo Otoni, and in 1900 settled in the village of Capelinha. It was in this neglected part of Brazil that he took on his role as doctor. For ten years, he looked after this vast region that included several villages northeast of Minas Gerais. Then, in 1903, he married Maria de Conceição Guimarães. The couple would go on to have fifteen children!
Minas Gerais means “general mines,” and the area was the chief producer of iron and precious stones in Brazil. For a long time, the capital was Ouro Preto, founded toward the end of the 17th century by the bandeirantes, and which had unquestionable and undisputed charms. From 1590, the bandeirantes made incursions from São Paolo into the interior of the territory to conquer the region that was still scarcely known to the Portuguese. They were looking for gold and Indian slaves. About ten years later, an important goldfield was discovered that yielded 1200 metric tons of gold. A special feature of this gold was the black film of iron oxide that covered the nuggets and gave them their name: ouro preto (black gold). The town grew rapidly, erected sumptuous churches adorned with statues glittering with powdered gold, built stately residences, raised sculptured fountains, and adopted the name Vila Rica, which in the 19th century became Ouro Preto. Proud of its gilded past, built on the tracks of the old gold seekers, Ouro Preto boasts some of the most important treasures of Brazilian baroque. The whole town was classified as a monument and national cultural heritage by President Getulio Vargas in 1933. At the end of the 19th century, Ouro Preto declined as the gold veins ran out and further gold deposits could not be found, thus the city was dethroned by Belo Horizonte, which became the capital of Minas Gerais.
In 1904, Francisco Antonio Alves, president of the state of Minas Gerais, appointed Pavie head of the vaccination commission, and, in 1905, Rodrigues Alves, president of the Republic, promoted him to the rank of chief surgeon of the third brigade of infantry of the civil guard in the town of Novas Minas.

**Victor Pauchet, a bridge to current medical knowledge**

At this time, Alphonse Pavie began to correspond again with his family and former colleagues, and received French books, journals, and medical material. He began a busy correspondence, discussing medical experiments with several French doctors, in particular Victor Pauchet (1869-1936), one of Europe’s best surgeons. They had been fellow students at the Amiens Collège de la Providence and were colleagues at the Hôtel-Dieu in Amiens, and again later at the Paris Medical Faculty. In several of his letters, Victor Pauchet expressed great admiration for Pavie, and recalled that his friend had encouraged him to study medicine and to specialize in surgery. He insisted that Pavie should return to Paris so that they could work together at the Saint-Michel Hospital. This correspondence with Victor Pauchet was of great importance. It enabled Pavie, who was the only doctor in the vast region of Minas Gerais, to keep himself abreast of modern medicine in Europe. Meanwhile, Victor Pauchet, after defending his thesis at the Paris College of Medicine in 1897, settled in Amiens. There he became professor of anatomy and surgery at the College of Medicine, and built up a very successful surgical practice up until 1914. Thanks to his many medical publications, he became well known in France and abroad, and foreign surgeons came to consult him. In 1914, when the First World War broke out, Pauchet led a surgical group in a hospital camp at the front, and improved the amputation technique mainly used during the war. For his services, he was made a member of the Legion of Honor and was decorated with the Military Cross. After 1918, he became head of the department of surgery at the Saint-Michel Hospital in Paris, where he specialized in abdominal surgery. His skill was recognized worldwide and internationally known surgeons came to visit him. He then directed the top Paris surgical clinic, and became president of the Paris Society of Surgeons and the Paris Society of Medicine. He made original contributions to surgical techniques, in particular for amputations and gastrectomy. It was Pauchet who introduced regional anesthesia in France. His published work was considerable, and included books on anatomy, surgery, and regional anesthesia. He also compiled his classic 23-volume *Illustrated Practical Surgery*, which was illustrated by the gifted artist S. Dupret, who had also illustrated Testut’s classic *Treatise on Anatomy*. Victor Pauchet was well known in the town of Amiens where a clinic, square, and street are named after him. His dictum was: “the most productive work is that created by the hands of a happy man.”

**Itamarandiba and the Pasteur Institute**

In 1910, Pavie settled in Itamarandiba. His relations with Victor Pauchet, other doctors, and various institutes, particularly the Pasteur Institute in Paris, not to mention the manufacturers of medical materials, enabled his Itamarandiba hospital to receive the most advanced medical equipment available in France. This allowed a village to be equipped with a hospital, a pharmacy, X-ray equipment, and a laboratory for complementary examinations, all of a technical level well beyond that of Brazilian medicine at the start of the 20th century. The laboratory was installed in 1911 together with reagents and appliances that were ordered in Paris by friends who were specialists. The spare parts, pharmaceutical and biochemical essentials, and books imported from France were transported from Belo Horizonte to Itamarandiba on the back of mules, a journey that took 15 days. The heavier equipment, such as the operating table, the X-ray equipment, and material for the future electric lighting system were transported by oxcart. Thus, at Itamarandiba in 1911, patients benefited from medical treatment that was among the most high-tech of its time: sterilization, blood chemistry, hematology, bacteriology, and serodiagnosis of syphilis, typhus, and paratyphus A and B, as well as pathological anatomy (microscopic and microtomic), and microphotography.

Next to the laboratory, there was an annex where guinea pigs, rabbits, and sheep were kept for inoculation experiments and to provide serum-antiserum for the Wasserman reaction. Some of the antigen extracts were provided by the Pasteur Institute in Paris.
In 1880, Laveran demonstrated the presence in the blood of the etiological agent of malaria, *Plasmodium falciparum*, or “Laveran’s hematozoon,” the agent that kills. In 1912, Pavie carried out serological and etiological studies of the most frequent infectious and parasitological diseases in the region of Minas Gerais, including typhoid fever, syphilis, malaria, and Chagas disease. It was only two years after Carlos Chagas had discovered trypanosomiasis that Pavie in his Itamarandiba laboratory identified the trypanosome that caused it.

In 1911, Pavie conceived and carried out his *Santa Casa de Misericórdia de Itamarandiba* project (hospital for the poor modeled on the Hôtel-Dieu) in which he followed the revolutionary principles of Pasteur’s microbiology. Later, he established the Ladies of the Red Cross Association, the members of which were taught how to give nursing care, and then worked at the Santa Casa hospital. In this way, he improved medical teaching and in addition gave unflagging assistance to much of the population concerning questions of medical care. Like Albert Schweitzer (1875-1965), who established a hospital to treat thousands of people in Africa, he was a precursor of advanced technology that was to have international repercussions.

In 1920, Brazilian surgeons recommended that Jose Pessoa, the nephew of Epitácio Pessoa, president of the Republic of Brazil from 1919 to 1922, should be operated on by Pauchet in Paris. After the successful operation, Pauchet asked the patient’s brother, João Pessoa (president of the state of Paraíbas, in Brazil) whether, instead of paying him fees, he would arrange for the most up-to-date operating table to be sent to his great friend Alphonse Pavie in Minas Gerais. The table arrived safely at Itamarandiba on a stretcher drawn by two mules.

**Pavie’s final decision, and introduction of local anesthesia**

After having spent the greater part of his life under conditions of pure abnegation, treating poverty-stricken patients in the northeast of Minas Gerais and trying to provide for his large family, Pavie considered he had paid for his youthful sins. On the insistence of his family and the archbishop of Diamantina (a town in Minas Gerais), he started reusing his family name. Nevertheless, he never returned to France, despite repeated requests from his family and Victor Pauchet.

The piecing together of the works of Pavie was simplified thanks to the great number of written documents and photographs he left behind. Already in 1911, he had a laboratory for developing photographs. More than 500 pictures of his medical activities have been preserved. In 1911, he began to treat the lepers of Itamarandiba and the local villages, and settled them in small cabins one-and-a-half miles from the town. Despite the isolated setting, using his up-to-date equipment, Pavie was able to give them advanced scientific treatment at a time when the diagnosis and treatment of leprosy did not exist in Brazil.

The sick from the whole area came to Itamarandiba, drawn by the fame of Pavie and his new techniques, making the town a center of reference for treatment in the region. All urgent surgical cases were referred to Pavie, and the hospital gradually enlarged to 104 beds. Finally, in 1924, thanks to equipment imported from France, he installed electricity in the town, the first to do so in the northeast of Minas Gerais.

Pavie, who was isolated in the Sertão region in the state of Minas Gerais, where many villages were not yet connected to the city by roads, and where mule caravans were the only method of transport and communication, nonetheless managed to keep up-to-date with medical knowledge as a result of French books and journals and through his correspondence with his colleagues in Paris. He performed numerous surgical operations using local anesthesia, which he had studied under Paul Reclus (1847-1914), professor of clinical surgery at the Paris Medical Faculty and initiator of local anesthesia using infiltration. In 1904, Pavie received cocaine from Paris so he could perform local anesthesia. He noted, “I have been acquainted with local anesthesia ever since it was born. Already in 1888, Reclus never stopped telling us: local anesthesia is the anesthesia of the future.” In 1884, inspired by a work of Sigmund Freud reporting that cocaine anesthetized his mucous membranes, Karl Köller performed the first local anesthesia of the conjunctiva and cornea. In 1886, Reclus used injected cocaine for carrying out local anesthesia and infiltrations, and...
thereafter devoted practically the rest of his life to furthering anesthesia. In this way, a big step forward was taken to perfect this technique that is still today one of the most frequently used in surgery. This is echoed by Littré in his preface to the History of Medicine in Brazil, written by Pedro Salles, one of the forerunners of infantile and orthopedic surgery who practiced in Belo Horizonte: “There is nothing even in the most advanced modern medicine whose roots cannot be found in the medicine of the past.” In 1906, Einhorn synthesized novocaine, and in 1912, after corresponding with Victor Pauchet, Pavie began to use it for regional anesthesia. Victor Pauchet then published the first edition of his Regional Anesthesia, which was reprinted many times and translated into numerous languages.

 Barely had two years passed since the introduction of regional anesthesia in France than Pavie began to make use of it in Itamarandiba. In 1923, he published in the French journal La Clinique his practical experience in the use of regional anesthesia, spinal anesthesia, and narcosis. This article was very favorably received by his surgical colleagues in France.

 In 1931, he published other articles in the journal Publication Médicales relating his long surgical experience and his use of regional anesthesia. In 1935, he published an article in the Review of Medicine and Surgery. Some of his surgical cases, accompanied by descriptions and photographs, were sent to Victor Pauchet and were presented at a meeting of the Paris Society of Surgeons.

 A busy retirement
 From 1925 on, with considerable surgical experience behind him, Pavie decided to interrupt his work and for about twenty years spent his time visiting the medical departments of Belo Horizonte and Rio de Janeiro and attending surgical conferences given by the principal specialists of the time. In Belo Horizonte, he visited the department of Borges da Costa in the Radium Institute. Borga da Costa’s aesthetic eye had enabled him to give the hospital a Hellenic look with its Greek column facade. He also visited the department of Hugo Werneck at the Santa Casa hospital. Pavie renewed his contacts with his great friend Juscelino Kubitschek who at that time was a federal deputy and chief of police in Belo Horizonte. The future president introduced Pavie as “a highly competent physician with whom I am linked by a profound friendship.”

 From 1947 onwards, his increasing years and gradual loss of vision resulted in Pavie progressively reducing his medical activities, and he left the running of Santa Casa Hospital to José Pavie, his son. Alphonse Pavie died on October 3, 1954 at the age of 86. Pavie was a pioneer who succeeded in using all the major technological advances, almost as soon as they appeared in Europe, despite being in a region far from the great industrial centers. Thus, from 1910 to 1912, he set up a hospital with all the technical equipment available in Europe. Today, due to reduced financial means, the Itamarandiba Hospital has lost some of its grandeur, but the memory of Alphonse Pavie lives on among the inhabitants of the region.

The prolongation of a life’s work
 Thus, one can say that Alphonse Pavie will remain one of the remarkable figures in the long history of Franco-Brazilian relations. He was a pioneer in a collaboration that today continues to grow between the agencies and associations of the two countries, in domains as varied as scientific research and technology, university cooperation and teaching, information technology, microelectronics, agronomic development and research, space, and health. Through his dedication and selfless work, Alphonse Pavie contributed to the building up of an effective medicine in Brazil that was at the forefront of the technologies of the day, thus initiating cooperation that has continued to flourish. This cooperation between France and Brazil dates back some considerable time. After the creation in 1826 of the Academy of Literature, the Faculty of Philosophy was established a few years later, and numerous French intellectuals taught there. The current educational, cultural, and scientific exchanges between Brazil and France reaffirm the intellectual cooperation of the past. This has enabled us to develop projects of common interest according to the re-
spective competence of each country, and allows us to take advantage both of our differences and our cultural similarities. The life of Alphonse Pavie has gradually taken its place among the annals of history, even though it is not well known in France. However, in Brazil he has left indelible traces that contribute in no small way to advancing the history of medicine and of Brazil itself. As Littré said: “The science of medicine, if it does not want to be reduced to the rank of a job, must take care of its history and look after the old monuments that the past has bequeathed us.”

Today, the friendship continues
At the present time, Franco-Brazilian agreements are resulting in numerous solid and fruitful exchanges between the two countries. Thus, the Oswaldo Cruz (Fiocruz) Foundation, a direct descendent of the institute of the same name, signed a general agreement for cooperation with the Pasteur Institute in October 2004. This agreement aims at strengthening the links with Fiocruz that have existed for nearly a hundred years—ever since, in the early nineteenth century, Oswaldo Cruz worked for several years in the Pasteur Institute, then returned to Brazil to devote himself to public health by founding his institute.

The many events in 2005 reuniting France and Brazil certainly illustrate the value of these exchanges and indeed have consolidated them, so that in the future Franco-Brazilian cooperation will be even more effective and will benefit our two countries.

The author would like to acknowledge the contribution of Professor Sebastião Gusmão of the Universidade Federal de Minas Gerais, Belo Horizonte, in making known the life and work of Alphonse Pavie. This article is partly based on material written by Ludovic Hubler, available at: www.sekoymag.com/nouveausite/SPIP/breve.php?id_breve=86
When the Portuguese navigator Pedro Alvares Cabral discovered Brazil in 1500, Portugal did not immediately show much interest in this new land which they named Vera Cruz or Santa Cruz. In contrast, French fishermen took an immediate interest in this mysterious terra incognita.

Norman and Breton shipowners make friends with the Indians

At the dawn of the 16th century, Normans and Bretons were already setting sail for Brazil. Since they were accustomed to fishing for cod, they began crossing the Atlantic to fish in the Brazilian waters and returned with rich cargoes. The first French expedition dates back to 1503, when Captain Paulmier de Gonneville left Honfleur in the Espoir with a crew of sixty and dropped anchor in a “southern land.” He returned accompanied by Essomericq, the son of an Indian chief, and the first of his race to set foot in France. Gonneville had promised to take him back to his home land at the end of twenty moons. However, Essomericq married a close relation of Gonneville and never returned across the Atlantic.

Throughout the 16th century, the merchants of Dieppe, Rouen, and Honfleur (Jean Alfonse, Guillaume le Testu, the Ango brothers, and others) crossed the South Atlantic and established special relations with several Indian tribes. They organized a very lucrative trade, returning with cargoes of pau brasil (Brazil wood), parrots, monkeys, cotton, pepper, and medicinal oils. These they bartered for sheets, mirrors, weapons, and tools (shovels, spades, scythes, hammers, etc). Pau brasil, “wood the color of red-hot embers” (from which Brazil takes its name), was very much in demand for the painting and construction of sailing ships. The French adventurers made friends with the Indian tribes, principally the Tamoios, the Tupinambas, and the Tapuias, who received them with warmth because of the way they were treated.

Every year France pays homage to another country, an event that highlights the cultural, historical, and other relations that link France and the guest country. 2005 was the year of France-Brazil, and the many events, exhibitions, concerts, symposiums, and conferences on numerous subjects emphasized the special nature of the relations that France has enjoyed and continues to enjoy with Brazil. And Brazil, a nation on the other side of the Atlantic, expressed wholeheartedly its friendship for France. Though relations from 1555 to 1711 were somewhat turbulent—since France was hoping to found a colony—from the Age of Enlightenment to the end of the Second World War, France was a reference for Brazilian intellectuals and a model at the time of the empire and the young republic.
France dreams of founding a colony in Brazil

In the first half of the 16th century, the French developed mainly commercial relations with Brazil, but with the passing of time they began to foster the ambition of founding a colony there. Francis I (1515-1547), the father of Henry II, had objected to the treaty of Tordesillas, signed in 1494 between Portugal and Castile (Spain) that had previously been sanctioned by a bull of Pope Alexander VI: “The lands discovered in the Occidental Hemisphere will be Portuguese and will extend for 370 leagues to the west of Cape Verde.” It was like dividing the world in two. Francis I rejected this territorial sovereignty and roared: “Show me God’s testament conferring on the kings of Portugal and Castile the right to divide the land between them.” According to other historians, the king is, in fact, reputed to have said: “I would like to see the clause in Adam’s testament that excludes France from the deal.” Francis I maintained that it was not “the discovery of a territory that conferred possession, but its permanent occupation and the construction of fixed establishments.” It was not until 1530, when they became aware of the French presence along the Brazilian coasts, that Portugal began to construct the bases that would one day become Brazil.

Villegaignon’s “French Antarctic” colony (1555-1560)

In 1555, Admiral Villegaignon, a knight of the Maltese order and vice admiral of Brittany, sailed out of Le Havre with three ships. The expedition had, among others, a religious goal. It was inspired by Admiral de Coligny, who although not yet an open Calvinist, had the idea of a place of exile for the Huguenots. Since 1551, a number of them had been imprisoned as heretics when they refused to renounce their Protestantism. Coligny considered that Catholics and Protestants could settle in a French Antarctic colony where, thanks to the principle of tolerance, they would be able to practice their faith in peace. After a rough crossing, Villegaignon, with 600 settlers, arrived in the bay of Guanabara where he set up camp on an island, today named after him. He constructed Fort Coligny, and life settled down. However, the isolation gradually became unbearable and the settlers staged a rebellion which was put down by Villegaignon. He demanded “spiritual” reinforcements, and Jean Calvin sent fourteen Calvinists including Jean de Lery. Very soon, religious quarrels broke out between Villegaignon and the Calvinists, whom he expelled in a boat that sank. Some managed to return to the island where Villegaignon had them shackled in irons, and those who refused to renounce their beliefs were drowned. Aware of his failure, Villegaignon returned to France and left the colony in the hands of his nephew Bois-le-Comte.

Since 1548, the Portuguese governor-general, Men de Sá, had presided over his domain from Bahia, the first capital of Brazil. In March 1560, despite the support of the Tamoios Indians, the French colony was seized by the Portuguese squadron of Men de Sá. However, it can be said that in a certain manner the French “founded” Rio de Janeiro. The Portuguese began building the embryo of the town that would become the capital in 1763. The failure of Villegaignon stirred considerable controversy in France where Brazil was famous, popular, and fashionable. Indeed, the dream of many people was to go there: which could be considered a posthumous victory for Villegaignon.

The short-lived France-Equinoctial colony (1612-1615)

Despite the failure of the French Antarctic colony, French shipowners continued their trade with Brazil. The land to the north of Recife had never been visited by any European, and a Dieppe navigator, Jacques Riffault, undisputedly the most adventurous French merchant, established himself on an island at Maranhão with the help of the Tupinambas, at the northern extremity of Brazil. Riffault fortified several posts along the coast and built warehouses in order to maintain more regular commerce with the Indians. In 1605, the French king agreed to send an expedition led by Daniel de la Touche, Seigneur de la Ravardière, in company with the king’s geographer, Jean Mocquet, whose mission was to map the coast of Brazil. On their return, they were so enthusiastic that the idea of creating a colony was launched. However, during their absence the king had been assassinated.
La Ravardière was joined in his project by François de Razilly. The new king, Louis XIII, approved the expedition, and subscriptions were invited at the port of Cancale. Everyone wanted to subscribe: both shipowners and the great families (the Richelieu, Condé, and Guise families). On March 19, 1612, three ships left Cancale with five hundred settlers on board. They dropped anchor at the island of Maranhão, which the Portuguese had never seized. On their arrival, the settlers built a fort, two chapels, a wooden warehouse, and a wharf for unloading. By the end of the year, the island colony was protected by several small forts and the French Brazilian colony became a reality. In 1614, reinforcements arrived from France (500 settlers, 200 soldiers, 10 Capuchin monks, and numerous craftsmen). The French explored the region and made numerous contacts with the local tribes. At the end of the year, the Portuguese reacted and Philip III, king of Portugal and Spain, ordered the governor to expel the French.

In October 1615, a Portuguese squadron besieged the island. France did not respond quickly enough and the following month la Ravardière capitulated. Bitter at being let down by France, la Ravardière remained in Brazil and decided he would allow the Portuguese to take advantage of his knowledge of the

Two panels of sculpted oak showing the importance of wood as a trading commodity between Brazil and France in the 16th century. They are thought to date from around 1530 and come from a house in Rouen that was destroyed around 1837 to make way for road construction. They probably belonged to a shipowner who brought cargoes of Brazil wood back to France. At that time, Brazil wood was much in demand for the construction of sailing ships. The panels depict the various stages in the process from the cutting down of trees by the natives to the loading of the chopped wood onto the ship bound for France. Musée départemental des Antiquités – Rouen. Photograph by Yohann Deslandes.

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Amazon basin. The Portuguese established a fort at Belém, and the Amazonian highway was henceforth open to them. The Capuchin missionaries Claude d’Abeville and Yves d’Evreux wrote the story of their stay from 1613 to 1614 on Maranhão and the surrounding islands, and their *Voyage to the North of Brazil* was published in 1615. The work captures brilliantly the wonder of the authors confronted by this virgin territory. The buildings erected in the north by la Ravardière on his first voyage in 1605 were maintained and strengthened by the local population. From them was born Guiana, a particularly hostile region that interested neither the Spanish nor the Portuguese nor the Dutch. From this French adventure, only the name São Luís remains, and is the present capital of Maranhão with its undeniable charms.

The discovery of gold in Brazil, in the Minas Gerais (1695), initially renewed French ambitions, but the king eventually lost interest in Brazil.

**The Entry of Henry II and Catherine de Medicis into Rouen (1550), a Dazzling “Brazilian Festival”**

In the time of the monarchy, the announcement that a king would visit a town was always an exceptional event. The town welcomed the monarch with a series of festivities and each city strove to outdo the others in originality. The people of Rouen brought off a major coup in this field by deciding to organize a “Brazilian festival,” and 50 Indians made the voyage from Brazil to France. With the support and cooperation of 250 Norman and Breton seamen accustomed to life in Brazil, they staged an unforgettable spectacle: naked, painted all colors, and speaking Tupi, they simulated hunting, and ate and danced against a background of tropical décor, with artificial fruits fixed to trees, and brilliantly colored parrots and monkeys fresh from Brazil. This spectacle, whose history has been preserved thanks to a precious illuminated manuscript (conserved in Rouen Municipal Library), made a great impression on the court. It contributed to the decision of Henry II to favor the project of Admiral de Villegaignon that was sponsored by the king’s favorite, Admiral de Coligny. Up until this time, it was only the shipowners who had been interested in Brazil. Now the king decided to take the project of establishing a French presence in the New World seriously; it was to be named “Antarctic France.”

**The 18th century: the Age of Enlightenment and the philosophers**

The Age of Enlightenment heralded a new vision of the world: science became a priority in the minds of the intelligentsia who lauded study and knowledge.

The expedition of the scientist La Condamine inaugurated a new kind of venture. The Paris Academy of Science wanted to test the theories of Newton concerning the size of the terrestrial globe. Newton had hypothesized that the earth was an “ellipsoid with a flattened rotation,” that is to say, that the equatorial radius was longer than the polar radius. This theory was not accepted by Paris, notably by the astronomer Cassini. Thus, the Academy of Science decided to dispatch two expeditions, one to Lapland and the other to the equator, to determine the shape of the earth by measuring the length of a meridian arc. The astronomer, geographer, and naturalist, Charles-Marie de La Condamine (1701-1774) took part with six other scientists in the expedition of Godin and Bouguer to the equator (1735).

In 1743, after 8 years of research in the Andes, La Condamine left his companions after having measured the equatorial meridian arc (which led to the modern term equator). He decided to return to France by descending the Amazon from Peru down to Guiana. By pirogue, mules, with trunks filled with notes, and accompanied by his colleague and friend Don Pedro Maldonado, he pursued his adventure guided by the Indians. The voyage was of considerable interest. In his role of naturalist, La Condamine carried out an in-depth study of the terrain. He discovered rubber as well as a tree he called “quinquina,” and took notes on the myths of the Amazon, the famous republic of warrior women, and on the fabled Lake Parimé.

**The Ouro Preto conspiracy**

The Brazilians secretly dreamed of independence. The great liberal leader Joaquim de Nabuco said: “All our revolutions (before independence) were waves that began in Paris.” The books of the philosophers such as Diderot, Montesquieu, Voltaire, and Abbé Reynal influenced the idea of national independence, as did the French revolution of 1789. The main attempt to liberate the country, the miners’ uprising known as the *inconfidencia mineira* (1789), was an event in the history of Brazil resulting from a plot hatched in Paris by three Brazilian students. They adopted the same inspirational ideas as the philosophers and laced them with republican aspirations. The same was true for the conspiracies of Rio de Janeiro (1794), Bahia (1798), and the republican revolution of Pernambouc (1817).
Curiously, the independence of Brazil was influenced by two events in the history of France: the revolution of 1789 and the invasion of Portugal by Napoleon I. As a result of the latter, the Prince-Regent, João VI, had no choice but to abandon the banks of the Tagus and take refuge in Brazil.

**The exile of the Portuguese royal family to Rio, or the break with France**

In March 1808, the Portuguese royal family disembarked in Rio de Janeiro. This exile was to have an unexpected impact on the Brazilians. The year 1808 in fact marked a new era in the relations between Brazil and Europe. The viceroy's headquarters in the city became the seat of the Portuguese court, and the French occupation of Portugal enabled the colony to slowly gain its economic independence. The commercial monopoly imposed by Portugal on the colony had prohibited trading with all other nations. However, the first decree promulgated by the prince regent was “Our ports will be open to all friendly nations.” The following year a new decree made it possible for foreigners to be granted land under exactly the same conditions as the Portuguese.

**The French artistic mission of 1816**

After the abdication of Napoleon (1814-1815), relations between France and Portugal improved considerably, and Brazilian ports were opened to French trade. Dom João VI returned to Portugal leaving his son Dom Pedro, the prince regent, with the task of administering Brazil. Several years later, in 1822, under the influence of proponents of independence and the inauguration of a constitutional government, Dom Pedro proclaimed the independence of Brazil.
After the restoration of the Bourbons in France, French culture became the reference for the Portuguese monarchy living in Brazil. As a result, Dom João VI decided to invite a French artistic mission to Brazil to help in the founding of the Rio de Janeiro Academy of Fine Arts. Headed by le Breton, the mission consisted of two painters (Nicolas Taunay and Jean-Baptiste Debret), a sculptor (Antoine Taunay), an architect (Gérard Granjean de Montigny), and an engraver (Charles S. Pradier). The task of the mission was to plan a new urban landscape in the capital, lay out a network of streets, construct public buildings, and organize the Royal School of Science, Arts, and Crafts, to be inaugurated in 1826 under the name Imperial Academy of Fine Arts. The mission was also expected to liven up the cultural and social life of Rio and the forthcoming national celebrations: the marriage of Dom Pedro with Maria-Leopoldina of Habsburg, Archduchess of Austria, in 1817, the acclamation of Dom João VI as king the following year, and later the coronation of the Emperor Pedro I of Brazil. Throughout, the influence of the French artists was decisive. Maria-Leopoldina, a devotee of art and science, in her turn invited a mission of scholars and artists. The Portuguese court and the social elite very rapidly adopted the French way of life. In the 1820s, Ouvidor Street was a French street in Rio. It was the epitome of fashion, with haute couture, perfumes, and hairstylists, with only one English shoe shop to spoil the French monopoly. This quarter became the centre of elegance and the favorite haunt of the aristocracy.

**French naturalists and voyagers continue the tradition of traveling to Brazil**

The botanist Auguste de Saint-Hilaire was the first French scientist to penetrate and describe the interior of Brazil. His works were to give birth to a significant Brazilian cult in France. His great admirer was Ferdinand Denis (1817-1890), whose office in the Sainte-Geneviève Library in Paris was, during the Second Empire, the holy-of-holies for French admirers of Brazil. From 1810 on, numerous illustrated albums were published in Europe, initially by English voyagers due to England’s alliance with the Portuguese monarchy: *Travels to the Interior of Brazil* (1812), by the mineralogist John Mave; *Views and Customs of the City and Neighborhood of Rio de Janeiro* (1822), by Henry Chamberlain; and *Brazilian Journal* (1818), by the German geologist Wilhelm Eschwege.

The first illustrated French edition *Brazil, or the History of the Morals, Habits, and Customs of the Inhabitants of the Kingdom* (1822), by Ferdinand Denis and Hippolyte Taunay, was not published until after the fall of Napoleon. *The Picturesque and Historic Voyage to Brazil* (1831-1837), published in three volumes by Jean-Baptiste Debret, professor of the painting of history in the French Artistic Mission, is a document of great importance. This precious work summarizes Debret’s stay of fifteen years in Brazil. He describes the daily life, the customs at the court, and the Indians. Without this work, we would not have such a complete and lively vision of Brazil at that time. It remains the most important source of illustrations of the time of Dom João VI and of his son Dom Pedro I. Debret’s engravings have profoundly marked the Brazilian imagination: they
are found in all the school textbooks, and have inspired the themes in the processions of samba dancers. In 1849, Édouard Manet, aged 17, disembarked in Rio. He acknowledged that he had learned much from observing nature there, and especially the variation in light, which he considered “the most important character on the canvas.”

There was also the extraordinary voyage of Hercule Florence, a French draftsman, in the expedition of Baron Von Langsdorff, a naturalist and chargé d’affaires of Czar Alexander I. Florence also developed a form of photography before Daguerre, but it is the latter who would go down in history as the inventor of photography.

The Orleans-Bragança families
The two marriages between the princes of the Orleans family and the princesses of the imperial family of Brazil resulted in very close links that united the royal families of France and Portugal for two centuries. The two most famous Frenchmen in Brazil were the Prince of Joinville (1818-1900) and Gaston d’Orléans (1842-1922). The Prince of Joinville, third son of Louis-Philippe, married, in 1843, Princess Francisca-Carolina (1824-1898), daughter of Dom Pedro I. The princess possessed the lands of Santa Catarina, in the south of Brazil, where a town called Joinville arose. The prince had to leave France during the Second Empire (1851-1870), and took refuge for some time in Hamburg, in England, and then in the United States. This explains why Joinville was mainly inhabited by Germans, who emigrated there at that time, rather than by the French. Gaston d’Orléans, count of the town of Eu, eldest son of the Duke of Nemours and grandson of Louis-Philippe, married, in 1864, princess Isabel of Bragança (1841-1921), heiress to the throne of Portugal.

Hercule Florence was born in Nice, in 1804, the son of a tax collector and a minor noblewoman. He showed talent as a child for drawing and science and by the age of 14 was working as a calligrapher and draftsman in Monaco. After some experience at sea, he set sail for Brazil on board the French ship Marie Thérèse and arrived in Rio de Janeiro in May, 1824 aged 20. He worked for a spell as a lithographer in a bookstore and printer’s office before replying to newspaper advertisement for an illustrator and topographic draftsman on a scientific expedition to the Amazon. This was being organized by Baron von Langsdorff, the consul general of the Russian embassy in Brazil, for the Russian Imperial Academy of Sciences, and the expedition team also included Florence’s compatriot, the illustrator Adrien Taunay. During the four years that the expedition lasted, Florence made many illustrations, drawings, and watercolors of the flora and fauna, landscapes, and inhabitants of the Amazon region. He later recounted his adventures in a work entitled A Fluvial Voyage from Tietê to Amazon Rivers, through the Brazilian Provinces of São Paulo, Mato Grosso and Grand-Pará (1825-1829) which was only published for the first time in 1977. During the expedition, he developed a system of musical notation to record the songs of birds and sounds of other animals, a technique that he called “zoophonia.”

After the expedition, Florence married a Brazilian woman and settled in the province of São Paulo and became a businessman. He continued to put his talents as an inventor to good use. He invented a technique called “polygraphia,” a printing technique that he tried to use on his textiles that he sold in his shop. In 1832, he developed a method that he termed “photographia” which allowed camera obscura images to be fixed permanently on sheets of paper. He later used silver nitrate and paper to do this, recording his experiments in his diary dated 15th January 1833, and thus invented a process very similar to the one developed by Daguerre, who is considered the founder of photography. Unfortunately, none of his images have ever been found. Florence did not publish details about his invention and thus was never given the credit he deserved as one of the inventors of photography.
of Brazil and daughter of the emperor, Pedro II. On arrival in Rio, Gaston d’Orléans was appointed marshal in the Brazilian army, and subsequently featured in one of the most glorious pages in the military history of Brazil. The country went to war with Paraguay, and Gaston d’Orléans led the Brazilian expeditionary corps and contributed in 1870 to the victory.

France, an intellectual reference for Brazil

In the aftermath of independence (1822), Brazil looked for cultural models in Europe and, discarding Lisbon and London, the very Francophile if not Francophone Brazilian elite chose Paris. French was spoken in the drawing rooms, and the most-read foreign authors were French—Chateaubriand, Benjamin Constant, Balzac, Verlaine, Zola, Mallarmé, Victor Hugo, and many others. After the proclamation of the Brazilian Republic in 1889, the Brazilian people sang the Marseillaise, and the 14th of July was declared a national holiday, which says much concerning the links with France. Indeed, throughout the nineteenth century, Brazilian politicians and intellectuals were greatly influenced by the French Age of Enlightenment, the Revolution, and the swirl of ideas that confronted each other in Europe. Victor Hugo, a friend of Emperor Pedro II, and Auguste Comte (1798-1857), were considered the leading thinkers by the progressive Brazilian intellectuals, who yearned for a social and political revolution in their country. It was thanks to mathematics that the positivism of Comte penetrated Brazil—thus the military and the engineers were the first to be influenced by it. The positivist slogan: “Love as principle, Order as foundation, and Progress as the aim,” impressed republican Brazilians so much that the motto “ordem e progresso” (order and progress) features on the Brazilian flag.

The influence of French scientists and doctors contributed largely to research in human and experimental science, as well as the advances in hygiene and the battle against epidemics led by Gary and Revy. Moreover, the Pasteur model adopted by Oswaldo Cruz and the first laboratory of physiology created by Louis Coutil were crucial. While staying in Paris, Emperor Pedro II visited the Mining School and recruited a young professor of geology, Claude-Henri Gorceix, who founded the Mining School of Ouro Preto. Camille Cléau, a historian, was director of the imperial and the public library of Rio de Janeiro from 1850 to 1867, and Emmanuel Liais, a physician, established an observatory outside the city in 1865. Another influential person, and who remains so today, was Allan Kardec (1804-1869), founder of the doctrine of spiritualism, and author of the Book of Spirits (1857).

Brazilians in Paris

It was the duty of every good Brazilian intellectual and artist to go to Paris. Mario Carelli wrote: “Paris was the uncontested example of progress and the mythical reference of artists.” Many intellectuals made the trip to Paris: the statesman Joaquim Nabuco (1849-1910) stayed there from 1873 to 1874 and became so Francophile that he began to write in French. Eduardo Prado (1860-1901), pamphleteer and journalist, who inherited one of the largest fortunes in São Paulo, settled in Paris. For many Brazilians, the 1900s were a time of prosperity: the Brazilian currency was strong thanks to the export of coffee and rich Brazilians readily made the journey to France. Alceu Amoroso de Lima was fascinated by the Universal Exposition of 1900 where he discovered “fairy-like electricity.”
Oswald de Andrade visited Paris several times, notably in 1925, with his painter wife Tarsila de Amaral. In their studio in Montmartre, they gave exotic dinners attended by Brazilian friends and the French artistic avant-garde. Blaise Cendrars was the sponsor of Tarsila’s first exhibition in Paris, and a poem, Paysage, from his Feuilles de Route illustrated her catalog. The Black Anthology by Cendrars was considered by the “modernists of Rio and São Paulo to be the manifesto of their own nascent identity.” In 1924, the avant-garde invited Cendrars to Brazil and proclaimed him as the model and master of modernity.

The Brazilian composer Heitor Villa-Lobos was interpreted by Rubinstein at the Salle Gaveau, and was well received. The painter Cicero Dias was the last to go to Paris before the Second World War, and though he was influenced by the French school of painting, he remained inspired by his homeland of Pernambouc.

Santos Dumont (1873-1932), after developing several dirigibles, became well known as an aviation pioneer and on 23rd October 1906, made the first official propelled flight in Europe. He wrote his memoirs In the Air in French (1904).

BRAZIL, FRANCE’S MAIN PARTNER IN LATIN AMERICA

The problem of infectious diseases, and more particularly yellow fever, prompted Oswald Cruz (1872-1917) to make the voyage to France (1896). He joined the Pasteur Institute where he became convinced of the importance of the Pasteur scientific method. On his return to Brazil, he created the Institute of Medical Experimentation, later named the Oswald Cruz Institute, today a famous research center.

In 1936, the French architect Le Corbusier spent six weeks in Brazil where he traveled with Lucius Costa and his team; Oscar Niemeyer, Reidy, and others. This meeting led to the construction of the first modern edifice, the Ministry of Education, and the emergence of a new generation of architects.

The great transfer of knowledge from Europe to Brazil and the blooming of scientific cooperation began in 1934/1935, during the development of the University of São Paulo and the University of the Federal District. At that time, Brazil called for a large delegation of European researchers in the social sciences, and those who responded were mainly French. Thus, the anthropologist Lévi-Strauss, the sociologist Roger Bastide, and the historian Fernand Braudel headed to São Paulo. Today, there is a significant collaboration between Brazil and the Center of Nuclear Studies in Grenoble and the GRESIL group, whose vocation is to develop works in the field of nuclear energy.

The university teaching of human geography in Brazil is based on the works of two key French figures: professors Pierre Deffontaines and Pierre Monbeig. Research on man, his thoughts and his cultures, unknown yesterday and under threat today, was carried out by the Musée de l’Homme in Paris, had a great impact on the anthropologists, ethnologists, and prehistorians of the world. Paulo Duarte, a young Brazilian humanist, created along with his French director, Paul Rivet, a center of Brazilian studies. He launched the study of prehistory and in the 1950s founded the Institute of Prehistory. The Franco-Brazilian research program led to excavations and the discovery of prehistoric rock art in the Mato Grosso and Paran Basin.

In 1967, the governments of Brazil and France signed an agreement for technical and scientific cooperation that involved several different domains (geology, astronomy, aeronautical and spatial activities, postal services, exploration of the sea and its hydraulic resources, as well as conservation of forests). In 1948, a cultural agreement was signed between the two countries, and since 1996 a Franco-Brazilian general commission has coordinated bilateral relations.

The many faces of this cooperation demonstrate the common advantages of exchanging knowledge and expertise. A remarkable study on this subject was carried out by Luiz Claudio Cardoso and Guy Martinière: France-Brazil, Twenty Years of Cooperation (science and technology), published in 1989 by IHEAL (Institute of Higher Latin American Studies), in both France and Brazil.
The French airmail service and the military mission (1919-1939)

At the beginning of the 1920s, thanks to the airmail pioneers (Pierre Latécoère and Jean Mermoz), France created a transatlantic airmail service between the two countries that became regular in 1935. Shortly after the end of the First World War, the Brazilian government requested Clemenceau to send a military mission to Rio in order to inspire young Brazilian officers with the Saint-Cyr spirit. The French instructors found themselves teaching officers and reorganizing the management of supplies and veterinary services. Up until 1939, they were rewriting certain regulations, forming staff officers and cavalrymen, and training pilots of the young air force.

In 1922, France participated in the celebration of Brazil’s centenary of independence and contributed to the International Exhibition in Rio. The French pavilion, a replica of the Petit Trianon, was presented to Brazil at the end of the exhibition. Today, it houses the seat of the Brazilian Academy of Letters, modeled on the French Academy. The same year the Frenchman Paul Landowski was commissioned to sculpt the famous statue of Cristo Redentor (Christ the Redeemer) on the top of Corcovado (hunchback) mountain. The Brazilian Heitor da Silva Costa was the engineer, and the statue was inaugurated in 1931.

Brazil and France share five centuries of eventful history, and over the course of time this has enabled the two countries to establish a deep and reciprocal friendship. The French were fascinated very early by this continental country that managed, depending on the era, to fascinate merchants, artists, botanists, and scientists. Brazilians were, in turn, fascinated by French culture and the voyage to Paris that was also part of the dream. So, let us hope that in the future, this respect for each other will continue to improve the friendly links that exist between the two countries.

LA FRANCE ET LE BRÉSIL : REGARDS SUR CINQ SIÈCLES D’HISTOIRE

Chaque année la France rend hommage à un pays, un événement qui permet de mettre en avant les relations culturelles, historiques, ou autres qui ont existé entre la France et le pays célèbré. L’année 2005 a été l’année France–Brésil et le grand nombre de manifestations, d’expositions, de concerts, de colloques, de conférences, etc, sur les sujets les plus divers montrent le caractère privilégié des relations que la France a entretenues et entretient toujours avec le Brésil, pays qui a de l’autre côté de l’Atlantique, largement mis en avant, cette année, son attachement à la France. Si les relations, de 1555 à 1711, ont été mouvementées – la France espérant y fonder une colonie – en revanche, à partir du siècle des Lumières jusqu’au lendemain de la seconde guerre mondiale, la France a été pour le Brésil une référence constante pour les intellectuels, l’époque impériale et la jeune république.
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