The Venous Valve and Primary Chronic Venous Disease

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EDITORIAL
VENOUS VALVE INCOMPETENCE: THE FIRST CULPRIT IN THE PATHOPHYSIOLOGY OF PRIMARY CHRONIC VENOUS INSUFFICIENCY. INSUFFISANCE VALVULAIRE VEINEUSE : PREMIER CHÂINON DANS LA GÉNÈSE DE LA MALADIE VEINEUSE CHRONIQUE PRIMAIRE

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Venous valve incompetence: the first culprit in the pathophysiology of primary chronic venous insufficiency

by J. Bergan, USA

CHRONIC VENOUS INSUFFICIENCY (CVI) IS MANIFESTED IN THE lower extremities. Its most obvious sign is protuberant, saccular varicose veins. These fail to fulfill their assigned function of transporting blood from the lower extremities to the heart. Instead, they allow the weight of the column of blood from the right atrium as it is transmitted through the valveless vena cava and iliac veins to be expressed in the thigh and leg. There, the venous hypertension initiates a cascade of inflammatory reactions that may progress to edema, venous eczema, ankle skin hyperpigmentation, atrophie blanche, and other manifestations such as lipodermatosclerosis and venous leg ulcers.

Recently, considerable progress has been made in understanding the pathophysiological processes at the cellular and molecular level that cause these diverse manifestations. These may become targets for preventative pharmacologic intervention. If so, there will be a change in focus from ablation to preservation. The goal of this editorial is to explain how the processes of venous insufficiency begin because of initial venous valve failure and how they are perpetuated by that valve failure.

Venous hypertension
In spite of the diversity of signs and symptoms associated with CVI, it is likely that they are all related to venous hypertension. Venous hypertension involves reflux through incompetent valves. Pressure in the veins of the leg is determined by two components, a hydrostatic component, described above, and a hydrodynamic component related to pressure generated by contraction of the skeletal muscles of the leg that is transmitted to the venular capillary network. Both components are profoundly modified by the action of the venous valves. During standing without skeletal muscle activity, venous pressures in the leg are determined by the hydrostatic component and capillary flow. Skeletal muscle contractions, as during ambulation or exercise, increase pressure within the deep leg veins. Competent venous valves ensure that the resulting blood flow is toward the heart, leading to emptying of the deep and superficial venous systems and a fall in venous pressure. Even quite small leg movements can provide significant pumping action. However, in the absence of competent valves, venous pressure fails to fall with leg movements, and the pressures generated by muscle contraction are transmitted to the skin microcirculation. Skin changes in CVI stem from venous pressures in the leg that reach higher than normal levels and are elevated for abnormally prolonged periods of time.

Valvular incompetence
Venous valve incompetence is a central feature of venous hypertension that in turn underlies most of the signs characteristic of chronic venous disease (CVD). Alterations and damage to valves have been noted angiographically. These include stretching, splitting, tearing, thinning, and adhesion of valve leaflets. Reduction in the number of valves has been observed in segments of saphenous veins from patients with CVI.
These observations do not reveal the mechanism of valvular disappearance or how such remodeling fits into the pathophysiologic sequence of events in CVD. However, an important step forward came when we examined valves from great saphenous veins removed from patients with CVD. Using a monoclonal antibody specific for monocytes and tissue macrophages, we found infiltration of valve leaflets and the venous wall by monocytes and macrophages in all vein specimens from CVD patients and in none from controls with normal veins. Infiltration was greater in the valve sinus and proximal venous wall than in the distal aspect of the valve leaflet and distal vein wall (Figure 1A). This suggested a link with elevated venous pressure. Further investigations have shown that inflammation and subsequent remodeling of the venous valves and wall are the fundamental mechanisms underlying valve damage and the lesions seen angioscopically.

Molecular mechanisms

Hemodynamic forces, such as blood pressure changes in the wall and shear stress, as well as varying planes of laminar and turbulent flow, induce activation of the leukocytes and endothelial cells. Integrins appear to act as intermediaries, and expression of adhesion molecules has been observed. Breakdown of the extracellular matrix of the media and adventitia through activation of matrix metalloproteases (MMPs) has been observed. In particular, expression of MMP-1, MMP-2, MMP-9, and tissue inhibitors of metalloproteinase (TIMP) have been studied. Telangiectasias, reticular veins, and true varicose veins appear to be a consequence of the changes induced by venous hypertension and shear stress (Figure 1B). As described above, when saphenous vein valves are observed angioscopically at the time of vein stripping, they show severe deformities. The animal model of induced venous hypertension that we have worked with demonstrates early venous valve changes that replicate those observed in humans.

This observation provides a link from venous hypertension to an induced inflammatory reaction that stimulates the valve damage. Thus the model has been useful for defining the fundamental mechanisms that cause venous valve failure and varicose veins. In the future it may prove useful in pharmacologic testing to identify agents that will be useful to prevent or treat venous insufficiency.

Primary venous insufficiency

A dysfunctional venous system is caused for the main part by functional failure of venous valves. The molecular mechanisms uncovered recently that enter into functional valve failure are mentioned above. Other factors are traditionally cited as contributing to venous valve failure; these include female sex, pregnancy, obesity, a standing occupation in women, and heredity. An increase in vein diameter is one cause of valve dysfunction and reflux. Progesterone inhibits smooth muscle contraction. This is useful in preventing uterine contraction and spontaneous abortion in pregnancy. However, preventing vein wall smooth muscle contraction allows passive dilation of veins and when a critical diameter is reached, a functioning venous valve becomes dysfunctional or incompetent. As half of a women’s adult lifetime is under the influence of progesterone, and this is exacerbated markedly during pregnancy, it is no wonder that primary venous insufficiency is twice as common in women than in men.

The effect of persistent valvular reflux is a chronic increase in distal venous pressure. This venous pressure increases as one proceeds from the inguinal ligament past the knee to the ankle. The prolonged venous hypertension initiates a cascade of pathologic events. These manifest themselves clinically as lower extremity edema, pain, itching, skin discoloration, and ulceration. The earliest signs of venous insufficiency are often varicose veins in the epidermis and dermis, and these are called telangiectasias (Figure 2). Slightly deeper, are flat, blue-green veins of the reticular (network) system. These may become varicose as well. Finally, deeper yet, are the varicose veins themselves. All of these abnormal veins and venules have one thing in common: they are elongated, tortuous, and have dysfunctional venous valves.

Manifestations of telangiectasias, reticular varicosities, and varicose veins are grouped together under the term primary venous insufficiency.
Chronic venous insufficiency

Skin changes of hyperpigmentation, scarring from previous ulceration, and active ulcerations are grouped together under the term CVI. Numerous theories have been postulated regarding the cause of CVI and that of venous ulceration.10,11

Some theories proposed in the last century have shown remarkable prescience. An example is the theory of venous stasis first published in a manuscript by John Homans of Harvard in 1917.12 It was a treatise on diagnosis and management of patients with CVI, and in it, Dr Homans coined the term “postphlebitic syndrome” to describe the skin changes of CVI. He stated that, “Overstretching of the vein walls and destruction of the valves... interferes with the nutrition of the skin... therefore, skin which is bathed under pressure with stagnant venous blood will form permanent open sores or ulcers.” That he called attention to destruction of valves was remarkable. However, that statement, like many others that describe venous conditions and their treatments, is steeped in dogma, and apart from the description of damaged valves, is short on observational fact. Actually, it is unlikely that Homans observed valve damage as we know it in primary venous insufficiency. He may have seen the ravages of the phlebitic valve destruction with adherence of leaflets to one another and to the vein wall. The term stasis ulcer honors that misconception, as do the terms venous stasis disease and stasis dermatitis.

Alfred Blalock, who later developed pericardiac surgery, disproved the theory of stagnant blood by studying oxygen content from varicose veins and normal veins.13 He pointed out that the oxygen content of the femoral vein in patients with severe CVI was greater than the oxygen content of the contralateral nonaffected limb. Because oxygen content was higher, some investigators thought that arteriovenous fistulas caused venous stasis and varicose veins. That theory, though disproved, has some basis in fact, since the entire thermoregulatory apparatus in limbs depends on the opening and closing of arterial venous shunts (Figure 3). These shunts are important, as they explain some terrible accidents that happen during sclerotherapy when sclerosant entering a vein is shunted into the arterial system and distributed in its normal arborization.14 Microsphere investigations have failed to show such shunting, and the theory of arteriovenous communications has died despite the fact that these shunts actually exist and do open and close under the influence of venous hypertension and ambient temperature.

Hypoxia and its part in causation of CVI were investigated throughout the last 25 years of the 20th century. English investigators thought that a fibrin cuff, observed histologically, blocked transport of oxygen and was responsible for skin changes in CVI at the ankles and distally.15 That theory has been abandoned.

There are two elements that interact to cause all of the manifestations of lower extremity severe CVI. These are failure of the vein valves, the first culprit, and subsequently the skin changes of hyperpigmentation, atrophie blanche, and skin ulceration at the ankles. Both of these are related to venous hypertension. Our work suggests that venous hypertension causes a shear stress–dependent leukocyte-endothelial interaction, which has all of the manifestations of chronic inflammation.16 These are leukocyte rolling, firm adhesion to endothelium, and subsequent migration of the cells through the endothelial...
barrier into parenchyma of valves and vein walls. There, macrophages elaborate MMPs, which destroy elastin and possibly collagen as well. Vein walls become stretched and elongated. Vein valves become perforated, torn, and even scarred to the point of near total absence. These changes are seen both macroscopically and angioscopically and have been produced experimentally by constructing an arteriovenous fistula.

The second manifestation of CVI is expressed in the skin. Therefore, future therapy must be directed at preventing such venous hypertension by preventing valve failure.

Conclusions

The processes of valve and vein wall damage and the advanced skin changes of CVI are the result of sterile inflammatory reactions. Valve failure is triggered by venous hypertension and, in turn, causes distal venous hypertension. Therefore, future therapy must be directed at preventing such venous hypertension by preventing valve failure.

REFERENCES


Keywords: venous valve incompetence; venous hypertension; venous insufficiency; molecular mechanisms; inflammation
INSUFFISANCE VEINEUSE CHRONIQUE (IVC) SE MANIFESTE dans les membres inférieurs. Son signe le plus évident est la présence de veines variqueuses saillantes et sacciformes. Ces veines n’arrivent pas à remplir leur fonction, qui consiste à transporter le sang des membres inférieurs vers le cœur. Au lieu de cela, elles permettent au poids de la colonne de sang provenant de l’oreillette droite par l’intermédiaire de la veine cave et des veines iliaques sans valvules de se manifester dans la cuisse et la jambe. Là, l’hypertension veineuse amorce une cascade de réactions inflammatoires susceptibles de progresser vers un œdème, un eczéma veineux, une hyperpigmentation cutanée de la cheville, une atrophie blanche et d’autres manifestations telles qu’une lipodermatosclérose et des ulcères veineux de jambes.

Ces derniers temps, des progrès considérables ont été faits dans la compréhension des processus physiopathologiques à l’origine de ces diverses manifestations aux niveaux cellulaire et moléculaire. Ces processus sont susceptibles de devenir les cibles d’une intervention pharmacologique préventive faisant glisser le traitement de l’ablation à la conservation. L’objectif de cet éditorial est d’expliquer comment l’insuffisance veineuse enclenche et entretient une insuffisance valvulaire veineuse initiale.

Hypertension veineuse

Il est probable que tous les signes et symptômes associés à l’IVC soient liés à l’hypertension veineuse. L’hypertension veineuse implique un reflux dû à une insuffisance valvulaire. La pression dans les veines de la jambe est déterminée par deux composantes, une composante hydrostatique, décrite ci-dessus, et une composante hydrodynamique en rapport avec la pression générée par la contraction des muscles squelettiques de la jambe et transmise jusqu’au réseau capillaire (formé de veinules). Ces deux composantes sont profondément modifiées par l’action des valvules veineuses. En position debout sans activité des muscles squelettiques, les pressions veineuses de la jambe sont déterminées par la composante hydrostatique et le débit capillaire. Les contractions des muscles squelettiques, telles qu’elles existent pendant la marche ou l’exercice, augmentent la pression à l’intérieur des veines profondes de la jambe. L’étanchéité des valvules veineuses garantit que le flux sanguin qui en résulte est dirigé vers le cœur, ce qui conduit à la vidange des systèmes veineux profond et superficiel et à une chute de la pression veineuse. Même des mouvements de jambe relativement petits peuvent faire fonctionner la pompe de façon significative.

Cependant, en l’absence de valvules étanches, la pression veineuse ne chute pas avec les mouvements de la jambe et les pressions générées par la contraction musculaire sont transmises à la microcirculation cutanée. Les changements cutanés de l’IVC sont dus aux pressions veineuses de la jambe, qui atteignent des niveaux supérieurs à la normale et restent élevés pendant des durées anormalement prolongées.
Insuffisance veineuse

L’insuffisance valvulaire veineuse est une caractéristique centrale de l’hypertension veineuse qui, à son tour, est une cause sous-jacente de la plupart des signes caractéristiques de la maladie veineuse chronique (MVC). Des modifications et des lésions des valvules ont été observées par angioscopie. Celles-ci incluent l’étirement, la rupture, la déchirure, l’amincissement et l’adhérence des valvules. Une réduction du nombre des valves a été observée dans des segments de veines saphènes de patients présentant une insuffisance veineuse chronique.

Ces observations n’expliquent pas comment les valves disparaissent ni comment ce remodelage s’intègre dans l’enchaînement des événements qui aboutissent à la MVC. Cependant, un pas important a été fait lorsque nous avons examiné les valvules des grands veines saphènes de patients atteints de MVC. En nous servant d’un anticorps monoclonal spécifique pour les monocytes et les macrophages tissulaires, nous avons trouvé une infiltration des valvules des valvules et de la paroi veineuse par des monocytes et des macrophages dans tous les échantillons de veines provenant de patients atteints de MVC, alors qu’aucune n’a été retrouvée dans les échantillons des témoins avec des veines normales. L’infiltration était plus importante dans le sinus valvulaire et la paroi veineuse proximale que dans le côté distal de la valve de la valvule et la paroi veineuse distale (Figure 1A). Cette découverte nous a fait envisager l’existence d’un lien avec une pression veineuse élevée. D’autres recherches ont fait apparaître l’inflammation et le remodelage ultérieur des valvules veineuses et de la paroi veineuse comme les mécanismes fondamentaux sous-jacents à l’atteinte et aux lésions valvulaires observées par angioscopie.

Mécanismes moléculaires

Des forces hémodynamiques, telles que des changements de la pression sanguine dans la paroi et la contrainte de cisaillement, ainsi que des plans changeants d’écoulement laminaire et turbulent, inducing l’activation des leucocytes et des cellules endothéliales. Les intégrines semblent agir comme des intermédiaires et l’expression de molécules d’adhésion a été observée. Une dégradation de la matrice extracellulaire de la média et de l’adventice au travers de l’activation des métalloprotéases matricielles (MMPs) a été observée. En particulier, les expressions des MMP-1, MMP-2, MMP-9 et des inhibiteurs tissulaires des métalloprotéïnases (TIMP) ont été étudiée. Les télangiectasies, les veines réticulaires et les véritables varices semblent être une conséquence des changements induits par l’hypertension veineuse et par la contrainte de cisaillement (Figure 1B). Comme indiqué ci-dessus, l’observation angioscopique des valvules des veines saphènes lors de l’éveinage des veines a fait apparaître les sévères déformations décrites. Le modèle animal de l’hypertension veineuse induite sur lequel nous avons travaillé démontre des changements précoces dans les valvules veineuses qui reproduisent ceux observés chez les humains.

Cette observation lie l’hypertension veineuse et la réaction inflammatoire induite qui stimule l’atteinte valvulaire. Par conséquent, le modèle s’est révélé utile pour définir les mécanismes fondamentaux à l’origine de l’insuffisance valvulaire veineuse et des varices. À l’avenir, il pourrait se révéler utile lors des essais pharmacologiques pour identifier les agents susceptibles d’être efficaces dans la prévention ou le traitement de l’insuffisance veineuse.

Insuffisance veineuse primaire

Toutefois, l’obstacle à la contraction des muscles lisses de la paroi veineuse entraîne une dilatation passive des veines et, lorsqu’un diamètre critique est atteint, une valve veineuse jusqu’alors fonctionnelle présente un dysfonctionnement ou une insuffisance. Dans la mesure où la moitié de la vie adulte des femmes est sous l’influence de la progestérone et où celle-ci est fortement exacerbée pendant la grossesse, on ne s’étonnera pas que l’insuffisance veineuse primaire soit deux fois plus fréquente chez les femmes que chez les hommes.

Le reflux valvulaire persistant entraîne une augmentation chronique de la pression veineuse distale. Cette pression veineuse augmente à mesure que l’on passe du pilier du canal inguinal à la cheville, en passant par le genou. L’hypertension veineuse prolongée amorce une cascade d’événements pathologiques. Ces événements se manifestent cliniquement sous forme d’aédomes, de douleurs, de démangeaisons, de décoloration cutanée et d’ulcération des membres inférieurs.


Les manifestations des télangiectasies, les varicosités réticulaires et les varices sont regroupées sous le même terme d’insuffisance veineuse primaire.

Insuffisance veineuse chronique

Les changements cutanés liés à l’hyperpigmentation, les cicatrices dues à une ulceration antérieure et les ulcerations actives sont regroupés sous le même terme d’insuffisance veineuse chronique (IVC). De nombreuses théories ont été avancées sur la cause de l’insuffisance veineuse chronique et des ulcères veineux.

Certaines des théories proposées au siècle dernier ont fait preuve d’une remarquable perspicacité. À titre d’exemple, la théorie de la stase veineuse, publiée pour la première fois dans un manuscrit de John Homans, de Harvard, en 1917. Il s’agissait d’un traité portant sur le diagnostic et la prise en charge de patients présentant une insuffisance veineuse chronique, dans lequel le Dr Homans a inventé le terme de « syndrome post-phlébitique » pour décrire les changements cutanés de l’IVC. Il affirmait alors que « L’étirement excessif des parois veineuses et la destruction des valves… interfèrent avec la nutrition de la peau… par conséquent, la peau soumise à un bain sous pression avec du sang veineux stagnant forme des plaies ouvertes permanentes ou des ulcères ». Le fait d’avoir attiré l’attention sur la destruction des valves était remarquable. Cependant, cette affirmation, comme de nombreuses autres qui décrivent les pathologies veineuses et leurs traitements, relève du dogme et, à l’exception de la description de l’atteinte des valves, manque de faits d’observation. En fait, il est peu probable que Homans ait observé les atteintes valvulaires telles que nous les connaissions dans l’insuffisance veineuse primaire. Il est possible qu’il ait vu les ravages de la destruction valvulaire phlébique avec adhérence des valves l’une sur l’autre et sur le paroi veineuse. Le terme d’ulcère de stase fait honneur à cette idée fausse, tout comme les termes de maladie de stase veineuse et de dermite de stase.

Alfred Blalock, qui, plus tard, a développé la chirurgie péricardique, a contesté la théorie du sang stagnant en étudiant la teneur en oxygène des varices et des veines normales. Il a notamment fait remarquer que la teneur en oxygène de la veine fémorale des patients présentant une insuffisance veineuse chronique sévère était supérieure à la teneur en oxygène du membre opposé non atteint. La teneur en oxygène étant plus élevée, certains investigateurs ont pensé que les fistules artério-veineuses pouvaient être à l’origine de la stase veineuse et des varices. Cette théorie, bien que réfutée, n’est pas dénuée de fondement, dans la mesure où l’inté-
gralité de l’appareil thermorégulateur des membres dépend de l’ouverture et de la fermeture de shunts artérioveineux (Figure 3). Ces shunts sont importants, dans la mesure où ils expliquent certains accidents terribles qui se produisent pendant les injections sclérosantes lorsque le produit sclérosant qui pénètre dans une veine est dérivé dans le système artériel et distribué dans sa ramification normale. Des études sur microphères n’ont pas permis de mettre en évidence une telle dérivation et la théorie des communications artérioveineuses a été abandonnée bien que ces shunts existent réellement et qu’ils se ferment sous l’influence de l’hypertension veineuse et de la température ambiante.


**Conclusions**

Les processus d’atteinte des parois des valves et des veines, ainsi que les changements cutanés avancés de l’IVC, sont la conséquence de réactions inflammatoires stériles. L’insuffisance valvulaire est une maladie veineuse primaire et secondaire, décelée par une hypertension veineuse et, à son tour, provoque une hypertension veineuse à distance. Par conséquent, les traitements futurs devront s’orienter vers la prévention d’une telle hypertension veineuse, en empêchant l’insuffisance valvulaire.
The challenge to this concept came centuries later, when direct observation of valve movements and in vivo measurement of blood flow velocity revealed some intriguing phenomena. In 1926, E. B. Carrier described an intricate blood flow pattern around the venous valve leaflets, by direct observation of red blood cell movement in the wing of the bat.3 This was exactly the same pattern as predicted by Leonardo da Vinci, and confirmed by K. D. Kele for a geometrically similar aortic valve.4 While the role of this flow phenomenon in the functioning of the aortic valve was understood, in the case of the venous valve, it was simply ignored. Carrier’s observations that venous valve leaflets do not open all the way out to touch the sinus wall were confirmed by in vitro experimentation with human saphenous valves.5 These findings demonstrated the complexity of the hemodynamics around the valve that far exceeded the simple sequence of forward and backward flow, and challenged the simplicity of the then current concept of the physics behind the closing of the venous valve.

Development of modern diagnostic ultrasound techniques opened up the opportunity to detect valvular incompetence in patients with chronic venous diseases.6 At the time of the original work in this area, ultrasound equipment did not allow reliable visualization of the valve itself. Instead, Doppler-based registration of reverse blood flow in the venous segment in response to Valsalva or rapid compression-decompression maneuvers was used to define valvular insufficiency. This approach advanced venous diagnosis by providing a reliable tool for reflux detection that is used to this day. Unfortunately, the indirect approach also created confusion between the presence of reverse flow in the vein and the function of the valve itself. The terms “reflux time” and “valve closure time” were incorrectly used interchangeably. As a consequence, the view that reverse flow through the valve is necessary for valve closure was promulgated.7

Increasing awareness of chronic venous disease as a growing public health problem in an aging population has uncovered significant gaps in our understanding of the physiology and pathophysiology of the venous system. Among the many features distinguishing the venous system from other vasculature, is the unique and most intriguing delicate structure of the venous valve.

The apparent simplicity of this apparatus leaves very little room for speculation regarding its function. Long before Harvey, the venous valve was viewed as a passive membrane that opened and closed the vessel’s lumen.1 An elegant and convincing demonstration of unidirectional venous flow, first formulated in Excercitarto Anatomicae de Motu Cordis et Sanguinis in Animalibus, was an essential part of the modern understanding of the cardiovascular system.2

Based on recent observations, a new concept of the mechanism of venous valve closure and the role of valves in the circulation has been proposed. In healthy individuals, valve geometry and pulsatile venous flow determine the mechanical forces that act on the valve’s cusps, causing their movements. Under physiological conditions, the venous valve creates a complex local flow pattern that facilitates forward movement of blood, increases the supply of oxygenated blood to valve pockets, and causes the cyclic closure of the valve itself, securing the pulsatile nature of venous flow. In rare circumstances of reverse flow, valves close, securing unidirectional flow. Dysfunction of the valve can lead to disruption of a normal flow pattern. This changes the oxygenation of valve pockets, potentially leading to thrombi formation, or causes asymmetrical jets of reverse flow through an incompetent valve, producing shear stress–mediated pro-inflammatory and pro-thrombotic endothelial transformations.


Keywords: venous valve function; physiology; reverse flow; pathology

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A new generation of ultrasound equipment, particularly the introduction of B-flow modality, has made it possible to observe venous valves and blood flow in the area of the valve in undisturbed physiologic conditions. Artificial maneuvers to force the blood backward to check the competency of the valve are no longer needed for normal valve observations. One can simultaneously observe the motions of valve leaflets, changes in venous sinus shape and size, and blood flow through the valve during a normal respiratory cycle, in different positions of the body and during exercises such as dorsal and plantar flexion of the foot.

**Function of the normal valve**

*Valve closure by reverse flow*

The ability of the venous valve to close in reaction to reverse flow or a distally directed pressure gradient has been used for the diagnosis of venous insufficiency ever since Brodie and Trendelenburg developed their simple and useful clinical test.10,11 20s century plethysmographic techniques involved changing the patient’s position from horizontal to vertical to measure the refill time as an indicator of valvular competency. A more physiologic method of emptying the calf veins using exercise was added later. These techniques were not convenient for ultrasound-based investigations, however, and were replaced by the Valsalva maneuver, compression of the extremity proximal to the segment of interest, or compression of the extremity distally, followed by rapid decompression.10

Widespread use of ultrasound-based diagnostics exposed the existence of retrograde flow in clinically healthy extremities under test conditions. To resolve this issue, cut-off values were proposed to differentiate pathologic reflux from physiologically normal reverse flow.11 Surprisingly, very little attention had been paid to such an interesting phenomenon as the existence of reverse flow in veins. The exception is a single report postulating that an apparent mechanism of emptying the calf veins using exercise was added later. These techniques were not convenient for ultrasound-based investigations, however, and were replaced by the Valsalva maneuver, compression of the extremity proximal to the segment of interest, or compression of the extremity distally, followed by rapid decompression.10

During the opening phase, the cusps move from the closed position toward the sinus wall. This phase lasts on average for 0.3 seconds when the patient is in the horizontal position.

*Equilibrium phase*

After reaching a certain point in this phase, the valves cease opening and enter the equilibrium phase. During this phase, the leading edges remain suspended in the flowing stream and undergo oscillations that resemble the flutter of flags in the wind. The valve is maximally open during this phase. Still cusps maintain their position at some distance from the wall, creating a funnel-like narrowing of the lumen. The cross-sectional area between the leaflets is about two thirds of the cross-sectional area of the vein distal to the valve. The flow accelerates in this stenotic area, forming a proximally-directed jet. Upon impact of the jet against a layer of much slower-moving blood proximal to the valve, reflection of flow occurs in the mural parts of the stream. While the larger stream located in the center of the vessel is directed proximally along the axis of the vein, the smaller part of the flow turns into the sinus pocket behind the valve cusp. This part of the stream forms a vortex along the sinus wall and the mural side of the valve cusp before re-emerging into the main stream in the vein.

As vortical flow persists, it applies pressure upon the mural surface of the valve cusps. When the pressure on the mural side of the cusp and the pressure on the luminal side of the cusp are in equilibrium, the valve remains open and the cusps float in the stream. This dynamic equilibrium is sustained by an equilibrium in the velocities of the two streams—
vortex on the mural side, and axial flow on the luminal side of the valve cusps. Changes in either of these streams can lead to the closure of the valve. Self-excited oscillations of the leading edges of the leaflets that occur during this equilibrium phase make this balance unstable and very sensitive to small changes in flow.

closing phase and closed phase
When the venous flow rate increases distal to the valve, as occurs during foot movements, the velocity of the flow between the valve cusps rapidly increases. This causes a fall in the pressure on the luminal side of the cusp, and the cusps start moving toward the axis of the vessel, further constricting the lumen (Figure 2). With rising pressures on the mural side and falling pressures on the luminal side of the cusps, valve closure is favored. The closing phase ensues. The leaflets move synchronously toward the center. The cusps of the valve assume a symmetrical position at an equal distance from the walls on both sides of the sinus. This phase lasts 0.4 seconds when the subject is at rest, and is shorter when foot movements are performed. The last phase is the closed phase, during which, the cusps remain closed.

The duration of the valve cycle and each of its four phases depends upon the position of the body. In the standing position, we found that the duration of the cycle was from 2.9 seconds to 3.2 seconds (95% confidence interval [CI]), which corresponds to a frequency of 18.8 to 20.4 cycles per minute (similar to respiration frequency). In a horizontal position, the duration of the cycle was from 1.7 seconds to 1.8 seconds (95% CI). This rhythm (34.2 to 36.1 cycles per minute) is most likely influenced by both respiratory and cardiac cycles. Muscle activity (dorsal and plantar flexions of the foot) causes shortening of the closing phase. As we observed, every single foot movement causes a significant increase in velocity and closure of the valve.

Based on our observations, we proposed a new concept of the mechanism of venous valve closure and the role of the valve in circulation. In the absence of forced reverse flow, the valve cusps consistently undergo the four phases constituting the valve cycle. The local hemodynamic events, such as vortical flow in the sinus pocket, play important roles in the valve operation. These hemodynamic events are predetermined by the shape and mechanical properties of the sinus and the valve cusps, and they constitute a self-sustained mechanism for competent valve operation.

Valve functions other than prevention of reflux
The blood flow in peripheral veins is much more complex than that in arteries and capillaries. At any given time, it can be continuous, pulsatile, or absent. The transitions from one state to another produce even more complex fluid dynamic phenomena. The presence of valves complicates this even further, as valves are not only moved by the flow, but participate in flow changes. In this sense, we can postulate that the venous valve has physiologic functions other than securing unidirectional flow, broadly characterized as flow modulation. Responsibility for the central role in providing this function belongs to the geometry of the valve and to the distinct mechanical properties of leaflets, walls of the sinus, and walls of adjoining segments.

During the opening and equilibrium phases of the valve cycle, a proximally-directed jet forms in the valve orifice. The shape of this orifice with fused leaflets on both sides and gradual widening toward the center significantly differs from a circular cross-section of adjoining venous segments. As blood passes through the valve orifice, its velocity profile flattens. This makes possible the formation of organized flow patterns, for example spiral flow in the great saphenous vein where valves are positioned at a small angle to one another, thus rotating the flow as it passes proximally. This is more likely to happen in segments with several closely located valves, such as crural veins. The existence of such organized flow patterns may conserve a significant amount of energy, facilitating venous return. As of now, this remains a theoretical construct awaiting experimental confirmation.

The flow inside the valve pocket deserves special attention. It is essential for keeping valve leaflets away from the venous wall, and for closing the valve. It also provides “flushing” of the valve leaflets during each valve cycle. Experiments have shown that when this flushing does not happen regularly, the oxygen content of the blood inside the valve pockets drops. This occurs during a period of continuous flow. With pulsatile flow, the flushing happens regularly, and the oxygen content in valve pockets is not different from the rest of the venous blood. Avascularity of the valve leaflets predisposes them to ischemic damage, thus, prolonged time periods of continuous flow followed by reperfusion of valve pockets may play an important role in the formation of venous thrombi.

This is one of the likely explanations for the established fact that valve pockets are often the site of initial thrombus develop-
The functioning of venous valves in normal and pathological conditions – Lurie

The venous valve and primary chronic venous disease

Figure 3. B-flow image of reflux jet directed toward the venous wall.

Figure 4. B-flow image of reflux jet in a saphenous aneurysm.

The predominant concept of venous valve physiology holds that the venous valve reacts to reverse flow by closing, ensuring unidirectional flow in veins. Not surprisingly, the role of the venous valve in the development of chronic venous disease is viewed as a simple failure to close, leading to recirculation, venous hypertension, or both. Ceaseless discussion of whether changes in the venous wall lead to valvular incompetence or whether valves undergo independent pathological changes, rarely, if ever, concentrates on the third possible scenario — namely, that valvular incompetence causes changes in the venous wall. This is despite existing evidence that in superficial veins, varices and dilations are located distally to valves, and not proximally, as one would expect if the hydrostatic pressure induced primary incompetence not only leads to recirculation and venous hypertension, or both. Ceaseless discussion of whether changes in the venous wall and valves in such a model are caused by closing, ensuring unidirectional flow in veins.

The abnormal valve

By closing in reaction to increasing flow velocity, venous valves interrupt continuous flow converting it into pulsatile flow, which secures adequate oxygenation of valve pockets and prevents formation of thrombi.

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**Le fonctionnement des valvules en conditions normales et pathologiques**

Un nouveau concept du mécanisme de fermeture des valvules et de leur rôle dans la circulation, fondé sur des observations récentes, a été pro-
posé. Chez les personnes en bonne santé, la géométrie valvulaire et le débit veineux pulsatile déterminent les forces mécaniques qui interviennent sur les valvules, provoquant leurs mouvements. En conditions physiologiques, les valvules créent un débit local complexe qui favorise un mouve-
ment sanguin vers l’avant, augmente l’apport de sang oxygéné aux cavités val-
vulaires et prorroque la fermeture cyclique des valvules elles-mêmes, préservant
la nature pulsatile du débit veineux. En cas de reflux, les valvules se ferment,
garantissant un débit unidirectionnel. Le dysfonctionnement d’une valvule peut conduire à la perturbation du débit normal. Ceci modifie l’oxygénation
des cavités valvulaires, pouvant conduire à la formation de thrombi, ou pro-
voque des jets asymétriques de reflux inverse dans une valvule incontinente,
produisant des transformations endothéliales prothrombotiques et pro-inflam-
matoires méditées par des contraintes de cisaillement.
Embryology and distribution of lower limb venous valves in humans

by A. Caggiati, Italy

Venous valves (VVs) were first mentioned in 1544 by the Spanish anatomist Ludovicus Vassaeus in his De Anatomen Corporis Humani tabulae quator.1 Sylvius Ambianus (1478-1555) is quoted as being the first to describe the presence of valves in the veins of the lower limbs. The function of VVs was clearly identified in 1559 by Andrea Cesalpino in his De Re Anatomica: “...certain membranes placed at the openings of the vessels prevent the blood from returning.”2 The German Salomon Alberti published the first drawings of a VV in 1585. In 1603, Hyeronimus Fabricius ab Aquapendente (1533-1619) published the first treatise on VVs entitled De Venarum Ostiolis. Fabricius meticulously described VV anatomy and topography in the whole venous system. More importantly, Fabricius described a test to evaluate VV competence (Figure 1) that led his student William Harvey (De Motu Cordis, 1628) to discover the circulation of the blood.2

Historical background

Venous valves appear in the embryo after the heart begins to beat and the primordial muscles begin to move the limb buds. The pressure gradient along the vein triggers a five-step process of valve development. Prenatal and perinatal morphological and numerical rearrangements have been described, but they have still to be clearly demonstrated. The cusps of the venous valves consist of thin collagen half-moon-shaped folds covered by endothelium, which spring from the wall of the vein very close to each other. The vein wall is thicker at the base of the valve cusps, due to larger quantities of smooth muscle cells of the media. With increasing age, the loose areolar collagen stroma of the cusp is gradually replaced by thick and fibrous tissue. Data from different authors regarding the distribution of valves in the deep, superficial, and perforating veins of the lower limbs are summarized. Finally, valves located in the microveins of the skin of the lower limbs are described.

Keywords: embryology; human venous valve; morphology; aging; microvein; varicose disease

Selected abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>GSV</td>
<td>great saphenous vein</td>
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<tr>
<td>MVV</td>
<td>microscopic venous valve</td>
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<tr>
<td>PTV</td>
<td>preterminal valve</td>
</tr>
<tr>
<td>SFJ</td>
<td>saphenofemoral junction</td>
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<td>VV</td>
<td>venous valve</td>
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(e-mail: alberto.caggiati@uniroma1.it)
According to Kampmeier and Birch, the pressure gradient along the vein triggers a five-step process of valve development (Figure 2): (i) thickening of the endothelium, which forms a pair of ridges placed transverse to the axis of the vessel; (ii) growth of the endothelial ridges due to their invasion by the underlying mesenchyma, which bulges out of the valvular anlage; (iii) the evolving valve directs itself toward the heart; (iv) the valvular cusps widen into a nodular shape, while the valvular sac gains in capacity; and (v) the venous wall thins down considerably in the region of the valvular sinus, mainly due to thickening of the media.

VVs increase in number during prenatal life. Differences with regard to their distribution and characteristics in different areas of the human body start immediately after birth. In 1981, Maros pointed out that “Certain findings suggest a reorganization after birth of the venous valves which are frequently met in fetus. The close relation between hemodynamic mechanisms and the blood guiding structures may explain the changes (disappearance or persistence) of venous valves in some areas after birth.”

Morphology of the venous valves

“The shape of valves is such that they resemble the nail of the index or other three fingers.”

Hyeronimus Fabricius ab Aquapendente, 1603.

According to Saphir and Lev (1952), the cusps of the VV consist of thin collagen half moon–shaped folds covered by endothelium, which spring from the wall of the vein very close to each other. Their free margins diverge to become attached again at the opposite section of the vein wall. The space between the attachment of the free margins of the cusps is called the commissure (Figure 3, page 102). The commissure itself is slightly raised because of a thickening of the vein wall in that area. The cusps are thicker at their bases, where they join the wall of the vein. This thickened attachment of the cusp framework was named “agger” by Franklin, and “limbus” or “tuberculum” by others. It is shaped like a double horseshoe, with the convex sides arranged distally, and contains smooth muscle cells. The continuations of the free border of the cusp where it meets the vein wall are named “cornua.” The valvular sinus (or pocket) is the space between the cusps and venous wall, which at that level is particularly thin (Figure 4, page 102). According to Franklin, the vertical length of the cusps will often be twice the diameter of the vessel (Figures 3 and 4).

The cusps can be designated into two faces: luminalis, that part of the cusp close to the lumen of the vein and facing the circulating blood stream, and parietalis, that part of the cusp facing the vein wall of the sinus. The luminalis is lined by one layer of endothelial cells, which is elongated along the major axis of the vessel. Beneath this layer of endothelial cells is a small amount of connective tissue that is especially noticeable in childhood. Immediately beneath the tissue, there are moderately thick, slightly wavy elastic lamellae, the continuations of the internal elastic lamina. The parietalis is lined by a layer of endothelial cells, which are elongated transversely. The remainder of the parietalis consists of loose connective tissue. At the base of the cusp, the parietalis contains scattered smooth muscle cells extended from the longitudinal muscular bundles of the vein intima. The luminalis and the parietalis join or fuse at the distal end of the cusp, which is thinner than the rest of the cusp; elastic and connective fibers are thinner here too. No blood vessels are found within the cusps.
Hyeronimus Fabricius ab Acquaipendente: “Quoque venarum distensionemuisse ostiola a Summo Opifice fabrefacta” (“The Supreme Artificer made valves to prevent venous distension”). Moreover, the tissue organization of the valve sites suggests that the action of valves is not merely that of passive flaps, but that they can also actively regulate the flow, especially in conditions of low velocity. According to Fegan:9

Contraction of the circular bundles at the base of the cusps reduces the diameter of the vein. Contraction of the longitudinal muscular fibers of the cusps reduces their length and increases their thickness. In addition, the cusps are drawn down towards their roots, and away from each other, but the sphincteric action of the circular bundles compensates for this. The upper free parts of the cusps press against the vein wall at the lateral attachments of the valve, and thus, with the intimal cushions, help to seal the potential leaks.

Age-related structural changes of venous valves

Age-related morphological changes in VV leaflets were comprehensively described by Saphir and Lev:7

Starting after the age of 30, the loose areolar collagen stroma of the cusp is gradually replaced by thick and fibrous tissue. After 40, an increase in elastic tissue starts at the base of the cusp, to gradually spar the free margin. In the parietal portion of the leaflet, accumulation of dense-collagenous fibers. In the luminal, deposition of collagen between endothelium and elastic membrane.

These changes are similar to those described in the superficial veins of aged individuals. They can be attributed to the physiologic hemodynamic stress related to standing and muscular contractions. However, changes related to senility do not imply VV dysfunction with significant reflux.

Distribution of venous valves in the lower limbs

Kampmeier and Birch correctly stated that, as a general rule, “Valves are present in those vessels which are subject to pressure from without and in those in the immediate sphere of muscular performance, such as in the veins of the extremities and stomach.” Many studies have dealt with the number and location of VVs in the inferior vena cava region.11-18 Data provided by different authors regarding the distribution of valves in the veins of the lower limbs are summarized in the following paragraphs. Unfortunately, these data are difficult to compare, mainly due to the different topographic designation of the veins.

Addomino-pelvic region

The inferior vena cava is without VVs. Sporadic monocuspid valves have been exceptionally reported. Occasionally, one sporadic and mostly incomplete valve, similar to a spur, is reported in the common iliac vein (in 1% to 7% of limbs).15,16 One VV is located in the external iliac vein of about a quarter of white subjects. Friedericin noted in 1882 that one VV is located in about 35% of external iliac veins, “but often mainly decadent.”17 La Page and colleagues reported one well-developed VV located within 2 cm distal to the entrance of the internal iliac vein in 26% of legs.18 The right external iliac vein has almost three times as many valves as the left (39.6% vs 14.6%). According to Kampmeier and Birch, the internal iliac vein is avulvalar, whereas its main tributaries (gluteal, sacral, and obturator veins) are valvular.1 By contrast, more recently La Page and colleagues stated that in 7.6% of individuals, a well-developed ostial valve is present, and parietal valves are found in only 2.2%. Finally, its tributaries will be valvular in only 10% of cases.

Deep veins

The common femoral vein shows one VV above the saphenofemoral junction (SFJ), known as the “supra-saphenic valve.” It protects the saphenous axis against rises in intra-abdominal venous pressure. According to Basmajian, two VVs are located in the same tract in about 5% of normal limbs.11 The femoral vein shows about three valves. The most constant valve (found in about 90%-100% of cases, according to Banjo), is located just below the conjunction of the deep femoral vein.14 No data are available with regard to the lateral and medial circumflex veins. The deep femoral vein and the deep femoral perforators are valvular.20 The popliteal vein displays one to three VVs. Finally, the deep
The veins of the leg are richly valvular. According to Gottlob and May, 8 to 19 VVs are located in each of the posterior tibial veins, and 8 to 11 VVs in both the anterior tibial and peroneal veins.20

Superficial veins
Cotton calculated that 7.2 ±2.3 valves are located along the entire length of the GSV.21 According to Raivio, between 1 and 7 valves are located along the thigh portion of the GSV (mean number, 3.5), 2 to 6 valves are located along the leg (mean number, 4), and finally 1 to 4 valves are located at the foot (along the marginal veins).22 The valves of the SFJ are of particular clinical relevance. In 1603, Fabricius stated that the terminal portion of the GSV has a bicuspid valve at the orifice, then at two fingers’ distance, a further set of twin valves (Figure 5).

The first is the well-known terminal valve situated at the termination of the GSV to prevent reflux from the femoral vein. The more distal one is the preterminal valve (PTV), which lies just below the openings of the SFJ tributaries. The PTV prevents venous reflux from the tributaries of the SFJ into the GSV trunk while the terminal valve is closed. Incompetence of the PTV is the reason for reflux into the GSV in cases in which the terminal valve is still competent.19 The terminal valve is present in 98% to 99% of normal legs, whereas the PTV is present in only about 70% to 85%. Finally, in about 2% of limbs, no valves are present in the last portion of the GSV.23

According to Raivio, the global number of VVs along the small saphenous vein is an average of 8.2.22 The terminal valve is located in all legs with a saphenopopliteal junction. No data are available on the presence of VVs along the thigh extension of the small saphenous vein, which shows, in normal conditions, an antegrade flow directed toward the GSV or toward tributaries of the internal iliac vein (inferior gluteal or ischiatic veins).

Saphenous accessories and other superficial veins
Fabricius affirmed that smaller superficial veins (saphenous tributaries, communicating veins, and reticular veins) are avalvular. By contrast, Bouchet affirmed that they are valvular at their end, along their course, and at the point of entry of a smaller vein.24 Avalvular superficial veins connect main valvular superficial veins (oscillating veins).25

Perforating veins
It is well known that perforating veins are furnished with valves. The number of VVs in perforating veins ranges between 1 and 5 (the mean is 2). In 1978, Pirner affirmed that “all valves were found in the subfascial part of the perforating veins.”26 In the same year, Van Limborgh and Hage noted that “the number of valves in the epifascial part of the perforators was significantly less in those (perforating) veins which frequently become incompetent.”27

However, Raivio reported that only 75% of the perforating veins are valvular.22 Avalvular perforating veins are found mainly in the foot, hand, and forearm. However, avalvular perforating veins are reported elsewhere in the human body, and work like oscillating veins connecting deep and superficial districts. This was confirmed by duplex investigations that demonstrated bidirectional flow in perforating veins of people without any sign of venous disease.28-30

Number of venous valves and varicose disease
While valvular agenesis is a known, but rare cause of venous insufficiency, the relationship between the number of VVs and varicose disease has been poorly investigated. Sales and colleagues demonstrated that the mean number of valves in varicose saphenous veins differed from that of nonvaricose ones (2.3 ±0.83 vs 4.8 ±2.01, respectively).31 Banjo comparatively evaluated the presence of VVs in whites and black Africans, and demonstrated that the number of valves is higher in the latter.16 This may account for the high prevalence of varicose veins (between 10% and 18%) in whites, and the low prevalence (1% to 2%) of the condition in Africans.

Age-related changes in the number of venous valves
A reduction in the number of VVs as a function of aging is a debated topic. The theory proposed by
Bardeleben in 1880\textsuperscript{2} and reconsidered by Powell and Linn in 1951,\textsuperscript{3} which proposed a lifelong and progressive reduction in the number of VVs due to involutive noninflammatory phenomena, was strongly denied by Leu and colleagues in 1979,\textsuperscript{4} and has been definitively abandoned. Leu and colleagues confirmed what Klotz demonstrated in 1887; ie, the number of VVs does not decrease with age, but the number of incompetent VVs increases with age.\textsuperscript{5}

According to Gottlob and May, “venous valves cannot disappear but pathological processes may cause them to become incompetent.”\textsuperscript{6} This can be a result of the well-known effects of a massive thrombosis, but also because of subclinical localized thrombosis of the valvular sinus, as described by Sevitt in 1974,\textsuperscript{7} dilation of the valvular anlage (as in varicose veins), and other regressive phenomena currently not well defined.

Senile involution of VVs was investigated in depth by Marinov in 1973.\textsuperscript{8} He established that in parallel with aging, the number of fully developed valves reduces, while that of “partial” valves increases, with the highest intensity of the process being recorded during the period between 25 and 60 years of age.\textsuperscript{9} In subjects older than 60 years, the number of partial valves represents between one fifth and one tenth of their total quantity of VVs; in the superficial veins, the amount is 1.5 to 2 times higher than in the deep veins.\textsuperscript{10} These regressive phenomena are subject to regional differences. According to Gottlob and May, “venous systems, in which unidirectional flow conditions are prevalent, tend to lose their ‘superfluous’ valves more readily, whereas systems, in which heavier strain is exerted on the valves due to hydrostatic stress or reversed flow, preserve their valves throughout life.”\textsuperscript{11}

### Valves in microveins

Anatomists, physiologists, and clinicians consider the venous bed to be “valveless” from the venular level up to 2 mm large veins. On the contrary, microscopic venous valves (MVVs) have been described in the microvascular bed (postcapillary venules and venulae efferents of arteriovenous anastomoses), in collecting venules, and in small caliber veins (with diameters up to 800 to 1000 μM).\textsuperscript{12} MVVs have been found in the subcutaneous layer and in muscles of various areas of the human body (Table I).

Generally, MVVs are described as bicuspid. MVVs are arranged in series along a vein or are situated at the merging point of two veins. The valves always point in the direction of the larger vessel, as in the collecting veins. Two layers of endothelial cells surround a core of basement membrane material, in which bundles of collagen fibrils are embedded.

MVVs are identical in structure, location, and orientation to the VVs of the leg macroscopic veins. This has led to the hypothesis that their role is to resist blood reflux in small sized veins and collecting venulae, and to prevent reflux from postcapillary venulae to the capillary bed and arteriovenous anastomosis.\textsuperscript{13} This hypothesis is corroborated by two pieces of evidence: (i) the absence of MVVs in regions with a favorable venous return; and (ii) the abundance of MVVs in regions subject to gravitational backflow and where blood flow is irregular or altered by muscular contraction, as with VVs. The absence of MVVs, as well as their incompetence, could explain clinical syndromes characterized by signs and symptoms of chronic venous insufficiency in limbs with competent VVs in large veins.\textsuperscript{14}

### Table I. Areas of the human body found to contain microscopic venous valves.

<table>
<thead>
<tr>
<th>Author (year discovered)</th>
<th>Area of the body</th>
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<tbody>
<tr>
<td>Popoff (1934)</td>
<td>Digital skin</td>
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<tr>
<td>Pirro (1950)</td>
<td>Calf muscles</td>
</tr>
<tr>
<td>Miani and Ruberti (1958)</td>
<td>Foot sole skin</td>
</tr>
<tr>
<td>Braverman, et al. (1983)</td>
<td>Abdominal wall</td>
</tr>
<tr>
<td>Curri, et al. (1987)</td>
<td>Vastus lateralis, Gastrocnemius</td>
</tr>
<tr>
<td>Caggiati, et al. (1987)</td>
<td>Vastus lateralis</td>
</tr>
<tr>
<td>Miyake, et al. (1996)</td>
<td>Human maxillo face</td>
</tr>
<tr>
<td>Aharinejad, et al. (1997)</td>
<td>Human dorsal thoracic fascia</td>
</tr>
<tr>
<td>Aharinejad, et al. (1998)</td>
<td>Skin of the scapular area</td>
</tr>
<tr>
<td>Aharinejad, et al. (2001)</td>
<td>Skin of the inferior limb</td>
</tr>
<tr>
<td>Shangjuan, et al. (2001)</td>
<td>Tongue</td>
</tr>
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### REFERENCES

EMBRIOLOGIE ET RÉPARTITION DES VALVULES VEINEUSES DU MEMBRE INFÉRIEUR CHEZ L'HOMME

En embryologie, les valvules veineuses apparaissent après les premiers battements cardiaques et les premiers mouvements des bourgeois des membres commandés par les principaux muscles. Le gradient de pression le long de la veine déclenche le développement de la valvule en cinq étapes. Les arrangements morphologiques et numériques prénataux et périnataux, déjà décrits, demandent à être démontrés. Les valvules veineuses sont constituées de fins replis de collagène, en demi-lune, recouverts d'endothélium, qui surgissent de la paroi veineuse, très proches l'un de l'autre. La paroi veineuse est plus fine à la base des valvules en raison du plus grand nombre de cellules musculaires lisses de la média. Avec l'âge, le stroma collagène aréolaire de la valvule disparaît progressivement au profit d'un tissu épais et fibreux. Sont résumées ici les données de différents auteurs sur la répartition des valvules dans les veines profondes, superficielles et perforantes des membres inférieurs. Enfin, les valvules des microveines cutanées des membres inférieurs sont décrites.
This literature review, which includes some of our own work, sets out to show that chronic venous insufficiency (CVI) can begin very early in childhood and adolescence and that reflux is an excellent indicator of its progression. Although hemodynamics is our main concern, we shall also discuss epidemiology and heredity, before advocating the grading of CVI based on hemodynamic and clinical characteristics.

**Epidemiology**

Venous angiodyplasia and deep vein thrombosis dominate the venous disease literature. Few recent studies have specifically addressed CVI in children and adolescents. Most cohorts range in age from 18 years to over 90 years, as if CVI only starts after adolescence. A few large-scale studies have included subjects from the ages of 12 or 15 years upward, but without drawing any conclusions specific to this age group. However, clinical signs such as small varices, and even hyperplasia of the great saphenous vein (GSV), began to be recognized as heralding CVI when continuous-wave Doppler entered standard practice.

A key epidemiological study in the young was that of Heede in 1989, carried out in 8- to 18-year-olds. Clinical examination revealed varices or telangiectases from the foot to the groin, with 52% in the popliteal region, confirming results of a 1978 Prague study. The overall prevalence of varicose veins was 14% and appeared to increase with age: 2.3% of the overall population showed reflux at the sapheno-femoral junction (SFJ) versus 3.2% in the 14- to 18-year-old subgroup, consistent with the 1981 study by Fischer.

The prospective Bochum Study monitored 740 pupils aged 10 to 12 years from 11 secondary schools for 9 years from 1982. It combined clinical examination with photoplethysmography and continuous-wave Doppler assessment of reflux. Results were identical to those of Heede, with GSV reflux being observed in 2.9% of the youngest subjects in Bochum Study I. Four years later, in Bochum Study II, reflux had risen to 10.4%, with primary valve failure being diagnosed in 1% to 2%. The authors considered reflux to be the first sign of truncal varicosis, while the mainly popliteal reticular varices were earlier in onset but not directly related to the reflux observed later. Another 1989 study, in 741 6- to 14-year-olds, found truncal perforator incompetence in 13.9%, but failed to detail the methods used. In 2006, we published a clinical and duplex ultrasound study of 142 young subjects, consistent with the 1981 study by Fischer.

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with significant GSV reflux (>0.5 seconds) in 92 cases, and none in the remaining 50 cases. The affected population comprised 77 girls (83.7%) and 15 boys (16.3%) aged 14±2 (8-18) years. We divided the leg into seven segments: reflux was found to extend over more than two segments of the thigh or leg in 16 patients (Group 1), and it was confined to one segment (short reflux) in 76 patients (Group 2). All patients were classified by age and Clinical-Etiology-Anatomy-Pathophysiology (CEAP) score, ranging from asymptomatic C0 (C0a) to symptomatic C2 (C2s). Scores differed significantly between the groups, with 0.0% C0a in Group 1 versus 58.7% in Group 2 (P<0.0001), and 56.3% C2s in Group 1 versus 2.7% in Group 2 (P<0.0001) (Figure IA). Division into three age groups (8-13 years old, 14-15 years old, and 16-18 years old) showed a correlation between age and CVI severity (P<0.01) (Figure IB), confirmed by the anatomical, clinical, and disability scores (Figure IC).

**Heredity**

Heredity has been considered to play a major role in CVI, with well-established evidence of transmission, although acquired factors have remained paramount for some authors. In 1937, Troisier and Le Bayon (cited by Merlen et al18) postulated sex-linked inheritance with female predominance, although most authors at that time believed that what was inherited was a susceptibility syndrome rather than CVI itself. However, the epidemiological data on which inheritance hypotheses were based were obtained largely by interview, not examination. In 1994, a French case-control study provided a clear answer to the inheritance issue by examining 402 subjects from 134 families.19 It included the non-varicose spouses of affected cases in an attempt to control for confounders such as diet and lifestyle. Clinical examination in children and parents was complemented in many cases by Doppler ultrasound (although these results were not an inclusion criterion). Statistical analysis showed that the risk of CVI in children, depending on the presence or absence of parental disease, was 20% if neither parent was affected, 25% in boys and 62% in girls (mean 45%) if one parent was affected, and 90% if both parents were affected. Inheritance is therefore a significant factor (P<0.001), and an indication for the monitoring of children with a strong family history.

**Investigations**

Prospective randomized controlled trials are not feasible in children. We were initially confined to hemodynamic observations that were empirical.
rather than strictly scientific. Clinical examination was the cornerstone procedure, as it is now. Over the years, it has been complemented by three types of investigation.

**Photoplethysmography**
This technique failed to improve understanding of CVI in the young. Even in combination with Doppler ultrasound, it could not differentiate between normal results and various forms of incipient CVI. The consensus is that muscle immaturity in the young makes it impossible to use the data collected.

**Ultrasound**
Ultrasound soon replaced radiology as the standard structural investigation. It maps the anatomy of the diseased superficial venous system and identifies the defective valves. It provides an initial score, which can be supplemented by vessel diameter values. Intima-media thickness (IMT) provides a measure of the vein wall changes induced by the disease, and is significantly increased in affected young subjects compared with normal adults.

**Doppler ultrasound**
Ever since its introduction, Doppler ultrasound has been the essential hemodynamic investigation for confirming the diagnosis of CVI. From 1985 to 1990, it was used in continuous-wave mode, but according to no standard technique or specific recommendations. The patient’s position during the examination and the maneuvers employed were not clearly specified. Only the Valsalva maneuver was regularly mentioned. This explains why patients were generally examined for reflux at the SFJ or saphenopopliteal junction. The duration of significant reflux was not considered an important parameter. Nevertheless, it was the hemodynamic studies using continuous-wave Doppler that yielded the epidemiological results cited above.

Today, not only do we have color duplex scanning, we also have a consensus document, *Duplex ultrasound investigation of the veins in chronic venous disease of the lower limbs*, which lays down clear and detailed instructions for examining venous regions of interest. It defines significant pathological reflux in the great or small saphenous vein as being retrograde flow in the anti-physiological direction lasting for more than 0.5 seconds. This is the only information on reflux in the consensus document. However, retrograde reflux does not necessarily imply true reflux, still less valve incompetence. It is also important to know whether the superficial venous reflux is spontaneous or induced, transient or permanent, and where it occurs. These are all hemodynamic parameters that we need to consider if we are to make as comprehensive an analysis as possible. They are as applicable to young subjects as to adults.

**Reflux**

**Spontaneous and induced reflux**
Color Doppler scanning may reveal spontaneous reflux when the subject is mobilized. It can be confirmed and assessed using compression-decompression maneuvers. Reflux in young people is often found below the knee along the GSV trajectory. Compression of the muscle compartments drained by the GSV will demonstrate its actual origin. However, this may require displacing a substantial volume of blood, which should not be repeated too forcefully in somewhat timid young subjects, for fear of triggering a vasovagal reaction.

**Intervalvular and commissural reflux**
Intervalvular reflux is associated with incompetent valve leaflets that are damaged and no longer functional. Reflux is always pathological if it lasts more than 0.5 seconds.

Commissural reflux through one or both spaces between the valve leaflets can often be demonstrated in the standing position in the lower third of the thigh. This high-intensity reflux shows as frequency saturation in pulsed Doppler mode and as a brightly colored stream on one or both sides of the valve in color Doppler mode. Endoscopy can corroborate commissural reflux. Although it mimics pathological reflux hemodynamically in that its duration greatly exceeds 0.5 seconds, it remains localized to the valve, with no distal extension, making it difficult to interpret. It could be that it reflects no more than slow closure of the commissural space, in no way heralding the development of CVI. It is therefore essential to recognize it for what it is and not mistake it for pathology.

**Transient and permanent reflux**
It is important to differentiate between transient and permanent reflux in the young, as one is a harmless sign, while the other marks the onset of irreversible CVI.

Reversible transient reflux always exceeds 1 second but is not consistently reproducible. It can occur after prolonged standing, and may be present one day and absent the next. It fully meets the definition of reflux through a healthy valve demonstrated in the GSV terminal segment. It reflects no more than functional dilatation of the perivalvu-
lar wall ring with no valve lesion. Such reflux is readily identified using continuous-wave Doppler, but is more difficult in pulsed Doppler mode.

Permanent and irreversible reflux reflects a structural valve lesion, and is therefore present at every examination.

**Reflux topography**

Superficial venous reflux arises from various sources, including the saphenous veins, accessory saphenous veins, perforators, pelvic veins, and nonsaphenous veins. In children, it can also originate from collateral branches mainly below the knee. Reflux often begins at the knee or anywhere along the course of the GSV and its branches. In a prospective clinical and Doppler study in 81 5- to 18-year-olds (89% girls) with a positive family history, we identified the site of reflux by compression-decompression of the thigh or calf. Reflux was significant in 38% of cases, and was distributed along the entire GSV. In 55.5% of cases, it occurred on either side of the knee, where it was slow and confined to a single interavalvular interval. The very low incidence of SFJ reflux (5.7%) would seem to eliminate femoral reflux as a cause of saphenous reflux. A fuller study 6 years later in 161 subjects amply confirmed these results, with reflux around the knee in 75.3% of cases, and proximal reflux up to the SFJ in the remainder.

Detailed hemodynamic analysis at the SFJ is relatively recent. There have been no specific studies of terminal and/or subterminal valve lesions in young patients, although we have observed several cases of terminal valve incompetence. Saphenous reflux in youths may also be associated with a varicosele.

**Height of reflux**

By dividing the limb into seven segments, three above and three below the knee, and one for the ankle and below, reflux height can be used to compare two successive investigations and plot the disease course. Height reflects severity. An ultrasound study used height to define three types of reflux in young subjects: type 0, no reflux; type 1, reflux limited to one limb segment; type 2, reflux stretching over more than one segment. The authors combined these data with other anatomical or structural parameters into a composite disease score that can be used in monitoring and, above all, in detecting CVI as early as possible. We have also included height as an indication for ultrasound-guided sclerotherapy when reflux reaches or exceeds two limb segments.

**Age and reflux topography**

Longitudinal monitoring is difficult in practice, but we have monitored pathological reflux in several young patients at yearly intervals. The reflux underwent progressively proximal ascent to the SFJ confirmed statistically by the correlation between subject age and ascending reflux topography. Children with reflux in the terminal GSV segment were older than those with reflux either side of the knee (14.4 years versus 13.2 years). The mean age of our general population, including normal and pathological subjects, was 13.7 years; this compared with 14.4 years for those with reflux, and 16.2 years for those with reflux involving two limb segments. These results are consistent with those showing a correlation between SFJ reflux and higher age in adults. Puberty, which was long assumed to be an important determinant of reflux, has an inconclusive role: in 156 adolescent girls, 77 had significant reflux, of whom 53.3% were prepubertal and 59.5% postpubertal.

**Management**

Based on the epidemiological and genetic data, and the current structural and hemodynamic studies of early-onset CVI, we propose the following management guidelines:

- Mandatory screening for all girls with one CVI-positive parent and all children with two affected parents.
- Diagnostic structural and hemodynamic studies to confirm reflux and determine its topography, height, origin, and score severity in conjunction with the CEAP classification as a basis for a rational management strategy.
- Follow-up at 6 or 12 months to confirm initial findings and check for progression.
- Curative treatment for adolescents with documented GSV incompetence in the absence of other consensus as to treatment indications and modalities. Ultrasound-guided sclerotherapy was successful in 15 out of 16 of our patients with reflux exceeding two limb segments; the remaining patient required surgery. This approach remains rel-
CIV cannot be scored on the basis of reflux alone, but only as a composite, in combination with the structural data, CEAP classification, and genetic factors.

Although no consensus exists as to treatment indications or modalities, we consider that GSV ablation can be offered from age 14 upward, given the data established by the few published studies, namely: the evidence in the young of ineluctable CVI progression with age,14,16,17,20 the body weight and height of affected adolescents (which generally exceed those of adult controls),24 and their sometimes grossly dilated GSV diameters (5-10 mm). Although these indications require further discussion, since few patients have been treated to date, even intensive monitoring should not delay curative treatment that may alone be able to prevent disease progression.

Conclusion

Doppler ultrasound has transformed our understanding of CIV in children and adolescents in recent years, although the topic remains generally understudied. Analysis of valve incompetence in the GSV has revealed a number of useful parameters for diagnosing and monitoring early reflux, itself a key parameter in the diagnosis and grading of CIV. This can then be combined with the CEAP classification and the structural and genetic data to produce a composite severity score giving an accurate prognosis. This approach is a precondition for reaching a consensus on treatment indications and modalities.

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L’INCONTINENCE VALVAIRE VEINEUSE ET LE REFLUX CHEZ L’ENFANT

La maladie veineuse chronique de l’enfant et de l’adolescent (MVC) est une pathologie qui commence très tôt, et le reflux représente un élément majeur dans l’évaluation initiale et sa surveillance. Dans cet article, nous proposons une méthodologie d’examen et une conduite à tenir. Comme le montrent de rares études épidémiologiques, le Doppler continu permet d’évaluer le pourcentage de jeunes présentant un reflux au niveau des grandes saphènes et de montrer que cette pathologie progresse avec l’âge. La classification CEAP (Clinique; Étiologique; Anatomique; Physiopathologique) confirme cette évolution. Malgré l’absence d’une véritable quantification du reflux, l’écho-Doppler peut définir son type, sa nature, sa topographie, son évolution, son « age ». Associée à l’examen morphologique, ces différents paramètres permettent d’établir un score initial de sévérité et d’observer ainsi l’évolution de la MVC. Il apparaît ainsi que la fréquence de cette maladie chez le jeune dépend de la population étudiée et varie de 3 à 10% en fonction de l’âge du patient. Chez les jeunes dont un ou deux parents sont variqueux, cette fréquence peut dépasser 50%. Le reflux débute généralement au niveau du genou. Sa progression est en rapport avec l’âge, tout en sachant qu’il peut apparaître avant la puberté. Au total, la MVC débute très tôt chez le jeune et évolue avec l’âge. L’analyse du reflux associée à l’étude morphologique permet d’établir un score de sévérité de la pathologie. Toutefois, il n’existe à ce jour aucun consensus sur l’attitude thérapeutique.
The study of the saphenofemoral junction to understand the distribution of refluxes in chronic venous disease

by L. Tessari and M. Cappelli, Italy

Some of the techniques currently in use for the treatment of the varices of the lower extremities were introduced at the beginning of the 20th century: the Narath technique in 1904 (multiple stab incisions phlebectomy), the Keller technique in 1905 (imaginated stripping on thread), the Mayo technique in 1906 (external stripping), and the Babcock technique in 1907 (internal stripping).¹

Before any decision can be made regarding the appropriate therapeutic technique for a varicose patient, it is necessary to define how a specific area (for instance, the saphenofemoral complex) should be assessed in the patient. We are going to consider two different aspects: first, how to study an incontinent segment, and second, how to study the saphenofemoral complex (on the basis of the general criteria described for an incontinent segment). Valvular continence must be studied in the orthostatic position so as to develop a transvalvular retrograde gradient (opposite to the orientation of valvular planes). Retrograde gradients are studied in two different ways: (i) a high pressure test, such as the Valsalva test; and (ii) a gravitational test, which exploits the weight of the hematic column once it has been mobilized. Analysis of 1294 patients with incontinent great saphenous vein crosses (saphenofemoral complexes) revealed complete incontinence of the saphenofemoral junction in only 55% of cases. In 6% of cases, a dissociation pattern was noted. Using the same criteria, the proximal femoral valve (ie, the valve in the common femoral vein located above the saphenofemoral junction) was also studied. This turned out to be continent in the saphenofemoral junction and in the saphenous vein arch in 58.4% of complete incontinence cases. In cases of continence of the upper femoral valve, the saphenous trunks (measured at the mid thigh area) mostly exhibit a diameter that is less than 7 mm.

Keywords: assessment; saphenofemoral complex; reflux; valvular continence; Valsalva maneuver; gravitational test

In the first years of the 21st century, several new techniques for varicose vein treatment have also been developed, both in the surgical field (hemodynamic conservative surgery according to the Conservative Hemodynamic treatment of Incompetent Varicose veins in Ambulatory patients [CHIVA] strategy) and in the sclerotherapy area. The latter has recently been gaining great success, thanks to echographic techniques and the use of foam.

At present, the most commonly used techniques for treatment of the saphenous varices are those involving endovascular obliteration (laser, radiofrequency, and sclerosant foam with either a long or short catheter). These techniques have in common the inability to completely occlude the saphenous junction properly, and they therefore expose the patient to a risk of possible relapse, traditional sclerotherapy with liquid being a notable example. This is what happens whenever the surgical disconnection of the saphenofemoral junction is not performed completely flush on the femoral vein. The remaining stump can be the cause of a possible evolution of the varicose disease. On the other hand, it must be pointed out that many surgical procedures involving the saphenofemoral junction do not show any evolution signs, even if they have not been correctly performed.

These differences can be explained by the fact that endovascular procedures as well as surgery are frequently performed without any preventive hemodynamic analysis, so the same therapeutic plan is

Selected abbreviations and acronyms

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<th>CHIVA</th>
<th>Conservative Hemodynamic treatment of Incompetent Varicose veins in Ambulatory patients (French acronym)</th>
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<td>C/R (test)</td>
<td>compression release (test)</td>
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applied in different hemodynamic conditions, resulting in different long-term outcomes. The often animated discussion regarding how to determine the best therapeutic technique has resulted in a series of publications about personalized technological approaches.

Unfortunately, these studies have often not been supported by accurate color-duplex ultrasound research of valvular functions and reflux dynamics, which could have otherwise helped to plan a more conservative and personalized therapeutic strategy. A personalized therapy should be based on an accurate color-duplex ultrasound analysis of the patient’s varicose situation; this assessment leads to a morphological and, in particular, hemodynamic map, which represents the basic element for defining the therapeutic plan.

Before any decision can be made regarding the appropriate therapeutic technique to use, it is necessary to define how a specific area (eg, the saphenofemoral complex) should be studied in a varicose patient. We are going to consider two different aspects: (i) how to study an incontinent segment; and (ii) how to study the saphenofemoral complex according to the general criteria listed in point (i).

### Study of an incontinent segment

Valvular continence must be studied with the subject in the orthostatic position, to develop a transvalvular retrograde gradient (opposite to the orientation of valvular planes). Retrograde gradients are of two different types; either that with a high pressure test, such as the Valsalva test, or that with a gravitational test, which exploits the weight of the hematic column once it has been mobilized. The mobilization of the column may occur in a static way through the compression/release (C/R) test (static test) or in a dynamic manner through activation of the muscular pump using any of the following: (i) Parana test; (ii) Oscillation test; (iii) Lifting on Tiptoes test; and (iv) Toes Dorsiflexion test.

#### High pressure gradient (Valsalva maneuver)

The high pressure charge developed during the Valsalva maneuver is transmitted in a distal way independent of the continence of the proximal valvular planes. This is possible thanks to the closure inerteria of valvular planes, which permits the passage of the pressure wave. Its propagation speed is definitively superior to the speed of the hematic flux, as is clearly shown in the arterial system. We can see that the Valsalva test always determines the transmission of the pressure wave. When valvular incontinence among different compartments is present (eg, between the deep and the superficial nets), the pressure wave is associated with the appearance of transcompartmental reflux. The passages among compartments (between the deep and superficial nets and between the saphenous system and its secondary ramifications), which are incontinent with the Valsalva test, are called points of reflux.

The evaluation of the correct execution of the Valsalva test is shown by the appearance of an anterograde flux, that is, the restarting of the flux as soon as the maneuver is completed. This shows that the hypertensive charge (ie, the blocking of anterograde physiologic flux) has been properly performed. It is essential to highlight here that transcompartmental reflux assessment can only be performed if at the moment of application of a retrograde gradient, a re-entry system toward a compartment with lower pressure is present (which could be the deep venous system too), and the lower pressure in the “recipient” system is possible thanks to the closure of its valvular planes (dynamic subdivision of the pressure column).

The above statement can be tested in every patient. Closure through digital compression of the reflux re-entry, eg, the saphenous trunk, brings about the disappearance of the reflux in many tests, mostly the gravitational ones.

#### Gravitational gradient

It must be underlined that dynamic tests, through the activation of muscle-joint pumps, will mobilize much more blood at a deeper level than the C/R test, particularly in big dimension calves. We will therefore have a larger subdivision of the deep hydrostatic column through the closure of the valvular planes, with a consequent decrease in pressure, and consequently there will be the development of a much higher re-entry gradient (in the case of incontinence of the superficial net) than the one developed in the C/R test. Hence, in order to detect reflux, the dynamic tests will be much more effective than the C/R test.

Gravitational tests will point out valvular incontinence in a zone distal to the position of the Doppler sample. They will not give any information on the functioning of the proximal valvular plane. Thus one must position the Doppler sample on the proximal side of the valve that is to be studied (eg, on the femoral side if we are going to analyze the functioning of the terminal saphenous valve). We can therefore state that the gravitational tests point out valvular incontinence in general, while a positive Valsalva test shows how this incontinence is mostly associated with points of reflux, which are in fact the incontinent compartment passages. Furthermore, it should be remembered that the incontinence of the venous axes is not always associated with points of reflux, in which case there will be negative Valsalva reflexes. As a consequence of these findings, it is argued that the multiple tests we currently use aimed at the elicitation of the reflux cannot be used indiscriminately in order to establish a diagnosis of valvular incontinence. Some valves show either commissural or complete incontinence during the Valsalva maneuver, but they turn out to be continent if exposed to a transvalvular gradient of the gravitational type.

The observation of this different valvular behavior during the execution of different tests can indicate a partial incontinence of valvular planes. These valves may as a result be continent to normal gravitational gradients caused by movement, while they “leak” under the high-pressure gradients developed with the Valsalva maneuver. These valves are thus not completely incontinent, and they have a high
probability of recovery with reduction of the diameter of the venous axis through targeted surgical interventions on saphenous collaterals.  

Study of the saphenofemoral complex

It must be pointed out that the saphenofemoral junction is just a part of the so-called “saphenofemoral complex.” The hemodynamics of this region are both physiologically and pathologically influenced by other structures. By saphenofemoral complex we mean:

- The saphenous arch (saphenofemoral cross with its two valves—the terminal valve and the preterminal valve, differently positioned). The saphenofemoral junction is part of the cross. It represents the passage between the great saphenous vein and the common femoral vein.

- The femoral valve proximal to (above) the saphenofemoral junction. This valve may not be present in 20% to 24% of patients.  

- The femoral valve distal to (under) the saphenofemoral junction.

- The upper tributaries of the saphenous arch, which in a variable way drain the superficial blood from the lower half of the abdomen. In fact, physiologically, a descending flow toward the arch can be observed. The physiological direction of flux is stated by the orientation of valvular planes.  

The hemodynamic study of the saphenofemoral complex consists in the positioning of the Doppler sample above and below the valve to be studied and in the application of all the aforementioned investigative methods. All these tests should point out valvular incontinence in the various parts of the complex. In this way, the hemodynamics of the region can be exactly described. The purpose of these tests is to determine a targeted therapeutic approach, which may help to avoid either incomplete or useless radical surgery, which can in fact accelerate the evolution of the varicose disease, commonly called “relapse.” The study of the hemodynamics of the saphenofemoral complex must determine:

- The presence of points of reflux represented not only by the incontinence of the saphenofemoral junction but also by the connection that some pelvic points of reflux have with the great saphenous vein through the arch tributaries. In such cases, we will find arch tributaries that show a Valsalva positive reflux. The exact position of pelvic shunts must also be pointed out on the map of the leg.

- The incontinence/continence state of the terminal valve—that is, the valve situated in the area of the saphenofemoral junction. This can vary; we may have: (i) complete continence both in the Valsalva and dynamic tests performed with the Doppler sample positioned on the femoral side of the valve. In this case, both tests will be negative; (ii) complete incontinence, when both tests are positive; or (iii) dissociated findings with a leaking terminal valve under a high pressure charge, but a resisting terminal valve when gravitational gradients are applied. In this case, we have a positive Valsalva test and a negative gravitational test, particularly when a dynamic test is applied.

- The extension of the incontinence, ie, whether the reflux is limited to the preterminal, terminal or femoral valve. The study of either the continence or the incontinence/absence of the proximal femoral valve is performed by positioning the Doppler sample under the inguinal ligament. The probe must be directed from the groin upward in order to be in a proximal position with respect to the femoral valve and for subsequent application of a combination of the two maneuvers: the Valsalva and dynamic tests. The incontinence extension will condition different pressure columns, with a consequent difference in the reflux hydrodynamic energy; indeed pressure is one of the energy components, together with the retrograde volume (energy = pressure × volume). The hydrodynamic energy, together with parietal factors, determines the vessel diameter. In fact there is a correlation between the incontinence extension and the saphenous vein diameter.

- The level at which the upper arch tributaries drain toward the saphenofemoral junction. This level has been defined as the “geometrical discharge height of the upper arch tributaries.” The disconnection of tributaries at a high geometrical height could cause the formation of a collateral circle that is vicarious because of the obstruction (iatrogenic-surgical), and this could be the source of retrograde flow either after crossectomy or after stripping-crossectomy. In such cases, the reflux is not associated with points of reflux, as is often shown in maps referring to patients operated on with excessively ablative methods. In fact, in these tributaries, the pressure components are represented not only by the residual venular pressure, but also by a high hydrostatic column. By contrast, the hydrostatic column is very low in the tributaries that are located at low geometrical height. The evolution of these collateral circles can cause cavernomas (“neovascularization”), which represent the re-entry of the relapse itself. These are negative Valsalva cavernomas. In subsequent years, these areas can become reflux points from the common femoral vein, and they can therefore become Valsalva positive reflux points. Valsalva positive reflux points can also be those cavernomas that originate from tributary disconnection from a pelvic shunt.

As a consequence of the aforementioned speculations and findings, it could be argued that the study of inflow level of the tributaries may condition the choice between tie/no tie of these arch tributaries and, in the case of their conservation, it will be of importance to decide where to let them drain—either in the common femoral vein or in the saphenous vein.

In an analysis of 1294 patients with incontinent great saphenous vein crosses (saphenofemoral complexes), complete incontinence of the saphenofemoral junction was noticed in only 55% of cases.  

In 6% of cases, a dissociation pattern (see above) was noted. Using the same criteria, the proximal femoral valve (ie, the valve in the common femoral vein located above the saphenofemoral junction) was also studied. In 58.4% of complete incontinence cases, it was found to be continent in the saphenofemoral junction and the saphenous vein arch. In

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Tessari and Cappelli

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Study of the saphenofemoral junction to understand reflux distribution in CVD – Tessari and Cappelli

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ÉTUDE DE LA JONCTION SAPHÉNOFÉMORALE
POUR COMPRENDRE LA DISTRIBUTION DES REFLUX
DANS LA MALADIE VEINEUSE CHRONIQUE

A vant de prendre une décision concernant le traitement adéquat pour un patient variqueux, il est nécessaire de définir comment une aire spécifique (par exemple le complexe saphénofémoral) peut être évaluée chez le patient. Nous allons envisager deux aspects différents : d’abord, comment étudier un segment incontinent, ensuite, comment observer le complexe saphénofémoral, en se fondant sur les critères généraux décrits pour un segment incontinent. La continence valvulaire doit être étudiée en orthostatisme de façon à développer un gradient transvalvulaire rétrograde (opposé à l’orientation du plan valvulaire). Le gradient rétrograde est étudié de deux façons différentes : 1) un test de haute pression, tel que le test de Valsalva ; et 2) un test de gravitation, qui exploite le poids de la colonne sanguine une fois qu’elle a été mobilisée. L’analyse de 1294 patients ayant une incontinence de la crosse de la grande veine saphène (complexe saphénofémoral) n’a révélé l’incontinence complète de la jonction saphénofémorale que dans seulement 55 % des cas. Une dissociation n’était notée que dans 6 % des cas. La valve fémorale proximale a aussi été étudiée en utilisant les mêmes critères (par ex. la valve de la veine fémorale commune située au-dessus de la jonction saphénofémorale). Elle s’est avérée être continent à la jonction saphénofémorale et au niveau de la voûte de la veine saphène dans 58,4 % des cas d’incontinence complète. Lorsque la valve fémorale supérieure est continent, les troncs saphènes (mesurés au milieu de la cuisse) présentent un diamètre inférieur à 7 mm.
Imaging of venous valves: B-Flow

by F. Ferrara and M. Midiri, Italy

Diagnosis of the different pathological conditions of the lower limb venous system is complicated, because of the anatomical and physiological characteristics of this region. A total of 6% of individuals have an anatomical anomaly of the internal or external saphena (i.e., double or triple saphena, irregularities of calibre or position), and in addition, there are physiological aspects that need to be considered regarding the return of blood to the right atrium, which is important for the equilibrium between the centrifugal and centripetal forces. In the 1930s, engineering and medical research was based on diagnostic systems that detected anatomical and hemodynamic alterations. The introduction of the echo-color Doppler systems represented an important evolution. Nevertheless, conventional B-mode and color flow imaging have inherent limitations that degrade their utility: B-mode and color flow involve compromises in either axial resolution or penetration; in addition, acoustic noise artifacts may mask out the extremely weak echoes from red blood cells. This is an important limitation, especially in the evaluation of the venous system. B-Flow imaging is a new technique that uses digitally encoded sono- graphic technology to provide direct visualization of blood echoes in grayscale. This technique allows simultaneous imaging of blood flow, vessel walls, and neighboring tissues. Compared with color Doppler sonography, B-Flow sonography has a higher frame rate and better spatial resolution. Major limitations of color Doppler sonography, such as aliasing, signal dropout at high Doppler angles, color flash, and perivascular color artifacts, are eliminated with this technique.

Keywords: venous valve; blood echo; color flow Doppler; B-Flow imaging; spatial resolution

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however. It was not able to demonstrate the morphological alterations of the vein walls, and it could not identify all of the low-velocity flow.

**B-mode and color flow Doppler**

In subsequent years, the introduction of the echocolor Doppler systems represented an important evolution, especially when new tools were used with color module and pulsed wave Doppler. These tools can directly and immediately identify alterations in the morphology of the vein wall and valves, and can study the venous flow, even with the Valsalva test or A-sound and S-sound squashing applications. Nevertheless, despite many improvements over the past two decades, conventional B-mode and color flow Doppler imaging have a number of inherent limitations that degrade their utility for assessing hemodynamics in major blood vessels.

**Limitations**

First, both B-mode and color flow imaging involve compromises in either axial resolution or penetration. This fundamental trade-off is illustrated in Figure 1. In general, the shorter the transmit pulse, the better the axial resolution (ability to resolve two closely spaced objects). On the other hand, in order to improve penetration, more signal energy is needed. The problem is that the pulse amplitude (instantaneous sound pressure) must be kept within some maximum allowable limit in accordance with regulatory requirements. This means that the only way to increase the energy of the pulse is to transmit a longer pulse. As a result, improved penetration invariably compromises axial resolution. In addition, in B-mode, acoustic noise artifacts may mask out the extremely weak echoes from red blood cells—echoes that are typically 1/1000th the strength of signals from the vessel wall and surrounding tissue. This is an important limitation in the evaluation of the venous system.

By using large “packets” of longer transmit pulses, along with special filtering and signal processing, color flow imaging is able to offer far better visualization of weak blood echoes. However, there are drawbacks to this improvement in flow sensitivity: the large packets limit frame rate, and the longer transmit pulses degrade spatial resolution. So while color flow imaging may be very sensitive to flow signals, thereby yielding valuable quantitative velocity and power information, its temporal and spatial resolution is very limited. In an attempt to combine the better aspects of each mode, the conventional approach is to acquire and overlay color flow data on B-mode data. But this approach also poses significant snags. Alternating between these two modes inevitably compromises the scanner’s frame rate. In addition, any large tissue motion in the color flow overlay may be displayed as a “color flash artifact,” overshadowing the true flow data. Finally, because color flow has lower resolution, filling in the vessels with color will almost always result in some overwriting of the vessel walls in the B-mode image, which can conceal subtle lesions in the vessel being studied.

**B-Flow imaging**

B-Flow imaging is a relatively new technique that uses digitally encoded sonographic technology to provide direct visualization of blood echoes in grayscale. This technique allows simultaneous imaging of blood flow, vessel walls, and neighboring tissues. When compared with color Doppler sonography, B-Flow sonography has a higher frame rate and better spatial resolution. Major limitations of color Doppler sonography, such as aliasing, signal drop-out at high Doppler angles, color flash, and perivascular color artifacts, are eliminated with this technique.

With B-Flow imaging, we enhance weak signals and suppress unwanted echoes. As illustrated in Figure 2, the digitally encoded ultrasound beam-
The Venous Valve and Primary Chronic Venous Disease

The venous valve and primary chronic venous disease

B-Flow pixel brightness

Two primary factors determine the pixel brightness in B-Flow images: the strength of echoes from the blood, and the velocity of blood. In arterial flow, the blood echo in each pixel represents the summed effect of backscattered sound waves from tens of


Imaging of venous valves: B-Flow – Ferrara and Midiri


Figure 4. Superiority of B-Flow (B and C) over color Doppler imaging (A) in the visualization of venous flow and the venous wall.
In these situations, but it may also reveal hemodynamics that have yet to be understood and used for diagnosis. B-Flow offers a number of advantages over conventional imaging techniques. Compared with conventional color techniques, B-Flow delivers superior spatial resolution and frame rate, allowing far better appreciation of the venous hemodynamics. B-Flow is much less dependent on the user or scanning angle.16 There is no need to manipulate complex color control parameters such as packet size, wall filters, and color write-priority threshold—in fact, the vessel-wall overwriting problem is completely eliminated, as B-Flow is not an overlay technique.

Although Doppler processing can clearly provide valuable diagnostic information in terms of detecting blood flow, it is susceptible to such limitations as aliasing, signal dropout at orthogonal detection angles, and wall-filter limitations. As a B-mode imaging technique, B-Flow provides direct visualization of blood echoes without these limitations.17

Clinical applications

B-Flow has especially been used to demonstrate ulcerated plaque and vessel-wall irregularities, as well as being used to measure stenoses.18,19 It should permit clinicians to measure the progression of stenoses with greater precision, which will help to better determine the appropriate follow-up intervals. B-Flow also has the potential to minimize the need for angiography as well as its inherent costs and risks.20,21

B-Flow’s ability to scan at high frame rates is important for visualizing not only vascular hemodynamics, but also the interaction of blood flow with thousands of red blood cells. The fine-grained appearance of the blood echoes is therefore similar to the “speckle” texture one sees in conventional B-mode images of soft tissue.

In general, blood echogenicity varies with a number of interrelated blood conditions, including hematocrit, the degree of red blood cell aggregation14 (rouleaux formation), and flow state (laminar or turbulent).15 For example, the extensive red blood cell aggregations that occur in low shear venous flow can significantly enhance blood echoes.

The velocity of blood relative to the ultrasound beam determines the degree of similarity between echoes from successive coded sequences. As the blood velocity increases, the red blood cells will move in and out of each resolution volume of the ultrasound beam faster. As a result, the echoes from the resolution volume will change by a greater amount from one coded sequence to the next. Since the change in echo information is used by the decoder to achieve tissue-blood equalization, the B-Flow pixel brightness generally varies with both the speed and direction of blood flow relative to the ultrasound beam. In general, as flow velocity increases, the B-Flow signal tends to increase. As the velocity becomes so high that the signal samples from successive firings are uncorrelated, the corresponding B-Flow pixel brightness approaches a maximum.

Finally, extra care should be exercised in interpreting B-Flow images of disturbed or diseased flow states. For example, rouleaux formation may be promoted in the stagnant flow regions around a major blockage, which can enhance the B-Flow signal. Flow turbulence that occurs distal to a significant occlusion can, in theory, also enhance blood echogenicity. B-Flow interpretation is clearly more challenging in these situations, but it may also reveal hemodynamics that have yet to be understood and used for diagnosis. B-Flow offers a number of advantages over conventional imaging techniques. Compared with conventional color techniques, B-Flow delivers superior spatial resolution and frame rate, allowing far better appreciation of the venous hemodynamics. B-Flow is much less dependent on the user or scanning angle.14 There is no need to manipulate complex color control parameters such as packet size, wall filters, and color write-priority threshold—in fact, the vessel-wall overwriting problem is completely eliminated, as B-Flow is not an overlay technique.

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Image: Figure 5. Ability of B-Flow imaging to highlight slow venous flow. Panels A and B show color Doppler images with A-sound and S-sound maneuvering, while panels C and D show B-Flow images.
Les structures anatômiques situées à l’intérieur de la veine telle que les valve cusps et thrombi. Ces structures fines sont souvent masquées par la couleur sur l’imagerie en flux Doppler. En outre, elle améliore la qualité d’imagerie et peut représenter le flux veineux et les contours de la veine. B-Flow technique améliore les veines veineuses, empêchant la visualisation des valves veineuses.

Figure 4A (page 118), la mise en évidence de flux veineux qui n’est pas contenu dans la veine, tandis que la flèche effacera les artefacts de l’observation, et évite de recourir à l’aide de la technique de Valsalva. Figure 4B illustre l’évaluation de B-Flow avant le manœuvres de Valsalva, et Figure 4C illustre l’évaluation de B-Flow après le manœuvres de Valsalva. De plus, les flèches, la veine veineuse peut être vue comme un flèche hypochoïde linéaire (blanc flèche)

Une autre avantage de B-Flow est que c’est un allumeur de flux qui peut visualiser un flux veineux élevé (Figures 5C et D, page 119), qui ne peut être visualisé par le Doppler sans l’aide de l’audition-A et l’audition-S veineuses manœuvres (Figures 5A et B). Cela permet une analyse anatomique et fonctionnelle de l’appareil veineux et les veines hémodynamiques dans les conditions fonctionnelles dans lesquelles l’appareil est trouvé au moment de l’observation, et évite le besoin de recourir à l’aide de différentes accélérations du flux qui peut conduire à un surévaluation de l’importance de la veine veineuse.


Imagerie des valves veineuses : le mode B

La distinction des différentes pathologies du système veineux du membre inférieur est compliqué en raison des caractéristiques anatomiques et physiologiques de cette région. Six pour cent d’individus au total présentent des anomalies anatomiques des saphènes interne ou externe (par exemple, saphène triple ou double, des irrégularités du calibre ou de position) et en plus, certains aspects physiologiques doivent être pris en compte en ce qui concerne le retour veineux dans l’oreillette droite, important pour l’équilibre entre les forces centrifuge et centripète. Dans les années 30, la recherche industrielle et médicale était basée sur des systèmes de diagnostic qui détectaient les altérations anatomiques et hémodynamiques. L’introduction de l’écho-Doppler couleurs est une évolution importante. Les limites inhérentes à l’imagerie en mode B conventionnel et en couleur diminuent néanmoins leur utilité : le Doppler couleur et en mode B font un compromis entre la résolution axiale ou la pénétration ; de plus, les artefacts acoustiques sonores peuvent masquer les échos extrêmement faibles venant des globules rouges. Cette limite est importante surtout dans l’évaluation du système veineux. L’imagerie en mode B est une nouvelle technique qui utilise une technologie échographique numérisée qui permet de visualiser directement les échos sanguins en échelle de gris. Elle permet d’obtenir simultanément des images du flux sanguin, de la paroi des vaisseaux et des tissus environnants. Comparée à l’écho-Doppler couleurs, l’écho en mode B a une vitesse de lecture d’images supérieure et une meilleure résolution spatiale. Elle élimine les principales limites de l’écho-Doppler couleur, tels le repliement spectral, la disparition du signal aux angles Doppler élevés, le flash couleur et les artefacts de couleur périvascularières.
Robust evidence has now been gathered to indicate that chronic venous disease (CVD) of the lower limb is a noninfectious inflammatory disease. This picture has opened the door to further investigation that may lead to an understanding of the trigger mechanisms of inflammation in CVD—the cause of its earliest manifestations—to form a basis for prevention and design of new interventions. Markers of inflammation accompany every stage of the disease—from telangiectasia, venous eczema, ankle skin hyperpigmentation, atrophie blanche, and lipodermatosclerosis, to the most severe forms involving varicose veins and venous leg ulcers. This picture facilitates our understanding of the pathophysiological processes that underlie these diverse manifestations, particularly at the cellular and molecular levels.

The inflammatory process is a repair mechanism

As a background to the following discussion, it is important to remember that the inflammatory cascade, with its stereotypic steps, is designed to achieve the initial removal of damaged tissue and the eventual generation and deposition of new tissue in the “resolution of the inflammation.” As such, it serves as the main biological repair mechanism in living organisms. Every tissue can mount an inflammatory cascade and it is the only repair mechanism present in mammalian tissue; it is used over and over again, from birth and through all the injuries sustained over a lifetime. Many individual steps in the inflammatory cascade are required to achieve resolution of the inflammation. For example, the generation of new proteins, such as acute phase proteins, cytokines, chemokines, or growth factors, forms part of the repair aspect of the inflammatory cascade. If markers of inflammation persist over time, and CVD is a prime example in this regard as it may last for many years, we have to ask the question as to what mechanisms exist to prevent resolution of the inflammation and instead continue to cause injury. It is not until we understand the initial injury mechanisms that we will be able to find the most effective intervention. Otherwise, we are relegated to treatment of the disease symptoms only.

Early microvascular manifestations of inflammation

One of the early signs of CVD at the microvascular level is elevated endothelial permeability, a state that tends to be caused by the opening of interendothelial tight junctions as well as endothelial pore formation. This can be readily observed in acute
models of venous hypertension. There are a large number of mediators (histamine, complement protein, platelet activating factor, vascular endothelial growth factor [VEGF], cytokines) with the ability to elevate endothelial permeability; most of them when applied to a venule, act transiently via nitric oxide, actin polymerization, and selected small GTPases. These early events in CVD may already be driven by mechanisms that have the ability to produce chronic inflammation. Elevation of endothelial permeability, with the opening of leakage sites between endothelial cells, depends on the interendothelial adhesion molecule VE-cadherin, an endothelial glycopexy layer that is sensitive to enzyme degradation, the specific venular genotypes, and on exercise training. Thus, the reduction of endothelial permeability may be a target opportunity for early intervention in CVD.

**Angiogenesis and microvascular restructuring**

A rich record exists of the relatively early event in the inflammatory process in CVD that involves liposclerotic skin formed via capillary angiogenesis and apoptosis in superficial layers of the skin. Areas of white atrophy, known as atrophy blanche, may show a loss of capillaries, while in other areas, the capillaries become dilated, elongated, coiled, and tortuous. This goes hand in hand with the occurrence of lesions in endothelial cells, with irregular cell shapes and distortion of the luminal surface, increased intracytoplasmic vesicles, and intracellular edema. Basement membranes fuse with the surrounding tissue. Pericapillary spaces are filled with a fluid that can contain cellular fragments and proteins. Fibrinogen deposits known as fibrin cuffs can be observed in the pericapillary spaces and around capillaries.

In lipodermatosclerosis, the skin capillaries are elongated and tortuous, and even have a glomerular appearance with proliferation of the capillary endothelium. VEGF is an obvious candidate for involvement in these changes, a factor that has also been shown to increase microvascular permeability. Plasma levels of VEGF increase during acute venous hypertension and are higher in CVD patients than in CVD patients with normal skin. Both VEGF expression and expression of its receptor, Flk-1, are influenced by blood shear stress and an inflammatory reaction. VEGF levels increase with the severity of the disease and the CEAP score (Clinical condition, Etiology, Anatomic location and Pathophysiology).

It should be mentioned that in CVD, the skin is associated with dermal tissue fibrosis. Immunocytochemical analysis of punch biopsy specimens has shown that skin from the lower calf of CVD patients has significantly elevated active transforming growth factor β–1 (TGFβ1) levels compared with normal skin or skin taken from the thigh region of the same patients. The TGFβ1 is located in leukocytes and fibroblasts, and on collagen fibrils. Activated leukocytes migrate out of the vasculature (see next section) and release TGFβ1, stimulating increased collagen production by dermal fibroblasts, leading to dermal fibrosis.

**Circulating cell entrapment and membrane adhesion**

The structural changes in the capillary network are also accompanied by erythrocyte packing in the lumen of capillaries, leukocyte entrapment within capillaries and adhesion to the venular endothelium and valve leaflets, and even white cell/platelet aggregate formation that can fill the lumen of microvessels. Leukocytes may be found in pericapillary tissue in patients with CVD. Skin biopsies from CVD limbs show elevated numbers of macrophages, T-lymphocytes, and mast cells. The same pattern has been observed in both acute and chronic experimental rat models of venous hypertension that depend predominantly on pressure and fluid shear, with elevated levels of tissue leukocytes in skin samples from affected limbs, but not from sham-operated controls.

The leukocyte entrapment within capillaries is a result of the stiff cytoplasmic properties of the leukocytes and their ability to express membrane adhesion molecules. As a consequence, leukocytes (eg, neutrophils, monocytes, T-lymphocytes) accumulate in the lower extremities under conditions of high venous pressure. Their accumulation in microvessels is enhanced by the fact that the cells may already be activated in the central circulation in patients with CVD, a process that further enhances the stiffness of the cytoplasm as well as the membrane adhesion. At the microvascular level, there are important details to consider regarding microvascular entrapment in the skin. Leukocyte entrapment in the narrow, single file capillaries can be caused by a simple stiffening of the cytoplasm or by projection of cytoplasmic pseudopods. No membrane adhesion is required. Since entrapment of leukocytes by cytoplasmic stiffening is limited to capillaries, the cytotoxic properties of leukocytes have a bearing on the tissue parenchyma that surrounds the capillary network.

By contrast, attachment of leukocytes to postcapillary venules in the skin microcirculation requires membrane adhesion to the endothelium via L-selectin on the leukocyte membrane and E-selectin on endothelial cells. In this case, the venules are the major site for the cytotoxic activity of leukocytes. The initial transient membrane attachment is followed by firm adhesion via integrins, the starting point for leukocyte migration out of the vasculature and degranulation. In CVD, the evidence suggests that a variety of membrane adhesion molecules on endothelial cells and leukocytes (intercellular adhesion molecule-1 [ICAM-1], vascular cell adhesion molecule-1 [VCAM-1], lymphocyte function–associated antigen–1 [LFA-1], very late antigen–4 [VLA-4], Mac 1, and others) appear to facilitate the adhesion and stimulate the projection of pseudopodia as a requirement for transmigration of the leukocyte into the venous wall. Basal plasma levels of the adhesion molecules ICAM-1, endothelial leukocyte adhesion molecule–1 (ELAM-1) and VCAM-1 are higher in CVD patients than in controls, and are increased significantly in response to venous hypertension provoked by standing. Any combination of leukocyte cytoplasmic stiffening...
and pseudopod formation together with enhanced membrane adhesion molecule expression serves to further enhance leukocyte trapping both in capillaries and in venules.

Little is currently known about the adhesion molecules expressed on venous valve leaflets, although it is known that the valves require specific transcription factors to be formed and that the endothelium on valve leaflets may have a different phenotype to that of the endothelium on adjacent blood vessels.21

**Leukocyte activation**

Leukocytes that accumulate in the microcirculation become activated and are key players in the inflammatory reaction, provoking skin changes in CVD. Although cytokines are part of the inflammatory reaction in CVD,22 no clear picture exists about their exact role. For example, treatment with granulocyte/monocyte colony stimulating factor (GM-CSF) to heal ulcers leads to mixed results. Tumor necrosis factor-α (TNFα), whose expression is enhanced in many inflammatory reactions, stimulates the expression of inflammatory adhesion molecules, the synthesis and release of other cytokines, and the chemotaxis of neutrophils and macrophages. The expression of TNFα appears to be upregulated in patients with venous ulcers, and healing of the ulcer may reduce the level of TNFα.22 It is important to remember that cytokine expression forms part of the repair aspect of the inflammatory cascade, and therefore no clear correlation with the degree of the disease may exist.

Treatment of CVD patients by compression bandage wrapped around the diseased leg has a distinct anti-inflammatory effect.21 Although the exact mechanism by which compression therapy operates is unknown, the evidence indicates that we need to consider mechanical stress as a mechanism for inflammation. Indeed, the transition from a normal inactivated state to an activated state may not only be facilitated by inflammatory mediators released from the endothelium or from adjacent tissue (e.g., release of platelet activating factor, TNFα, and others) but also be caused by mechanical fluid shear stress25 in the absence of chemical mediators.

Fluid shear stress is a tangential force (per unit area), and it is present in all parts of a venule; on the endothelium, in the wall of the venule, in the valve leaflets, and elsewhere. Among the many mechanisms responsible, it can be produced by the movement of blood acting on the endothelial surface, in which case it is a function of the velocity gradient of blood near the endothelial surface and the blood viscosity. This particular fluid shear stress is relatively low, i.e., of the order of 10 dyn/cm², a quantity that is ~1/100th of the stress caused by the weight of 1 cm H2O! Yet the lack of such low, but still physiologically relevant, levels of fluid shear stress can lead to leukocyte activation even in the absence of biochemical inflammatory mediators.27 The ability of leukocytes and other cardiovascular cells to respond either to chemical or physical stimulation has led to a significant deviation from past thinking regarding trigger mechanisms for inflammation.

The sensing mechanisms that allow cells to respond to such small fluid mechanical forces involve G-protein–coupled receptors.27 The phenomenon may be quite relevant with respect to CVD, because of the strong hemodynamic components of the disease. In the presence of a biophysical response to fluid shear stress, a mere shift in the blood flow field in venules may itself be a proinflammatory stimulus.

There is now a large body of evidence to suggest that virtually all functions of endothelial cells are controlled by fluid shear stress.26,28 Steady shear stress within a normal physiological range of about 10 dyn/cm² is largely anti-inflammatory. In contrast, low flow or flow disturbances, especially if they involve instances of reversed flow direction with forward and backward shear, cause a loss of this phenotype. Instead, the endothelial cell becomes more susceptible to inflammatory mediators. Stretch of endothelial cells and smooth muscle cells also has a direct effect on many aspects of their biology,27 including synthesis and release of inflammatory molecules such as leukotrienes, prostaglandin, bradykinin, free oxygen radicals, and cytokines.

Finally, we should note that in addition to local biochemical or biophysical factors operating during venous hypertension, CVD patients have a tendency toward systemically elevated leukocyte adhesion outside the veins in the affected leg. Central venous plasma obtained from CVD patients has been shown to induce higher degrees of activation (assessed by oxygen-free radical production and pseudopod formation) in healthy, naive granulocytes than did plasma taken from normal subjects.17 The nature of the plasma factor(s) responsible for the activation is currently unknown.

**Valve failure**

A key event in CVD is the loss of the ability to properly close venous valves. Failure of valves may be brought about by dilation of the venous wall and the valvular annulus with remodeling of the valve leaflets, bulging and stretching of valve leaflets, commissural dilation, shortening, tearing and perforation of leaflets and, finally, complete destruction of the valve.31,32 Furthermore, ultrastructural and immunohistochemical studies of valves and the venous wall have revealed the presence of leukocytes adhering and transmigrating into the venous wall.17,32 The leukocyte infiltration of the venous parenchyma is accompanied by remodeling of the extracellular matrix, a process that may in part be responsible for the destruction of venous valves.

**Tissue proteolytic activity**

Chronic dermal ulcers involve proteolytic activity that degrades extracellular matrix proteins. Proteases are also of major interest in this context, because of their involvement in both the inflammatory reaction and the remodeling of cutaneous tissue.34,35 The overexpression of Ca/Zn-dependent endoproteinas (matrix metalloproteinases, MMPs), MMP-3 (stromelysin-1), and MMP-13 (collagenase-3) is as-
Figure 1. A schematic diagram illustrating selected mechanisms that may control inflammation of the vein wall and valve leaflet. Normal vein and valve leaflets (A). Valve leaflets may be subject to inflammatory damage by alteration in magnitude and direction of fluid shear stress on the endothelium (B). Venous valves may become unable to close their leaflets due to vein wall distension by (C) elevated venous pressure or by (D) weakening of the vein wall due to proteolytic degradation of its extracellular matrix. MMP, matrix metalloproteinase.

**Trigger mechanisms for inflammation in chronic venous disease**

Inflammation in CVD may continue without resolution for months and years. Our understanding of the mechanisms that serve to maintain such an inflammatory state needs to be improved. The discussion above suggests that elevation of venous pressure per se, eg, after the loss of venous valves, with stretching of endothelial cells and development of an abnormal fluid shear stress pattern, may itself be an injurious inflammatory stimulus. The available evidence is compatible with this proposal, but detailed analysis with realistic models of the mechanical pattern of fluid in human veins is not currently available.

But one is compelled to ask the question “What mechanisms may lead to destruction of a venous valve in the first place?” (Figure 1). There is the possibility of venous wall distension by blood pressure elevation, caused by posture or inadequate lower limb activity (prolonged standing with lack of venous compression by muscle contraction). Some patients may have obstructed proximal venous pathways (eg, due to obesity) that cause chronically elevated pressure in veins of the lower limbs, and associated with nonhealing wounds. There is increased expression of MMP-2 and tissue inhibitor of metalloproteinase (TIMP)-1 in liposclerotic skin, venous leg ulcers, and wound fluid from nonhealing venous ulcers. An upregulation of the expression of MMP-9 has been observed on the edges of venous ulcers, and the plasma of patients with severe CVD has an increased rate of MMP-9 activation. Levels of TIMP-2 are lower in lipodermatosclerotic skin and ulcers. Uncontrolled MMP activity may contribute to extracellular matrix protein breakdown, which impairs healing.

MMPs are positioned on extracellular matrix proteins, and may be released from preexisting pools or may be newly synthesized. The inactive pro-enzymes are activated by other proteases, including those produced by mast cells. Neutrophils have gelatinolytic activity discharged by MMP-9, MMP-8 (a neutrophil collagenase), and leukolysin (a membrane-type MMP). Knockout experiments suggest that MMP-9 acts upstream of neutrophil elastase by proteolytically inactivating neutrophil elastase inhibitor AIP1, and that it can activate other MMPs. Extracellular MMP inducer (EMMPRIN; CD147) has been observed to increase MMP expression, and membrane type 1 MMP (MT1-MMP) was implicated in the activation of MMPs. Venous leg ulcers have elevated expression of EMMPRIN, MMP-2, MT1-MMP, and MT2-MMP.

An important issue is the activation of inactive proenzymes in CVD. As discussed above, leukocyte activation in patients with chronic venous insufficiency manifests itself in the form of degranulation, with an increase in neutrophil elastase and lactoferrin release. The enzymes have been proposed to be effective activators of other proenzymes, such as MMPs. Other mechanisms by which MMPs are activated may involve serine proteases, such as trypsin, pro-MMP-3, and MMP-13. Plasmin stimulates pro-MMP enzyme conversion to the active form. Plasmin hyperactivity caused by decreased plasminogen activator inhibitor–1 (PAI-1) may thus cause uncontrolled MMP activity. Elevated venous pressure in CVD causes stretch not only of the veins and venules, but also of the capillary network feeding the venules. An issue quite relevant, therefore, is the fact that the expression levels of MMPs can be controlled by mechanical stretch of cells in a way that depends on the time course of the strain. This has been studied in vitro in smooth muscle cells subjected to oscillatory and constant strain. Stationary strain significantly increases MMP-2 mRNA levels at all time points, whereas cyclic strain decreases it after 48 hours. Both secreted and cell-associated pro-MMP-2 levels are increased by stationary strain at all time points, whereas cyclic strain decreases secreted levels after 48 hours. MMP-9 mRNA levels and pro-MMP-9 protein are increased after 48 hours of stationary strain compared with no strain and cyclic strain. Endothelial cells also respond to stretch by restructuring the cell cytoplasm.
may thus be candidates for venous stents. Long-term measurements in real-life environments are required to fully understand the role of such factors in the disease. The venous wall may also be distended because its mechanical properties are weakened or because its smooth muscle is dilated. The underlying mechanisms may be derived from a genetic defect or the presence of a hormonal load during early pregnancy (e.g., progesterone) or the distension of veins after pregnancy may remain without recovery if during pregnancy the extracellular matrix was restructured. Over the period of time required to develop manifestations of CVD, it is likely that more than one mechanism may be responsible for the injury and inflammation in veins. The challenge is to identify the prevailing mechanisms underlying CVD in each individual.

Acknowledgement: I would like to thank my colleagues, Drs John J. Bergan, Luigi Pascarella, Shinya Takase, Takeshi Ono, Thomas Alaigh, and Alexander Penn who carried out the experimental studies summarized in this report.

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**Mécanismes déclenchant l’incontinence valvulaire veineuse**

Les mécanismes conduisant à la cascade d’événements associés à l’inflammation aseptique au cours de l’insuffisance veineuse chronique sont les facteurs de risque génétiques, l’imprégnation hormonale, la pression hydrostatique prolongée et la contrainte liquide de cisaillement anormale. L’inflammation se manifeste par l’activation endothéliale, l’adhésion leucocytaire à l’endothélium et la migration dans les tissus, la dégranulation des mastocytes et l’infiltration des monocytes et des T-lymphocytes avec transformation des macrophages. Les fibroblastes colorent la matrice extracellulaire ainsi que les cellules parenchymateuses, et produisent un ensemble de métabolites et de médiateurs inflammatoires, de molécules d’adhésion des membranes cellulaires, de récepteurs prothrombotiques, de facteurs de croissance et d’agents chimiotactiques. La cascade inflammatoire sert de façon fondamentale comme mécanisme de réparation tissulaire. Cependant, en cas d’insuffisance veineuse chronique associée au développement d’une incontinence valvulaire, l’inflammation ne résoud pas et au contraire conduit à des manifestations cliniques pouvant aller de la présence de varicosités à d’éventuels ulcères. Les facteurs déclenchant l’inflammation dans l’insuffisance veineuse chronique restent encore incertains.
Venous valve incompetence: the role of genetic factors

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The role of inheritance in primary varicose veins is now well recognized, although uncertainty persists as to the type of inheritance involved. Clear understanding of the mode of transmission is essential in informing genetic research strategy. When the disease mechanism is known, direct methods can be used, but this does not apply to varicose veins; indirect methods must be used instead. As in other common diseases, several types of inheritance may be involved. In some families, transmission is dominant, strongly expressed, and with a homogeneous phenotype. In such cases, a reverse genetic technique can be applied known as linkage analysis, based on the study of large families.

We have used this to identify several loci potentially related to varicose veins, but despite the presence of candidate genes within these regions of interest, we have not yet identified a mutation within these families. At the same time, other methods of investigation (transcription products of tissue samples, differential expression studies using deoxyribonucleic acid chips) may help to identify new candidate genes. However, in most cases, the mode of segregation appears non-Mendelian, and associated with the environmental factors traditionally described. This suggests polygenic or multifactorial inheritance. The molecular genetic techniques that can be used to identify one or more susceptibility genes are more complex (sib-pair and association methods) and require a large number of samples.

Medicographia. 2008;30:127-130. (see French abstract on page 130)

Keywords: extracellular matrix; genetics; inheritance; smooth muscle cell; transmission; varicose vein disease

Types of inheritance: the hypotheses

Predispensing factors play a currently well-recognized role in varicose veins. The clinical consensus is that primary varicose disease is probably genetic in origin. As early as 1851, Rudolf Virchow (1821-1902) observed an excess of family cases, and in 1868, the pedigrees of two affected families were reported. However, nongenetic factors seem to an important modulating role, compensating the task of analysis. Late onset is entirely compatible with a genetic origin, as has been shown in other common diseases (eg, familial atrioventricular block). The few twin studies provide additional information: what data are available show markedly higher concordance rates in monozygotic twins (75%) than in dizygotic twins (52%), although the difference is not statistically significant given the small sample size. Impedance plethysmography of venous distensibility in twins has also revealed that heredity plays an important role.

The genetic factor thus appears to weigh heavily, but its nature remains unelucidated. What is the mode of transmission? Clues from family tree studies point to different types of inheritance: some early investigators suggested an autosomal dominant mode of transmission, whereas others reported findings more consistent with recessive transmission. It may therefore be that mode of transmission differs between families. Indeed, in 1969, Hauge and Gundersen proposed a polygenic inheritance hypothesis, based on cooperation between a number of independent genes each having minor pathogenic effect, but which collectively, when present in sufficient numbers, resulted in varicose vein disease, just as in other common diseases in which inheritance plays a major role. The literature on varicose vein inheritance allows little in the way of robust conclusions, given the numerous forms of bias in data collection depending on the diagnostic criteria used, the population selected, and whether data about previous family members have been obtained by questioning the patient or by examining the relative concerned. The reference study by Corru-Thénard et al was based on 134 families whose members were examined. Even if the multifactorial hypothesis readily accounts for a large number of family patterns, this does not mean that this is the actual mode of transmission. In 1998, a Chinese study attempted a conclusive breakdown of modes of varicose disease transmission; nuclear family analysis was consistent with dominant autosomal transmission with 70% to 92% penetrance; other pedigrees were consistent with autosomal recessive transmission, and 37% of cases were sporadic. These family transmission studies are fundamental because they inform molecular genetic strategy, which can be either direct or indirect.

Selected abbreviations and acronyms

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<th>Abbreviation</th>
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<tr>
<td>ECM</td>
<td>extracellular matrix</td>
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<td>MMP</td>
<td>matrix metalloproteinase</td>
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<td>SMC</td>
<td>smooth muscle cell</td>
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Molecular genetic strategy

Direct methods
Direct methods can be used if the pathophysiology of a particular disease has been elucidated, as when an abnormal protein is shown to have a direct pathological role, and gene sequencing identifies a mutation (eg, hereditary hemoglobinopathy). Such methods do not extrapolate to varicose veins, because the molecular mechanism is complex and remains unelucidated. Numerous pathophysiological mechanisms have been described. Some investigators have differentiated primary changes that begin in the vessel wall from those that begin in the valves. Such an approach appears oversimplified, since the situation is rarely unambiguous. Even if valve lesions are recognized to be early and crucial in varicose disease, more widespread changes have been identified in varicose patients, involving valve insertions in the vein wall, changes in the vein wall itself, and even the skin. Varicose disease is a pathological entity in its own right. It is not secondary to physiological aging, but an instance of genuine vascular dysplasia, comprising disorganization of the vessel wall and a specific ratio of fibrillar to basement membrane collagen that remains stable over time.

The first and most visible changes to have been identified were abnormalities in extracellular matrix (ECM) metabolism, notably with a well-documented imbalance between types I and III collagen. This dysregulation in connective tissue synthesis concerns abnormalities in ECM remodeling, mainly dependent on matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). Abnormalities of MMP expression have been identified in varicose compared with control vessel wall: increased expression of MMP1, and decreased expression of MMP9, each unevenly distributed within the wall and varying between varicose segments. MMP imbalance within the ECM (in particular with an accumulation of type I collagen and a decrease in type III collagen) is found in the varicose wall (myocytes), but also in the skin (fibroblasts), indicating a more general disorder of connective tissue synthesis in varicose patients.

After the ECM, the next most obvious abnormalities involve the smooth muscle cell (SMC) itself, given its major role in ECM metabolism. Many changes, both morphological and functional, have been demonstrated in varicose SMC. In addition, specific mutations may affect the complex, two-way, integrin pathway relationships between SMC and ECM, with major potential impact on remodeling of the ECM and reorganization of the SMC cytoskeleton. More recently, the importance has been emphasized of cell infiltration of the varicose wall, in particular by monocytes and macrophages. The detailed role of this inflammatory infiltrate in varicose vein remodeling has been elucidated: venous hypertension induces a leukocytic and endothelial inflammatory cascade via a mechanism that combines valvular and vein wall hypoxia and slowing of blood flow (decreased shear stress). This induces the expression of leukocyte adhesion molecules, leading to valvular and vein wall infiltration by mononuclear cells (monocytes and mast cells), which in turn are responsible for the production of growth factors, including transforming growth factor β1 (TGFβ1). TGFβ1 is an important modulator of MMP/TIMP balance and is actually involved in the regulation of cellular apoptosis and proliferation, a pivotal element in vascular remodeling. Several studies have in fact documented inhibition of apoptosis in varicose wall myocytes.

Many variations have been described in the expression of various proteins in varicose vein disease, but differential gene expression has been less studied. Nevertheless, certain recently targeted abnormalities deserve our attention: what is the impact of variations in the repeated nucleotide sequences modulating the expression of structural genes (eg, for connective tissue and elastic tissue) in the development of primary varicose veins? What is the role of the transcriptional changes in vascular endothelial growth factor (VEGF) and its receptors, or of the mutations recently identified in the gene coding for forkhead box C2 (FOXC2), a transcription factor specifically involved in valve development and maintenance? Other mutations or polymorphisms of candidate genes have been described in the literature: MMP3 (stromelysin-1) polymorphism, the spordin 1 gene, or the thrombomodulin gene promoter, although with no conclusive evidence identified pathophysiological implications. Each of these molecular targets represents a potential line of research, such as in functional SMC studies (messenger ribonucleic acid, proteins), or comparative studies between varicose and healthy veins, whether of differential ECM and SMC gene expression or of the signaling pathways involved. Direct study of the molecular mechanism(s) leading to varicose veins thus offers multiple interesting leads but has limitations: what is the primary abnormality? Is it single or multiple? Are we not too focused on disruption of a secondary control system?

Reverse genetics
When the pathophysiological mechanism behind a condition is unknown, we can use a reverse genetic approach that identifies a potential culprit gene by studying patients; once a gene is identified, we can then elucidate the molecular mechanism behind the disease concerned. The multifactorial hypothesis accounts for a number of situations but, as in other common diseases, there also appear to be other modes of transmission. Several molecular biology strategies are complementary and therefore need to be conducted in parallel.

Bearing in mind the genetic heterogeneity seen in other common conditions, we cannot rule out the involvement in certain families of a single or major gene with dominant effect, whose expression is modulated by age and sex. Such families show a clearly dominant and strongly expressed mode of transmission, with a strikingly homogeneous phenotype. The reverse genetic technique of linkage analysis can then be used. It is based on the study of large data-rich families, with plenty of affected individuals and healthy controls, stretching over sev-
eral generations. Linkage analysis is an indirect statistical method based on two fundamental biological phenomena: meiotic recombination (i.e., the intense exchange of chromosome segments at meiosis), and the presence of polymorphic markers throughout the genome (these are repeat sequences that vary in length between individuals and are found at regular intervals throughout the genome). The analysis searches for a statistical relationship between one of these markers and the culprit gene, reflected in the family tree by an affected phenotype. The result, expressed as the logarithm of the odds (LOD) score, reflects the probability of a statistical linkage for each marker. The next step, which is essential in pursuing the search for candidate genes, consists of recruiting new families in order to narrow these broad regions of interest by determining the shortest linkage interval shared by the different families. Once narrowed to a minimum, these regions of interest can be searched for candidate genes using computerized databases, using sequencing to detect a mutation in one of them.

From theory to practice: our experience

In 2000, we began our study of six extended families in whom varicose disease segregated according to a strongly expressed autosomal dominant mode of transmission, with a particularly homogeneous phenotype and high penetrance. We have managed to identify several loci potentially associated with varicose disease, based on the phenocopy hypothesis (subjects with the same phenotype based on a different genetic abnormality—a plausible hypothesis given the high frequency of the disease in the general population) and the assumption of non-penetration in some subjects (i.e., carriers of the mutant gene who do not express the disease). However, despite the presence of candidate genes within these regions of interest (genes involved in ECM metabolism, such as those coding for TIMP2, spondin-1, elastases, integrins, and different types of collagen), we have not yet identified a mutation in our families. Nor have our families shown the mutations we have not yet identified a mutation in our families. Alternatively, new candidate genes can be identified using parallel and complementary techniques, such as studies of tissue sample transcription products or of differential expression using deoxyribonucleic acid chips. Varicose vein disease also appears to be heterogeneous, both clinically and genetically. Like others, we consider it to be a highly heterogeneous entity in terms of inheritance: isolated reticular varicoses that remain stable despite several pregnancies have little in common with severe, early-onset, progressive great vein incompetence. Some families or twin pairs can show remarkable anatomical and morphological concordance at the start of the disease. It is also worth noting that the loci of interest that we have identified differ between families, which again indicates that the disease may be genetically heterogeneous.

On the other hand, in most of the population, clinical presentation is more polymorphous and variable, and the number of family members affected is low or quite low, making it impossible to conclude that a single genetic abnormality is present, and even less that it is dominant. The mode of segregation appears non-Mendelian, and associated with the environmental factors traditionally described. This suggests that inheritance is polygenic (involving major and minor genes) or multifactorial (involving environmental determinants). The molecular genetic techniques available for identifying one or more susceptibility genes are more complex, but do not require a mode of transmission to be specified in advance. Their main drawback lies in the number of samples needed for this kind of analysis (300 to 500, depending on the epidemiological and hereditary characteristics of the disease concerned). Options include sib-pair and association methods. The sib-pair method screens genetic marker allele frequencies in affected and healthy sibs for an imbalance, in one or more given markers, between the expected theoretical frequencies and those actually observed, to identify a locus (genome region) potentially related to the disease. Association methods screen markers close to selected candidate genes for a binding imbalance, or study marker allele frequencies in affected and healthy subjects in small families (nuclear families). These complementary approaches are currently under development.

Conclusion

Despite its methodological limitations, genetic research heralds the time when we will eventually elucidate the process(ies) leading to varicose disease. This should enable us to identify subjects at risk who could benefit from prevention, given that varicose disease is associated with some long and expensive complications, but it should also enable us to explore new drug therapy avenues, or even consider gene therapy.

REFERENCES


Venous valve incompetence: the role of genetic factors – Pistorius
L'importance de l'hérédité dans l'origine des varices primitives est actuellement admise. Des incertitudes persistent cependant concernant le mode d'hérédité en cause. Une bonne connaissance du mode de transmission est cependant indispensable car cette étape guide la stratégie de recherche génétique. Les méthodes directes peuvent être appliquées lorsque le mécanisme d'une maladie est connu, ce qui n'est pas le cas de la maladie variqueuse. Le recours aux méthodes indirectes s'impose. Comme dans d'autres maladies communes, plusieurs modes d'hérédité semblent exister. On observe en effet dans certaines familles une transmission de type dominant, avec une expression forte et un phénotype homogène. On peut alors appliquer une technique de génétique inverse appelée « analyse de liaison », menée à partir de l'étude de grandes familles. Elle a permis d'identifier plusieurs locus potentiellement liés à la maladie variqueuse ; cependant, malgré la présence de gènes candidats au sein de ces régions d'intérêt, aucune mutation n'a été identifiée pour l'instant au sein de ces familles. Parallèlement, d'autres méthodes d'investigation (pro- duits de transcription à partir de prélèvements tissulaires, étude de l'expression différentielle sur puces à DNA), sont actuellement en cours et pourraient contribuer à identifier de nouveaux gènes candidats. Cependant, dans la majorité des cas, le mode de ségrégation semble non mendélien, associé aux facteurs environnementaux classiquement décrits. Ceci fait appel aux notions d'hérédité polygénique ou multifactorielle. Les méthodes de génétique moléculaire que l'on peut mettre en œuvre pour identifier un ou plusieurs gènes de prédisposition sont plus complexes (méthode des « sib-pairs », méthode d'association) et nécessitent un grand nombre d'échantillons.
Improving the management of chronic venous disorders is a timely topic, and our knowledge of the disease remains incomplete. This is acknowledged by many experts in venous disease worldwide. With this in mind, I will attempt to establish a parallel in this paper between research and advances in peptic ulcer disease and those in chronic venous disease. The idea is to demonstrate that today, we have become “reflux hunters,” but the causes of diseased veins most probably lie elsewhere, and might be approached via genetics, molecular biology, or pharmacogenotherapy. This is clearly the future, yet today, state-of-the-art treatment in venous disease mirrors that of gastric surgery 25 years ago, when gastric resection was the method of choice for all patients with a peptic ulcer. I do not know if our achievement in the next 25 years within the venous field will be comparable to that achieved in gastric and duodenal ulcer therapy, but certainly our patients will expect us to make much bigger progress in the avoidance of surgery and the improvement of varicose vein treatment to make it improving the management of chronic venous disorders.

The aim of this article is to establish a parallel between the dramatic evolution of treatment for peptic ulcer disease and that of refluxing veins. Treatment of acid peptic disease has involved a series of attempts to control gastric acid secretion in order to heal and prevent recurrence of duodenal ulcers. Likewise, it is believed that repair of refluxing valves and even more prevention of valve damage are the future of chronic venous disease treatment. To come back to acid peptic disease, surgeons like Pean, Rydygier, and Billroth began performing gastric resections in the second half of the 19th century. In 1943, the first truncal vagotomy was performed to limit cholinergic stimulation of gastric acid secretion. This led to surgery that combined gastric resections with vagotomy. In 1970, the first microsurgical technique was performed, consisting of parietal cell vagotomy. This was able to limit vagal initiation of acid secretion, while minimizing the impact on other gastrointestinal functions. By the 1960s, pharmacological intervention included antacids to neutralize acid, and anticholinergics to reduce the amount of acid produced. In 1976, treatment of acid peptic disease began a new phase, with the introduction of the first $H_2$ receptor antagonist. Since 1982, the discovery of Helicobacter pylori has dramatically altered the role of surgery in the management of peptic ulcer disease. In most cases, medical treatment is undertaken with the use of specific drugs aimed at managing Helicobacter pylori and acid secretion, and interventional methods are mostly reserved for the treatment of ulcer perforation. Today, surgeons are left only with surgical treatment of gastric ulcer complications (e.g., perforations, bleeding, or neoplastic transformation of gastric ulcers). With regard to management of venous disease, a similar evolution over time has been seen. For years, the method used for the elimination of superficial refluxes has been the stripping of the veins in which the diseased valves were located. The high recurrence rate after great saphenous vein surgery, together with the dramatic improvement in the imaging of venous valves by means of sophisticated duplex scanning methods, has made it possible to reconstruct the diseased valve rather than remove it. The future remains to be determined in the field of venous disease management. Strategies focused on the prevention of valve damage rather than its repair or resection might be envisaged. Similar to peptic ulcer disease management, it is possible to contemplate that specific drugs aimed at correcting genetic defects, reinforcing venous tone or preventing the inflammatory events that cause damage to the valves could replace current treatment methods.

Keywords: acid peptic disease; venous valve incompetence; reflux; pharmacological intervention; proton pump inhibitor; progress
more pleasant and effective, and with less recurrence. This raises the questions: what do we know, what do we not know, what should we know to progress in the management of venous disease, and what can be contemplated in the near future to improve the management of our patients?

The history of peptic ulcer therapy

The history of the treatment of acid peptic disease has involved a series of attempts to control gastric acid secretion in order to heal gastric and duodenal ulcers and prevent their recurrence (Figure 1). Gastric secretion is mediated by way of the vagus nerves, gastrin, and protein derivatives of the digestion process.

◆ Early treatment
Early treatment attempted to heal the disease by neutralizing gastric acid with diet modification—the Sippy diet, and Doll’s milk drip. Just before the turn of the century, surgeons began performing gastric resections.

◆ Resection procedures
Blalock gave a very good review of the history of peptic ulcer surgery. On November 21, 1881, the Polish surgeon, Ludwik Rydygier (Figure 2), became the first to excise the pylorus of a 30-year-old woman with a gastric ulcer and successfully anastomose the stomach with the duodenum. This was the first successful gastric resection ever performed for a gastric ulcer, and the patient lived for the next 17 years without any clinical symptoms or signs. At almost the same time, an Austrian surgeon, Theodor Billroth, performed a similar operation and later introduced another type of gastric resection consisting of a gastroenterostomy with oversewing of the duodenal stump (known today as a Billroth II gastric resection). Following the observation that only partial gastrectomy made a hyperacid stomach permanently anacid, by the 1930s, the removal of 66% to 75% of the distal stomach became the standard operation for peptic ulcer disease.2

In addition to many other people, Dragstedt knew that peptic ulcers were caused by excess acid in the stomach. Because of the known action of the vagus nerves on gastric secretion, in 1943, he performed the first truncal vagotomy to limit cholinergic stimulation of gastric acid secretion. This operation reduced 12-hour overnight gastric secretion by 50% to 60% in all patients. After Dragstedt’s introduction of the vagotomy, it was simply a matter of time before it was combined with gastric resections.2

In the early 1900s, Edkins reported that an antral hormone, which he named gastrin, caused gastric antrectomy caused a marked reduction in gastric secretion. In 1976, Herrington published the results of a large series of vagotomies and antrectomies, following which, a more conservative vagotomy was performed to prevent the nerves of the antrum and pylorus from being injured. In 1970, the first partial cell vagotomy was performed. This microsurgical technique limited vagal initiation of acid secretion, while minimizing the impact on other gastrointestinal functions.2

Today, surgery for intractable or chronic ulcer disease is rarely necessary; as a consequence, such complex procedures as vagotomy with antrectomy or highly selective vagotomy are virtually nonexistent. Surgery is now reserved for the treatment of
complications of the acute ulcer (eg, bleeding, perforation, and obstruction).3 Regarding duodenal ulcer perforation, the most common operative treatment is an omental (Graham) patch. More definitive management is rarely necessary.

**Pharmacological intervention**
Progress in gastroenterological research over the past century started as a consequence of the discoveries by Prout in the early 18th century of the presence of inorganic hydrochloric acid in the stomach and Pavlov at the end of the 19th century of the neuroreflex stimulation of its secretion, for which he was awarded the Nobel prize in 1904. The discovery of H2 receptor antagonists by Black (Figure 3) and their usefulness in the control of gastric secretion and ulcer healing, was a real breakthrough both for the elucidation of gastric secretory mechanisms and for ulcer therapy. He was awarded the Nobel Prize for this discovery, which opened the path to pharmacological intervention for gastric ulcers.

By the 1960s, pharmacological intervention included antacids to neutralize acid and anticholinergics to reduce the amount of acid produced. These treatments varied in their effectiveness, and some of them caused significant side effects. In 1976, treatment of acid peptic disease began a new phase, with the introduction of the first H2 receptor antagonist, cimetidine, which partially suppresses basal and meal-stimulated acid secretion. Ranitidine, the second H2 receptor antagonist, produced greater acid suppression capable of inducing an intragastric pH level greater than 3, lasting for approximately 10 hours per day when given twice daily at recommended doses. This level of acid suppression can facilitate the healing of duodenal ulcers, but has limited efficacy for other indications (eg, gastrointestinal bleeding). The knowledge that there is a circadian pattern in acid production, with higher levels between 10 PM and 2 AM, further resulted in the development and use of a single evening dose of ranitidine.4

Research continued to be carried out to investigate the effects of dose timing and the influence of more potent acid-suppressing agents. In the late 1980s, a more potent class of acid-suppressing agents was developed, the proton pump inhibitors (PPIs). PPIs can induce an intragastric pH above 3 that lasts for approximately 17 hours per day, and an intragastric pH above 5 that lasts for approximately 9 hours per day after once-daily oral administration of recommended doses. It is possible to attain even higher target pH values with large doses and with continuous intravenous infusion. Thus, PPIs are the agents of choice for the treatment of many acid-related disorders, including peptic ulcer disease and moderate-to-severe gastroesophageal reflux disease, and for prevention of rebleeding in patients with upper gastrointestinal bleeding. Availability of an intravenous formulation, pantoprazole, enables hospitalized patients for whom oral administration is not feasible to benefit from the superior potency of PPIs. It was suggested that intravenous PPIs may be more effective than H2 receptor antagonist prophylaxis against stress-related ulcer bleeding for intensive care patients, and should facilitate healing in those with bleeding ulcers of the upper gastrointestinal tract. A great step forward was made when two Australian clinical researchers, Warren and Marshall, discovered spiral bacteria in the stomach, named *Helicobacter pylori* (H. pylori) (Figure 4). They received the third Nobel prize in the field of gastrology in the past century for the finding that this bacterium is related to the pathogenesis of gastritis and peptic ulcer. They documented that the eradication of *H. pylori* from the stomach, using antibiotics and potent gastric inhibitors, not only accelerates healing of the ulcer but also prevents its recurrence, a finding considered to be the greatest practical discovery in gastrology during the last century. Thus, the outstanding achievements in gastroenterology during the last century have resulted in three Nobel prizes and have been appreciated by millions of ulcer patients all over the world. Infection with *H. pylori* causes most duodenal ulcers (95%) and gastric ulcers (70%). It is also likely to cause around 9% of dyspepsia cases in which no ulcers are detected.5

The dramatic success of pharmacological acid suppression in the healing of peptic ulcers and the management of patients with gastroesophageal reflux disease has been reflected in the virtual abolition of elective surgery for ulcer disease, a reduction in nonsteroidal anti-inflammatory drug–associated gastropathy, and the decision by most patients with reflux symptoms to continue medical therapy rather than undergo surgical intervention. The latter is currently reserved only for gastric ulcer complications, namely perforation, bleeding, and neoplastic transformation of a gastric ulcer. A number of challenges remain in the management of acid-related disorders, however, and a number of new drugs are currently being investigated to provide a significant advance on current treatments. Some of them (namely, potassium-competitive acid blockers and cholecystokinin 2 [CCK2]–

Figure 3. Sir James W. Black, who developed the first clinically useful H2 receptor antagonist, cimetidine, for the treatment of gastric ulcer. Copyright © The Nobel Foundation.

Figure 4. *Helicobacter pylori*, discovered in the early 1980s by Robin Warren and Barrie Marshall to be the cause of the majority of gastric and duodenal ulcers via infection of the lower stomach and upper duodenum. Copyright © 2006, Australian Academy of Science.
receptor antagonists) have already reached the clinical testing stage, while others (for instance, the antigastrin vaccine, H₂-receptor ligands, and gastrin-releasing peptide receptor antagonists) are still in preclinical development, requiring proof-of-concept in human beings. Of the current approaches to acid secretion reduction, potassium-competitive acid blockers and CCK2-receptor antagonists certainly hold the greatest promise, with several compounds already in clinical trials.

A parallel with the treatment of superficial venous valve incompetence

The aim of treatment in chronic venous disease is to eliminate sources of venous hypertension.9

◆ Resection of the diseased superficial vein

In superficial venous insufficiency, the aim of treatment is to suppress reflux in the superficial diseased veins (varicose veins).10 Reflux in superficial veins is mostly responsible for venous hypertension. Until 10 years ago, the usual way to suppress reflux in diseased superficial veins was the following: first, suppress leakage points in the deep venous network that could be responsible for reflux in the superficial system; next, strip pathologic superficial veins, either by stripping the great saphenous vein (GSV) of the thigh or at the other end of the spectrum, stripping the entire saphenous vein from the ankle to the groin, along with stab avulsion of varices. In France, the two most performed procedures in 2001 were high ligation plus saphenous trunk stripping and tributary stab avulsion (71.9%), and high ligation plus saphenous trunk stripping (17.3%).11 By contrast, in the USA, high ligation alone at the saphenofemoral junction has been widely practiced.5

Thus, type of procedures varied greatly depending on countries and the dominant thinking among phlebologists and surgeons. For a long time and until recently, saphenofemoral ligation (Figure 5) associated with stripping of the GSV was considered the best procedure to achieve the goal of suppressing reflux in the superficial system.

Recurrent varicose veins after surgery are acknowledged to be a major problem for patients and society. In an attempt to perform less bloody surgery procedures, endovenous ablation was developed in the 1990s. This procedure was found to be safe and effective in eliminating the GSV from the venous circulation. The two currently available methods used to achieve ablation of the GSV are the Closure Procedure using a radiofrequency catheter and generator, and endovenous laser ablation using a laser fiber and generator (Figure 6). Both systems use electromagnetic energy to destroy the GSV in situ. We are presently lacking follow-up data to verify whether these endovenous procedures lead to less neovascularization than open surgery, but patient acceptance of these minimally invasive procedures is overwhelmingly better than with stripping. In this regard, one can say that a step forward has been made in the treatment of venous insufficiency, with less invasive methods that are more comfortable for patients.

◆ Valve repair in superficial and deep venous insufficiency

Specialists in venous disease dreamt of a valve repair or valve restoration process that could spare the vein itself, much like the patches that were developed for perforation of duodenal ulcers. Direct and indirect restoration of valve function was eventually performed.

Methods for indirect valve function restoration all have in common the fact that they preserve the saphenous trunk and restore its valve function via modification of the hemodynamics. Conservative Hemodinamic treatment of Incompetent Varicose veins in Ambulatory patients (CHIVA) is a technique that seeks to normalize venous pressure by ligation of points of venous reflux at re-entry perforators.9

High ligation plus tributary phlebectomy plus/mi-

nus a perforator ablation procedure was first report-
ed by Hammarsten, and was only used for treating GSV insufficiency. The CHIVA procedure was later further developed and popularized by Franchesci, Zamboni, and Cappelli (see article by Perrin in the current issue). Another vein-sparing technique is external banding, which aims to restore proximal valvular competence of the GSV. These procedures are not widely practiced, however.

For deep venous insufficiency, the goal is to correct the deep venous reflux (DVR) at the subinguinal level. This reflux leads to a permanent increase in venous pressure, unaffected by the activity of the calf venousmuscular pump. But it must be kept in mind that DVR is frequently combined with superficial and perforator reflux, consequently all these mechanisms have to be corrected in order to reduce the permanent increased venous pressure. Several methods are used: internal valvuloplasty, venous segment transfer, vein valve transplantation, neo valve, and allograft. All these methods are associated with phlebectomy, while valvuloplasty and percutaneous placed devices do not need associat-
ed phlebectomy.

◆ Chemical interventions: sclerotherapy

Until now, chemical intervention has been limited to liquid and foam sclerotherapy. Liquid sclerother-

apy is mostly used in the treatment of telangiec-

terms of fundamental research. Recent studies in chronic venous disease have illuminated our understanding of the underlying mechanisms responsible for the progression of such disease to the extent that it was useful for us to review current knowledge, with particular regard to the roles of the key players namely the leukocyte, its inflammatory products, and biomechanical factors.

It appears that inflammatory processes involving leukocyte/endothelial interactions, triggered largely in response to abnormal venous flow, are important in causing the adverse changes in venous valves and vein walls. Elevated venous pressure and changes in shear stress are involved in the control of inflammatory reactions in endothelial cells and circulating leukocytes. Decreased shear stress modifies gene expression at the endothelial surface, promoting an inflammatory endothelial phenotype. Normal shear stress prevents leukocyte adhesion to valves, while inflammatory mediators suppress the response of leukocytes to shear stress. Thus the interaction between leukocytes and valve endothelium is facilitated. Inflammation unmasks cell adhesion molecules at the surface of the endothelium, promoting leukocyte adhesion to the endothelium. In addition, chronic venous disease patients have a tendency for systematically elevated leukocyte adhesion.

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Conclusion

If dramatic progress has been made over the last decade in the treatment of venous insufficiency, moving from open surgery to minimally invasive interventions, a great step remains if we are to accomplish an advance that is comparable with that achieved in the treatment of peptic ulcers. This is in large part due to a lack of research into the fundamental mechanisms of chronic venous disease progression. As says Professor John Bergan, the first author of an outstanding review on chronic venous disease: 

It is an unfortunate fact that research interest and funding attracted by chronic venous disease has been in inverse proportion to its prevalence and socioeconomic burden. It has enormous capacity to impair the quality of patients’ lives, mildly in most cases, moderately in many, and severely in the cases of the significant number with leg ulceration. This state of affairs is unwarranted, not simply for humanitarian reasons, but also in terms of fundamental research. Recent studies in chronic venous disease have illuminated our understanding of the underlying mechanisms responsible for the progression of such disease to the extent that it was useful for us to review current knowledge, with particular regard to the roles of the key players namely the leukocyte, its inflammatory products, and biomechanical factors.

It appears that inflammatory processes involving leukocyte/endothelial interactions, triggered largely in response to abnormal venous flow, are important in causing the adverse changes in venous valves and vein walls. Elevated venous pressure and changes in shear stress are involved in the control of inflammatory reactions in endothelial cells and circulating leukocytes. Decreased shear stress modifies gene expression at the endothelial surface, promoting an inflammatory endothelial phenotype. Normal shear stress prevents leukocyte adhesion to valves, while inflammatory mediators suppress the response of leukocytes to shear stress. Thus the interaction between leukocytes and valve endothelium is facilitated. Inflammation unmasks cell adhesion molecules at the surface of the endothelium, promoting leukocyte adhesion to the endothelium. In addition, chronic venous disease patients have a tendency for systematically elevated leukocyte adhesion.

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, has focused attention on available molecules with known activity to modify this chain of events. It is high time we stopped our role as venous reflux hunters and became wise, modern pharmacogeno-healers, armed with new molecular biology and nanotechnology tools. Let us hope that this will be realized in the coming years.
Cet article veut établir un parallèle entre l'évolution remarquable du traitement de l'ulcère gastroduodénal et celui des veines refluentes. Pour traiter la maladie acido-peptique, on a tenté de contrôler la sécrétion gastrique acide afin de guérir et prévenir la récidive d'ulcères duodénaux. De même, la réparation de valves refluentes et même plus, la prévention des lésions valvulaires sont présentées comme l'avenir du traitement de la maladie veineuse chronique. Pour revenir à la maladie acido-peptique, des chirurgiens comme Pean, Rydggier et Billroth ont réalisé leurs premières résections gastriques dans la deuxième moitié du XIXe siècle. En 1943, la première vagotomie tronculaire a été effectuée pour limiter la stimulation cholinergique de la sécrétion gastrique acide. Ceci a mené à une chirurgie qui a associé résections gastriques et vagotomie. En 1970, la première technique microchirurgicale est apparue sous la forme d'une vagotomie cellulaire pariétale. Elle permettait de limiter la composante vagale de départ de la sécrétion acide en minimisant l'impact sur les autres fonctions gastro-intestinales. Dans les années 60, les antacides pour neutraliser l'acide et les anticholinergiques pour diminuer la quantité d'acide produite ont fait partie des traitements pharmacologiques. En 1976, une nouvelle phase du traitement de la maladie acido-peptique voit le jour avec l'introduction du premier antagoniste des récepteurs H2. Depuis 1992, la découverte d'Helicobacter pylori a complètement bouleversé le rôle de la chirurgie dans la prise en charge de l'ulcère gastroduodénal. Dans la plupart des cas, le traitement médical est entrepris avec des molécules spécifiques destinées à Helicobacter pylori et la sécrétion acide et les méthodes interventionnelles sont principalement réservées au traitement de l'ulcère perforé. De nos jours, les chirurgiens ne s'occupent que du traitement chirurgical des complications de l'ulcère gastrique (par exemple, perforations, saignement ou transformation maligne des ulcères gastriques). La même évolution au cours du temps a eu lieu en ce qui concerne la prise en charge de la maladie veineuse. Depuis des années, le stripping des veines abritant des valves pathologiques a été la méthode utilisée pour l'élimination des reflux superficiels. Le taux élevé de récidive après chirurgie de la grande veine saphène associé à l'amélioration très importante de l’imagerie des valves veineuses grâce à des méthodes sophistiquées d’écho-Doppler pulsé, ont permis d’envisager la reconstruction de la valve malade plutôt que sa résection. Les perspectives dans le cadre de la prise en charge de la maladie veineuse restent à préciser et il faudrait créer des stratégies de prévention des lésions valvulaires plutôt que la résection ou la réparation. Comme pour l’ulcère gastroduodénal, il est possible de considérer que les médicaments spécifiques destinés à corriger les défauts génétiques, renforcer le tonus veineux ou prévenir l’inflammation qui endommage les valves, pourraient remplacer les méthodes de traitement actuelles.

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TRAITEMENT DE L’INSUFFISANCE VALVULAIRE VEINEUSE : PASSÉ, PRÉSENT ET FUTUR
UNE RÉFLEXION SUR SON ÉVOLUTION COMPARÉE À L’ULCÈRE GASTRODUODÉNAL

THE VENOUS VALVE AND PRIMARY CHRONIC VENOUS DISEASE

MEDICOGRAPHIA, VOL 30, No. 2, 2008
The saphenofemoral junction: to ligate or not to ligate?

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Ligation of the saphenofemoral junction (SFJ) was first proposed by Trendelenburg in 1890 and modified to its current form by Moore and Thomas in 1896. Extended flush high ligation (HL), taking care to cauterize or tie all the tributaries right up to the first or second level, is the current recommended technique. HL with removal of the great saphenous vein (GSV) has been the universally accepted surgical treatment of axial venous reflux for almost a century. HL alone aimed at preserving the GSV for future use is associated with poor results, because reflux persists, resulting in recurrent varicose veins. HL with stripping of the thigh GSV gives better results than HL with sclerotherapy or stab avulsions. These results suggest that removal of the thigh portion of the GSV with detachment of its perforator tributaries is more important than HL itself and it remains a crucial step in the treatment of axial reflux. Two issues now threaten this procedure after almost 100 years. First, there is the need among surgeons who treat venous reflux to use minimally invasive methods, ablating only the GSV and leaving the SFJ untouched. The second is the duplex ultrasonography (DUS)-based observation that significant varicose vein recurrence is due to neovascularization, even after technically correct HL. Several aspects need to be answered in deciding for or against HL: (i) what are the causes of recurrence after SFJ ligation? (ii) is the risk of neovascularization sufficient to abandon the procedure? (iii) does neovascularization also occur if the SFJ is left untouched? and (iv) what are the alternative procedures available? Most recurrence is due to technical failure. Viani et al. reported that in 61 patients with recurrence, 50.8% had an intact SFJ, 44.2% had intact tributaries coming from the SFJ, and only 3.2% showed neovascularization. Bradbury et al. found that of 71 patients undergoing repeat groin dissection, only 20 (28%) had a ligated SFJ, 31 (44%) had intact major tributaries, and 52 (73%) had an intact GSV in the thigh. Neovascularization is considered to be the cause of recurrence when HL is technically perfect. However, Egan et al. found that DUS identified neovascularization in only 8.2% limbs with recurrence. Surgical exploration revealed a residual GSV stump with one or more significant tributaries in 27 out of 41 recurrent limbs. Each of the remaining 14 limbs had a residual incompetent thigh GSV. Two prospective studies by De Maeseneer et al. suggested that the incidence of neovascularization after SFJ ligation is much higher in both the short term (14% of cases at 1 year) and long term (88% of cases at 3 years). Neovascularization is also seen after radiofrequency ablation of the GSV and, surprisingly, is more common when the SFJ is not ligated (67% vs 34% when ligated). Neovascularization after HL may be reduced by using barrier techniques such as polytetrafluoroethylene (PTFE), silicon, and explantation of the intima of the ligated SFJ stump by under-running the mouth with prolene sutures. In summary, at this stage, it may be premature to condemn HL as a cause of neovascularization and/or recurrence. Technical modifications with better preoperative assessment to identify other factors responsible for high hydrostatic and hemodynamic forces will probably give better recurrence-free results after HL. More prospective randomized trials with periodic and regular DUS follow-up are needed before the concept of sparing the SFJ can be proved to be effective and acceptable.

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A main aim of venous surgery is to eliminate venous reflux. However, with all treatment modalities, long-term recurrence remains a challenging problem, and one with a relatively high incidence, for reasons that have attracted many explanations, in particular poor surgical technique and neovascularisation. During my surgical residency 25 years ago, “To ligate or not to ligate”? was not a question that would ever have been proposed. Saphenofemoral flush ligation, with meticulous ligation of all tributaries at that level, was combined with great saphenous vein (GSV) stripping as the standard surgical technique. The growing trend toward less invasive low-morbidity intervention, day surgery, and outpatient procedures has combined with the refinement of endoluminal vascular instruments to favor the introduction and increased use of endoluminal ablation for GSV reflux. It was these emerging techniques that prompted the question “To ligate or not to ligate”? since it became impossible to ligate the saphenofemoral junction (SFJ) and we therefore ignored the numerous venous tributaries around it. Research sought to determine the effect of ligation and nonligation on the incidence of recurrence, and was pushed a step forward to postulate that if recurrence was caused by neovascularization, then the solution was to avoid surgical groin hematoma. In the case of conventional surgery, we have long-term studies of patients’ groins up to 14 years postoperatively. The consensus is that neovascularization is the cause of recurrence in such cases, in the absence of surgical error. By contrast, only short-term follow-up is available for patients treated with radiofrequency ablation, and very few studies after endolaser ablation. Compared with stripping and SFJ ligation, radiofrequency ablation leaves physiologic tributary flow relatively undisturbed. Two year follow-up showed no evidence of inguinal neovascularization. We would do well to ask whether longer follow-up would produce the same results. Descriptive analysis of ultrasound findings after radiofrequency ablation showed small-vessel networks adjacent or connected to the ablated GSV in most cases. SFJ ligation, on the other hand, was associated with fewer small-vessel networks and proximal GSV recanalization when examined after a similar follow-up period. Whether these small networks will develop into large-caliber refluxing veins needs long-term follow-up. At present, the trend not to ligate the SFJ and its tributaries is strongly supported by the growing endoluminal ablation market. The technique is definitely less invasive and gives results comparable to conventional surgery in terms of venous reflux elimination and patient satisfaction. Only time will tell its effect on late recurrence. As the pendulum swings between different emerging techniques, it is clear that the ideal treatment for varicose veins, based on a proper understanding of the underlying pathology and hemodynamics, continues to elude us.

REFERENCES


The saphenofemoral junction: to ligate or not to ligate?

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Various interventions have been described to correct the underlying pathophysiological abnormalities that lead to varicose veins. Appropriate patient selection is crucial for success. Treatment planning should be directed by the presence/absence and location of axial reflux, and the extent and location of the superficial venous pathology. Duplex ultrasonography (DUS) has become the gold standard for this purpose and in most patients is the only diagnostic investigation necessary in selecting the most appropriate intervention. The parameters evaluated by DUS comprise: patency of the deep venous system, evidence of prior deep vein thrombosis or deep venous system reflux, great saphenous vein (GSV) reflux and anatomy (eg, double GSV), GSV diameter and distance from skin, small saphenous vein reflux, anatomy of the saphenopopliteal junction, and perforator incompetence and location. Treatment options include (i) for GSV reflux: ligation and stripping, radiofrequency or laser endovenous thermal ablation, and endovenous chemical ablation with a foam detergent; (ii) for perforator incompetence: minimally invasive ligation, subfascial endoscopic perforator surgery, sclerotherapy or even the Linton procedure; and (iii) for superficial varicocities and varicose veins: stab avulsion phlebectomy, sclerotherapy and/or laser therapy. Management of GSV incompetence has historically been treated with high ligation of the GSV at the saphenofemoral junction, ligation of all tributaries, and groin-toANKLE stripping of the saphenous vein. This surgery was highly invasive and associated with severe pain and bruising, swelling, and disfiguring scars. However, modern stripping techniques have greatly reduced the associated trauma and morbidity. Stripping can now be performed as an outpatient procedure in the above-knee segment of the GSV without a distal incision for a better cosmetic result. Early ambulation with elastic stockings is encouraged. Endoluminal laser or radiofrequency thermal ablation requires percutaneous access to the vein lumen. Initially, in these ambulatory procedures, there was a concern to use limited energy to restore competence to the saphenofemoral valve, but this did not prove effective in the long term. Intraoperative and postoperative complications are infrequent, generally well tolerated, and include difficult device access or advancement, transient heat, bruising, pain, paresthesia, thermal skin damage, superficial thrombophlebitis, lymphedema, and deep vein thrombosis. Some randomized trials have concluded that endoluminal thermal vein ablation is as effective as conventional stripping. Some enthusiasts of ultrasound guidance and intravenous foam injection have expanded the indications for conventional sclerotherapy to include treatment of an incompetent GSV. They argue that saphenofemoral occlusion using external compression or a balloon-tipped catheter permits retention of foam sclerosant in the vein long enough to produce sufficient damage to cause sclerosis. Side effects are infrequent, usually resolve spontaneously, and can include chest discomfort, nausea, dry cough, headache, dizziness, visual disturbance, and psychogenic reactions. Recently some authors have shown that ultrasound-guided foam sclerotherapy can be effective even if GSV diameter at the saphenofemoral junction exceeds 10 mm, to a maximum of 16 mm, but further information is needed regarding bubble emboli and long-term follow-up. Procedure costs appear highest for radiofrequency ablation, somewhat lower for laser ablation, and significantly lower for chemical ablation. The answer to the question “To ligate or not to ligate?” hangs on the definition of neovascularization or recurrence. Some authors agree that neovascularization is secondary to “frustrated” venous drainage from the abdominal wall and perineum, while others believe that recurrence is the issue, due to the enlargement of previously existing veins that were ineffectively ligated and consequently cause recurrent reflux in the thigh. The literature contains various reports of neovascularization or recurrence after ligation and stripping and also after radiofrequency/laser procedures. In my view the answer also depends on the definition of successful treatment, including the entire procedure, the method of screening for treatment failure, and the reporting of results. Recent advances in ultrasound technology allow more critical evaluation of clinical results than in the past. We need more high-quality randomized multicenter studies, and long-term follow-up of endoluminal ablation, both thermal and chemical, before we can define their role and costs compared with modern minimally-invasive GSV stripping.

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CONTRAVERSIAL QUESTION

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In cases of great saphenous vein (GSV) reflux, the ostial valve is often competent. The frequency of subsostial or more distal trunk reflux is estimated at around 50% in the literature.1-6 Endovenous treatments for GSV reflux that spare the saphenofemoral junction (SFJ) during GSV ablation have called into question the principle of high ligation of the SFJ.7-9 Midterm results using endovenous techniques show anterograde drainage of the SFJ collaterals toward the deep vein in 85% to 100% of cases.9-11 Yet high ligation of the SFJ remains the rule when stripping the GSV. Since October 2003, given the results of endovenous treatment, we have stopped combining high ligation with surgical stripping, even in cases of ostial reflux. We recently reported the hemodynamic and clinical results of this new approach at the 19th Annual Congress of the American Venous Forum, in San Diego, CA, USA. We observed no reflux in the preserved SFJ in 98% of cases over a mean follow-up of 24.4 months. These results are at least comparable with, or even superior to, the 80% to 97% absence of SFJ reflux reported 2 years after endovenous radiofrequency or laser treatment.9-11 This prompts the question: Does surgical stripping combined with extensive phlebectomy improve the hemodynamics of the preserved SFJ, given that the GSV cannot recanalize and, perhaps especially, that the varicose reservoir has been ablated? The hemodynamic benefits of varicose reservoir ablation are mentioned in the literature.11 Despite inguinal surgery, the rate of inguinal neovascularization was very low in our series (1.8% at 2 years). This figure is no higher than the 0% to 2.8% recorded after endovenous treatment,6-8 and much lower than in surgical studies of extended high ligation with rates of 20% to 53%.12-17 Preserving the superficial abdominal and perineal venous drainage by not dissecting the SFJ and not disconnecting the collaterals appears to avoid neovascularization. Using a limited inguinal approach without dissecting the SFJ does not therefore seem to cause more neovascularization since it preserves the drainage of SFJ collaterals into the femoral vein. Our clinical recurrence rate (6.3%) can be compared with stripping combined with extended high ligation, where the figures vary from 10% to 25% after 2 years.13,14 Our recurrence rate is also better than the 12% to 15% observed after endovenous treatment with an identical follow-up.9-11 It is difficult to compare the different studies because none have quantified either the preoperative varices or varicose reservoir resection. Moreover, in our study, clinical recurrence was independent of SFJ reflux in 6 cases out of 7, just as GSV ablation did not lead to recurrence in the studies of endovenous treatment.11 These observations support the increasingly propounded theory that varicose disease develops from the superficial distal venous network,7,8,10 rather than downwards from the junctions between deep and superficial venous networks, as in the conventional view.20,21 However, we did observe one serious postoperative complication: SFJ thrombosis extending into the femoral vein, with pulmonary embolism, but fortunately no further serious sequelae. This potentially serious complication has been reported after endovenous treatment for years, and should probably be taken into account by targeted prevention when preserving the SFJ, for example by using low molecular weight heparin or conventional high ligation with multiple phlebectomy in patients with thrombophilia, a history of thrombosis, or a very dilated junction (>20 mm). Early postoperative Doppler ultrasonography (after 24-48 hours) could also be recommended for detecting thromboembolic complications.22 In endovenous treatment, conserving the SFJ is beneficial during surgical ablation of the GSV because it preserves physiological venous drainage of the inguinal region and minimizes the mid-term risk of neovascularization and varicose recurrence. Further studies are needed in order to assess the postoperative risk of SFJ thrombosis and the long-term hemodynamic results of this surgical approach and of SFJ-preserving endovenous techniques.

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Ligation of the saphenofemoral junction (SFJ) has for many years been considered a mandatory part of the surgical treatment for varicose veins. The need to ligate the great saphenous vein (GSV) at this level is being questioned on the basis of better awareness of neovascularization in the groin and the development of alternative techniques. The conventional and perhaps oversimplified view is that neovascularization results from poor surgical technique. However, the evidence now suggests that it can occur despite correct surgical technique. It is therefore important to determine its frequency and identify its causes, with particular regard to the following factors: stimulation of angiogenesis by the endothelium in the GSV stump, the role of inguinal lymphovenous connections, the vasa vasorum of the femoral vein, altered physiological drainage of inguinal GSV tributaries, and constitutional factors. Color Doppler ultrasonography is a particularly useful monitoring tool. In a follow-up of 1326 patients, Allegra et al found no residual reflux in the GSV trunk 3 weeks after varicose vein surgery, but a 13% relapse rate at the SFJ after 5 years. Using the same technique in 100 patients, De Maeseneer et al noted that neovascularization was unlikely ever to develop in those in whom it was not present at 1 year, thus giving an idea of the odds of long-term relapse at the SFJ. Winterborn et al monitored outcome 11 years after surgery in 51 out of an original population of 106 patients, concluding that recurrence and the need for reintervention were due to incompetence in the groin, the commonest cause being neovascularization. They suggested that the presence of a residual GSV may be contributory, a view confirmed by Egan et al who observed that all recurrent varicose veins associated with duplex-diagnosed neovascularization are also associated with persistent reflux in the GSV stump tributaries, thigh GSV, or both. These data force the conclusion that so long as we continue to ligate the SFJ, we must use correct surgical technique, avoid leaving tributaries or incompetent GSV segments in the thigh, develop a better understanding of neovascularization, and use postoperative color Doppler ultrasonography in follow-up. Some authors believe that the use of physical barriers, such as silicone patches, may diminish neovascularization, particularly in repeat recurrence. Techniques such as endoluminal radiofrequency, laser or sclerosing foam ablation of the GSV avoid SFJ ligation. They have yielded promising short-term results, but only long-term comparative studies will ultimately determine whether SFJ ligation is unnecessary.

**REFERENCES**

Duplex scanning has greatly enhanced phlebotherapy in recent years. New endoluminal techniques such as duplex-guided foam sclerotherapy have been developed or modified for treating great saphenous vein (GSV) incompetence. Current treatment options include minimally invasive surgery with flush ligation of the saphenofemoral junction (SFJ) and all the tributaries, inversion stripping, mini-phlebectomy, and various ultrasound-guided endovascular procedures using heat (produced by laser, radiofrequency, immersion, or steam) or sclerosant foam, each of which approximates and shrinks the vein walls, resulting in occlusion of the incompetent GSV trunk. These procedures dispense with the conventional surgical practice of ligating all tributaries. Irrespective of the option chosen, every phlebologist faces the problem of recurrence. Published recurrence rates vary from 5% to 60% depending on method and time frame, but all treatments aim to eradicate venous insufficiency. Recurrence can be due to disease progression and technical error, but also to neovascularization, since Nature seeks ways to rebuild what surgeons extirpate. Angiogenesis is a feature of all healing wounds and the remaining intimal cells of the saphenous produce endothelial growth factor. The main advantage of endovenous obliteration is that it does not excise the incompetent trunk or shed endothelial cells into tissue. Short- and midterm outcome is comparable to that of minimally invasive surgery, and with less recurrence, even if the tributaries remain. El Wajeh et al and Egan et al have suggested that a main factor in recurrence, rather than or in addition to neovascularization, lies in the abnormal hemodynamic forces in the saphenofemoral area, such as the high pressure in the first femoral segment distal to the inguinal ligament and above the proximal femoral valve, the so-called “unprotected venous segment.” Activity-induced peaks of abdominal pressure impact this unprotected venous segment and escape through neovascular capillaries, resulting in recurrent varicose veins. Another argument favoring endovenous obliteration is the rapid recovery from a minor procedure under local or regional anesthesia, hence an improved quality of life. Our experience has also shown similarly good results after minimally invasive surgery under tumescent anesthesia. We would confirm the long periods of pain along the GSV reported by Proebstle et al after endovenous laser treatment, even if most studies have found less pain than after conventional surgery. Whether the phlebologist chooses to ligate or not to ligate is mainly a question of anatomy, and it is solved by duplex scanning. In our experience, a diameter >10 mm, aneurysm, or non-linear GSV close to the SFJ are indications for minimally invasive surgery. In very slim patients with light skin, hyperpigmentation may be a negative cosmetic side effect of endovascular obliteration. As for duplex-guided foam sclerotherapy, we use it routinely in the elderly, patients with comorbidities, and those who refuse a minimally invasive technique. Short-term success can be measured by various parameters, include closure of the culprit venous valves, venous reflux; visible varicose veins, quality of life, recovery time, and pain. The main parameter of long-term success is the recurrence rate, diagnosed by duplex scanning and described by the presence of venous reflux. Although the short- and midterm results of endovenous obliteration are good, we know that the recurrence rate after venous surgery increases significantly after 10 years. Accurate comparison will require long-term results. Provided that endovenous GSV obliteration works, the new nonligation techniques are highly promising because they do not appear to induce neovascularization and recurrence is lower. It is therefore extremely astonishing that some practitioners combine GSV obliteration with saphenofemoral ligation. Combining two great methods may not end up with a result that is greater still, but with complete cancellation of their respective benefits!
The saphenofemoral junction: to ligate or not to ligate?

The most common source of ambulatory venous hypertension is an incompetent superficial system, usually the great saphenous vein (GSV). Alternatively, vein reflux may originate from the deep veins, perforating veins, or any combination of the superficial, perforating, and deep vein systems. It is critical to identify the origin of venous hypertension and the most proximal point of reflux by performing a thorough evaluation with duplex ultrasound imaging. Superficial axial vein reflux may be corrected by surgical, thermal, or chemical means. Interventions on the GSV at the saphenofemoral junction (SFJ) have been widely performed in the belief that this could control gravitational reflux and remove the hydrodynamic forces of perforator vein reflux. A cornerstone of varicose vein surgery is high ligation of the GSV with tributary ligation of the GSV at the SFJ. Neovascularization after correct SFJ ligation: angiogenic stimulation that could explain how new veins can develop to focus on the pathophysiological mechanisms responsible for recurrence. Attention eventually focused on the saphenous nerve injury associated with ankle to groin stripping. It was concluded that stripping from groin to ankle, or to the knee, caused less nerve injury and did not adversely affect early venous hemodynamic improvement. One disappointing outcome for surgeons and patients is recurrence, defined as the presence of varicose veins in a lower limb previously operated on for varices, with or without adjuvant therapies. This clinical definition includes true recurrence, residual veins, and varicose veins due to disease progression. Some causes are obvious: insufficient understanding of venous anatomy and hemodynamics, inadequate preoperative assessment, and incorrect or insufficient surgery. In the absence of surgical error, junctional recurrence is found in less than one third of re-examined extremities. Duplex ultrasound or re-exploration of the groin at the level of the SFJ frequently shows neovascularization as the cause of recurrence.

Research needs to focus on the pathophysiological mechanisms that could explain how new veins can develop after correct SFJ ligation: angiogenic stimulation in the free endothelium of the ligated stump, transnodal lymphovenous connection, dilatation of small adventitial vessels in the vasa vasorum of the femoral vein, or disturbed venous drainage of the ligated tributaries of the SFJ. Neovascularization in the groin has been reduced by over-sewing the ligated SFJ with prolene to prevent contact with surrounding tissue, inserting a polytetrafluoroethylene (PTFE) patch over the ligated junction, and closing the cribriform fascia. In recent years, endovenous ablation of the GSV without ligation has proved safe and effective in eliminating the proximal portion of the GSV from the venous circulation, giving even faster recovery and better cosmetic results than stripping. The two currently available methods are the Closure procedure using a radiofrequency catheter and generator (VNUS Medical Technologies) and endovenous laser ablation, using a laser fiber and generator (various manufacturers). The goal of endovenous treatment is the ablation of abnormal blood reflux by durable occlusion of the vein lumen. This can be achieved either by shrinking the vein until the lumen has vanished completely, or by substantially damaging the endothelium and inner vein wall leading to secondary occlusion of the lumen by thrombus, similar to the effect of a sclerosant. The degree of vein wall shrinkage appears important because the residual lumen occluded by endovascular thrombus could be recanalized. The larger the thrombus, the higher the risk of recanalization. Results are promising, both early (GSV occlusion was achieved in >90% of cases after both procedures at 1 month) and in the midterm (recurrence at 36 months appeared similar to that after conventional surgical management), although long-term follow-up and comparison with standard GSV stripping are required to confirm the durability of these endovenous procedures. However, the absence of neovascularization is striking, and these minimally invasive procedures are also well accepted by both doctors and patients. The literature emphasizes the need for early ultrasound scanning in all patients after endovenous GSV ablation: veins still occluded 1 year after the procedure remained occluded at further follow-up to 3 years. Relevant complications reported with endovenous treatment are rare. The most important is deep vein thrombosis, which further emphasizes the need for ultrasound B-scanning after surgery. Thrombus protrusion into the femoral vein is an indication for antithrombotic therapy. Deep vein thrombosis prophylaxis may be considered in patients >50 years old. In the absence of significant complications, endovenous procedures have important advantages in selected patients, offering less postoperative pain, earlier return to work and normal activities, and apparent cost-effectiveness. Endovenous treatment can be combined with any other technique (Muller’s phlebectomy, all forms of sclerotherapy, perforator surgery, subfascial endoscopic perforator surgery, and endovenous laser occlusion of incompetent perforators). Concomitant tumescent anesthesia enables the vast majority of patients to be treated in-office without general anesthesia or surgical incisions, at
the same time as maximizing outcome and minimizing recurrence. Ultrasound-guided foam sclerotherapy was introduced as a third alternative treatment. Foam is more effective than liquid sclerotherapy and can be used to treat large-diameter veins and even main superficial trunks. Most vascular surgeons agree that sclerotherapy has been used for a very long time for treating recurrent veins. The results are promising but still inconclusive. Thus endovenous methods may be promising but GSV ligation and stripping remains the gold standard. However, there is an urgent need for prospective randomized trials of endovenous laser therapy against conventional surgery, high ligation at the same treatment session, and other endovenous techniques such as radiofrequency closure and sclerotherapy.

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Optimal treatment of varicose veins requires exact identification of the source of venous reflux. One of the biggest problems in treatment is recurrence, which can reach 65% within 5 years and currently accounts for 25% of all varicose vein surgery. The best guarantee of a good result lies in accurately identifying the source of reflux and in removing it in the first surgical procedure. Duplex scanning of the lower extremity plays an important role in reducing the rate of varicose recurrence. Duplex ultrasound mapping is much more accurate than other methods of venous system examination. However, it is still not accepted by all general or vascular surgeons because of the time and expense involved.

In my view, clinical examination and manual Doppler ultrasound are insufficient in patients with primary varicose veins. Duplex ultrasound should be considered as standard, and as absolutely essential in patients with varicose recurrence. The problem of angiogenesis in the saphenofemoral junction (SFJ) stump following ligation of the great saphenous vein (GSV) is a hot topic. Experience tells us that primary surgery is often incorrectly performed, predisposing to recurrence. On the other hand, all surgeons have a proportion of patients with recurrence, whether or not they believe the procedure they performed was flawless. Perfect anatomical knowledge is essential, given the multiplicity of venous variants in the SFJ region. The GSV has tributaries subinguinally — the medial and lateral accessory saphenous veins — as well as inguinally — superficial circumflex iliac vein, superficial epigastric vein, and external pudendal vein, including its superficial and deep branches. The external pudendal vein can be double or triple, as can the GSV (18.1% of cases). The number of SFJ tributaries is also not constant. In 33.4% of cases, one or more (functional) tributaries join the GSV or common femoral vein deep to the deep fascia. Anatomical variation in the SFJ is important in ensuring safe and appropriate management.

Venous insufficiency is best treated using the least invasive methods, such as percutaneous endovenous techniques which improve patient comfort and accelerate return to work. Endovascular therapy gives promising midterm results for GSV reflux. However, it also has certain pitfalls and is therefore not suitable for all patients. One limitation is the diameter and tortuosity of the treated vein. The risk of thermal damage to surrounding structures should also be taken into account. There are two schools of surgeons: one performs standard ligation of the GSV followed by endovenous therapy, the other omits ligation, but both claim comparable midterm results. No long-term studies are available. Radiofrequency ablation (the Closure procedure) is based on endoluminal destruction of the endothelium and does not comprise GSV ligation. In my experience, endovascular methods are often confined to patients in stage C2 with no symptoms of chronic venous insufficiency, thus clearly biasing results in the method’s favor. Supporters of endovascular methods without GSV ligation claim that they avoid neovascularization. However, Labropoulos et al failed to confirm this.

Improved diagnostic methods give us a more accurate overview of the hemodynamics, anatomy, and pathophysiology of the venous system of the lower extremities and thus help us to select the appropriate therapeutic method. Crossectomy, conventional stripping and external stenting to the SFJ will definitely remain irreplaceable treatments for certain groups of patients, particularly in the light of their favorable long-term results. Endovascular procedures have proved to be good alternatives to stripping, while sclerotherapy continues to play an irreplaceable role. In addition, the therapeutic spectrum comprises venotonics and compression therapy. Treatment choice also depends on the specific anatomic characteristics of the patient’s venous system. The optimal procedure is the one that most improves a particular patient’s quality of life. Only long-term comparative studies that include a quality of life measure can provide a conclusive answer to the question “To ligate or not to ligate.”

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The aim of varicose vein surgery is to remove reflux and visible varicosities in order to achieve the most favorable hemodynamic and cosmetic result. High ligation is the crucial step because it restores normal hemodynamics. However, if the incompetent saphenous trunk in the thigh is not stripped at the same time, it remains patent and incompetent after surgery, and may provoke recurrent reflux. For this reason, high ligation combined with stripping became the standard treatment for truncal varicosities. On the other hand, venous grafts retrieved from the great saphenous vein (GSV) are the best conduits for vascular and some coronary reconstructions. The demand for such grafts is continuously rising as the population ages, confronting surgeons with the problem of whether the saphenous trunk in patients with varicose veins may be used for grafting or not, and if yes, what is the price to be paid for preserving it? Hammarsten et al showed that 78% of preserved saphenous veins were suitable for use as arterial conduits almost 5 years after high ligation, although lowering the radicality of varicose vein surgery increases recurrence. The saphenous trunk in primary varicose veins is not always degenerate, and may basically be compatible for use as a vascular or coronary artery conduit. Interestingly, it does not dilate aneurysmatically when transplanted into the arterial circulation. We performed a prospective study to evaluate the long-term results of GSV-sparing surgery compared with above-knee stripping. Fifty patients with varicose veins were randomly treated with standard stripping of the GSV or high ligation. In both groups, miniphlebectomies were carried out and incompetent perforators ligated on the basis of physical examination and duplex findings. Follow-up at 42±5 months showed recurrence rates, defined by clinical and duplex findings, of 12% in the stripping group vs 20% in the high ligation group (P<0.05). However, duplex scanning showed that the preserved GSV was suitable for use as an arterial conduit in most cases. These results suggest that it is possible to perform elective vein surgery for varicose veins with reasonably good results and preserve the GSV for eventual arterial reconstruction. What is the role of crossectomy and stripping in the modern era? Revascularization in the strip track after GSV stripping is a new concept in recurrence, and it occurred in 3 of our 50 patients. Munasinghe et al reported strip-track revascularization in 23% of patients at 1 year, all with duplex-proven reflux. As an alternative to crossectomy and stripping, minimally invasive saphenous ablation, using endovenous radiofrequency or laser treatment, corrects and/or significantly improves the hemodynamic abnormality and clinical symptoms associated with superficial venous reflux in over 95% of cases. These techniques may also reduce neovascularization in the groin. The critical question is what is the role of simple high ligation in preserving the GSV? Despite current recommendations, we still tend to perform this procedure on patients with severe saphenofemoral junction reflux, below-knee varicosities, and a near normal-sized and normal-looking GSV. We also discuss the situation with the patient and explain the higher rate of recurrence. In the event of recurrence, endovenous laser or radiofrequency obliteration is readily performed as an outpatient procedure after high ligation of the saphenofemoral junction.

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Until recently, saphenofemoral junction (SFJ) ligation, with or without great saphenous vein (GSV) stripping, was considered the treatment of choice for varicose veins in the presence of an incompetent GSV, despite the persistent and unacceptably high recurrence rate after surgery.1-3 Endovenous laser treatment (EVLT) and radiofrequency ablation (RFA) of the GSV have brought new perspectives and new questions concerning chronic venous disease intervention.4 Backed by the success and safety of the first published results using these techniques, most practitioners now perform these procedures in the office setting under vascular ultrasound guidance without SFJ ligation, to greater patient satisfaction in terms of simplicity, comfort, and cosmetic outcome.5-11 Nevertheless, the immediate fate of the SFJ after endovenous treatment remains unclear, with many questions still unanswered. What is the real risk of pulmonary embolism with these new procedures? What is the exact role of dissection and high ligation of the SFJ as a cause of recurrent varicose veins?

Deep venous thrombosis and pulmonary embolism

With EVLT or RFA, the SFJ can be occluded and ligated under direct vision through an inguinal incision, or the catheter can be advanced under duplex scanning control to just below the SFJ, without the inguinal region needing to be surgically accessed. The duplex-guided procedure is simpler, faster, and more esthetic, but it carries the risk of extending the thrombus from the SFJ into the common femoral vein and may cause pulmonary embolism. In the literature, RFA has been associated with 21 cases of deep vein thrombosis (DVT) and at least two episodes of pulmonary embolism: Hingorani et al reported a 16% incidence of DVT in 66 patients,12 while Mozes et al estimated the cumulative incidence of DVT as 2.1% and of pulmonary embolism as 0.2%.13 As for EVLT, a Mayo Clinic report cited three cases of DVT, equivalent to 2.3% in 130 treated limbs.14 Conventional varicose surgery was associated with 5.7% DVT in 377 patients in a study by van Rij et al.15 Other studies using duplex scanning cited rates of 3% and 5%.16,17 Most cases associated with conventional surgery are distal DVT in the calf veins with a low tendency for propagation, whereas those associated with EVLT and RFA involve the protrusion of thrombus originating in the SFJ into the common femoral vein, representing a theoretical risk of pulmonary embolism. Some reports have advocated the use of temporary vena cava filters and prophylactic anticoagulation.

For these reasons, further studies are still necessary for a better understanding of the postoperative clinical course of GSV ablation and the mechanisms underlying postoperative thrombosis.12,13,15

Neovascularization and recurrence

Recurrence is a common problem in the treatment of chronic venous disease.19 The use of minimally invasive techniques has led to a debate over the role of inguinal surgical access and tributary ligation as causes of neovascularization and recurrent varicose veins. Neovascularization is an essential component of wound healing.19 New vessels arise due to angiogenic stimuli produced during surgery; arteriovenous connections develop, promoting wound perfusion and healing. Van Rij et al have argued that neovascularization occurs not only at major ligation sites but also wherever superficial veins are stripped, avulsed, or injected with adjuvant sclerotherapy.20 New vessels can extend significant distances in the lower limb to make their reconnections and develop varicosities, although this process is still the subject of debate and skepticism. Neovascularization has been implicated as the cause of recurrence in up to 94% of cases. Occluding the SFJ using an endovascular technique free of the potential angiogenic stimuli in conventional surgery is a very attractive option, at least in theory.20 Early results of EVLT and RFA do suggest that recurrence is reduced. Even so, there are reports of recurrent incompetence at the SFJ and of ultrasound evidence of neovascularization.21,22 Labropoulos et al found a 5% prevalence of small arteriovenous fistulas following endovascular treatments of the GSV. Such fistulas may be responsible for recanalizing ablated venous segments and subsequent recurrence.22 Winterborn et al showed that neovascularization is a dynamic and continuous phenomenon not restricted to the healing period after surgery. They found increasing rates of neovascularization as a cause of recurrence: 36%, 54%, and 65% at 2, 5, and 11 years of follow-up, respectively.23 Some authors argue that ligation of competent tributaries is unnecessary and can promote neovascularization.22 Theivacumar et al showed that despite SFJ tributaries remaining patent and competent in 59% of 81 EVLT procedures, the overall number of recurrences did not increase after 1 year of follow-up.23 In conclusion, longer-term results from prospective randomized studies comparing stripping with new minimally invasive methods are needed to determine the ultimate fate of the GSV after EVLT and RFA. We still do not know if SFJ ligation will become the villain or hero.
CONTROVERSIAL QUESTION

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MEDICOGRAPHIA, VOL 30, No. 2, 2008


Chronic venous disease (CVD) is an umbrella term that encompasses a variety of clinical presentations, which include venous symptoms and signs. A review of the literature shows that the most commonly expressed CVD-related symptoms are heaviness, pain, sensation of swelling, restless legs, paresthesias, night time cramps, tiredness, throbbing, and itching. The signs of chronic venous disorders are described in the Clinical, Etiological, Anatomical, Pathophysiological (CEAP) classification and comprise telangiectasia, varicose veins, edema, skin changes, and healed and active venous leg ulcers.

It seems likely that the progression of CVD stems from prolonged periods of increased venous pressure in the legs. The abnormally elevated venous pressure is called venous hypertension, and this links all theories regarding the pathogenesis of the disease.

Hypertension is central to the pathogenesis of chronic venous disease

During periods of standing without skeletal muscle activity, venous pressures in the legs are determined by capillary flow and the hydrostatic component that is related to the weight of the column of blood from the right atrium to the foot. The pressure may reach 80 to 90 mm Hg. In addition to the hydrostatic component, distal veins are submitted to transiently increased pressures generated by contractions of the skeletal muscles of the leg that may reach 150 mm Hg. Proximal veins may also be submitted to peaks of pressures, generated in this case by abdominal pressure. Both components are profoundly influenced by the action of the venous valves.

Many factors may play a role in raising hydrostatic pressure in the superficial venous system of the lower limbs; in particular, prolonged standing or sitting occupations, pathologic conditions of increased abdominal pressure and decreased calf pump as is found in morbid obesity, and hormonal status. Genetic inheritance must be considered, because CVD is seen in patients with a family history of varicose veins. In line with the observations regarding genetic influence, a deficiency has been found in collagen type III in cultured venous smooth muscle cells from patients with varicose veins. The defect was found to be generalized within different tissues in the same patients. One of the theories thus put forward regarding the development of varicose veins is that the veins of affected individuals are genetically more distensible than those of people with normal veins.

Primary chronic venous disease is a widespread disorder. Its manifestations include symptoms in the form of pain and heaviness, and signs in the form of telangiectasia, varicose veins, skin changes, and chronic leg ulcers. Recent advances in the understanding of its pathophysiology have shown that molecular mechanisms in the inflammatory cascade underlie these diverse manifestations. Venous hypertension and alteration of hemodynamic forces, such as blood pressure changes in the wall and shear stress, induce activation of leukocytes and endothelial cells. This may initiate the cascade of inflammation that results in adverse changes in the venous valve, venous wall, and skin and leads to the many clinical manifestations of the disease. The disease symptoms and the telangiectasia, varicose veins, and eventual venous leg ulcers appear to be a consequence of the changes induced by venous hypertension and shear stress. Treatment to inhibit inflammation may offer the greatest opportunity to prevent progression of the disease and its related complications. Daflon 500 mg, an oral phlebotropic medication, attenuates various elements of the inflammatory cascade, particularly the leukocyte-endothelium interactions that are important in many aspects of the disease. Such medication deserves more detailed study to confirm its protective effect on venous structures.

Medicographia. 2008;30:149-153. (see French abstract on page 153)

Keywords: primary chronic venous disease; venous valve failure; inflammatory cascade; leukocyte-endothelium interaction; protective effect; Daflon 500 mg
There might also be a genetic component to the alteration of remodeling in venous valves. A theory linking the various observations to describe the chronology of venous valve failure and venous insufficiency is, however, lacking.

**A strong link is evoked between venous hypertension and valve failure**

In most cases, venous hypertension is caused by reflux through incompetent venous valves. Examination of surgical specimens removed from limbs with chronic venous insufficiency and, more recently, the direct observation offered by angioscopy, has revealed lesions involving the venous wall, the valvar annulus, and the valve cusps. Failure of the valve and its annulus is responsible for progression of the disease via maintenance and further increase of venous hypertension. Immunohistochemical studies using monoclonal antibodies 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 that leukocyte infiltration is greater within the base of the valve leaflets and in the proximal venous wall. 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.

Ultimately, macrophages become the instrument of tissue damage that softens the venous wall and favors valve destruction. Venous valve failure and subsequent reflux causing distal venous hypertension may contribute to the sustained and chronic hypertension that is responsible for leukocyte activation within the endothelium and leukocyte destruction of skin and subcutaneous tissues at the ankle. In addition to leukocyte activation, increased mast cell infiltration into the venous wall may have a role to play in the development of varicose veins. Increased expression of intercellular adhesion molecule-1 (ICAM-1) and the presence of CD-68 on the endothelial surface of venous walls in patients with venous insufficiency has been confirmed and may be related to this. These findings suggest a continuing inflammatory reaction that is related to venous wall remodeling. On the other hand, endothelial cells must be activated to allow leukocytes to migrate through the cells into the tissue. It is believed that endothelial stretching may induce activation of the endothelium; as blood flow itself is affected, fluid shear stress may 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.

**Clinical observations are confirmed by animal models**

Since the mechanisms responsible for venous valve failure in primary CVD cannot be investigated in vivo in human beings, animal models were set up for the purpose of experimental research.

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*Also registered as Ardium®, Alvenor®, Arvenum® 500, Capiven®, Detralex®, Elatec®, Flebotropin®, Variton®, and Venitol®.

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**Figure 1. The vicious circle of venous hypertension/venous inflammation.**


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**To elucidate the possible mechanisms involved in the destruction of valves in chronic venous hypertension, Takase et al examined saphenous vein valves in a rat model in which femoral venous hypertension was elevated for a period of 3 weeks by a femoral arteriovenous fistula (AVF). In this model, venous reflux developed in response to venous hypertension. Examination of vein morphology revealed that valve failure occurred as a result of dilation of the venous wall and shortening of valve leaflets to the point of incomplete valve closure and subsequent reflux. Assessment of the valves for molecular inflammatory markers revealed enhanced leukocyte infiltration with granulocytes, monocytes, and T-lymphocytes. In addition, the expression of the endothelial cell membrane adhesion molecules P-selectin and ICAM-1 on the endothelial cells of the saphenous vein wall was increased. In this study, the leaflets were still able to close properly in the early stages after placement of the AVF, suggesting that pressure per se is not necessarily the variable that can compromise the leaflets. However, at the time the leaflets failed and reflux occurred, a reduction in the leaflet dimensions was observed. A possible explanation for the sequence of events that leads to the morphologic abnormalities in venous valves is that as the venous wall dilates, a point may be reached at which reflux develops across the leaflets. An abnormal fluid shear field produced at the surface of the leaflets during venous reflux would be highly inflammatory for the endothelial cells on the valve leaflets, and could trigger destruction of the leaflets, increasing venous hypertension. This would maintain a vicious circle of venous hypertension/venous inflammation (Figure 1).**

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**The inflammatory reaction in chronic venous disease might be a new target for drugs**

Intervention in the inflammatory reaction that occurs as part of the progress of the disease may be a new pharmacological target. For this reason, the model by Takase et al was used to assess the effect of a drug treatment: Daflon 500 mg.*
The ability of Daflon 500 mg to mitigate or even block the effects of chronic inflammation at the level of both the micro- and macrocirculation has been demonstrated in rat models of venous hypertension. In a model of venous occlusion and reperfusion, the subsequent elevation of venous blood pressure increased the inflammatory cascade and tissue injury. In Daflon 500 mg–treated animals, markers of inflammation were decreased in a dose-dependent manner. Daflon 500 mg also served to significantly reduce parenchymal cell death as well as leukocyte rolling, adhesion to postcapillary venules, and migration.17

Important data supporting the protective effect of Daflon 500 mg at the level of the macrocirculation have been provided by the rat fistula model of venous hypertension.18 In this model, the venous hypertension caused by a femoral AVF resulted in the development of venous reflux and an inflammatory reaction in venous valves. In animals treated with Daflon 500 mg, there was a significant, dose-dependent reduction in the reflux rate (Figure 2). Daflon 500 mg also reduced several indicators of the inflammatory reaction including expression of the endothelial cell adhesion molecules, P-selectin and ICAM-1, and leukocyte infiltration, and reduced the level of apoptosis in a dose-dependent manner. By delaying and even blocking the inflammatory reaction, these data suggest that Daflon 500 mg may delay the development of reflux and suppress damage to the valve structures in the rat model of venous hypertension. These observations were recently confirmed in a new study using the same animal model. The administration of Daflon 500 mg reduced the edema and the fistula blood flow produced by the acute AVF. Daflon 500 mg also reduced granulocyte and macrophage infiltration to the valves, in line with the previous study.19 Daflon 500 mg may be protective against valve alterations.

**Therapeutic consequences of the protective effect of Daflon 500 mg**

Daflon 500 mg is the only vеноactive drug with proven early protective properties on venous valves and the venous wall. This is probably one of the mechanisms by which Daflon 500 mg is efficient right from the early symptoms of CVD.

In one double-blind, placebo-controlled, randomized study including 40 patients with CVD, several symptoms were considered, and were 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). According to the intensity of each parameter and its repercussion on daily activities, the patient quantified the parameters using a 4-point scale. Global scores were calculated for functional and objective symptoms. In the Daflon 500 mg group, after a 2-month period of treatment, patients demonstrated a significantly better improvement in global ($P<0.001$ for functional score and $P=0.034$ for objective symptom score) and separated symptom scores ($P$ value 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 efficacy were confirmed by testing parameters using strain gauge plethysmography and edema measurement.

Another double-blind, placebo-controlled, randomized study included 160 symptomatic patients with CVD related to either post-thrombotic syndrome (24 patients), primary varicose veins (59 patients) or other conditions (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 symptoms without repercussion on daily activities), 2 (appreciable symptoms but allowing daily activities) or 3 (severe symptoms, 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 (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 edema/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 Reflex assayEssment and quality of life improvement with micronized flavonoids (RELIEF) study involved 5052 symptomatic patients from...
The skin is the final target of chronic venous hypertension

The complications of CVD are expressed in the skin and are related to chronic venous hypertension. The skin is the final target of chronic venous hypertension. The hypertension is a cause of chronic inflammation manifested by persistent and sustained injury. Ultimately it is the capillary circulation that is most severely impaired in limbs with chronic venous insufficiency. (chronic venous insufficiency implies that reflux is present). Although other theories exist, the fundamental cause of skin damage in CVD has been ascribed to leukocyte trapping, adhesion of leukocytes to the endothelium and neutrophils, and their subsequent activation. It is hypothesized that the primary injury to the skin is caused by extravasation of macromolecules such as fibrinogen, α-macroglobulin, and red blood cells into the dermal interstitium. Red blood cell degradation products and interstitial protein extravasation are potent chemoattractants and presumably present the initial inflammatory signal that results in leukocyte recruitment and migration into the dermis. The cascade of pathologic events occurs during leukocyte migration into the dermis, and the end product of these is dermal fibrosis.

Systemic medications have been used in addition to standard treatments, because of a theoretical ability to address one or more of the factors that have been identified in the pathophysiology of venous ulceration. A small number of drugs have been used with varying success. The way in which Daflon 500 mg speeds ulcer healing might be to modulate leukocyte-L-selectin interaction with endothelial selectins responsible for the initial stages of adhesion. By reducing the likelihood of leukocyte adhesion, Daflon 500 mg presumably acts through an anti-inflammatory mechanism. Thus, among the many mechanisms at work in the pathogenesis of venous ulceration, the mechanism involving leukocyte activation and interaction with the endothelium seems currently to be the one most responsive to pharmacological treatment.

A meta-analysis of randomized prospective studies using Daflon 500 mg in conjunction with conventional treatment confirmed the results of previous trials; namely, that such oral medication accelerates the healing of leg ulcers. Five prospective, randomized, controlled studies involving 723 patients with venous ulcers who had received treatment between 1996 and 2001 were included in the analy-
La maladie veineuse chronique essentielle est très répandue. Elle est définie par la présence de symptômes tels que douleurs et lourdeurs de jambes, étouffées de signes tels que télangiectasies, varices, troubles trophiques et ulcère veineux. La physiopathologie de cette maladie reste encore mal connue mais de récentes avancées ont mis le doigt sur le rôle déterminant des mécanismes inflammatoires dans son déclenchement et sa progression. L'action conjuguée de l'hypertension veineuse et des modifications des forces hémodynamiques exercées sur la paroi des veines et des valves peuvent induire une activation des leucocytes et de l'endothélium pariétal, initiant une cascade inflammatoire. Il en résulte un profond remodelage des structures valvulaires et pariétales, puis des capillaires de la peau, ce remodelage se traduit par les diverses manifestations cliniques décrites dans cette maladie. Ainsi les symptômes veineux, les télangiectasies, les varices puis les complications ulcéreuses sont-ils la conséquence des changements induits par les modifications des forces hémodynamiques et de pression. Le rôle prédéterminant de l'inflammation dans la genèse et la progression de cette maladie pourrait avoir d'importantes implications thérapeutiques. Des traitements pharmacologiques capables d'enrayer le cercle vicieux de l'inflammation permettraient de prévenir les complications. Daflon 500 mg, un phlébotrope largement utilisé dans le traitement des maladies veineuses et plus particulièrement les valvulaires et pariétales, peut avoir une action protectrice contre la maladie valvulaire veineuse.

**Venous valve protection is to be closely studied since it opens up the perspective of 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 has focused attention on available molecules with known ability to modify this chain of events. Daflon 500 mg currently possesses the most appropriate profile, since the previously published observations of an anti-inflammatory effect of Daflon 500 mg under acute situations show that it may have a protective effect on the venous valves in chronic conditions of venous hypertension.

**Daflon 500 mg : protège contre la maladie valvulaire veineuse**

La maladie veineuse chronique essentielle est très répandue. Elle est définie par la présence de symptômes tels que douleurs et lourdeurs de jambes, étouffées de signes tels que télangiectasies, varices, troubles trophiques et ulcère veineux. La physiopathologie de cette maladie reste encore mal connue mais de récentes avancées ont mis le doigt sur le rôle déterminant des mécanismes inflammatoires dans son déclenchement et sa progression. L'action conjuguée de l'hypertension veineuse et des modifications des forces hémodynamiques exercées sur la paroi des veines et des valves peuvent induire une activation des leucocytes et de l'endothélium pariétal, initiant une cascade inflammatoire. Il en résulte un profond remodelage des structures valvulaires et pariétales, puis des capillaires de la peau, ce remodelage se traduit par les diverses manifestations cliniques décrites dans cette maladie. Ainsi les symptômes veineux, les télangiectasies, les varices puis les complications ulcéreuses sont-ils la conséquence des changements induits par les modifications des forces hémodynamiques et de pression. Le rôle prédéterminant de l'inflammation dans la genèse et la progression de cette maladie pourrait avoir d'importantes implications thérapeutiques. Des traitements pharmacologiques capables d'enrayer le cercle vicieux de l'inflammation permettraient de prévenir les complications. Daflon 500 mg, un phlébotrope largement utilisé dans le traitement des symptômes et de l’œdème liés à la maladie veineuse, a démontré sa capacité à atténuer l’inflammation veineuse, et plus particulièrement l’intéraction leucocyte-endothélium dont on connaît l’impact dans le mécanisme de développement de la maladie. Ce mécanisme d’action prometteur nécessite d’être approfondi pour confirmer les effets protecteurs du produit sur les structures veineuses et plus particulièrement les valves.
Tell us about the animal model you have set up

Our group is interested in the pathobiology of varicose veins. In order to study the complete time course of this condition, it is necessary to examine veins early in their pathogenesis and preferably with reference to control material. Clearly it is not possible to use human material for such studies, and a suitable animal model has, therefore, been sought. Unfortunately varicose veins do not occur spontaneously in lower animals and it has been necessary to develop experimental animal models in an attempt to mimic the human state. As such, we have aimed to establish a chronic, large animal model of primary superficial varicose veins. It is important to be aware that there have been a number of animal models for venous disease developed by other investigators, and there is a need to be very clear as to which condition each model is trying to mimic.

Our model, which is of the chronic superficial varicose vein, involves the fashioning of a femoral arteriovenous fistula in adult pigs. The fistula is fashioned adjacent to the intact saphenofemoral junction (SFJ). It is interesting that in the pig, the saphenous vein is formed by superficial tributaries and passes more deeply into its own fascial compartment in the thigh before penetrating the fascia cruris and joining the femoral vein. Unlike the human situation, the saphenous vein runs parallel to a small saphenous artery, forming a saphenous bundle within its own fascia. What is also slightly unusual about the pig is that this particular length of saphenous vein has numerous (8–10) valves. We believe that these valves are critical to the model, as they appear to fail sequentially following creation of the femoral fistulae. As such, they appear to “protect” the vessels within the superficial compartment from direct arteriализation in the acute phase of fistula maturation. After approximately 1 to 2 weeks, the superficial saphenous tributaries begin to become varicose in a consistent pattern radiating out from the saphenous vein. These veins progressively enlarge, resulting in the formation of an extensive network of large (1.5 mm in diameter), tortuous, superficial varicose veins overlying the medial thigh and extending into the superficial epigastric veins. Although animals are initially operated upon at a body weight of 35 kg, they grow rapidly and are typically 80 to 100 kg by the time measurements are made (8–15 weeks postoperatively). An advantage of this model is that the size of the animal and associated veins allows for physiological (pressure and ultrasound) evaluation, which would not be possible in smaller animals.

Physiologically, these vessels are characterized by retrograde flow with a mild nonpulsatile venous hypertension (20–35 mm Hg in a supine position). Venous pressures decline with increased distance from the fistula-fed saphenous vein. Increased intra-abdominal pressure elevates

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Selected abbreviations and acronyms

- **AVF**: arteriovenous fistulae
- **SFJ**: saphenofemoral junction

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Previous animal models of venous disease, while suited to the study of venous hypertension and valvular insufficiency, do not produce superficial varicose veins. Our group aimed to develop a pig-based model of superficial varicose veins. The pathophysiology of this model was assessed by intravenous blood pressure measurement, duplex ultrasound, and histology, and was compared with that of the human condition. Right femoral arteriovenous fistulae were surgically fashioned in adult pigs. Patency of the fistulae was confirmed by transcutaneous ultrasound. Animals were re-examined postoperatively for up to 15 weeks to determine both pressure and blood flow velocities within the superficial thigh veins. Histology was used to characterize the resulting structural venous alterations with those of human superficial varicose veins. In this model, gross superficial varicosities developed after an initial lag period of 1 to 2 weeks. Varices appeared to have a postural component to their filling and were associated with a mild (nonpulsatile) venous hypertension. This physiological profile is distinct from the near-arterial pressure profiles typically observed in smaller animals with arteriovenous fistulae. Venous blood flow velocities were elevated to 15 to 25 cm/second in varicose veins. Structurally, pig varicose veins were enlarged, tortuous, had focal medial atrophy with or without overlying intimal thickening, and valvular degeneration. In conclusion, the superficial varicose veins, which developed within this porcine model, have a pathophysiology that is consistent with that observed in humans. The suitability of other animal models of venous disease for the evaluation of therapeutic agents for the treatment of varicose veins is discussed.

**Keywords**: animal model; arteriovenous fistula; chronic venous disease; superficial varicose vein; therapeutic evaluation

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superficial venous pressures. Supine superficial venous blood flow velocities were elevated from approximately 1 to 4 cm/second in controls to 15 to 25 cm/second in animals with patent fistulae. While duplex waveforms within the saphenous vein displayed an arterialized pattern, particularly at the proximal end near the fistula, the waveforms within the superficial veins indicated continuous (elevated) flow.

An important feature of this model is the intermittent distension noted in relation to posture. In the supine anesthetized pigs, the enlarged superficial veins are clearly visible but not distended. When the unconscious animal is lifted into an erect position, the veins become noticeably more filled. Lateral flank varicose veins were only observed in ambulating animals, particularly postexercise. The most pronounced, distended veins were noted in conscious animals placed in an erect position; this induced a Val- 

salva-like maneuver in all animals, result-

ing in extensive bulging of the superfi-

cial varices.

We examined the global soluble protein expression profile of pig varicose veins using two-dimensional electrophoresis. An advantage of conducting such exper-

iments in an animal model system was the availability of completely healthy ve-

nous tissue for use as reference materi-

al. Proteins upregulated in pig varicose veins included smooth muscle motility-

related proteins, heat shock proteins, and ATP synthases. Taken together, this pro-

file suggests a process of inflammatory-

induced fibrosis in the developing pig varicose veins. These observations are en-

couraging as they match the reported gene expression profiles of human pri-

mary varicose veins.2

Histopathological changes in superfi-

cial vein structure included increased diameter and tortuosity of veins within the hypodermis, focal medial atrophy with or without overlying intimal thickening, valve degeneration (tearing and fibrosis), mild periadventitial inflammation, and loss of elastic tissue constituents in both the media and adventitia. Alterations were not limited to the large hypodermal venous drainage network, but also extended into tributaries of these veins. Corrosion vascular casts demonstrated terminal tributary valvular incompetence leading to reflux in incompetent micro-

venous networks. As such, this model may not only have utility with regard to primary varicose veins, but also chronic venous insufficiency. All these histopathological changes were consistent with those typically observed in human primary varicose veins.2,4

Tell us about previous animal models of venous disease

Previous animal models of ve-

nous disease can be categorized into four groups; those utilizing (i) ves-

sel occlusion/obstruction; (ii) valvular incompetence; (iii) augmented hemody-

namics; or (iv) a combination of these models. Depending on the desired out-

come, each method has its own strengths and weaknesses. Our approach has been to focus on the development of a model of varicose veins, and only secondarily on the generation of tissue changes of chronic venous insufficiency. Unfor-

unately, other models have not achieved this, although they have contributed to the study of other venous conditions, such as acute venous obstruction, throm-

bophlebitis or valvular insufficiency.

Since chronic venous hypertension is widely accepted as a key pathological mechanism of chronic venous insufficiency, venous occlusion models have been employed in an attempt to raise venous pressures by limiting outflow. Despite an acute elevation, venous occlusion models in themselves do not appear to maintain chronically elevated venous pressures.3 Burnand concluded that this was due to the formation of collat-

eral drainage, which he demonstrated on phlebograms.5

Valvular incompetence is a common feature of chronic venous insufficiency. Lalka, Dalsing, and colleagues6 described a simple, reproducible model of hind-

limb valve disruption (in the greyhound) that represents a useful model of venous valvular insufficiency, particularly in the evaluation of valve reconstruction pro-

cedures. Animals developed an immedi-

ate increase in post-stimulation seg-

mental venous pressure that persisted for as long as 14 weeks. While phlebog-

raphy demonstrated reflux in the seg-

ments with the disrupted valves, there was no indication of extension into trib-

utaries and no evidence of varicose veins, even at the most chronic time point. Other aspects that should be considered when assessing this model’s suitability include the acute nature of the valve de-

generation, which abruptly exposes the vein to increased pressure, and the rela-

tively short hydrostatic column present in the quadruped hind limb. The third group of venous disease models involves the fashioning of arteriovenous fistulae (AVF). Dart and colleagues formed acute AVF in the dog, but noted an arterialized pressure profile within the distal veins. Burnand produced a more mild chronic venous hypertension in the greyhound that was associated with sustained rest-

ing and ambulatory pressures.6 Unfortu-

nately, the associated acute phase arte-

rial pressure profile is inconsistent with chronic venous disease. More important-

ly, none of these AVF venous disease models have reported the formation of associated superficial varicose veins.

Models combining the above mecha-

nisms have also been developed. Most notably, the combination of AVF and out-

flow obstruction has been used in order to produce sustained venous hyperten-

sion. Van Bemmelen applied this model to rats in order to study valve remodel-

ing.7 Although valve incompetence and remodeling were noted as early as 24 hours postoperatively, no pressure pro-

files were recorded and the animals did not develop varicosities. More recently, a detailed series of studies conducted by Bergan’s group has utilized the same model and reported arterial-like pressure profiles with mean venous pressures in the order of 100 mm Hg.8 Vein alterations reported included media atrophy, wall fibrosis, increased protease expression, progressive valve degeneration, and dila-

tion of the commissures. Using this rat model, valvular inflammation has been identified as a key pathologic feature in the development of reflux.9

What does this new model bring that the others did not?

The principal feature of the pig femoral AVF model is the for-

mation of chronic superficial varicose veins. Such pathological changes have not been reported in any previous mod-

el of venous disease. The heterogenous venous pathohistology of this model is consistent with the range of alterations observed in human superficial varicose veins, including medial atrophy, intimal thickening, connective tissue degenera-

tion, fibrosis, and chronic valvular de-

generation. These changes appear to be due to physiological alterations that are not simply an acute arterIALIZATION, but are more consistent with that associated with chronic varicose veins in humans. Venous filling has an intermittent pattern, influenced by posture, and driven by a mild nonpulsatile venous hypertension. The use of a human sized experimen-
tal animal allows for a greater range of physiological evaluations to be performed and results in much larger tissue vol-

umes for biochemical evaluation.

Another exciting feature is the sugges-

tion that venular changes also occur in the draining tissues, comparable with some of the changes seen in chronic
venous insufficiency. This does raise an important issue with regard to venous disease models and the likelihood of being able to produce skin changes that are comparable with those seen in humans. Most animals studied are young and have a very dense hypodermis, so that even in the presence of appropriate venous hypertension in the larger superficial veins, the microcirculation is extremely well protected.

In your opinion, which model is the most appropriate for the study of drugs?

This depends of course on what particular action of a drug is to be tested, whether it is to demonstrate effects on chronic degeneration of the venous valves and wall and the formation of varicose veins, or the effects on acute events of valve disruption or venous occlusion. The pig model is clearly preferred for the study of the effect of drugs on the formation of varicose veins.

In addition, smaller animals such as the rat, and to a lesser extent the dog, have always been considered to have an advantage for drug evaluation studies because large numbers can be evaluated at a reasonable cost. However, we would argue that the similar size and physiology of the pig to humans also makes them suitable for use in studying drug effects. Drug delivery and tissue/liquid sampling for bioavailability studies is straightforward, and large sample volumes can be obtained for analysis. Physiological and ultrasound evaluations are also not only more comparable but also more reliably done in the larger animal. While adult pigs are associated with a high per animal cost, we believe that in the case of our varicose vein model, this is easily countervailed by the quality and relevance of the resulting pathophysiological information compared with that obtained in other venous disease models in smaller animals.

Could results drawn from the new model be easily translated to human beings?

While no animal model is a perfect representation of the human pathophysiological state, we believe that drug evaluation study results based on our pig model of varicose veins will translate well to humans, because of the similarities in the underlying pathology. The model also has the distinct advantage that the primary outcomes, namely, the development and severity of superficial varicose veins, match the key clinical features that any phlebotrophic drug would aim to target.

REFERENCES
Most veins in the human body contain valves. The number and size of the valves vary with their location. Their function is to allow blood flow toward the heart and to prevent back flow. Normal valves in the lower extremity allow some retrograde flow (RF) before their closure. The duration of the RF varies with the location and size of the vein and valve. Reflux is a prolonged duration of RF beyond the normal limits. It occurs as a result of valve absence or incompetence from recanalization, dilatation or denervation. Several studies on the definition of reflux in the superficial and deep veins have reported cutoff values of >0.5 second or >1.0 second. The sample size of these reports has been small, however, and only a few sites have been assessed in the lower extremity veins. Limited work has been done to define perforator vein reflux. These veins—particularly in the calf and ankle—exhibit inward and outward flow, but incompetent perforating veins have shown a net flow toward the superficial veins. A later study from my group determined the upper limits of normal in terms of duration and maximum velocity of RF in lower extremity veins." The results of these and other recent relevant studies will be presented and discussed.

**Function of the venous valve**

The venous valves are stationed in different vein segments, some of which are constant such as the terminal valve in the saphenofemoral junction or the most proximal valve in the femoral vein. In order to better understand their function, the cycle of the venous valve has to be explained: this was carried out in detail by Lurie et al., who studied the most proximal femoral vein valve and a proximal vein valve from the great saphenous vein in 20 normal volunteers (10 males and 10 females). It was shown that the pattern of flow events was consistent in every cycle as the blood passes through the valves. The characteristics of this pattern were related to the variations in flow velocity in and around the valve. The flow pattern also varied with the body position and the limb activity. The valve cycle was defined as the time taken to complete two valve closures. Four phases were identified: the opening phase, during which the cusps move from the closed position toward the wall (mean duration 0.025±0.05 s). When the valves cease opening, they enter the equilibrium phase, during which the leaflets are suspended, with oscillations in the flowing blood (mean duration 0.65±0.08 s). Then the closing phase begins, during which the leaflets move toward the center of the lumen and take a symmetric position, having the same distance from the opposing walls (mean duration 0.41±0.07 s). At the end, the closed phase occurs, during which the cusps remain closed (mean duration 0.45±0.05 s).

**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CVD</td>
<td>chronic venous disease</td>
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<tr>
<td>DU</td>
<td>duplex ultrasound</td>
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<tr>
<td>RF</td>
<td>retrograde flow</td>
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**Keywords:** retrograde flow; pathophysiologic; reflux; venous valve; venous segment; cutoff point
The valve cycle and the duration of the four phases are affected by the position of the body. During standing, the cycle lasts 2.9 to 3.2 seconds, giving a frequency of 18.8 to 20.4 cycles per minute. In the supine position, the cycle duration is 1.7 to 1.8 seconds, giving a frequency of 34.2 to 36.1 cycles per minute. In the latter position, both respiration and the pressure in the right atrium influence the valve cycle. Dorsal and plantar flexion of the foot reduce the closing phase. The venous valve causes a stenosis that occupies about a third of the lumen. This leads to an increased velocity at the exit of the stenosis (end of leaflets), which enhances the outflow. The rhythmic activity of the valve cusps and the pulsatility of the venous flow create vortical streams and prevent stasis in the valve pockets, thus decreasing the chance for thrombus formation.

**Changes in venous valves**

Venous reflux is important in the development of venous hypertension, which is responsible for the signs and symptoms of chronic venous disease (CVD). Many studies have shown that valve dysfunction leads to venous reflux, which increases the ambulatory pressure in the lower extremity veins. Valvular dysfunction is most often primary and mediated by changes in the venous wall, the valve leaflets or a combination of both. With the use of an angioscope, changes and damage to the valves have been observed such as stretching, splitting, tearing, thinning, and adhesion of valve leaflets. Patients with CVD may have fewer valves per unit length. Infiltration of the venous wall and the valve leaflets by monocytes and macrophages has been demonstrated in all vein specimens from patients with CVD, but not in those specimens from controls. Infiltration from the inflammatory cells was found in areas of endothelium that expressed intercellular adhesion molecule-1 (ICAM-1).

Changes in the valves are also seen after vein thrombosis. This is due to the direct effect of thrombus on the valves and the vein wall. Many natural history studies have demonstrated the damaging effect of thrombosis on the valve/valve leading to reflux. Reflux is seen after both partial or complete recanalization of the previously thrombosed segments. More evidence regarding this has been provided by the effects of early thrombus removal with chemical and pharmacomechanical thrombolysis, which reduces the development of postthrombotic reflux.

Valve atrophy and aplasia have also been reported. In these cases, the affected vein segments are found to have severe reflux. The reasons for the failure of the valves to develop are not known, but this condition is very rare and only small series or cases reports have been published.

**Methods for diagnosing reflux**

There are both physiologic and imaging methods for diagnosing reflux. The physiologic evaluation includes invasive tests with direct vein pressure measurements, and plethysmographic tests such as air, strain gauge, and photoplethysmography, light reflection rheography, and foot volumetry. The plethysmographic tests measure the refilling time, and the percentage or absolute change in volume from the supine to standing position or after knee bends or tiptoe movements. The shorter the refilling time the more severe the amount of reflux. These methods are very good for evaluating the overall venous hemodynamics, and are great for use in natural history studies or to assess the effect of treatment. However, when used alone, they cannot guide treatment as they cannot evaluate which veins are affected.

The imaging tests involve phlebography and duplex ultrasound (DU). Descending and ascending phlebography are invasive and are used only in selected cases requiring deep vein reconstruction. Currently, the method of choice for detecting reflux in all the lower extremity veins is DU. The distribution and extent of reflux is determined so that treatment can be tailored to the individual patient needs. In addition, a differentiation between primary and secondary disease can be made. The names of the veins, the anatomic definitions as visualized by DU, and the methods of testing have been described in detail.

The best position for determining reflux with DU is standing. In this position, the hydrostatic column is highest and the veins have their largest diameter. Also, dilated veins and varicosities are more easily seen and it therefore makes the examination more accurate. With the patient rotating in various positions, it is best to access all areas in the lower extremity.

Different maneuvers are used to elicit reflux. Manual compression followed by sudden release below the tested vein segment is good to determine reflux in routine examinations. However, standardized pressure with the same inflation and deflation duration is necessary when longitudinal studies are performed, particularly when different types of treatment are tested. The Valsalva maneuver is used only in the groin. Other tests, such as dors/plantar flexion, are useful in the calf and ankle in patients with edema. Other factors that affect the duration of RF and that should be taken into consideration, are the time of day that the test is performed, the temperature of the examining room, and in females of childbearing age, the time of their menstrual cycle.

**Criteria for venous reflux**

Relatively few studies have been performed regarding the definition of venous reflux in the lower extremity veins and its standardization. All of the reports are in agreement regarding the best cutoff value in the superficial veins, which is >0.5 second. Even fewer studies have assessed the perforator, muscular, and deep axial veins. The results of the only study to have evaluated all of the veins is presented below.

**Patients and methods**

A total of 80 limbs in 40 healthy volunteers and 60 limbs in 45 patients with CVD were examined with DU in the standing and supine positions. Reflux was
assessed at 16 vein segments: the common femoral, deep femoral, and proximal and distal femoral veins; the proximal and distal popliteal veins; the gastrocnemial vein; the anterior and posterior tibial veins; the peroneal vein; the great saphenous vein at the saphenofemoral junction, thigh, upper calf, and lower calf; and the small saphenous vein at the saphenopopliteal junction and mid calf. Perforator veins detected along the course of these veins were also evaluated.

In healthy volunteers, 1553 vein segments were assessed, including 480 superficial vein segments, 800 deep vein segments, and 273 perforator vein segments. In the patients, 1272 vein segments were assessed, including 360 superficial vein segments, 600 deep vein segments, and 312 perforator vein segments. Rapid-inflation pneumatic cuffs (Aircast, Summit NJ) with pressure set at 80 mm Hg were used to elicit reflux. The cuffs were placed on the lower thigh for groin and proximal thigh vein measurements, and for the other veins, they were placed on the lower calf. The inflation time to maximal pressure was 0.3 second, inflation was maintained for 1.0 second, and deflation was achieved in less than 1.0 second.

The Doppler tracings were set so as not to have overgain, with the background appearing dark and the signal bright. The scale was reduced to the lowest necessary point to detect low flow velocities, and was optimized to show the whole trace. Immediately after release of compression, the tracings were allowed to run until the RF ended. At this point, the durations of RF and peak vein velocity were measured in both the standing and supine positions.

Results and interpretation

All data for each vein segment were analyzed individually for the supine and standing positions. The definition of abnormal RF was calculated at the best separation point and in comparison with the data from the healthy controls. Statistical analysis of the data was performed for the differences in proportions using the chi-squared test and with 95% confidence intervals (CI). Examples of different waveforms and flow patterns obtained are shown in Figures 1 to 8 (page 160).

Superficial veins

In the control group, the mean duration of RF was 210 ms (range, 0-2400 ms; 95% CI, 206-214), and in 16 vein segments (3.3%), RF was >500 ms. In the patients, RF was >500 ms in 202 segments (56%; \( P<0.0001 \) compared with controls). If other segments of the main saphenous veins, tributary vessels, and nonsaphenous superficial veins were included in the analysis, then 93% would have RF >500 ms. Varicose veins had RF >500 ms. It is important to note that of the 202 segments with RF >500 ms, 114 segments (56%) were dilated but had no varicosities, and 18 segments (9%) had a normal diameter or had a diameter of <2.5 mm.

From the above findings and in accord with others, RF >500 ms identifies reflux with great certainty. It has been shown that the larger the diameter of a vein, the higher the chance of it being incompetent. However, many vein segments with a normal diameter, and also some with a small diameter, can have reflux. This has been observed in all types of superficial veins (saphenous, accessory, tributaries, and nonsaphenous veins) in many locations in the lower extremity.

Perforator veins

Because it has been shown that perforator veins can exhibit bidirectional flow, the outward flow component was taken as the RF. Most perforator veins were found below the knee (n=214; thigh, n=59). The mean RF duration in the control group was 170 ms, ranging from 0 to 760 ms. Only 3 perforator veins (1%) in the calf and none in the thigh had RF >500 ms. RF duration in the calf (180 ms, 95% CI, 176-184) was longer than in the thigh (150 ms, 95% CI 145-155; \( P<0.0001 \)). The best cutoff value for reflux was RF >350 ms. In the patients, 71 of 312 perforator veins had RF >500 ms (\( P=0.0001 \) compared with controls). Setting the cutoff at 350 ms, 82 perforator veins would have had abnormal RF.

Incompetence in the perforator veins is controversial, as the impact of these veins on CVD is not clear. However, the number of incompetent perforator veins and their size increase with the severity of the disease.27,28 The diameter of a perforator vein has been found to correlate well with the presence of reflux, as those >3.0 mm are most often incompetent.29,30 However, as in the superficial veins, many incompetent perforators have a smaller diameter. In patients with primary CVD, the perforator reflux develops in continuity with that of the superficial veins.31 In the absence of superficial vein reflux, the perforator veins are normal.

Deep veins

In the deep veins, RF ranged from 0 to 2600 ms. Deep femoral and calf veins had a mean RF duration of 190 ms (95% CI, 188-192). The RF was >500 ms in only 1 deep femoral vein (1.2%) and 7 calf veins (2.2%). Common femoral, femoral, and popliteal veins had a mean RF duration of 280 ms (95% CI, 375-385), which was significantly longer than all other veins (\( P<0.0001 \)). In 21 of 400 femoropopliteal segments in controls, the RF duration ranged from 510 to 2600 ms, but in 99% of these veins, RF was <990 ms. Using 1000 ms as the cutoff for abnormal RF, only 4 of 400 segments (1%) would have reflux. In the patients, 152 of 600 segments had RF >500 ms (\( P=0.0001 \) compared with controls). In the femoropopliteal veins, the prevalence of RF >500 ms was 29% (87 of 300 veins; \( P=0.0001 \) compared with controls). Using a cutoff value of 1000 ms, the prevalence of abnormal RF was significantly reduced at 18% (54 of 300 veins; \( P=0.002 \)).

In primary CVD, reflux in deep veins is associated with reflux in superficial veins.21 In fact, it has been shown that correction of superficial vein reflux corrects deep vein reflux in most patients.22,23 The prevalence of deep vein reflux increases with severity of CVD, and is significantly more common in patients with skin damage.24 This is probably

Cut point on normal and pathological values of reflux – Labropoulos

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Figure 1. Normal popliteal vein, without any retrograde flow.

Figure 2. Normal popliteal vein with a retrograde flow duration of 820 ms.

Figure 3. Popliteal vein reflux with a retrograde flow duration of 1.4 seconds.

Figure 4. Proximal femoral vein reflux with a retrograde flow duration of 1.84 seconds.

Figure 5. Reflux in the saphenopopliteal junction with a retrograde flow duration of 3.5 seconds. The popliteal vein just distal to the junction is normal, whereas at the junctional level, it is incompetent. After treatment of the small saphenous vein, the popliteal vein became normal.

Figure 6. Reflux in the small saphenous vein in the upper calf with a retrograde flow duration of 1.8 seconds. The vein has a small diameter measuring only 2.2 mm.

Figure 7. Reflux in the great saphenous vein in continuity with a tributary in the lower thigh. On Doppler spectrum, the retrograde flow duration was 5.2 seconds and the peak flow velocity was 34 cm/s. The proximal incompetent vein segment has a larger diameter than the distal normal vein segment just below the tributary (4.6 mm vs 3.4 mm).

Figure 8. A nonfunctioning valve in a posteromedial tributary overlying the medial head of the gastrocnemius muscle. The valve in the near wall has become atrophic and in the far wall it is elongated and frozen.
because the extent of superficial disease and the duration of CVD are longer, and the prevalence of thrombosis is significantly higher compared with patients presenting with varicose veins.28

◆ Supine compared with standing position
In the control group, 37 vein segments (2.4%) had RF >500 ms in the supine position. Of these segments, only 22 (59%) had RF >500 ms in the standing position. Of the 48 vein segments (3.1%) with RF >500 ms in the standing position, RF was <500 ms in 6 of these (13%) in the supine position. Similar observations were noted in patient veins, where some vein segments with reflux in the supine position became normal in the standing position, and some others became worse in the standing position.

These findings indicate that both the specificity and sensitivity for detecting pathologic reflux are best in the standing position. Standing is a more physiologic position and more meaningful in clinical practice, as the hydrostatic pressure in the lower limbs is highest and the diameter of all veins is larger. This allows a longer period of RF to occur in diseased vein segments. During standing, there is a definitive closure of competent valves and clearly more challenge is offered to incompetent valves. A cutoff value of >2 seconds was suggested for veins tested in the supine position.34 Given our findings and the reasons discussed above, when possible, reflux should only be tested in the standing position. Another smaller study that examined patients in both positions also found that the standing position was superior for reflux testing.35

◆ Waveform characteristics
The peak RF velocity, which was identified immediately after the release of the compression, showed a wide range in both controls (8-35 cm/s) and patients (9-83 cm/s). Vein segments with reflux had higher peak velocity (mean 23.5 cm/s; 95% CI, 20.2-26.8) compared with normal vein segments (mean 15 cm/s; 95% CI, 14.8-15.2; P<0.0001). In the patients, vein segments with reflux had a mean peak RF velocity of 41 cm/s; 95% CI, 36-48.5, compared with 18 cm/s; 95% CI, 14.5-24.2, in the normal vein segments (P<0.0001). It was not possible to determine peak RF cutoff velocity values for reflux, as RF duration and peak RF velocity had great variation. More importantly, reflux occurred at both low and high peak RF velocities. In a previous study, no association was found between the peak RF velocity and reflux.36 Many factors are responsible for the velocity characteristics, such as the diameter and length of the incompetent vein segment, wall compliance, the network of veins where this segment empties, and the condition of other veins in contiguity. Also, the severity of the disease and the degree of inflammation may affect these values, as blood flow in the limb may be affected locally or in its entirety.29 Other RF parameters may be important for the severity of the disease, but do not discriminate between normal and pathologic values.34 It was shown that the RF duration has a qualitative value, whereas the peak RF velocity and the average flow velocity better reflect the severity of venous incompetence.

◆ Effect of different maneuvers
Manual compression or rapid inflation cuffs may not be adequate stimulus to elicit reflux in some patients. In 13 vein segments (great saphenous vein, 3; small saphenous vein, 1; femoral vein, 1; popliteal vein, 1; gastrocnemial veins, 2; peroneal vein, 1; perforator veins, 4) in patients with significant pitting edema, RF was normal. RF became abnormal only during active dorsiflexion or plantar flexion. We have also observed this in routine clinical practice, where some very obese patients and those with edema may need active dors/plantar flexion where the deep veins are compressed with higher force directly from the muscles. In the groin area, if the test is negative with distal compression, the Valsalva maneuver is performed, because the challenge to the valves at that level is stronger and reflux may only be demonstrated in this manner.

Progression of reflux
Reflux develops in an ascending, descending, and multifocal manner.30,31 It can also exist in independent locations that do not anatomically communicate. It has also been shown that the progression of reflux occurs in the same manner.30,31 All veins can be affected by reflux, but the superficial veins are most often involved in primary disease. In patients with thrombosis, reflux progresses in the post-thrombotic veins, but reflux in veins that were remote to thrombosis can be affected as well. Across the whole spectrum of CVD, reflux is most common in the superficial veins. Superficial vein reflux affects the perforator veins either in an ascending manner as progression of vein wall disease, in a descending manner at a re-entry point via the high flow rate that may dilate the perforator veins, or in both directions. In the descending path, wall disease may also be important, together with, or separate from, increased flow. The perforator veins, in turn, affect the deep veins that they are communicating with, and in time will render these incompetent as well. In a similar manner, the saphenous and gastrocunnel junctions can make the femoral and popliteal veins incompetent.

REFERENCES
Un reflux se prolongeant plus longtemps que ne le permettrait une fermeture valvulaire normale peut se développer dans les membres inférieurs. Des signes et symptômes de maladie veineuse chronique surviennent pendant l'activité à cause de l'augmentation de la pression veineuse. L'écho-Doppler, la meilleure méthode d'évaluation du reflux, a évalué sa durée dans quelques études, déterminant les situations normale et pathologique. La plus grande et seule étude prospective sur le sujet est analysée ici avec les résultats de ces études. La meilleure valeur seuil pour la durée d'un reflux anormal était supérieure à 500 ms pour les veines superficielles, les veines fémorales profondes et les veines profondes du mollet. Pour les veines perforantes, la plupart des experts ont extrapolé la même valeur que celle utilisée pour les veines superficielles. La meilleure valeur séparant le normal du pathologique est néanmoins celle supérieure à 350 ms. En ce qui concerne les veines fémorale commune, fémorale et poplitée, la meilleure valeur est celle supérieure à 1000 ms. L'orthostatisme est la meilleure position pour réaliser le test du reflux. La durée et la vitesse maximale du reflux sont très variables, la relation n'ayant aucun rapport avec la présence d'un reflux prolongé. La progression et le développement du reflux touchent toutes les veines et de façon ascendante, descendante et multifocale.
Valve dysfunction can be described as an abnormality that is responsible for reflux in the affected vein. Primary venous insufficiency is chronic venous dysfunction whose cause is neither congenital nor clearly identifiable. Valve dysfunction is the result of structural abnormalities in the vein wall and in the valve itself. Redundant, mal-opposed cusps and venous dilation permit valve prolapse and reflux. Unlike in the post-thrombotic syndrome, there is no evidence of previous thrombosis near the valve. A rare cause of reflux is the complete or partial absence of valves. This anomaly can be primary or congenital. Valvular incompetence can be identified in both the upper and lower limbs, the other veins in the thorax and abdomen being most-ly valveless, but the adverse consequences resulting in chronic venous disease are only found in the lower limbs.

Below the inguinal ligament, there are three venous systems: the superficial, perforator, and deep systems. Consequently, valve dysfunction can be identified in all of them, but restoration of valve function by surgery is only performed in the superficial and deep systems.

Surgical methods for treatment of valve dysfunction

Superficial venous system
In the superficial venous system, two kinds of treatment methods can be used—indirect and direct.

Indirect procedures
Indirect procedures have in common the preservation of the saphenous trunk with restoration of its valve function via modification of the hemodynamics (Figure 1, page 164). All of these procedures need a very precise preoperative duplex scanning (DS) evaluation and mapping.

Direct procedures
Direct valve repair in the superficial venous system can be achieved through vein external cuffing or bandaging at the valve station. Extensive deep venous system ablation is not possible without major perturbation of the venous return function, and ligation has proven to be ineffective. The most common procedure used in this situation is valve repair, with valve transfer or use of a prosthetic venous valve also used less frequently. Techniques, treatment outcomes, and indications for venous valve restoration by surgery will be discussed with respect to primary chronic venous disease.

Keywords: primary chronic venous disease; venous reflux, valvuloplasty; valve transfer; valve bandaging; venous surgery; phlebectomy; varicose vein

Address for correspondence: Michel R. Perrin, 26 Chemin de Décines, 69680 Chassieu, France (e-mail: m.perrin.chir.vasc@wanadoo.fr)
which involved stab avulsion of incompetent tributaries in patients presenting with incompetent valves in the saphenous trunk. He updated his experience in 1996. Recently, Pittaluga has promoted this technique with some refinement on the basis of information provided by DS investigation.

- Deep venous system
In the deep venous system, valve repair techniques for treating deep venous reflux (DVR) can be classified into three groups: those that involve phlebotomy, those that do not involve phlebotomy, and those utilizing percutaneous placed devices.

- Techniques with phlebotomy
  - Internal valvuloplasty
Since the first internal valvuloplasty procedure described in 1968 by Kistner, involving the use of a longitudinal phlebotomy (Figure 3), various procedures have been proposed. Raju advocated a supravalvular transverse venotomy, while Sottirai utilized a hybrid T-shaped supravalvular incision (Figure 4). In 2002, Tripalhi proposed the use of an internal trapdoor valvuloplasty. In all cases, the redundant valve cup is plicated to the vein wall using multiple interrupted or continuous 7-0 Prolene reefing sutures. It has been estimated that pllication of approximately 20% of the leaflet length should restore competence, although the best gauge remains visual inspection.

- Venous segment transfer
Venous segment transfer was devised for patients with a competent great saphenous or deep femoral vein valve in their proximal segment (Figure 5) and DVR in the femoropopliteal axis. The purpose of venous segment transfer is to transpose a competent valve-bearing venous segment into the axial deep venous system, ie, the femoropopliteal axis at the groin level. Several surgical variations of venous

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Figure 1. Hemodynamic techniques for restoration of the valves of the saphenous trunk. A shows a diagram of primary varicose veins; 1, deep vein; 2, great saphenous vein (GSV) or short saphenous vein (SSV trunk); 3, GSV or SSV tributaries; 4, perforator. B illustrates the CHIVA technique: high ligation plus ligation of the saphenous trunk below the re-entry perforator plus disconnection of the venous shunts or tributary phlebectomy. C illustrates valvuloplasty or wrapping (shown here) of the GSV termination plus tributary phlebectomy plus perforator ligation. D illustrates high ligation resection plus tributary phlebectomy plus perforator ligation. E shows tributary phlebectomy (ASVAL). X, vein resection; L, ligation.

Figure 2. External stenting. Left panel: above, the Venocuff II set. Below, schematics of incompetent venous valve (BEFORE) and competent valve following external stenting (AFTER). Right panel: angioscopic view after stenting.

Figure 3. Internal valvuloplasty according to Kistner. Using a longitudinal phlebotomy, each valve is repaired by interrupting a series of sutures placed at the commissures. Each suture progressively shortens the leading edge of the cusp.
was developed initially for saphenous vein incompetence, and later for primary deep vein incompetence.27,28

External valvuloplasty
The first step in external valvuloplasty consists of adventitial dissection until the valve's insertion lines are clearly identifiable as an inverted V shape. The commissural angle is normally acute, but in refluxive valves it is widened. Kistner introduced external valvuloplasty in 1990.29 In the transmural valvuloplasty technique, an external row of sutures is placed along the diverging margins of the valve cusp in the vein wall. Sutures for external repair are commenced at each commissure on both sides of the vein. The interrupted sutures are carried inferiorly until the valve becomes competent by strip testing (Figure 8, page 166).

Transcommissural valvuloplasty, developed by Raju, differs from transmural valvuloplasty by the use of a transluminal suture. As described in his paper: “A through-and-through transluminal resuspension suture (7-0 Prolene) was placed obliquely across the inverted V, traversing the valve cusps ‘blindly’ near their wall attachment to pull them up.”31

Vein valve transplantation
In vein valve transplantation (Figure 6), a 2-3 cm segment of axillary vein is inserted as an interposition graft at the termination of the femoral vein just below the junction between the deep femoral vein and the femoral vein or at the popliteal vein.

Neovalve creation
Maleti created a valvular cusp by dissection of the femoral venous wall to obtain a single or a bicuspid valve (Figure 7).26 He has used this technique mainly in cases of secondary etiology (post-thrombotic syndrome) but also in valvular agenesis that is probably not primary but congenital, but this original technique deserves to be mentioned.

Techniques without phlebotomy
- Wrapping, banding, cuffing, and external stenting

Segment transfer have been employed using end-to-end or side-to-end anastomosis according to the state of competence of the different valves in the veins of the groin.25

Vein valve transplantation (Figure 6), a 2-3 cm segment of axillary vein is inserted as an interposition graft at the termination of the femoral vein just below the junction between the deep femoral vein and the femoral vein or at the popliteal vein.

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Techniques without phlebotomy
- Wrapping, banding, cuffing, and external stenting

Wrapping, banding, cuffing, and external stenting

Venous valve dysfunction restoration by surgery in primary chronic venous disease – Perrin
Angioscopy-assisted external valve repair

In angioscopy-assisted external valve repair, the sutures are passed from outside to inside the lumen, directed by video-enhanced, magnified angioscopic imaging, allowing for precise approximation of the valve cusps.23

Percutaneous placed devices

The percutanous placed device, the Portland valve, consists of a square stent and porcine small intestinal submucosa covering, and is currently in a clinical phase I study.23

Clinical trial outcomes for surgical procedures

Superficial venous system

In all case series involving surgery to the superficial venous system in which the outcome on varices was reported, no assessment data is available on the value of the saphenous trunk as a potential arterial substitute.

Indirect procedures

Several nonrandomized controlled studies have been reported on the use of CHIVA, with both good clinical and hemodynamic outcomes at 3-year follow-up.3,4,34,35 Unfortunately, no randomized controlled trial (RCT) versus conventional surgery is available. With regard to high ligation plus tributaries phlebectomy plus/minus perforator ablation, two RCTs comparing this method with conventional surgery did not show any statistical difference in terms of clinical results at 4-year follow-up.5,6 Two case series using ASVAL have been reported with 7.8 (mean), and 36 months follow-up, respectively.5,6 The recurrence rate was found to be less than 10% in both.

Direct procedures

It is more difficult to assess the outcome of direct procedures, as a variety of procedures have been used. However, three RCTs comparing valve bandaging to classical surgery are available, with 9.4 (mean), 12, and 42 months of follow-up, respectively.5,6,10 No difference in terms of outcome—including varices recurrence—has been found.

Deep venous system

The results of DVR surgery are somewhat difficult to assess, as superficial venous surgery and/or perforator surgery are often performed in combination with DVR surgery. In primary DVR, the most frequent procedure used is valvuloplasty. Results are summarized in Table I.13,15,16 On the whole, valvuloplasty is credited with achieving a good result in 70% of cases in terms of clinical outcome, defined as freedom from ulcer recurrence and a reduction in pain, valve competence, and hemodynamic improvement over a follow-up period of more than 5 years. In all series, a good correlation was observed among these three criteria. External transmural valvuloplasty does not seem to be as reliable as internal valvuloplasty for providing long-term valve competence or ulcer-free survival.13

Only two series provide information about the outcome of patients presenting with severe chronic venous insufficiency without ulcer who are treated with valvuloplasty.10,42 No patients in either series developed an ulcer during the long-term follow-up, presumably due to successful prevention of disease progression by the operative intervention. Other procedures used in primary deep reflux, including angioscopic repair and wrapping, are more difficult to assess, because the case series have a relatively short follow-up, with the exception of Lane’s series (Table II).27,28,41,44

As valve transfer has been used mainly in post-thrombotic syndrome, the outcomes in primary DVR cannot be precisely assessed.

Recommended indications

Primary superficial venous insufficiency

As very few RCTs are available comparing direct or indirect valve restoration procedures to classical surgery, only weak recommendations can be stated concerning their use. Furthermore, new techniques such as echo-guided foam sclerotherapy and endovenous techniques such as radiofrequency and endovenous laser have recently emerged as valuable alternatives to traditional vein stripping.

It therefore looks difficult to recommend any particular procedure sparing the saphenous trunk (usually the great saphenous vein), but in young patients and particularly in women who have children and are considering future pregnancies, ablation surgery might not be the ideal recommendation.
must be less than 12 seconds, and the difference between pressure at rest and after standardized exercise in the standing position must be less than 40%.

The decision to operate should be based on the clinical status of the patient, not the noninvasive data, since the patient’s symptoms and signs may not correlate with the laboratory findings.46 In addition to meeting the clinical criteria, patients selected for surgery should be highly motivated to participate in their recovery, since ultimate success is dependent on their compliance with postoperative management.

In summary, primary reflux reconstructive surgery is recommended after failure of conservative treatment and in young and active patients reluctant to wear permanent compression. Valvuloplasty is the most suitable technique, with Tripathi, Kistner, Perrin, and Sottiurai favoring internal valvuloplasty,24,39,40,43 Raju recommends transcommissural external valvuloplasty31 and Rosales favors transmural valuloplasty.42 Some, but not all, authors recommend repairing several valves.24,42

### Table I. Valvuloplasty clinical study results.

<table>
<thead>
<tr>
<th>Study author</th>
<th>Surgical technique</th>
<th>Number of limbs treated (number of valves repaired)</th>
<th>Etiology</th>
<th>Follow-up months (mean)</th>
<th>Ulcer recurrence or unhealed ulcer (%)</th>
<th>Hemodynamic results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eriksson46</td>
<td></td>
<td>1 27</td>
<td>27/27</td>
<td>(49)</td>
<td>N/A</td>
<td>19/27 (70)</td>
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<tr>
<td>Masuda39</td>
<td></td>
<td>1 32</td>
<td>N/A</td>
<td>48-252 (127)</td>
<td>(28)</td>
<td>24/31 (77)*</td>
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<tr>
<td>Perrin30</td>
<td></td>
<td>1 85 (94)</td>
<td>65/85</td>
<td>12-96 (58)</td>
<td>10/35 (29)</td>
<td>64/83 (77)</td>
</tr>
<tr>
<td>Raju31,41</td>
<td>TMEV</td>
<td>68 (71)</td>
<td>N/A</td>
<td>12-144</td>
<td>16/68 (26)</td>
<td>30/71 (42)</td>
</tr>
<tr>
<td></td>
<td>TCEV</td>
<td>47 (111)</td>
<td>N/A</td>
<td>12-70</td>
<td>14/47 (30)</td>
<td>72/111 (59)</td>
</tr>
<tr>
<td>Rosales42</td>
<td>TMEV</td>
<td>17 (40)</td>
<td>17/17</td>
<td>3-122 (60)</td>
<td>3/7 (43)</td>
<td>(52)</td>
</tr>
<tr>
<td></td>
<td>TCEV</td>
<td>143</td>
<td>17/17</td>
<td>3-122 (60)</td>
<td>3/7 (43)</td>
<td>(52)</td>
</tr>
<tr>
<td>Tripathi24</td>
<td>TMEV</td>
<td>90 (144)</td>
<td>96/118</td>
<td>(24)</td>
<td>(372)</td>
<td>(79.8)</td>
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<tr>
<td></td>
<td>TCEV</td>
<td>12 (19)</td>
<td></td>
<td>(50)</td>
<td></td>
<td>(31.5)</td>
</tr>
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</table>

* no reflux or moderate reflux (<1 s) in 9 patients.

### Table II. Banding, cuffing, external stent, and wrapping clinical study results.

<table>
<thead>
<tr>
<th>Study author</th>
<th>Number of extremities treated (number of valves repaired)</th>
<th>Site</th>
<th>Etiology</th>
<th>Follow-up months (mean)</th>
<th>Ulcer recurrence or unhealed ulcer (%)</th>
<th>Hemodynamic results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akesson27</td>
<td>20 (27)</td>
<td>F, P</td>
<td>7/20</td>
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<td>2/10 (20) both PTS</td>
<td>PVI 7/7(100)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>PTS 7/10 (4)</td>
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<tr>
<td>Camilli44</td>
<td>54</td>
<td>F</td>
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<td>4-63</td>
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<tr>
<td>Lane28</td>
<td>42 (125)</td>
<td>F, P</td>
<td>36/42</td>
<td>64-141 (93)</td>
<td>(20)</td>
<td>(90)</td>
</tr>
<tr>
<td>Raju41</td>
<td>28</td>
<td>F, P, T</td>
<td>N/A</td>
<td>12-134</td>
<td>6/22 (27)</td>
<td>60/72 (83)</td>
</tr>
</tbody>
</table>

### Primary deep venous insufficiency

Indications for deep valve repair are based on clinical severity, hemodynamics, and imaging.

### Clinical severity

Most authors recommend surgery in patients classified as C6, and particularly with recurrent ulcer. In addition, given the good results associated with valve repair for primary reflux, I feel that valve repair should be considered in young and active patients presenting with severe edema or C4b findings, in order to avoid the lifetime use of compression garments. When superficial and perforator venous insufficiency occur in association with DVR, they must be treated as well, either as the first step in therapy or in a staged fashion. Contraindications to reconstructive surgery include uncorrectable hypercoagulable state or ineffective calf pump of any etiology.

### Hemodynamics and imaging

Only reflux that is considered grade 3 to 4 based on Kistner’s criteria45 is usually appropriate for DVR surgery. It is generally recognized that to be significantly abnormal, the value for venous refill time must be less than 12 seconds, and the difference between pressure at rest and after standardized exercise in the standing position must be less than 40%.

The decision to operate should be based on the clinical status of the patient, not the noninvasive data, since the patient’s symptoms and signs may not correlate with the laboratory findings.46 In addition to meeting the clinical criteria, patients selected for surgery should be highly motivated to participate in their recovery, since ultimate success is dependent on their compliance with postoperative management.

In summary, primary reflux reconstructive surgery is recommended after failure of conservative treatment and in young and active patients reluctant to wear permanent compression. Valvuloplasty is the most suitable technique, with Tripathi, Kistner, Perrin, and Sottiurai favoring internal valvuloplasty,24,39,40,43 Raju recommends transcommissural external valvuloplasty31 and Rosales favors transmural valuloplasty. Some, but not all, authors recommend repairing several valves.24,42
REFERENCES
Louis XVI was 20 years of age when he acceded to the throne of France and Navarre in 1774 on the death of his grandfather Louis XV the well-beloved (born in 1710). Born at Versailles on August 23, 1754, Louis XVI lost his father when he was 11 years old and his mother when he was 13 years old. As Duke of Berry, he received a strict religious education under the guardianship of the obscure Duke de La Vauguyon (1706-1772) and Bishop Jean Gilles de Coëtlosquet (1700-1784), who also saw to the education of his three brothers. He was a hard-working pupil whose favorite subjects were Latin, mathematics, physics, the maritime sciences, history, and geography. He was a frequent visitor to the workshop that Jean-Antoine Nollet (1700-1770), priest and experimental physicist, had installed in Versailles. He was the first French monarch to be fluent in English, reading House of Commons debates, translating English works, and building a collection of English periodicals and newspapers. In addition, and on his own initiative, he learned Italian and Spanish. Although his tutor, de La Vauguyon, took great care to isolate him from the philosophy of the Enlightenment, he nevertheless read *The Spirit of the Laws* (L’Esprit des Lois) by Montesquieu (1689-1785). The future Louis XVI was not keen on the military arts, despite his reputation as an excellent horseman.

The main political problem during the reign of Louis XVI, compounded by the expense of French aid during the American War of Independence, was the constant undermining by the nobility and senior clergy of attempts to abolish their privileges. The forces most hostile to change were forever marshaled against the King, who failed to attract support from the more enlightened elements of the nobility. Reserved, shy, and modest, Louis XVI knew what he wanted but was loath to give orders. He was a reluctant participant in Court ceremonial, thus indirectly depriving the nobility of their representational social role. His main failing was an inability to command. He was forever torn between the reformist ideas of the Enlightenment and deep attachment to tradition. Although respectful of the fundamental laws of the land and unwilling to contravene them, he appointed reforming ministers—only to dismiss them shortly afterward. The last absolute French monarch by divine right, he had a natural interest in scientific experiment, research, and discovery. He lost no opportunity of offering moral and financial support to new undertakings that might advance human knowledge and improve the condition of the masses: expansion of the Academy of Sciences, creation of the Royal Society of Medicine, the hot-air balloon and steam engine trials, the voyage of La Pérouse, implementation of hospital hygiene, and institutions for the blind and deaf-and-dumb. Long misunderstood in French history and often despised, the biographies of Louis XVI and Marie-Antoinette in the pre-Revolution political context are now being rewritten.

On May 16, 1770, he married Archduchess Marie-Antoinette of Austria (1755-1793), the younger daughter of Emperor Francis I of Lorraine. Husband and wife were 15 and 14 years of age. Their marriage embodied the alliance between the kingdoms of France and Austria. Louis XVI and Marie-Antoinette had four children: Marie Thérèse (1778-1851), known as Madame Royale, Louis Joseph (1781-1789), Louis Charles (1785-1795), the future Louis XVII, who was to meet a tragic fate, and Sophie Béatrice (1786-1787).

The years in waiting: an unconventional prince
When 2 years old, the young Duke had teething problems and was losing weight. The Genevan physician Théodore Tronchin (1709-1781), author of the article on “inoculation” in the Encyclopédie and senior physician to the Duke of Orléans, was visiting Versailles at the time. He recommended exposing the royal children to fresh air.

Tronchin had the ear of the Court, yet was also a friend of Voltaire (1694-1778), Denis Diderot (1713-1784), and Jean-Jacques Rousseau (1712-1778). He was an Enlightenment physician and an advocate of smallpox inoculation using Variola minor (variolation).

After staying nearby to Meudon Forest, the young Duke of Berry and his brothers returned to Versailles. Louis was brought up with his elder brother, the Duke of Burgundy, who died in 1761 from pulmonary tuberculosis aged 10, leaving Louis to inherit the crown by default. His childhood was marked by loneliness, lack of affection, and a succession of bereavements: after his elder brother, came his father (1765), mother (1767), and grandfather Louis XV (1774).

“My grandson is not very passionate,” Louis XV wrote the Infant of Parma in June 1770, deploring the future King’s lack of alacrity in consummating his marriage to Marie-Antoinette, “…[he is] unlike other men.” In July, 2 months after the wedding, the Dauphin was examined by Germain Pichault de la Martinière (1697-1783), surgeon to the King, for any anatomical abnormality that might explain the absence of sexual relations (the young Duke was almost 16 and Marie-Antoinette 14).

The surgeon found no abnormality, in particular no phimosis (“narrowness of the passage”). He suggested that “constitutional frigidity” might be responsible, a diagnosis confirmed in 1773 by the King’s physician, Jean-Marie François de Lassonne (1717-1778). We should recall that the young prince was being educated in the puritanical Jansenist moral code by a tutor who taught that “children conceived by too young a father are of a delicate constitution and do not live long,” and that “there is also a risk that their father becomes a libertine.” The unconsummated marriage became an affair of State and the focus of all malicious gossip at Court; the Count of Fuentès, the Spanish ambassador, saw it as a case of “constitutional frigidity induced by the teachings of Duke de La Vauguyon.”

Other factors included the fact that the young prince’s interests were not shared by his wife. Whereas her tastes ran to singing, dancing, balls, music, and fine clothes, Louis liked hunting and all kinds of manual work, with locks, clocks, and carpentry. His cabinet was equipped with a forge, workbench, a couple of anvils, and numerous tools. He took untold pleasure in joining craftsmen at their work “moving materials, planks, and cobblestones, and undertaking such heavy exercise for hours at a time that he sometimes came back more exhausted than any laborer forced into such work.” In 1773, de Lassonne prescribed the young prince some cinchona and “Mars balls” (alcoholic concoctions of iron filings and tartar) in an attempt to kick-start his libido.

As for the Dauphine, she was somewhat offhand in her compliance with the practices of the French court. She kept company with a coterie of young people with scant respect for etiquette. This attitude brought reprimands from her mother, Maria-Theresa, who wrote to her: “It is said that you are beginning to make fun of people, to burst out laughing in their faces… By going out of your way to please five or six young ladies or gentlemen, you risk alienating everyone else.”

On May 10, 1774, Louis XV died of smallpox, having refused to inoculate his family (only the Duke of Orléans, who was more open to modern ideas, had had variolation performed on his children). “The King is dead! Long live the King!”
Louis XVI was crowned in Reims on June 10, 1715. Four days later, he conducted the age-old ceremony of the royal touch, a time-honored rite performed by French kings since Robert the Pious in the 10th century. In the park of the abbey of Saint Rémi in Reims, bareheaded and wearing the cloak of the Holy Ghost, he touched some 2400 patients afflicted with scrofula, the “King’s evil,” making the sign of the Cross over them, and speaking the words: “The King toucheth thee; the Lord healeth thee” (the chronicle of the event recorded four cures). Louis XVI repeated this medieval ceremony five times in the course of his reign.4

Successes and setbacks in the reign

Louis’ grandfather, Louis XV, his father (the Dauphin), and his tutor, de La Vauguyon, inculcated the young prince with their patriarchal monarchy ethic. Kings were both shepherd and father to their flock. This conception of the exercise of royal power was influenced by a religiously inspired moral philosophy that taught the subservience of the temporal domain to the demands of its spiritual counterpart. Clearly, no such principle had been espoused by the Sun King, Louis XIV, for whom radiance of the monarch, reason of State, preeminence of law, and national prestige outweighed all other moral or religious considerations.

A diligent worker and regular attendee at the Council of Dispatches (which received administrative reports from provincial governors) and Council of State, Louis XVI set about becoming an exemplary “good king.” He sought to do good and keep to the fundamental laws of the kingdom. His reign was dotted with gestures of generosity: restoration of the regional or city parliaments (1774), creation of the pawnshop in Paris to discourage usury (1777), abolition of torture (1780), abolition of craft guild privileges and of the corvée royale, by which peasants donated their labor on royal highways (1780), institution of an extensive public works program, abolition of the poll tax on Jews (1784), and the granting of civil status to Protestants (1788).3

Louis XVI’s intelligence shone best in foreign policy. He built up a royal navy powerful enough to rival that of England, as shown during the American War of Independence. Signed at Versailles on September 3, 1783, the Treaty of Paris marked the creation of the United States of America. It reflected France’s military and economic commitment to the rebels and erased the humiliation of the Treaty of Paris signed 20 years previously, marking the loss of the French possessions in North America. It also signaled the return of France as an arbiter of European policy.2, 4

However clear-sighted he may have been in foreign policy, Louis XVI had difficulty in imposing his authority within France. He dismissed his ministers as soon...
as any obstacle emerged that appeared insurmountable, in particular, resistance by the parliaments. Yet he did not hesitate to appoint men of the Enlightenment as his ministers. Determined to push through fiscal reforms, he called on Jacques Turgot (1727-1781) in 1774, then on the Geneva banker Jacques Necker (1732-1804) in 1776, dismissing both before they could complete their stabilization of the royal finances. At the instigation of the Controller-General of Finance, Charles Alexandre de Calonne (1734-1802), the King convened the Assembly of Notables in 1787 with a view to carrying out fiscal and financial reform. King and minister sought to establish equality in taxation by seeking contributions from the notables themselves, setting up provincial assemblies that would rule on public finance issues, abolishing internal customs barriers, and freeing up the grain trade. The Assembly disbanded without reaching a conclusion. Senior clergy and nobility refused to pay the tax. Calonne was dismissed. His successor, Bishop Étienne Charles Loménie de Brienne (1727-1794), faced a parliamentary revolt. On the advice of Necker, Louis XVI convened the Estates-General, comprising clergy, nobility, and Third Estate (middle class). However, voting was to proceed by estate, enabling the clergy and nobility to outvote the Third Estate, rather than by overall poll, which would have enabled the numerically much superior Third Estate to carry the day.1,3,5

Louis XVI was not against a measure of reform. On July 17, 1789, 3 days after the Paris insurrection that followed the dismissal of Necker, the King went to the city hall proudly sporting the revolutionary cocarde (white, the French royal color, framed by red and blue, the colors of Paris). But this well-received gesture was marred on August 4 by his refusal to sign the Declaration of the Rights of Man or the decree abolishing feudal privileges. Forced back to Paris from Versailles, Louis XVI appeared to accept his role as constitutional monarch, no longer King of France by divine right, but King of the French. At the Champ-de-Mars, on July 14, 1790, the King went to the feast of the Federation, took his oath to the Constitution, and was acclaimed by the crowd. But his faith could not accept the transformation of the clergy into civil servants. His last hopes resting with an armed coup de force, he fled with his family in the night of June 20 to 21, 1791. His prestige and credit were at rock bottom, and he was imprisoned in the Temple prison. On August 10, 1792, he was condemned to death, then guillotined on January 21, 1793. His bravery in the face of death sent a wave of emotion sweeping through European courts and inspired the first military coalition against the fledgling republic.1,2,4,5

Influence of the Encyclopédie on the intellectual climate
With its 600 000 inhabitants, Paris was the largest city in the Western world after London. The Bourbon capital was the center of intellectual and financial life, a hub for the arts and sciences. It was only natural that Paris should have been the setting for a remarkable intellectual event: the publication of the sum of human knowledge, revised and corrected in the light of philosophical thought.

In the 1750s, triggered by the writings of Voltaire, a break occurred in the customs and traditions of conventional philosophical thought. Cornerstones of this enlightened thinking included: a belief in the elimination of ignorance through scientific progress; trust in observation and experimentation; aspiration to individual happiness; glorification of reason as opposed to religious dogma; and concern for a new civil and democratic morality.

This was the intellectual climate that welcomed the birth of a monument to Western knowledge. The first volume of the Encyclopédie (Encyclopedia, or a systematic dictionary of the sciences, arts, and crafts) appeared in 1751; 28 volumes of text and 15 volumes of plates were published up to 1780. This unprece-
dented publication comprised 17,000 articles written by 140 contributors of differing backgrounds and specialties. According to Diderot and Jean le Rond d’Alembert (1717-1783), the *Encyclopédie* aimed “to gather together the knowledge scattered across the surface of the globe and expose its general system to those who will come after us so that the work of centuries past will not have been in vain for the centuries that follow.” What was novel about the *Encyclopédie* was not only its exhaustive determination to record the sum of human knowledge, but to articulate theory closely with practice “in one and the same vision of progress.” The publication was also innovatory in its systemic cross-referencing, thereby emphasizing its determination to break down the barriers between the different disciplines within human knowledge. The *Encyclopédie* interpreted the sum of knowledge in the light of critical reason and integrated this knowledge into a consistent philosophical system. “All our direct knowledge can be reduced to what we receive through our senses,” wrote D’Alembert, “whence it follows that we owe all our ideas to our sensations.”

Financed by subscription, the work was published in Paris (first seven volumes), then from March 1759 onward in Neuchâtel (Switzerland). Because it espoused sensualist and materialist theories that questioned the spirituality of the soul and justified atheism, the *Encyclopédie* was not well received by the authorities. The Paris Parliament issued a ban in 1759 and ordered the seven volumes already published to be destroyed. Despite bans and other forms of obstruction, the *Encyclopédie* and its numerous pirated foreign versions found a wide public among notables, including magistrates, civil servants, cultured bourgeois, artists, merchants, and the enlightened nobility (i.e., those sectors who were to prove most active in the Revolution). It was even supported in many circles up to and including the Court: a portrait by Maurice Quentin de la Tour (1704-1788) depicted Louis XV’s favorite, Madame de Pompadour, turning the pages of the *Encyclopédie*. The Encyclopedists also received unfailing backing from Malesherbes (1721-1794), the director of the book trade and royal censorship from 1750 to 1763, who enjoyed the esteem of the young Louis XVI. After first reading the *Encyclopédie* in 1777, and recognizing its scientific and technical qualities, the King ordered the establishment of a Museum of Sciences and Technology in 1781. It was the forerunner of the present-day Museum of Arts and Crafts (*Musée des Arts et Métiers*). The philosophy of the Enlightenment, embodied in the *Encyclopédie*, bore within it the seeds of the 1789 revolution: the progress of universal knowledge would free mankind from the irrational beliefs responsible for fanaticism. The philosophers of the Enlightenment did not separate the order of reason and nature from the moral and social order. Men were born free and equal, and social rank was to be determined on merit alone. The implications behind an intellectual project of this kind could not escape the notice of those in power, and they also won over a number of enlightened minds.

On the other hand, there are historians who believe that the Revolution invented the Enlightenment in order to legitimize itself through a corpus of philosophical knowledge. In defense of this view, it must be recognized that the Enlightenment never addressed the masses.

The King as enlightened protector of the sciences

Under Louis XVI, the Academy of Sciences, which had been founded in 1666 by Jean-Baptiste Colbert (1619-1683), grew by three new sections: general physics, natural history, and mineralogy, thereby complementing its six other sections (geometry, astronomy, mechanics, anatomy, chemistry, and botany). Scientists from around the world working in the leading learned societies came to Paris to test and add to their knowledge. Between 1720 and 1780, the proportion of scientific publications doubled, to the detriment of their theological counterparts. In the spirit of the *Encyclopédie*, during the reign of Louis XVI, the 39 academies in Paris and the provinces were keen to report any scientific discoveries and innovations with the potential for directly transforming daily life. The King took a great interest in the activities of these engineers and scientists and encouraged their experiments and initiatives.

Louis XVI had been fascinated by science since childhood. He could handle calculations in algebra, had a solid grounding in physics, was acquainted with Boyle’s law, and knew how to do section drawings of buildings and instruments. Proud of his epoch’s discoveries, he had no hesitation in sporting a bouquet of...
Agronomist Antoine Augustin Parmentier presenting Louis XVI with a bunch of potato flowers. Potatoes were first grown in France in the sandy ground at Les Sablons, in Neuilly, near Paris. Legend has it that the crop was guarded by heavily armed royal troops so that the populace, very mistrustful of the palatability of this new plant, would be convinced it was very precious, for it to be so protected. © Roger-Viollet.

“Have we any news of Monsieur de la Pérouse?”

During his adolescence, Louis XVI read the account published in 1771 by Louis Antoine de Bougainville (1729-1811) of his circumnavigation of the globe (1766-1769). He was also interested in the archipelago that Yves-Joseph de Kerguelen de Trémarec (1734-1797) discovered in the southern Indian Ocean. In his apartments in Versailles, Louis XVI was surrounded by astrolabes, barometers, thermometers, chronometers, potato blossom in his buttonhole in honor of the tuber raised from pigsty to dining table by the chemist Antoine Parmentier (1737-1813). Following the recognition by the Paris Faculty of Medicine in 1772 (for which Parmentier was largely responsible) that the potato was harmless to human health, the King granted Parmentier the Sablons plain near Neuilly to develop his crop. Large-scale potato cultivation was to play a considerable role in eradicating the famines that periodically ravaged the French countryside when climatic disasters decimated the grain harvest; during such crises, potato replaced cereal in the baking of bread (the staple food of the French). Even so, during the Revolution, Louis XVI’s endorsement of Parmentier was to make the chemist suspect in the new regime’s eyes.8,9

In 1783, Louis XVI drew on his own resources to finance the hot-air balloon experiments by the Montgolfier brothers. The first test of a spherical balloon took place in Annonay on June 5. The 800 m³ balloon inflated with hot air weighed 225 kg. It rose 1000 meters into the sky and traveled 2 kilometers. Looking for financial backing, and supported by the Academy of Sciences, Jacques-Étienne Montgolfier (1745-1799) went to Paris and gave a demonstration at Versailles on September 19 before King and Court. This time, the blue taffeta balloon decorated with fleur-de-lis was larger (1000 m³), and carried a sheep, rooster, and duck in a basket. The King asked for explanations, and was shown the huge straw-fired stove that produced hot air to propel the balloon. The trial was successful, with the animals returning alive. The King gave permission for an experiment with a human being. On June 23, 1784, the Marie-Antoinette, a balloon decorated with the French and Swedish coats of arms, lifted off in Versailles in front of the royal family and Gustav III, King of Sweden. It transported its two passengers, Jean-François Pilâtre de Rozier (1754-1785) and Louis Proust (1754-1826), senior pharmacist at the Salpêtrière Hospital, all the way to the Forest of Chantilly, a distance of 52 kilometers. Bowled over by the invention, the King awarded Jacques-Étienne the ribbon of St Michael, gifted an annuity to his brother Joseph Michel (1740-1810), ennobled their father, and granted the two brothers a substantial sum to continue their hot-air experiments.8,10 Louis XVI also encouraged industrial applications of the steam engine. He would regularly arrange to be presented with novel ideas, in some cases supporting them from the privy purse. This was not the case for the Périer brothers, Jacques-Constantin (1742-1818) and Auguste Charles, who had to use their own funds to build a pump at Chaillot to supply Paris with water from the Seine; the pump was driven by two steam engines. The Périer brothers were skilled mechanics, and they applied their pressurized steam method to blast furnaces, enabling them to manufacture cylinders, pendulums, and new cotton spinning machines.8,11

In 1783, Louis XVI backed attempts by the Marquis Jouffroy d’Abbans (1751-1832) to fit the steam engine into boats. Newspapers of the time reported the progress of a paddle steamer, the Pyroscaphe, on the Saône near Mâcon. Unfortunately, opposition from the Academy of Sciences and the intervention of the Revolution meant that glory never came the way of Jouffroy d’Abbans.8,12
Louis XVI, on June 29, 1785, giving his instructions to La Pérouse about to set out on his voyage around the world. Painting by Monsiau Nicolas André, oil on canvas, 2.72×2.7 m, at the Musée du Château de Versailles, 1817. © Gérard Blot/RMN.

The King's creation of the Royal Society of Medicine

Numerous epidemics had ravaged France since the last visit by plague in 1720: smallpox (1776-1786), measles (1776-1786), dysentery (1779, 1792), and pneumonia (1784-1785). On April 29, 1776, in an attempt to study and prevent such afflictions, the King set up a Commission of medicine in Paris to maintain correspondence with physicians in the provinces on all that may pertain to human and animal epidemic disease. Turgot, Controller-General of Finances, entrusted the anatomist Félix Vicq d’Azyr (1748-1794) with the founding of the Commission that became the Royal Society of Medicine by letters patent on August 20, 1778. A member of the Academy of Sciences, Vicq d’Azyr was the author of the article on morbid anatomy in the Encyclopédie. The Royal Society of Medicine (half-way between academy and government thinktank) boasted the most progressive physicians of the Enlightenment era among its members. It met in the Louvre in the courtroom of the Secretary of State for the King’s Household. Attacked from its inception by the Paris Faculty of Medicine, the Society was inspired by a pioneering spirit. Its aim was to collect serial data on the epidemiology of infectious disease, the state of the soil and water supply, medical topography, and meteorology, all on a monthly basis, right across France. The survey was hugely ambitious in
that it sought not only to map French epidemiological risk but to lay down general principles of hygiene applicable to prisons, hospitals, schools, barracks, ports, and ships. In return, corresponding physicians in France and abroad were to receive information on the clinical aspects of infections and their treatment. Considered as the largest administrative survey ever undertaken in the 18th century, the study remained under the authority of the Controller-General of Finances who authorized no other institution, even the Academy of Sciences, to concern itself with statistics in its place. As a result, the conduct of the study remained under the supervision of royal civil servants.\textsuperscript{15-17}

To ensure that measurements were reliable, Vicq d’Azyr asked physicians to purchase mercury instruments from Paris or London and to calibrate them using the method of Charles Messier (1730-1817) in the case of barometers and the method of René de Réaumur (1683-1757) in the case of thermometers. In practice, many corresponding physicians did not have the instruments for recording temperature, hygrometry, pluviometry, or pressure three times a day, once a month, for 15 years (!). However, the archives of the Royal Society of Medicine \textit{reflect on the part of the physicians, despite their little training in data recording and management, a fierce determination to achieve accuracy, as if they were shot through by absolute confidence in the idea of progress. Of the near 200 physicians who took part in the survey, around 50 performed their measurements for nearly 10 years. From 1776 to 1792, the Society collected almost 8300 of the 35,000 anticipated report cards. The comments and observations that physicians included with their data contained much information on medical practice and the state of French society in the immediate pre-Revolutionary era.\textsuperscript{15-17}

Although the great disparity in responses made it impossible to draw up the comprehensive epidemiological map of France that the survey sponsors had intended, the partial information collected threw accurate light on the routes of contamination of certain infections. The reports received by the Royal Society of Medicine inspired Vicq d’Azyr in 1790 when he drafted his \textit{New plan for the constitution of medicine in France.}

Antoine de Fourcroy (1755-1809), physician, chemist, and Convention deputy, was to draw on this text when instigating the decree of 4 Frimaire Year III (December 4, 1794) that reopened the faculties of medicine in Paris, Montpellier, and Strasbourg as Schools of Health.

By demanding meticulous attention to measurement and emphasizing the importance of the results, the Royal Society of Medicine accelerated the switch from a medicine of philosophical and nosological speculation to one of enlightened scientific reasoning.\textsuperscript{15-17}

Medicine held little interest for Louis XVI as a “science”—unsurprisingly, in that the healing art, in the late 18th century, was still deeply enmeshed in abstruse philosophical considerations. As a profoundly religious person, the King was moved by the fate of the ill and infirm. The measures he took were dictated mainly by pragmatism, charity, and religiously inspired commiseration. In 1778, Louis gifted 6000 livres to Charles-Michel de l’Épée (Abbé de l’Épée) (1712-1789), the inventor of a more comprehensive signing language, to help found an institution to care for the young deaf-and-dumb. The same year, he made an identical grant to Valentin Hauy (1745-1822) to found a school for the blind; years later, on December 26, 1786, 26 blind youngsters who had learned to read and write were presented to the King at Versailles.

In 1780, the King commanded military hospitals to treat enemy wounded as “the King’s own subjects.”\textsuperscript{15-17} The same year, he ordered “light and well-ventilated infirmaries” to be constructed at his expense in the kingdom’s prisons.

In 1781, after an incognito visit to the Hôtel-Dieu Hospital in Paris, Louis was upset to see patients piled three or four to a bed in unhealthy rooms. He decided to set up a system of individual beds and to separate patients by type of infection. The same year, he approved the creation in Paris of a hospital for 26 blind youngsters who had learned to read and write. He decided to set up a system of individual beds and to separate patients by type of infection. The same year, he approved the creation in Paris of a hospital for children with infectious disease, the Sick Children’s Hospital. It was in this public health spirit, in 1785, after the Hôtel-Dieu Hospital was destroyed by fire, that Louis XVI entrusted the surgeon Jacques René Tenon (1724-1816) and seven other members of the Academy of Sciences with drafting a report on the reconstruction of the Hôtel-Dieu. This report inspired Tenon’s celebrated 1788 \textit{Memoirs on the hospitals of Paris itemizing the concrete measures to be applied for refitting Paris hospitals according to the new...

\textsuperscript{15-17}
principles of hygiene: ventilated wards with high ceilings and a fixed number of patients, reorganization of nursing duties, isolation of contagious patients, and special arrangements for obstetric deliveries, catering, staff and patient clothing, baths, showers, and disinfection facilities.\textsuperscript{4,17,18}

**Epilogue**

Militant hagiographies penned by die-hard monarchists aside, the royal couple suffers from an appalling image in French historiography. Studies offering an objective and subtle analysis of the personalities of the two monarchs are relatively rare. Louis XVI is often described as a somewhat weak and insignificant king whose sole hobbies were hunting and the dismantling and repairing of locks. When hunting, he preferred the company of his masters of hounds and stablemen to that of his guests. His master locksmith reported that he had to help the King hide from Court and Queen “to file and forge with me. (…) The King was good, shy, tolerant, and inquisitive.” Louis has also been depicted as improvident, indecisive, overburdened by responsibilities, and under the dual influence of courtiers’ intrigues and Marie-Antoinette.\textsuperscript{4}

During his lifetime, this image was bandied about (in amplified form) by the Court, the Paris circles close to the Viennese throne, and both his brothers, the Counts of Provence (the future Louis XVIII) and Artois (the future Charles X). The economic and institutional reforms proposed by his ministers (Turgot, Necker) threatened the privileges to which his 10 000 courtiers were so attached.\textsuperscript{2,3}

Louis XVI was unrestrainedly caricatured. Shortsightedness compounded his tendency to absentmindedness. He was sometimes unable to put a name to those he spoke to. His great height, chubbiness, and “noble features tinged by melancholy” increased the distance that he created with those who came into contact with him. The King’s personality was complex. He often appeared retiring. Liking jokes, he gave
an impression of familiarity, but in fact detested it. In 1774, Lord Stormont, the English ambassador to Paris, wrote: “As he is very reserved and indeed proud to be so, one guesses rather than knows what he is thinking.” His style was curt, terse, and plain. Often he did not answer those with whom he was speaking. “I prefer my silences to be interpreted rather than my words,” he told Malesherbes, who defended him at his trial in 1792. His memory was formidable, allowing him to correct and annotate memoranda and dispatches from his ministers and advisers with considerable ease and accuracy. However, his faults are hard to conceal: the King was shy and awkward in public and did not look his interlocutors in the eye. He lacked self-confidence and resolve. “There were two men in him, the man who knew and the man who wanted,” wrote his biographer, Jean-Louis Soulavie (1751-1813), priest, geologist, and historian. “The qualities of the first were most varied and extensive. But in the great affairs of state, the King who wanted and commanded was almost never to be found.” Louis’ excess of modesty and discretion probably aided the decline in the prestige and cult of the monarchy. The blurred image of Louis XVI is not helped by the meager writings he left behind him: a diary began as Dauphin in January 1766, and a diary continued as King, which ended on July 31, 1792 with the word “Nothing.” There is little if anything else. Both diaries were simply hunting notebooks. They were not diaries in the proper sense, nor chronicles of a reign. Louis also kept a book of the annuities and gifts he bestowed, and another for private expenditure. In the following centuries, the void was filled by a multitude of counterfeit manuscripts, circulated in attempts either to rehabilitate the King or to flesh out the portrait of a weak and conspiratorial monarch. 

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LES SCIENCES SOUS LOUIS XVI. UN ROI ENTRE LUMIÈRES ET RÉVOLUTION

Le problème politique majeur du règne de Louis XVI réside dans ce travail de saper incessant de la noblesse et du haut clergé contre l’abolition de certains de leurs privilèges. La question économique occupe une place essentielle dans ce règne marqué par la très coûteuse guerre d’Indépendance américaine (1776-1783). Le roi trouve toujours dressé devant lui les forces les plus hostiles au changement; il ne sait pas s’appuyer sur la frange éclairée de la noblesse. Secret, timide et modeste, Louis XVI veut mais n’ordonne pas. Le roi se plie difficilement au cérémonial de la cour privant indirectement la noblesse de son rôle social de représentation. Louis XVI présente le principal défaut de ne pas savoir commander les hommes; sensible à la modernité des Lumières, il est constamment écarté entre ses idées réformistes et son attachement profond à la tradition. Le roi demeure respectueux des lois fondamentales du royaume et refuse de les transgresser; il nomme pourtant des ministres réformateurs mais les congédie prématurément. Par goût et par nécessité, Louis XVI, dernier monarque français de droit divin au pouvoir absolu, se passionne pour les expériences, les recherches et les découvertes scientifiques. Il ne manque aucune occasion d’apporter son appui moral et financier à de nouveaux projets susceptibles de faire progresser les connaissances humaines et d’améliorer le sort de la multitude. C’est ainsi qu’il favorise le développement de l’Académie des sciences, la création de la Société Royale de Médecine, les expérimentations de l’aérostat et de la machine à vapeur, l’expédition maritime de La Pérouse, l’application des règles d’hygiène aux hôpitaux, la fondation d’institutions pour aveugles et sourds-muets. Personnages incompris et souvent méprisés de l’histoire de France, Louis XVI et Marie-Antoinette bénéficient aujourd’hui d’une réécriture de leurs biographies dans le contexte politique qui précède la Révolution française.
To reach the Petit Trianon, you need to leave the Château of Versailles behind you, leave the straight lines of the formal gardens, and bid farewell to the geometrical precision of the landscapes and vistas designed by Le Nôtre. Walk along the edge of the Ornamental Pools on the Terrace, go around the Latona Basin, make your way between the Chestnut Grove and the Dauphin’s Grove, carry on between the Colonnade Grove and the Dome Grove, head toward the Grand Canal, and turn off to the right. The Pavilion is straight ahead of you, at the end of the path. A masterpiece of neoclassical architecture, this modestly proportioned palace was built between 1763 and 1768 by Ange-Jacques Gabriel (1698-1782) at the request of Louis XV, who wanted to give it to Madame de Pompadour, his favorite. But the marquise died too soon and never had the chance to enjoy her beautiful gift. The Comtesse du Barry, another of the King’s mistresses, enjoyed it in her stead. With this stunning, square building, embellished with Corinthian pillars on the court side and columns overlooking the formal garden, the King’s architect, who also designed the buildings of the Place de la Concorde and the Ecole Militaire, as well as the “Grand Project” in Versailles, surpassed himself. The harmony is perfect. The accommodation is delightful, the rooms on the bel étage perfectly proportioned and tastefully decorated. The residence was designed, first and foremost, to be in harmony with nature. Surrounded by a veritable botanical laboratory entrusted from 1759 to the great naturalist Bernard Jussieu, who was commissioned to classify the species so carefully nurtured and maintained by the domain’s gardeners, the twenty-five minutes at a slow walking pace. That’s all it takes to pass from one world into another, to leave behind the glitz of the Château of Versailles and step into the simplicity of the Petit Trianon. It’s a journey that Queen Marie-Antoinette made a thousand times to escape the Court formalities. Here, just minutes from the salons where the courtiers conducted their intrigues, the Austrian princess born in Vienna on November 2, 1755 who became Queen of France on May 10, 1774 at the age of 19 years, created a small paradise for herself, away from the stringencies of etiquette that she found intolerable. Surrounded by the charm of the French Pavilion designed by Gabriel, the landscaped garden, and the contrived simplicity of the cottages in the Queen’s Hamlet where she played the shepherdess, Marie-Antoinette would say: “I am not the Queen, I am me.” The Petit Trianon was her personal domain, a thoughtful gift from Louis XVI that released his capricious bride from the yoke of monarchy. Today, despite the ravages of time and the Revolution, the place still reflects the Queen’s personality, tastes, and aspirations. “To know someone, you must visit their home. The Trianon is Marie-Antoinette,” notes historian Evelyne Lever. Here, in her carefully restored domain, in the exquisite apartments or the garden she loved so much, visitors come close to this beautiful woman who was so passionate about the arts and the pleasures of life, but whose life was changed from frivolity to martyrdom by history.
building is a celebration of the plant world even in its internal decor. The paneling in the great dining room is decorated with carvings of orange tree branches and bowls of fruit; and the drawing room walls are decorated with the cipher of Louis XV intertwined with a crown of wild lilies. Garlands of flowers, birds, and rustic motifs are a recurring theme in the fabrics, paneling, furniture, and wall paintings.

Marie-Antoinette received this magnificent gift from her husband on August 15, 1774, just a few months after his accession to the throne. “You love flowers, and I have a whole bouquet of them for you!” he said gallantly as he handed her a key encrusted with 531 diamonds. The Queen could not have imagined a more beautiful tribute. She who so detested the Court now reigned over a kingdom modeled in her image, where she could live as she wished.

Freedom to bloom

It was a relief. The young Queen struggled with the rigors of etiquette. In Versailles, closely watched by her Mistress of the Household, Madame de Noailles, life weighed heavily on her. The Queen found it difficult to accept “that she belonged not to herself but entirely to the kingdom of France,” explains Evelyne Lever. “Placed above mere mortals in a society organized along extreme hierarchical lines, her slightest gesture had the significance of a public act.” She could not get used to it.

From what she wore to what she ate, from the moment she got up in the morning to the moment she went to bed at night, her every gesture was scrutinized, and regulated down to the finest detail by immutable rules. The old nobility vied for her favors, and encroached upon her privacy. Her daily life took place under the eyes of a host of courtiers, ladies-in-waiting, valets, and footmen.

At the Trianon, she shut them out so that she could live as she wished and give free rein to her own desires and personality. She reclaimed her right to a private life and imposed her own style. Her kingdom belonged to her. Nothing and no one could enter this small, enchanted domain without her permission.

Even her husband was allowed in by her invitation only. As a rule, he came simply to dine. He was never to sleep in the bedroom with the red silk drapes that Marie-Antoinette had set aside for him on the second floor. To the great horror of all the courtiers, rules were posted in the gardens. They were rules set “by order of the Queen” and not “by order of the King.”

Marie-Antoinette withdrew, surrounding herself with a clique of young intriguers whom she liked to think of as her friends. Nobody spied on her, nobody judged her. So at least she thought. But tongues were wagging. Her solitary retreats displeased the Court, and its members distanced themselves, injured by her neglect. The Queen didn’t care. Ignoring all the gossip, she continued to assert her freedom as a woman. She even went as far as endowing a boudoir with “movable mirrors,” where an elaborate system of sliding panels enabled her to cover the windows. She restricted access to the sumptuous feasts she held in her haven of peace, even though the Court was, by tradition, public. She shut herself away.

Far from all the conventions, but also far from her subjects. “Trianon is a world in miniature,” wrote Austrian novelist Stefan Zweig in his classic biography of his compatriot, published in 1933. “From her windows—symbolically and literally—she could not see the town, or Paris, or the countryside, or anything that had any connection with real life. Her little patch of land could be crossed in a few moments, yet this
tiny space was of enormous significance and meant more to Marie-Antoinette than all of France and its twenty million inhabitants,” continued Zweig. Ah, the garden! Although, initially, the Queen did not alter the decor of the French Pavilion designed by Gabriel for Madame du Barry, the same did not apply to the parkland surrounding her new residence. She did not like the precision of Le Nôtre’s landscapes and vistas—his straight pathways and alleys, his contrived use of perspective, his trimmed boxwood, and artificial groves. Marie-Antoinette dreamed of intricate, fairytale landscapes. The squares of rare plants so scrupulously collected since 1759 by the botanist, Charles Jussieu, by the order of Louis XV, were too severe. They had to go. The young woman was a romantic. She fell in love with the landscaped gardens of the English, and adored a mass of rambling, untamed vegetation. She ordered her architect, Mique, to redesign the gardens, drawing inspiration from the works of the Comte de Caraman (whose designs included the Parc Monceau in Paris, which still exists today), and from the ancient ruins depicted in the paintings by Hubert Robert, who was enamored of Italy.

“Hurried on by the Queen’s impatience, hundreds of workers began to implement the architects’ and designers’ plans, undertaking works that would, like magic, make the real world disappear, to be replaced by the most natural and picturesque landscape imaginable,” wrote Stefan Zweig.

The place was transformed. A gentle stream meandered through fields where the air was now scented with the rare fragrances of plants from North America, such as the tulip tree from Virginia, cypress from Louisiana, massive oaks. Paths wound their way between overflowing flowerbeds. Broad clearings offered views of the follies built here and there according to the Queen’s fancy, ravishing buildings made for conversation and amusement. There was, for example, The Temple of Love, built on a little island surrounded by reeds; a charming octagonal belvedere overlooking an ornamental lake; and a Chinese tilting ring, a game in which players try to mount multicolored wooden horses made to look like peacocks or dragons.
And finally, the Grotto. Designed for romantic encounters and intimate conversations, the Grotto was Marie-Antoinette’s secret refuge. You approach it via a little hidden pathway that enables you to see before being seen. This is where she was, some 15 years later on October 5, 1789, when she received the news that the people were marching on Versailles.

A refined world

Meanwhile, with all its charm and contrived delicacy, this little patch of land just a few kilometers square became the Queen’s entire universe. Equipped even with its own theater, the “world in miniature” enchanted her. “Trianon is for Marie-Antoinette a secret, blessed land dedicated entirely to chivalry and pleasure,” noted Stefan Zweig ironically. For the whims of a frivolous girl barely 20 years old were not to everyone’s liking. The expenditure was profligate. To the extreme.

“I thought I had gone mad or was dreaming when I found that the large greenhouse (the most costly and best designed in Europe) had been replaced by tall mountains, a large rock, waterfalls, and a stream. Never have two acres of land been so totally changed, nor cost so much money,” lamented the Duc de Croÿ.

Marie-Antoinette knew nothing about painting. She judged artists’ talent simply by their ability to render her likeness or at least a reflection of her own notion of her beauty. Several well-known artists tried their hand. Liotard, Jean-Baptiste Charpentier, François-Hubert Drouais, and Joseph Krantzinger, whose depiction of the young Queen as an amazon so shocked Empress Maria Teresa. “I’m fated to find no painter able to capture my likeness,” the young Queen complained to her mother.

In 1778, Elisabeth Vigée-Lebrun, a fashionable young portrait artist, tried her luck. The initial meeting went well. “At the first sitting, I found the Queen’s imposing air prodigiously intimidating to begin with,” wrote the artist. “But Her Majesty spoke to me so kindly that her gentle good grace soon dispelled this feeling.” She forgot etiquette to focus on the gracious features and perfect figure of her model. “The most striking thing about her face was the radiance of her complexion,” she said later. The two young women were the same age. They became friends. During the long sittings, Elisabeth Vigée-Lebrun was to become the Queen’s confidante. They shared the same love of singing, and of freedom. It is to Madame Vigée-Lebrun that we owe a painting of the Queen wearing a simple muslin dress and a straw hat decorated with feathers and bound by a ribbon. This was the kind of costume that the Queen loved to wear in her gardens at the Trianon. Exhibited in 1783, the canvas was found shocking in its simplicity. It had to be quickly replaced by an identical picture of the Queen with a rose in her hand, but this time wearing a dress of blue-grey satin trimmed with an abundance of lace.

Marie-Antoinette and her Children, by Elisabeth Louise Vigée-Le Brun, painted as an attempt to portray the Queen as an affectionate mother and so ingratiate her with public opinion. The empty cradle alludes to the death of Sophie-Beatrix, who died while the painting was being executed. From left to right, daughter Madame Royale, and two sons, Louis-Joseph and the future Louis XVII.

Oil on canvas, 275 x 215 cm, Château de Versailles. © Bridgeman Art Library.

Portrait of Marie-Antoinette “À la Rose” by Elisabeth Louise Vigée-Le Brun, who was to become the confidante of the Queen. Oil on canvas, 113 x 87 cm, Château de Versailles. © Photo RMN.
when he discovered the extent of the works ordered by Marie-Antoinette. A style icon, obsessed by her clothes and appearance, infatuated with hairstyles, jewelry, finery, and especially herself, the Queen next launched herself with equal enthusiasm into redesigning the interior of her home. It was the ideal activity to stave off boredom and give meaning to her life, and she devoted herself to it wholeheartedly. Before tackling the refurbishment of her cherished Trianon, she began with a makeover of her apartments in the Château de Versailles. She fitted doors and windows with locks bearing her cipher, ordered new furniture,

**MONSTER OR MARTYR? FROM THE REVOLUTION TO SOFIA COPPOLA**

From feather-brained macaroon addict to a woman with a passion for pleasure and consumption, from “the Austrian woman” to the victim of the liturgy of Versailles, the public image of Marie-Antoinette is many-faceted and has constantly changed over the centuries.

The author of several biographies of the Queen, including “Marie-Antoinette, the last Queen of France” (Framan, Strauss & Giroux, 2000), which inspired film director Sofia Coppola, French historian Evelyne Lever takes stock of these shifts in public opinion.

Marie-Antoinette has always fascinated people. But perceptions of her have changed. In the 19th century, she was seen as a martyred queen whose cult was maintained by the nobility. They were not looking at her life; she was merely being held up as a symbol of a murderous Republic. This version was cultivated in every aristocratic family. At the same time, in Republican circles following the Second Empire, Marie-Antoinette was seen as a bad queen who sucked the people’s blood. The two currents of thought co-existed during the same period. They merely varied from one circle to another. In 1858, the Goncourt brothers published the first real biography of the Queen in this expiatory spirit. It was not until the end of the First World War that the historian and curator of Versailles, Pierre de Nolhac, did some proper research. He drew on several works by scholars who had begun to classify Marie-Antoinette’s letters. He succeeded in providing a coherent picture of the Queen, demonstrating that she was not simply a saint. Certainly she was a victim of the Republicans, but he stressed her political role, her sensitivity, and her growth into maturity.

It was the Austrian novelist Stefan Zweig, influenced by psychoanalysis, who wrote the finest biography in the 1930s. In the Viennese archives, he had discovered some letters that had been censored but cast a fascinating light on her sexual life, and on the problems she had had with Louis XVI before she succeeded in providing an heir to the throne of France. According to Zweig, Marie-Antoinette was a princess of unexceptional intelligence whose tragic destiny transformed her into an exceptional person. In his view, the Queen played a genuine political role from 1787 onwards.

In the 1950s, the French public fell in love with this woman who arrived in a carriage and was taken to the scaffold in a cart. Today, Sofia Coppola’s film has turned Marie-Antoinette into a fashion icon. The exaggerated frivolity and whirlwind of pleasure fascinates young people, who now appear to confuse the Queen’s fate with that of Lady Diana. Insufficiently loved in life, she is now never more adored than in death.
and selected the finest silks. In 1781, she transformed her library and refurbished the former cabinet of Queen Marie Leszcynska. Overlooking a dark and gloomy courtyard, the somber room became a charming boudoir lit up by the careful use of mirrors and pale-colored paneling. Known as “La Meridienne,” it is a model of elegance. Visitors can still admire the pretty little sofa tucked into its corner, the mirrors framed with stems of roses and bronze foliage accompanied by the eagle of the Hapsburgs and the attributes of Love. Of course, Marie-Antoinette often changed her mind. She hesitated, reconsidered, started again, spent fortunes, gave orders, and counter-orders. But the result was delightful.

In 1783, some 230 craftsmen were employed in transforming the inner Grand Cabinet (the Gold Room) at Versailles. In the Chamber of Ceremonies, Marie-Antoinette had the walls and chairs covered with sumptuous white satin brocaded with arabesques and embroidered with wild flowers. It was not to last. Four years later, she tired of it. The whole room was empanelled in white and gold.

Entranced by novelty, she bought lots of expensive trinkets. Chinese lacquers and porcelains, boxes, fans, seashells with gilt bronze mounts, jaspers, crystals, and fossilized wood littered every available surface. And every item of furniture bore a famous name. Jean-Henri Riesener was her cabinetmaker, supplying magnificent roll-top writing desks, tables of every shape and kind, and all sorts of corner pieces embellished with bronzes by Gouthière. Sofas, armchairs, and love seats bore the signatures of Georges Jacob, Foliot, and Boulard. The silks came from the workshops of Jean Charton. Faithful to her suppliers, Marie-Antoinette was midwife to a new style. Combining the elegant and the rococo, it was inspired by the classical world but adapted to offer the comfort and feminine grace of which she prided herself on being the finest example. Obsessed with her image, she reigned over the decorative arts with the same blend of sophistication and simplicity that she liked to express in her clothes. She imposed her tastes. “She doesn’t really deserve the credit,” Evelyne Lever reminded us.

“As Queen, she had only to choose among the items presented to her by the most talented craftsmen of the period. She never actually influenced them.” That may well be so. But she was their patron. She introduced new blood, swept away the cobwebs, did away with the heaviness of the rocaille style. She let in a breath of fresh, more lighthearted air. She loved simple lines, wall hangings, and foliage. She had bouquets embroidered on curtains, chairs, and bedscreens. Lightness, sophistication, and delicacy became her trademark.

In 1786 at Versailles, she had the Salon des Jeux stripped of its marble decor. She wanted to give the rooms “a light, clean feeling,” and banish the “mean and heavy feel of the bronze and lead” ornaments commissioned by Louis XV. She didn’t like Lebrun’s ceiling. So she had it painted over in sky blue.

At the Petit Trianon, she made few changes to the original decor. She contented herself with affirming a style, introducing daylight and delicacy. She had a preference for rustic designs, which she used and abused, both for her numerous sets of porcelain tableware with their background of gold, and for her famous “wheat-ear” furniture, whose polychromatic shapes are laden with lily of the valley, jasmine, and fir cones, while the chairs were covered with pale silk embroidered with bouquets and garlands of flowers.

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**MARIE-ANTOINETTE’s Estate at Versailles**

The creation of “Marie-Antoinette’s Estate” is part of the “Grand Versailles.” It includes access to the Petit Trianon, Chapel, French Pavilion, Queen’s Theatre, Belvedere, Temple of Love, Grotto, Landscaped Garden, Refreshments Dairy, Queen’s Hamlet, and Farm.

The Estate and Petit Trianon are open daily, except on some French public holidays and during official ceremonies. April 3 through October 31: noon to 7.30 pm.

Information: 01.30.83.78.00

[www.chateaushortes.fr](http://www.chateaushortes.fr)
There was nothing pompous or particularly sumptuous in her choices, rather “a perfect harmony, from bed to powder case, from harpsichord to ivory fan, from chaise longue to miniature, using only the finest materials in the most discreet forms, fragile in appearance yet long-lasting.” Incorrectly called Louis XVI, this style owes much to the Queen, since it is wholly associated with her light and elegant silhouette.

Too frivolous a game

In her Petit Trianon domain, known as the “little Schönbrunn” in acknowledgement of her Austrian origins, she wore charming muslin dresses and straw hats, favoring modesty. “Compared with the luxury of Versailles, the Petit Trianon seemed simplicity itself,” comments historian Jean-Christian Petitfils. “A bedroom full of muslin and silk embroideries, a boudoir, several cabinets and garde-robe, an elegant library, a bathroom with a white marble bath. And throughout, a symphony of soft pastel tones of green, lilac, blue, white, and gold.”

Her cardboard cutout haven became an obsession. Very soon, Gabriel’s French Pavilion, the garden, and its novelties were no longer enough for her. To “make the fantasy even more real,” joked Stefan Zweig, she commissioned her architect, Mique, to build eleven cottages and a tower to satisfy her need for rusticity. Thatched roofs, fake lizards on the walls, pigs, sheep, and peasants were all included in this puppet show in which the Queen entertained herself by playing the farmer. This final caprice cost her her throne. Wrapped up in her escapist dreams, she failed to face reality. The more she amused herself, the worse the political situation became. In 1785, the Low Countries revolted, putting the Franco-Austrian alliance severely to the test. Poverty knocked on the doors of her domain. She was deaf and blind to it all. After her difficulties in giving the realm an heir, her unbridled behavior and romantic escapades, whether real or imaginary, offended both Court and people. That same year, the “Diamond Necklace Affair,” a ludicrous conspiracy against her, marked the beginning of her fall from grace. Her private paradise could do nothing to save her. Lies proliferated. The people’s hatred multiplied tenfold. The nobility distanced itself. Despite the courage she was to show on October 6, 1789 before the market women who came to seek her and her family at the Château de Versailles, despite her years of imprisonment, her separation from her children, her isolation, and the dignity of her last moments before the scaffold, nothing could make people forget the heedlessness of her youth. She was to pay with her life, the symbol of her frivolity.

Marie-Antoinette, Queen of France, Queen of Style

Monting-cinq minutes en marchant à petits pas. Il n’en faut pas plus pour passer d’un monde à un autre, pour quitter les dorures du château de Versailles et rallier la simplicité du petit Trianon. Un trajet que la Reine Marie-Antoinette a fait maintes fois pour échapper à la rigidité de la Cour. Ici, à quelques minutes des salons où se disputaient les courtisans, la petite princesse autrichienne née à Vienne le 2 novembre 1755 et devenue Reine de France, le 10 mai 1774 à 19 ans, s’était aménagé un petit paradis intime loin des lourdeurs de l’étiquette qu’elle ne supportait pas. Entre le charme du pavillon Gabriel, les jardins à l’anglaise et la simplicité factice des chaumières du Hameau où elle se plaisait à jouer à la bergère, Marie-Antoinette aimait répéter « Je ne suis pas la reine, je suis moi ». Le petit Trianon, c’est son domaine. Louis XVI le lui avait offert en juin 1774, au début de son règne. L’attention était délicate. Le cadre était idéal pour permettre à sa jeune épouse capricieuse de se libérer du joug sacré de la monarchie. Aujourd’hui, malgré les assauts du temps et ceux de la révolution, ce domaine reste emprunt de la personnalité de la reine. Il reflète ses goûts, témoigne de ses aspirations. « Pour connaître quelqu’un, il faut visiter sa maison. Trianon, c’est la reine », rappelle l’historienne Evelyne Lever, spécialiste de Marie-Antoinette. Ici, dans son domaine réhabilité minutieusement, dans l’atmosphère exquise de ses appartenements ou dans ce jardin qu’elle chérissait, le visiteur fait véritablement connaissance avec cette jolie femme férue d’art et de plaisirs dont l’histoire bascula de la frivolité au martyr.
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