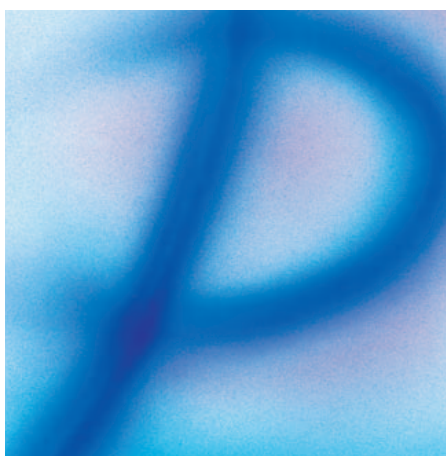


# PHLEBOLOGY

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# LYMPHOLOGY

## AIMS AND SCOPE

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

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

*Phlebology* is scientifically supported by a prestigious editorial board.

*Phlebology* has been published four times per year since 1994, and, thanks to its high scientific level, was included in several databases.

*Phlebology* comprises an editorial, articles on phlebology and lymphology, reviews, news, and a congress calendar.

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**Hugo Partsch**  
Editor in Chief

**D**ear Readers,

*This issue of Phlebology presents an interesting mixture of topics demonstrating the broad variety inherent to our discipline. Clinical physiology is a fascinating field in which Scandinavian medical schools have traditionally played an outstanding role.*

***Einar Stranden** from Oslo, one of the leading specialists in the pathophysiology of the peripheral circulation, gives a clear and clinically orientated review of the transcapillary fluid balance in venous edema and the complex mechanism of the venous pump, supplemented by highly educational illustrations and drawings. Reading the methodological details of measuring transcapillary pressure gradients governing Starling's equilibrium, one can understand that there is still uncertainty and dispute regarding how much fluid will be reabsorbed by the venules and how much by the initial lymphatics, especially in the dynamic situation of the lower leg.*

*A very moving report by **André Cornu-Thénard**, Paris, on the spectacular improvements achieved using compression therapy in African patients with severe lymphedema caused by filariasis. It is amazing what he and his colleagues accomplished in a short time during their charity mission. The impressive pictures clearly show that even self-treatment using sub-optimally applied bandages can produce dramatic improvements and save patients from leg amputations.*

*A review article on recent guidelines in the management of chronic venous disease and the place of venoactive drugs raises some key questions that need to be answered in order to improve protocols for good clinical trials and to draw up future guidelines on these agents. Regrettably, the terms "chronic venous disease" and "chronic venous disorder" are mixed up. Correct definitions can be found in the Veinterm article, reported by Michel Perrin in Phlebology 2009;16:299-305.*

***Cristobal Papendieck**, Buenos Aires, a world authority in pediatric surgery specialized in vascular malformations, gives us an excellent overview of the difficult problem of lymphatic dysplasia in children, which is illustrated by several very instructive pictures.*

*In his article on the treatment of vulvar and perineal varicose veins, **Jean-Francois van Cleef**, Paris, reports on favorable results with sclerotherapy using low concentrations of liquid sclerosant, even in patients with pelvic congestion syndrome. The recommended "class 2" compression stockings refer to the French classification system corresponding to a pressure between 15 and 20 mm Hg, which is lower than in other countries.*

*Two reports by **Michel Perrin**, Lyon, conclude this issue of Phlebology, one on the book on CHIVA by Franceschi and Zamboni and one on the last Meeting of the European Venous Forum held in Antwerp, Belgium, on June 2010.*

*Enjoy your reading!*



# Edema in venous insufficiency

Einar STRANDEN

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## ABSTRACT

Edema is a clinical state characterized by an accumulation of fluid in the interstitial or intracellular space. This accumulation develops when the net transcapillary filtration rate exceeds the lymphatic drainage rate over a period of time. In other words, increased filtration or reduced lymph flow or both. The present chapter focuses on the lower limb edema frequently associated with venous insufficiency. Because the key pathophysiological factor behind this edema is increased distal venous pressure in the upright position, much attention is given to the mechanisms leading to venous hypertension. Furthermore, because understanding edema mechanisms requires knowledge of the factors acting on transcapillary fluid balance, a basic review of these and how they may be measured experimentally is included.

## TRANSCAPILLARY FLUID BALANCE

Fluid exchange between the intra- and extravascular space takes place across the capillary wall. This structure is considered to be semipermeable: impermeable to plasma proteins and freely permeable to water and low-molecular-weight solutes. The interstitial fluid volume (IFV) is normally kept within narrow limits. Edema is likely due to an imbalance in the hydrostatic and colloid osmotic forces across the capillary wall, resulting in net transcapillary filtration exceeding lymphatic flow.<sup>1</sup> Net transcapillary filtration (F) (see “Revision of the Starling principle” at the end) is classically described by the so-called Starling equation:

$$F = CFC [(P_c - P_{if}) - \sigma(COP_{pl} - COP_{if})] = JI,$$

### Keywords:

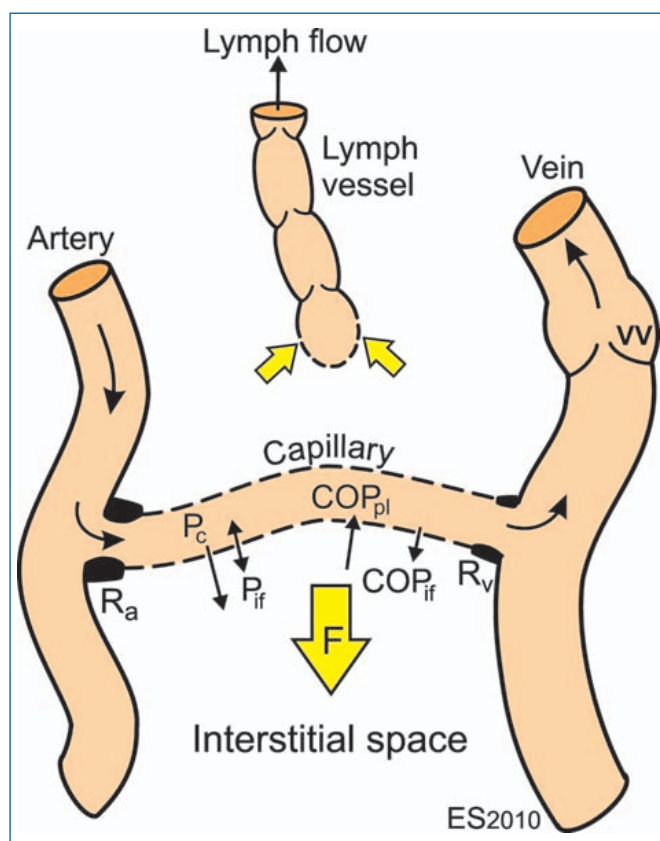
edema, venous insufficiency, transcapillary fluid balance, Starling forces, venodynamics, venous pumps, edema prevention

where CFC is the capillary filtration coefficient, which expresses the capillary permeability, ie, capillary “leakiness”. CFC is the product of capillary hydrodynamic conductivity ( $K_f$ ) and the available capillary surface area (SA). If the gaps between the endothelial cells widen, then  $K_f$  increases, and SA increases if an increased number of capillaries are perfused. An increased

CFC thus increases the rate of capillary filtration at a given net filtration pressure.

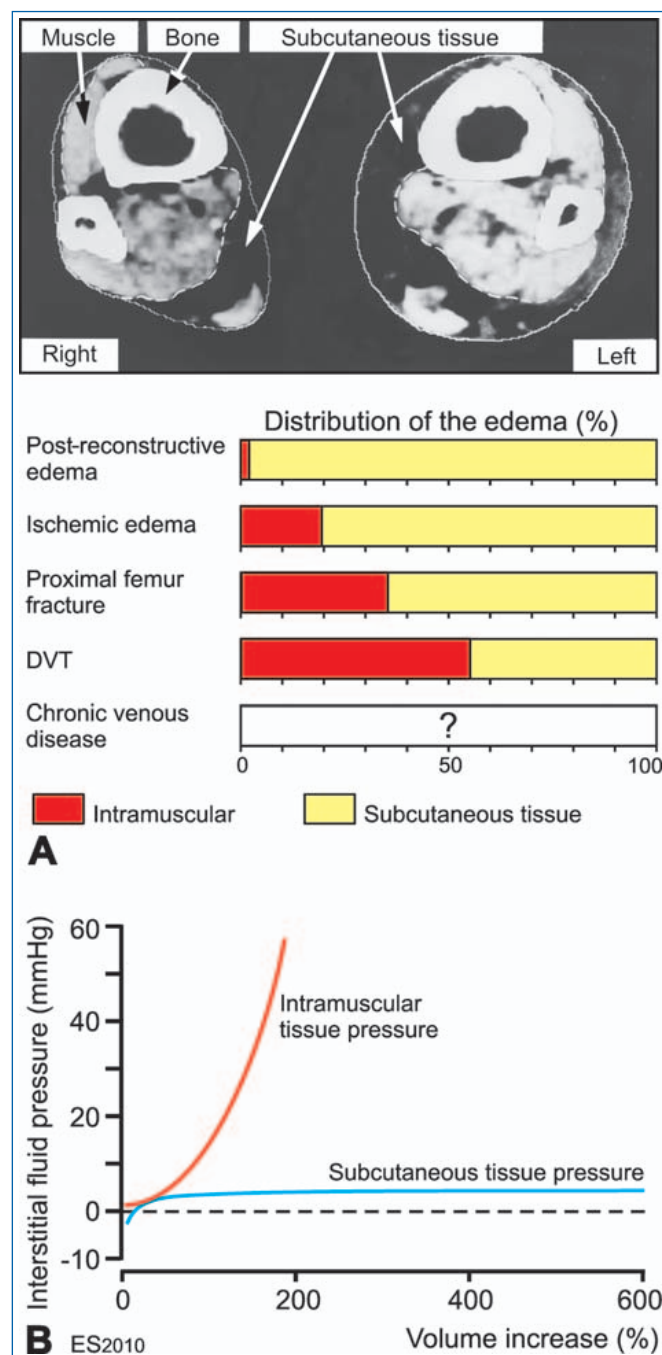
$P_c$  and  $P_{if}$  are the hydrostatic pressures of the capillaries and interstitial fluid, respectively (Figure 1).  $COP_{pl}$  and  $COP_{if}$  are the colloid osmotic pressures of plasma and interstitial fluid. The colloid osmotic pressures are caused by proteins, mainly albumin. Sigma ( $\sigma$ ) is the capillary reflection coefficient, expressing how efficiently the capillary wall is creating an osmotic pressure. For a capillary exchange system that is impermeable to proteins,  $\sigma = 1$ . If proteins pass freely, no osmotic pressure gradient is created and  $\sigma = 0$ . In subcutaneous tissue  $\sigma$  is probably between 0.9 and 1.0.<sup>2,3</sup>

Since the interstitial fluid volume is normally kept fairly constant, this implies that lymph flow (Jl) balances net transcapillary filtration (F).



**Figure 1.** Schematic illustration of the factors involved in transcapillary fluid transport.  $R_a$  and  $R_v$  are the pre- and postcapillary vascular resistances,  $P_c$  and  $P_{if}$  are the hydrostatic pressures in the capillary and the interstitial fluid, respectively,  $COP_{pl}$  and  $COP_{if}$  are the colloid osmotic pressures of plasma and interstitial fluid. VV denotes venous valve, and F is the net filtration of fluid.

The tissue pressure ( $P_{if}$ ) in normally hydrated leg subcutaneous tissue is weakly negative, but may increase to a few mm Hg in subcutaneous edema (Figure 1). In a study on patients with post-reconstructive edema, we found a low subcutaneous  $P_{if}$ , never above 5 mm Hg,



**Figure 2.** A. Distribution of edema within subcutaneous and muscle tissue measured from CT scans of the legs in different types of edema. The depicted cross-sectional CT scan was taken proximal to the ankle in a patient with mainly subcutaneous edema on the left side. B. Very different pressure/volume curves (compliance) are seen in muscle and subcutaneous tissues. For more explanation, see text.



even if subcutaneous tissue volume rose by more than 600% (*Figure 2B*). This indicates a very high compliance of that tissue, especially following the initial steep rise.<sup>4</sup> When edema develops in muscle tissue of the legs, however, the pressure may rise from normally a few mm Hg to well above 50 mm Hg due to the non-elastic fasciae limiting tissue expansion. At these high pressures the risk of tissue necrosis is elevated (ie, compartment syndrome). During volume expansion the two compartments thus behave very differently, as indicated in *Figure 2B*. In this illustration the curve for subcutaneous tissue is based on our study of patients with post-reconstructive edema<sup>4</sup> and the intramuscular pressure on our studies on patients with deep venous thrombosis.<sup>5</sup>

*Figure 2A* indicates the distribution of edema between muscle and subcutaneous tissue from our previous studies on patients with post-reconstructive edema,<sup>6</sup> critical ischemic edema,<sup>7</sup> edema following proximal femur fracture (manuscript in preparation), and leg edema in deep venous thrombosis.<sup>8</sup> The studies were based on CT scans proximal to the ankle (*Figure 2A, top*) and calf. From these scans, for unilateral edema, subcutaneous and intramuscular swelling could be calculated by planimetry and later by computer area measurement, as the difference between the edematous and the contralateral extremity. There was an increasing fraction of muscular edema from the post-reconstructive edema (2%) to deep vein thrombosis legs (55%) (*Figure 2A*). The higher fraction of intramuscular edema in deep vein thrombosis renders these patients more likely to develop high intramuscular pressure, which may provoke compartment syndrome (ie, intramuscular pressure >30 mm Hg), especially in the early edema forming phase.<sup>5</sup> In this group intramuscular  $P_{if}$  in some patients was above 50 mm Hg, but was reduced in the edema declining phase.

To the author's knowledge, systematic studies of edema distribution in patients with venous insufficiency have not yet been carried out. Such studies are desirable, because the filtration load in the upright position may be very large. Vaughan<sup>9</sup> did, however, report subcutaneous edema on CT scans in four patients with isolated superficial venous insufficiency. One might expect, though, that deep venous insufficiency represents a greater challenge in edema formation than a superficial disorder alone, because in the latter group the deep venous pump system may be partly intact.

## INFLAMMATORY SWELLING

Recent research suggests the presence of inflammation in legs with venous insufficiency, probably caused by the long-lasting venous hypertension in the upright position. The inflammation may be responsible for remodeling of the venous wall and valve restructuring.<sup>10</sup> Hemodynamic forces such as blood pressure elevation and mechanical stretching of the venous wall may activate both leukocytes and endothelial cells. Membrane adhesion molecules then facilitate adhesion of leukocytes and their transmigration through the vessel wall into the inflamed tissue. This leukocyte infiltration is followed by remodeling of the extracellular matrix, which again is responsible for the destruction of valves.<sup>10</sup>

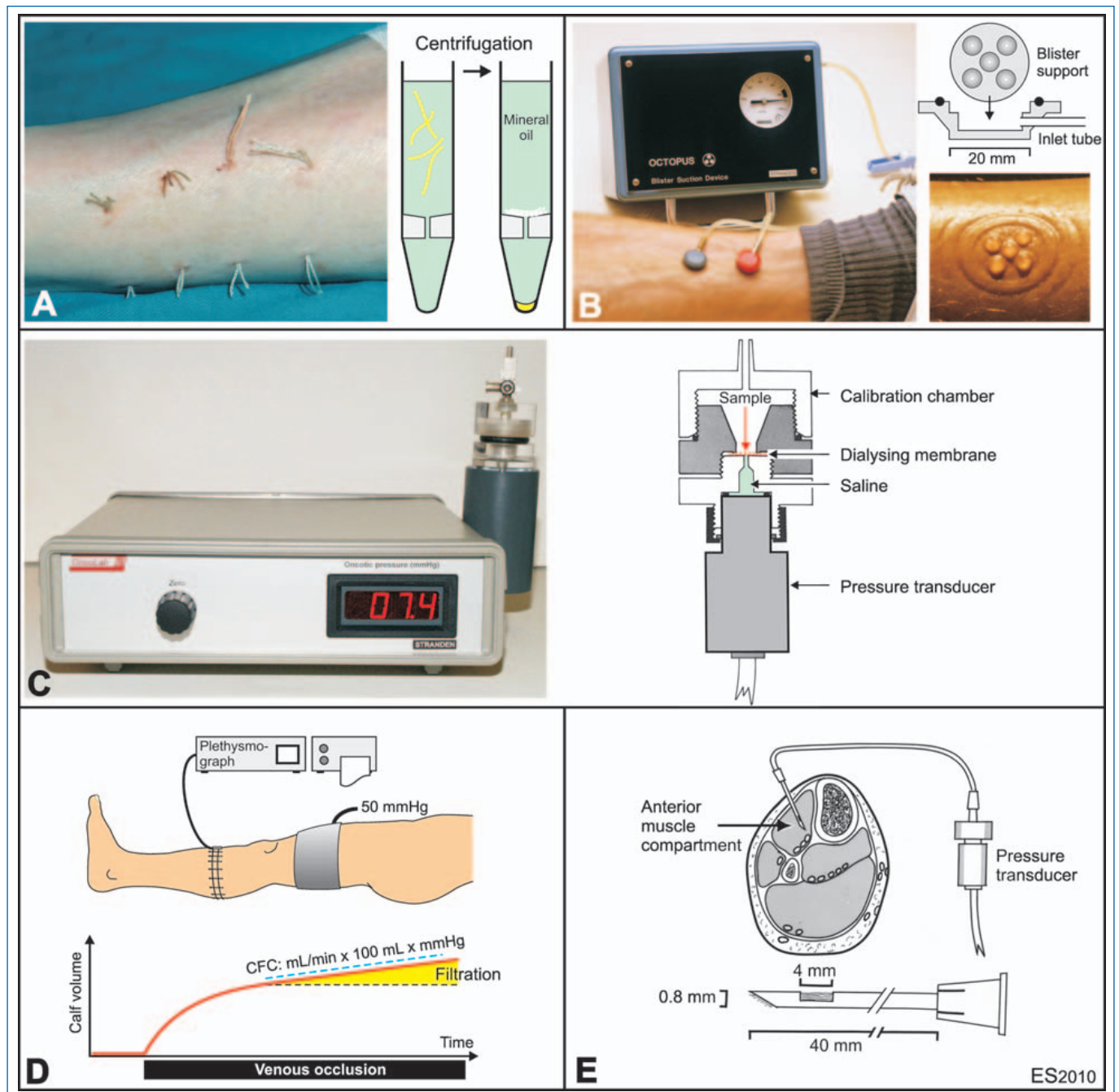
Inflammation also opens the gaps between the endothelial cells. Gap formation is most likely caused by contraction of actin and myosin filaments within the endothelial cells. The gap opening may become very large, greatly enhancing the hydraulic conductance of fluid. It also raises the permeability to plasma proteins into the interstitial space, which reduces the gradient of COP that opposes filtration. In addition, increased gap openings reduce the capillary wall protein reflection coefficient ( $\sigma$ ) to around 0.4, which further reduces the effective COP gradient (*Figure 1*).<sup>11</sup>

## MEASUREMENT OF THE "STARLING COMPONENTS"

### Measurement of interstitial fluid colloid osmotic pressure ( $COP_{if}$ )

The collection of interstitial fluid for protein analysis represents a challenge. We have used three approaches: 1) Direct sampling by catheters, 2) Technique based on fluid equilibrium ("wick method", *Figure 3A*), and 3) Blister method (*Figure 3B*).

The wick method (approach 2) is based on equilibrium between saline-soaked nylon threads (0.8 mm thick, 210 filaments) sewn subcutaneously at the antero-lateral part of the leg and left in place for one hour. During that time the wick equilibrates *osmotically* with the surrounding fluid, but does not reflect the true protein composition of interstitial fluid as the insertion trauma causes considerable efflux of proteins during the first 30 min. The wicks are then pulled out, protruding ends cut off, quickly transferred to centrifugation tubes filled with



**Figure 3.** Methods for studying "Starling components". Interstitial fluid for protein analysis may be collected by either the wick method A or the blister method B, blister suction device, Stranden). C. Colloid osmotic pressure in plasma and interstitial fluid is measured by a specially designed device (OncoLab, Stranden). D. Plethysmographic determination of the capillary filtration coefficient (CFC). E. Subcutaneous and intramuscular pressure may be measured using the "wick-in-needle" technique.

mineral oil and centrifuged. The small sample (2-10  $\mu$ L) is then transferred to an osmometer developed by the author for small samples ("OncoLab", Figure 3C). The osmometer was built with a dialyzing membrane with a cut-off of 30 000 Daltons, similar to that of the endothelial cells of leg capillaries. Interstitial fluid may be collected by a blister technique

(approach 3) as described by Kiistala and Mustakallio.<sup>12</sup> Subatmospheric pressure was obtained by a manually working pump (blister suction device, developed by the author) with two suction cups made of PVC. The 20 mm wide suction cups each has five concave 5 mm holes into which the blisters are formed. Blisters normally appear after 60-90 minutes of suction with a subatmospheric



pressure of 200 mm Hg. After puncture with a needle the blister fluid (approx. 20 µL) is collected in unheparinized glass capillaries and later transferred to the osmometer mentioned above.

### Blood sampling and plasma colloid osmotic pressures (COP<sub>pl</sub>)

Blood from antecubital veins can be collected for analysis. Following centrifugation, colloid osmotic pressure of plasma is measured by the osmometer technique described above.

### Measurement of capillary filtration coefficient (CFC)

CFC may be measured by plethysmography (*Figure 3D*). A venous occlusion cuff is applied proximal to the measuring site. Cuff pressure of 50 mm Hg (or stepwise increase in pressures) is maintained during the measurement. This permits unrestricted arterial flow into the limb while venous outflow is compromised, resulting in an increased leg volume. The volume curve reaches a steady state after approximately 3 minutes. The initial, relatively steep part of the calf volume recording coincides with the filling of veins. After the volume curve flattens, a secondary very small, but distinct increase in volume is measured, which signifies a limb volume increase due to transudation of fluid through the capillary wall. This increase in volume over time denotes CFC, and is expressed as mL/min · 100 mL of tissue · mm Hg increase in filtration pressure.

We have measured CFC for different types of lower limb edemas as listed below. The values refer to contralateral side, or healthy controls in bilateral edema:

	Increase
Post-reconstructive edema <sup>13</sup>	2.0-fold
Deep venous thrombosis <sup>14</sup>	1.4-fold
Idiopathic cyclic edema <sup>15</sup>	2.5-fold
Ischemic edema <sup>16</sup>	2.0-fold
Proximal femur fracture <sup>17</sup>	1.5-fold

There seem to be no studies so far focusing on CFC for patients with venous insufficiency. Capillaroscopy studies using a tracer technique have, however, revealed increased permeability in toe nailfold capillaries in patients with venous insufficiency.

### Interstitial fluid hydrostatic pressure (P<sub>if</sub>)

The interstitial fluid pressure may be measured by the “wick-in-needle” technique. The method is based on

fluid equilibrium between a pressure transducer and the interstitium (*Figure 3E*). Hypodermic needles (0.8 mm OD, 40 mm length) are provided with a 4 mm long side-hole approximately 7 mm from the tip. The needles are filled with cotton thread and sterilized by autoclave. The thread provides a continuous water connection between tissue and needle lumen. The pressure is adjusted to zero before insertion and checked after each measurement. By this technique P<sub>if</sub> may be measured in both subcutaneous and intramuscular tissue.

### Capillary pressure (P<sub>c</sub>)

Blood flow through the capillaries is primarily regulated by variation in the arteriolar/precapillary resistance (*Figure 1*, R<sub>a</sub>). This variation in vasoconstriction also influences capillary pressure, P<sub>c</sub>. Vasoconstriction reduces pressure; the pressure increases during dilatation. Hence, R<sub>a</sub> affects transcapillary filtration—higher pressure means higher filtration.

On the venous side of the capillary there is another site for adjusting vascular resistance R<sub>v</sub> (*Figure 1*). This is smaller than R<sub>a</sub>, but contributes to the regulation of filtration. When this resistance is high, the capillary pressure tends to rise, much the same way as the pressure build-up within a garden hose whose outlet is squeezed. Mean capillary pressure thus depends on the balance between the two, the pre- to postcapillary resistance ratio (R<sub>a</sub>/R<sub>v</sub>). R<sub>a</sub> is typically four times larger than R<sub>v</sub> and capillary pressure is therefore more sensitive to changes in venous pressure than arterial pressure.<sup>18</sup> This is why venous obstruction affects filtration rate so markedly (eg, deep vein thrombosis).

Increase in R<sub>a</sub>/R<sub>v</sub> is an important edema-limiting mechanism when standing up. Arteriolar constriction then normally limits the increase in capillary pressure to about 2/3 of the increase in arterial pressure because of the very potent veno-arteriolar response (VAR). There have been reports that the VAR is reduced in patients with chronic venous insufficiency,<sup>19</sup> which may in itself contribute to the formation of edema, in these patients.

The capillary pressure is not readily available in a clinical setting. However, because of the low post-capillary resistance, the level of venous pressure may to some extent mimic capillary pressure. High venous pressure is transmitted retrogradely to the capillaries; low venous pressure permits P<sub>c</sub> to remain relatively low. Because of the key role of P<sub>c</sub> in influencing transcapillary filtration,

and its dependency on venous pressure, a large part of this chapter is about the venodynamics of the lower limb in healthy limbs and in venous insufficiency.

## VENODYNAMICS OF THE LOWER LIMB

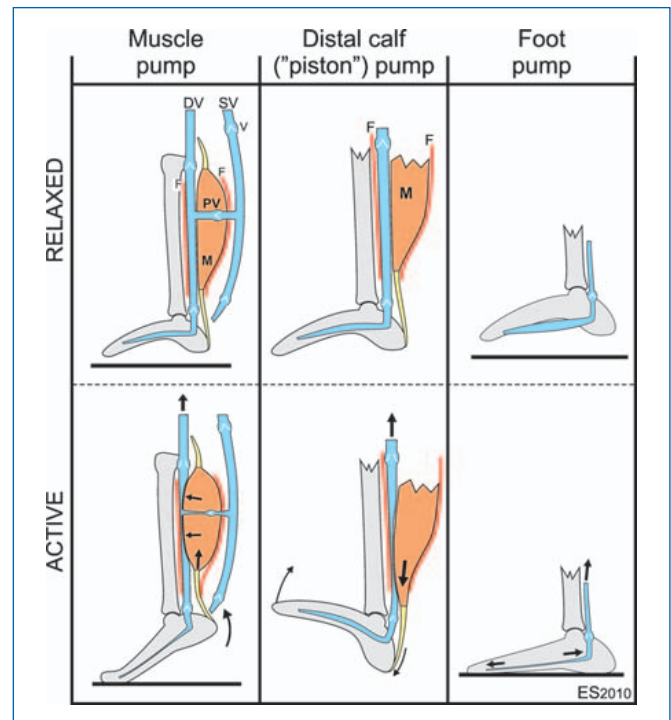
The venous system in the lower limb is composed of a subcutaneous superficial system, a deep system within the muscular fasciae, and connecting perforating veins. Dysfunction, mainly of the valves, may occur in each system and in combination. The great variability in venous anatomy and function makes pathophysiological understanding rather complex. The following description of four clinical conditions is therefore simplified. The pressure and flow curves of the examples summarize numerous published studies, eg, studies of venous pressure by CC Arnoldi,<sup>20-27</sup> the studies of pressure and flow by RI Björdal,<sup>28-34</sup> and noninvasive investigations.

## THE VENOUS PUMPS IN THE LOWER LIMB

In the upright position a significant amount of blood is translocated to the lower extremity veins. During quiet standing, the muscles in the lower extremity contract and relax rhythmically, causing a swaying motion of the body. During muscular contraction blood is squeezed in a proximal direction, and the veins are refilled during the relaxation phase. This cyclic muscular action and the venous valves form a powerful pumping system aiding the venous return to the heart.<sup>35</sup> The return of blood from the extremity does not totally depend upon properly functioning pumps; cardiac activity alone is sufficient to maintain return flow (vis-a-tergo blood flow). The pump system is, however, of vital importance in preserving the integrity of the microcirculation, by reducing distal capillary pressure when standing.<sup>36</sup>

Pumping occurs in all veins containing valves and is subject to oscillating surrounding pressure. Even without functioning venous valves, leg motion, by virtue of venous compression, promotes venous return.<sup>36</sup> The venous pumping system may be divided into three portions with different working mechanisms (Figure 4):

1. The muscle pumps<sup>27</sup>
2. The distal calf ("piston") pump<sup>35-37</sup>
3. The foot pump<sup>35, 38-40</sup>



**Figure 4.** Schematic illustration of the venous pump systems of the foot and calf in the relaxed and active states. The muscle pump unit consists of muscles (M) ensheathed by a common fascia (F) and veins within the same compartment. Contraction of the calf muscles (muscle systole), as in plantar flexion of the ankle joint during walking (below), expels blood into the proximal collecting vein. During relaxation (muscle diastole, above) the blood is drained from the superficial veins (SV) into the deep veins (DV) in addition to the arterial inflow, making the pump ready for the subsequent ejection. V: venous valve. The distal calf ("piston") pump is indicated in the middle. On dorsiflexion of the ankle (passive or active), the bulk of the calf muscle (M) descends within the fascial sheath (F), and expels blood in the distal veins like a piston. The foot vein pump is illustrated on the right. The plantar veins are connected like a bow-string from the base of the fourth metatarsal in front to the medial malleolus. On weight-bearing the tarso-metatarsal joints are extended and the tarsal arch is flattened. Thus the veins are stretched, causing them to eject their blood content.

During normal walking the three vein-pumping systems are synchronized to form a complete network of serial and parallel pumps aiding the return of blood towards the heart. The mechanism may be summarized as:

1. Before weight-bearing the ankle is dorsiflexed, emptying both the anterior muscle compartment (muscle pump) and the distal calf ("piston" pump).
2. At weight-bearing the foot veins are emptied (foot pump).
3. The plantar flexion of the foot to ensure forward locomotion activates the proximal calf pump of the posterior muscles (muscle pump).

### Normal venodynamics

In the upright position, the hydrostatic vascular pressure is greatly increased in the lower part of the body. The increase is similar in arteries and veins, and should per se have little effect on the overall blood flow through the lower limb. However, the very potent veno-arteriolar response initiated by distension of veins, at transmural pressures above 25 mm Hg, causes arteriolar vasoconstriction which reduces blood flow in the dependent limb by approximately 50%.

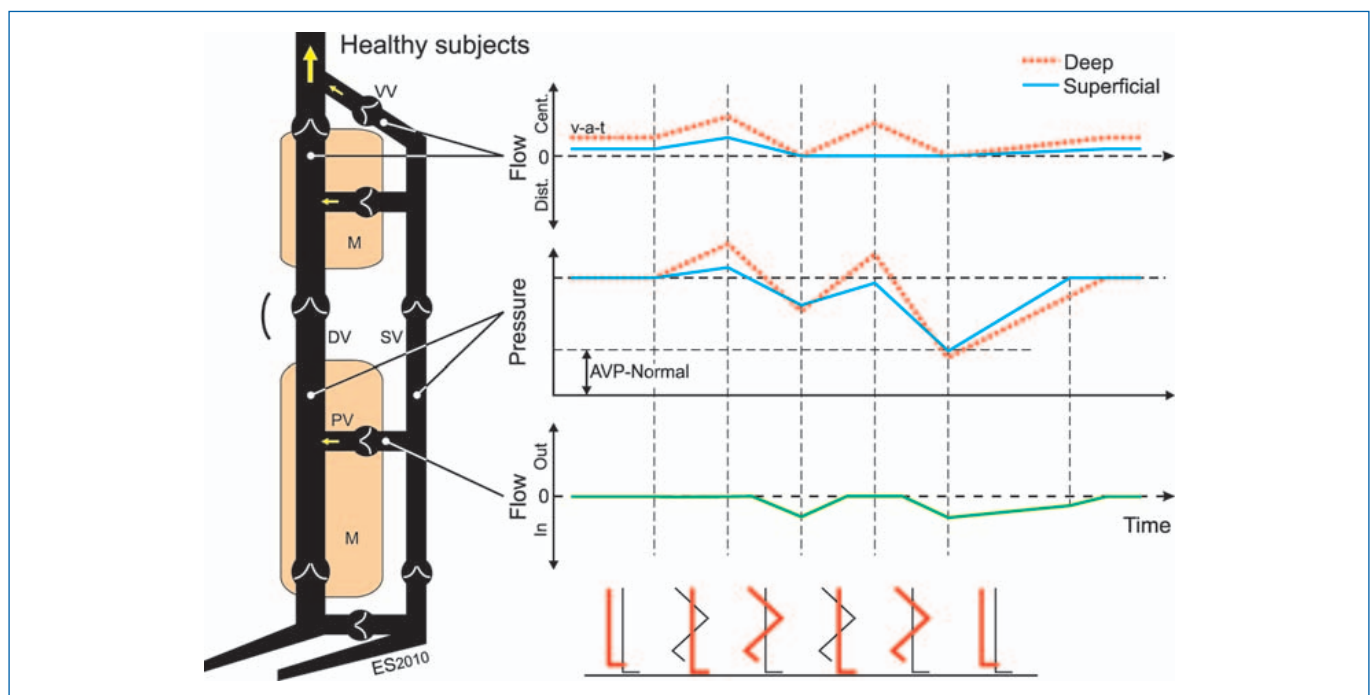
In passive dependent legs, the pressures in all veins at the same height are equal, and are approximately equal to (slightly higher than) the hydrostatic fluid pressure in a column of blood from the point of measurement to the level of the heart. In this state, phlebography indicates that blood returns to the heart through both deep and superficial veins (*Figure 5*).<sup>27</sup>

Muscle contraction (systole) at weight-bearing is accompanied by a rise in pressure in all veins of the limb (*Figure 5*). Within the muscular compartment the

increase is largest, typically 60-70 mm Hg, three times higher than the rise in superficial veins. During systole the muscle contraction may cause venous outflow obstruction, further enhancing deep systolic vein pressure. In extreme cases the pressure is raised by more than 200 mm Hg in a fraction of a second.<sup>27</sup> The systolic venous pressure increase in the collecting conduits is smaller (appr. 20 mm Hg, popliteal vein), and the resulting pressure gradient rushes blood from calf to thigh. Competent valves prevent distal flow or outward flow through the perforators. In addition, the higher deep venous pressure does not allow inward flow through the perforating veins during systole.

During muscle relaxation (diastole) the pressure falls below that at rest, especially in the deep veins (*Figure 5*), ensuing an inward flow through the perforating veins. In healthy subjects patent vein valves prevent flow in the distal direction in both deep and superficial veins.

In repeated muscle contractions, as in normal walking, the systolic pressures in the deep and superficial veins



**Figure 5.** Schematic representation of normal anatomy and dynamics of lower extremity veins. The simplified venous system consists of superficial veins (SV), deep veins (DV) within muscular compartments (M) of the calf and thigh, and perforating veins (PV). Venous valves (VV) ensure unidirectional flow of blood in central (cent.) direction in deep and superficial veins, and inward direction in the perforating veins. The diagram on the right depicts idealized pressure and flow characteristics of different areas of the veins during steady state at passive dependency (the leftmost walking-phase symbol) and two subsequent walking cycles—during weight-bearing (muscle systole) and elevation of the leg (muscle diastole). The red line indicates the extremity described. In a passive relaxed state the blood is forced almost solely through the deep system by the pumping action of the heart, often referred to as the vis-a-tergo (v-a-t) blood flow. AVP-Normal is the normal ambulatory venous pressure in superficial veins.

will gradually fall and fluctuate at levels considerably below the pressures during a single contraction (Figure 5). The superficial venous pressure in the ankle region during walking is typically 30 mm Hg and is referred to as the ambulatory venous pressure (AVP).

### Superficial and perforator dysfunction

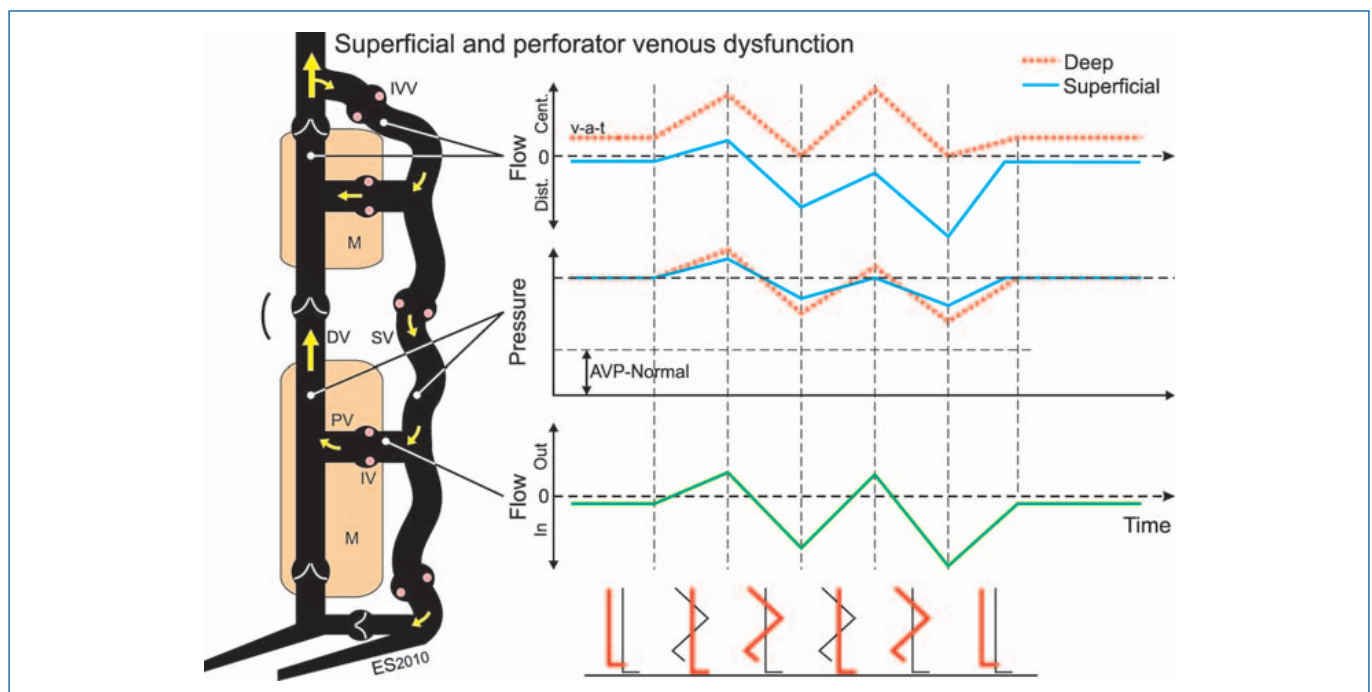
Relatively few patients referred to hospital have dysfunction of superficial veins combined with normal valvular function in the perforating veins. In this group the calf vein pumps are normal and ambulatory venous pressure in the deep veins at the ankle is low, which explains the absence of edema and trophic changes in the skin.<sup>27</sup>

Most patients with venous dysfunction have incompetent valves in both superficial and perforator veins. This causes a significant reflux in the superficial vein trunk and a smaller reduction in superficial venous pressure than normal, often referred to as "ambulatory venous hypertension". Although the venous pumps may be normal, the pressure in the deep veins is rapidly restored to the blood column pressure upon standing, because of backfill from the superficial veins (Figure 6). The clinical picture is varicose veins and sometimes leg

edema, often in combination with trophic changes. The more extensive and the more distal the venous reflux, the greater the probability of ulcer formation.

In steady state at passive dependency blood flows primarily through the deep veins, and the pressure in the veins corresponds, as in healthy subjects, to the hydrostatic pressure from the blood column to the heart. Consequently, the pressure at rest is not affected by valvular dysfunction. Weight-bearing with muscular contraction causes a steep rise in deep venous pressure, as in healthy subjects. The increase in superficial venous pressure is considerably higher than normal, due to the extensive retrograde flow from the deep venous system through incompetent dilated perforating veins in muscle systole.

During relaxation the pressure in the muscular deep veins falls abruptly, and to a larger extent than in popliteal and superficial veins. This causes an inward flow through the perforating veins, whereas reflux from the popliteal vein is prevented by valves. The absence of competent valves in the superficial system allows retrograde flow, most often through the saphenofemoral junction. Bjordal<sup>28</sup> quantified this reflux in the



**Figure 6.** Schematic representation of patients with superficial and perforator venous dysfunction. The most striking difference from healthy subjects is the distal (dist.) blood flow in the superficial veins due to incompetent venous valves (IVV). During ambulation there is oscillating flow in incompetent perforators, outward during muscle contraction and inward at muscle relaxation. Furthermore, the state is characterized by less reduction in venous pressure in superficial veins during walking ("ambulatory venous hypertension"). Annotations are as in Figure 5.



superficial main trunk during normal walking as an average of 300 mL/min, and thus verified the hypothesis of “a private circulation” as suggested by Trendelenburg. According to his finding a large fraction of the blood from the deep venous trunk is “spilled” through incompetent superficial veins and re-enters the deep veins at a lower part of the limb.

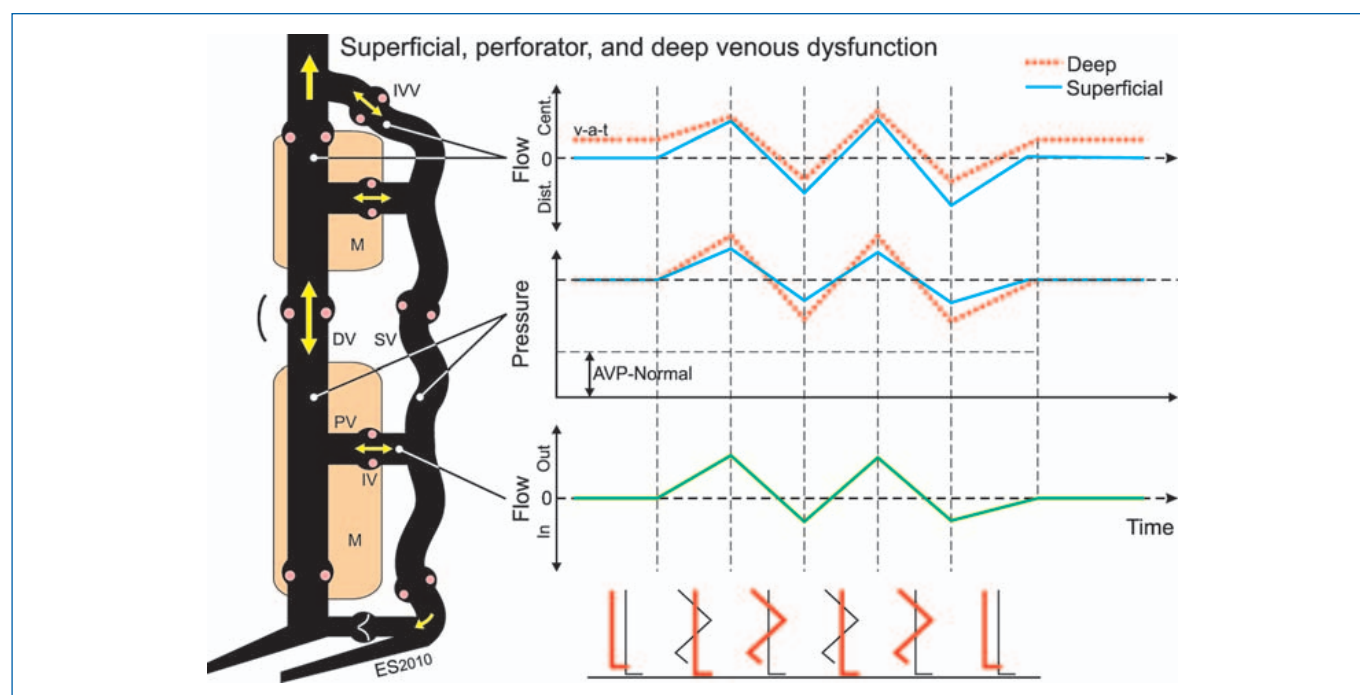
The high retrograde flow in superficial veins during walking refills the deep veins during muscle diastole, greatly enhancing the venous pump capacity by increasing the expelled volume. The net increase in expelled volume is, however, due to the superficial retrograde circuit and does not represent effectively increased drainage from the extremity. The result of this rapid back-flow is that the systolic pressures in the deep and superficial ankle veins remain high during walking.

Proximal occlusion of the superficial veins normalizes ambulatory venous pressure in these veins and the pressure recovery time after standstill. This effect is the dynamic basis for the detection of superficial venous dysfunction by venous pressure measurements. The pressure test does not, however, assess the patency of the perforating veins.

### Combined superficial, perforator, and deep dysfunction

The deep, perforating, and superficial veins of the leg may all be more or less involved in skin ulcer formation. Deep venous incompetence is usually secondary to previous deep venous thrombosis, although venous dilatation and subsequent valvular insufficiency may also be the result of increased pressure and flow load from isolated superficial insufficiency. The latter condition may be reversed following treatment of the superficial veins. The venodynamics are characterized by ambulatory venous hypertension in both superficial and deep veins. In this state the capillary pressure in the upright position is high, the only relief being elevation of the legs.

During walking, the pressures in superficial and deep veins oscillate around the level during passive standing, ie, with minimal net reduction in ambulatory venous pressure (*Figure 7*). Flow in perforating veins is bi-directional, with an outward net flow, as opposed to the situation with superficial and perforator incompetence only (*Figure 6*). The flow in superficial veins may be bi-directional, without net flow, or a net flow directed centrally or distally.



**Figure 7.** Venodynamics in patients with superficial, perforator, and deep venous dysfunction. During walking, the pressures in superficial and deep veins oscillate around the pressure in the passive upright position, ie, with minimal net reduction in ambulatory venous pressure. Flow in perforating veins is bi-directional, with outward net flow, the opposite of what is found in patients with superficial and perforator incompetence only (*Figure 6*). Annotations are as in *Figures 5 and 6*.

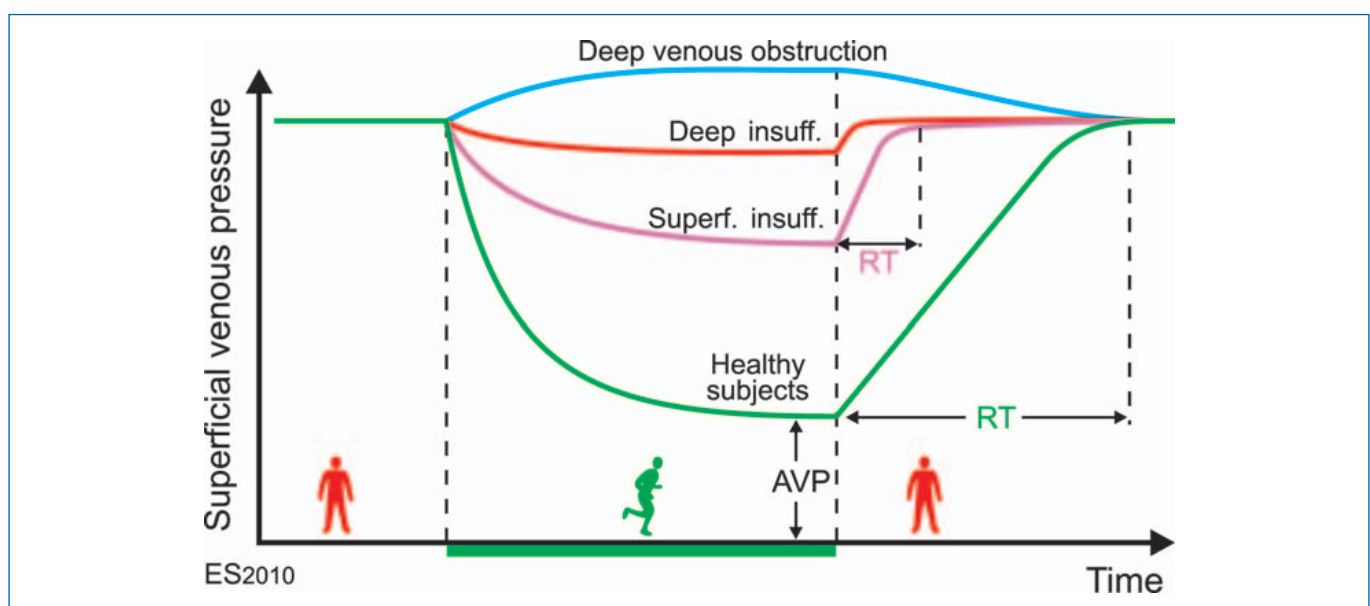


### Outflow obstruction

Venous outflow obstruction may be the result of occluded or partially recanalized veins subsequent to deep vein thrombosis. In proximal (outflow) venous thrombosis, increased outflow resistance and venous pressure during muscle contraction may lead to venous claudication (*Figure 8*).

Ambulatory venous hypertension often leads to distension of the perforators and valve dysfunction. The pressure and flow is then directed towards the superficial veins, which may become the principal venous conduits. A resulting overload of the superficial veins may lead to dysfunction, including varicose veins.

*Figure 8* shows mean pressure curves during and after ambulation in the four states listed. The ambulatory venous pressure typically increases from healthy subjects to patients with superficial and perforator dysfunction to those with additional deep venous dysfunction and to those with deep venous obstruction. These venous pressure profiles, along with the recovery times (time from end of walking until the vein pressure reaches the level of passive dependency), with and without superficial venous occlusion (occlusion test), form the diagnostic basis of venous pressure measurement.



**Figure 8.** Schematic illustration of the superficial venous pressure at rest, and during ambulation. The ambulatory venous pressure (AVP) represents the lowest mean pressure during walking at the site of measurement, and the recovery time (RT) is the time interval between the termination of walking until the vein pressure reaches the pressure level at passive dependency. In healthy subjects, AVP at the distal calf is about 30 mm Hg and RT is 20-30 s.

### REVISION OF THE STARLING PRINCIPLE

This traditional form of Starling's principle has recently been challenged. In a recent review article,<sup>41</sup> Levick and Michel argue that sustained fluid absorption into the capillaries from the interstitium does not normally take place (except in a few specialized regions like the kidneys and intestines). Rather there is merely a unidirectional fluid shift from the capillaries to the lymphatics via the interstitium. The structural basis for this idea is the endothelial glycocalyx small pore system covering the relatively wider intercellular clefts that form the semipermeable membrane of the capillary wall. Hence the area for colloid osmotic pressure build-up outside the

capillaries is not in the interstitium; it lies within the intercellular clefts. This has important functional consequences. During filtration, the interstitial proteins that may previously have entered the intercellular clefts are washed into the interstitium, effectively reducing the COP just underneath the glycocalyx to a very low level and rendering it insignificant in the fluid balance, and the filtration force is reduced. In the opposite situation, during the initial phase of absorption, interstitial proteins are trapped in the cleft, like in a sieve, thus building up a large COP which reduces and may stop the fluid transport. These new ideas challenge the relevance of the  $COP_{if}$  presented in studies so far.

## SUMMARY

### FACTORS INVOLVED IN VENOUS EDEMA FORMATION

- Edema promotion: Valvular incompetence and increased ambulatory venous pressure in the leg are the most important edema-promoting factors. Increased venous pressure increases capillary pressure and hence transcapillary filtration.
- Superficial insufficiency alone does not necessarily lead to leg edema—the key factor is the state of the venous pump systems of the foot and leg.
- Edema promotion: Local inflammation, assumed present in advanced venous insufficiency, further promotes edema formation through reduced precapillary resistance and increased capillary “leakiness”.
- Edema counteraction: Increased lymphatic drainage may, up to a certain level, cope with the extra filtration load.
- Edema counteraction: The extra filtration dilutes and “washes down” interstitial proteins through the lymph vessels, hence reducing effective interstitial fluid colloid osmotic pressure, and may increase the colloid osmotic absorption force by 5–6 mm Hg.
- Edema counteraction: Primarily at low and moderate capillary blood flow, the plasma becomes more concentrated due to increased fluid filtration. This leads to a rise in capillary plasma colloid osmotic pressure, probably in the order of 5–15 mm Hg, further increasing the colloid osmotic absorption force.
- Edema counteraction, interstitial fluid pressure in subcutaneous tissue: Initial steep rise in pressure (3–5 mm Hg) counteracts edema formation, but no further increase in pressure occurs as edema develops.
- Edema counteraction, interstitial fluid pressure in muscle tissue: Due to the non-elastic fasciae, the intramuscular tissue pressure may rise considerably, thereby counteracting edema formation within that tissue.

## ACKNOWLEDGEMENT

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# Discovery of lymphatic filariasis during a humanitarian aid mission to Burkina Faso

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## SUMMARY

Lymphatic filariasis affects 120 million persons worldwide, a third of whom live in Africa. It is caused by threadlike parasitic worms transmitted to humans by the bite of mosquitoes which are vectors of the disease. One of the effects resulting from a mosquito bite affecting a lower limb is the occurrence of lymphedema. When the latter becomes massive, it is known as elephantiasis. The purpose of the December 2009 aid mission was to treat patients with this disease by using compression therapy. Also, it was planned to study, in cooperation with the local health authorities, the possible setting up of a specific care facility to train nurses in the different methods of compression therapy, which remarkably is missing from the therapeutic arsenal in Burkina Faso. These nurses would care for the many patients affected: over 150 identified in 2000 in the city of Kaya alone, without counting cases of hydrocele, and involvement of the upper limbs, genital organs, and breasts.

The aim of our humanitarian aid mission was to take care of all cases of lymphatic disease using appropriate treatments.

Since 1998, the not-for-profit organization Contacts has been going to Kaya, Burkina Faso, a city located some 100 km north-east of the capital, Ouagadougou, in the framework of exchanges between young French aid workers and the Burkinabé (*Figure 1*). Contacts is non-political and non-



*Figure 1. Location of Burkina Faso in West Africa*

## Keywords:

Burkina Faso, elephantiasis, lymphatic filariasis, compression therapy.





**Figure 2a.** Patient 1 - Bilateral elephantiasis, right panel (January 2009).



**Figure 2b.** Patient 1 - Detailed view of right foot. Verrucous swelling on the dorsal aspect of the foot overlaps anteriorly and covers the toes.

denominational, which allows us to work with partners whether Christian, Moslem, or Animist. Three avenues of exchange with the population have been initiated: education and teaching, art and culture, and hygiene and health. Achievements hitherto are detailed on the French-language Web site [www.kontacts.org](http://www.kontacts.org).



**Figure 3a.** Patient 2 - Elephantiasis of the left foot



**Figure 3b.** Patient 2 - The first bandage

In January 2009, during another stay in Kaya, we discovered two young people with enormous lymphedema (Figure 2a, 2b and Figure 3a, 3b). Failure to recognize this vascular infectious disease led us to a surprising discovery, for which currently there are few details in our European manuals: lymphatic filariasis.

## LYMPHATIC FILARIASIS

### Epidemiology

Lymphatic filariasis is a threat in nearly 80 countries. Of 120 million persons already affected, over 40 million are seriously disabled. A third of those afflicted live in Africa, another third in India, and the remainder in South Asia, the Pacific islands, and in South America.<sup>1</sup> Lymphatic filariasis is the second leading cause of permanent disability worldwide,<sup>2</sup> in particular due to the fact that



generally it is acquired in early childhood ([www.filaria.org](http://www.filaria.org)). It results not only in major physical disabilities, but also in psychological and social ones. The social life of these young people is especially disastrous. The disease is considered as a curse, those afflicted hide and so have no family life, do not attend school, and have almost no friends.

### Cause

Lymphatic filariasis is caused by threadlike parasitic worms, *Wuchereria bancrofti* and *Brugia malayi*, which reside in the lymphatic system and for which humans are the only definitive host.

### Transmission

The disease is spread by mosquitoes (Figure 4).<sup>1-4</sup>

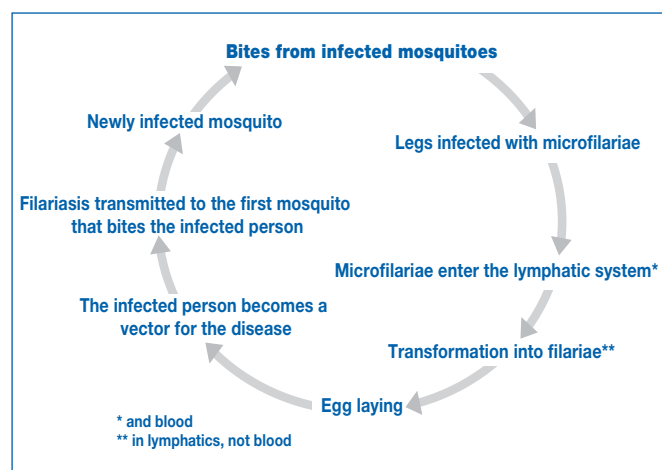


Figure 4. Transmission of the disease and the vicious circle.

### Signs

The disease usually develops in adults. In its most visible forms, lymphatic filariasis causes elephantiasis of the legs or arms, the genital organs (hydrocele), the vulva, or breasts. Subclinical alterations, in particular renal, are common.

### Diagnosis

Several methods of diagnosis are possible: the most conventional consists in examining a blood sample and visualizing the microfilaria. This examination must be conducted when the parasites are circulating in the bloodstream, ie, at night. A simple, sensitive, and specific test to detect the antigen, the ICT filariasis test, detects infection within a few minutes ([www.filaria.org](http://www.filaria.org)). Ultrasonography can visualize the adult worms, which can be 10 cm long.

### Treatment

A worldwide program of eradication of this disease was launched by the WHO in 2000.<sup>2</sup> Only a short time ago, only 48 out of 81 countries were applying these recommendations. The primary objective of treatment is to interrupt transmission of filariasis by administration of massive amounts of two medicinal products in a single dose. Three microfilaricides—diethylcarbamazine, ivermectin, and albendazole—can be prescribed in combination (called “DIA” treatment if all three are used). The macrofilaricide doxycycline at a dosage of 200 mg/day for 8 weeks can be used for individual treatment, but not mass eradication.<sup>5</sup> In Burkina Faso, the WHO program is re-launched every 2 to 3 years for treatment of the younger generations. The difficulty lies in reaching populations in isolated villages.

Once the disease is established, nothing really can be done: lower limb elephantiasis, hydrocele, swelling of the genital organs, and breast hypertrophy can take on proportions that today are difficult to imagine. In the city of Kaya alone over 600 cases of hydrocele, and 150 of elephantiasis of the foot, 30 of the arms, and 20 involving the breasts were identified in 2008.

For doctors who are vascular specialists, compression therapy, combined with sessions of manual lymphatic drainage and night-time postural drainage is the basic treatment for reduction of lymphedema. Our discussions with people at the Regional Hospital Center of Kaya suggested that compression therapy is unknown. Apart from elevating the affected limb, the only treatment applied in an emergency or when there are ulcer complications is amputation! This is probably also true in other countries of western Africa. The reason may lie in the fact that after the departure of the Europeans during the 1960s, compression therapy was abandoned, probably as the result of a lack of clinical supplies. Lastly, it should be noted that old case reports indicate that MPFF (micronized purified flavonoid fraction, Servier, France) seemed to be really effective on this type of lymphedema.<sup>6</sup>

## HUMANITARIAN AID MISSIONS 2009-2010

### January 2009: A discovery

This mission to “investigate areas of additional intervention” for Kontaks revealed no venous lymphatic disorder of the limbs. We did not imagine that such a

disease could exist in a population which has produced world class athletes, but through Father Theophile, the parish priest, we discovered two young men with massive lymphedema (*Figures 2a, 2b and 3a*).

In the first patient the disease was extensive and in particular affected both legs, preventing him from walking unaided (Patient 1, *Figure 2a*). The edema of the dorsal aspect of his right foot concealed his toes (Patient 1, *Figure 2b*). The second (Patient 2, *Figure 3a*) arrived on crutches.

Compression therapy was immediately initiated in both patients. Biflex® bandages (Laboratoires Thuasne), which we had brought at the request of a nurse during a previous trip, were applied (*Figure 3b*).<sup>7</sup> The improvement during the few days prior to our return to France was remarkable. Subsequently, videoconference monitoring (our thanks to the Skype Phone Service) was used to assess medical and psychological improvement in the condition of these two young patients (*Figure 5*).



**Figure 5.** Same patient (Patient 1) as in fig 2a and 2b, 6 months later (photo sent by video transmission)

### December 2009: A revolution

The aim of this trip was threefold: To see these two patients again, to treat other patients and, in particular, in cooperation with the local health authorities, to study the feasibility of creating a specific health care unit for treatment of elephantiasis. The group comprised 3 vascular specialists, 2 nurses, and 2 young men about 25 years old. Onsite expenses were paid for by a donation, but each person paid for his own airline ticket, in accordance with the principles of Contacts. In terms of preventive measures, each of us brought about fifteen kilos of bandages and elastic stockings, since it is not possible to find these items locally.

On our arrival, we were able to observe that the progress made by our two patients, followed up over the Internet, was in fact real.<sup>8</sup> They had resumed almost normal activity and self-sufficiency enabling them to walk easily (*Figure 6*). Much to the surprise of those who had not yet seen them, these 2 young men were taking care of themselves, performing careful hygienic care, and massages similar to those of lymphatic drainage, with karité (shea) butter (*Figures 7, 8, 9*), and in particular application of 3, 4, or 5 Cotton Short Stretch, Biflex 17, Urgoband, Medica 315 or Somos bandages (provided by the manufacturers prior to our departure). Very often, this bandage was covered with a medical compression stocking for purely cosmetic purposes. In these cases, an extensor often helped in placing the stocking over the bandage (*Figure 10*).<sup>9</sup>



**Figure 6.** Our two young patients were self-sufficient starting in August after 8-month treatment (photo of December 2009)





**Figure 7.** Same patient (Patient 1) performing massage similar to lymphatic drainage. Note the large decrease in size of the papilloma on the ankle joint.



**Figure 8.** Massaging with shea butter on left foot and leg: Note the position of both hands (Patient 1).



**Figure 9.** Detailed view of papillomatosis of left foot (December 2009).



**Figure 10.** Use of an extensor for placement of an elastic stocking over 2 bandages.

These two patients, who became “super nurses”, truly surprised us because, apart from a succinct demonstration that we gave them a year previously, they had not received any formal training. Everyone was also amazed by the excellent acceptance of such a bandage, so inelastic<sup>10,11</sup> and thick, in a country with high temperatures. During this stay, many other patients were examined, including a thirty-year-old male who presented with massive elephantiasis manifest as overlapping redundant skin folds, associated with a wound about 40 cm<sup>2</sup> in size (Patient 3, Figure 11).



**Figure 11.** Patient 3 - Elephantiasis with redundant skin folds, associated with a wound of about 40 cm<sup>2</sup> (December 2009). Patient was scheduled for amputation.

For the onsite medical staff, in particular Dr Mohamed Sidi, Deputy Medical Director of the District Hospital of Kaya, this compression therapy was an absolute novelty. He qualified it as “revolutionary”.

Enthusiastic, he encouraged us to continue the idea of creating a dispensary reserved for elephantiasis. The hospital might be able to make available to us a small building, the old maternity clinic unused for 5 years, which would have to be renovated (*Figures 12, 13*). It might also assign us a nurse whom we would train, and who, in our absence, would be in charge of maintaining continuity of care.

Upon our return, we received the following estimates: 8000€ for renovation of the building, 6000€ for installation costs, probably 4000€ for computer equipment, and 2000€ for annual operating costs. At the



Figure 12. Old hospital maternity ward, unused, to be renovated.



Figure 13. Need for renovation is obvious.

same time, we learned that we had received a 2500€ grant from the Ministry of Cooperation and French Culture (see [www.kontacts.fr](http://www.kontacts.fr)).

#### April 2010: Disappointment followed by joy

Our trip was planned to discuss these estimates for the renovation, while agreeing that some work could be postponed. Dr Sidi, still enthusiastic since he was participating in the setting up of the first center for elephantiasis in Burkina Faso, again welcomed us, but with less eagerness: A note from the Ministry of Health dated 7 April 2010, “*prohibited all foreign doctors from performing medical consultations without authorization signed by the Minister himself.*” Our enthusiasm collapsed, but just for a moment. As in December, we could perform consultations in a building made available to us by the church, and to speed up the implementation of the project we decided with Dr Sidi to create a Burkinabé Kontacts not-for-profit organization, which will make it possible for us to work in the hospital as soon as it is officially recognized.

This somewhat puzzling situation did not allow us to plan renovation of the building before the summer of 2010. Nevertheless, the planned operations were discussed:

- The dispensary would be the site from which an all-terrain vehicle would be dispatched to bring to the clinic patients with elephantiasis, identified by nurses in the corresponding villages. This vehicle could also be used by a specialist nurse to visit the bedside of patients unable to travel (so purchase of a vehicle and two motorcycles had to be added to the planned budget, ie, 4200€).
- On arrival, a team of nurses and doctors would examine the patients, explain the disease, check that they had in fact taken the treatment for the parasitic disease, start treatment of lymphedema, and explain how to use the bandages in the following weeks. The patients would then be driven back to their village.
- Villages would be visited in rotation, according to the instructions of the nurses working there (identification of the different disorders was performed regularly).

Medically, there were three undeniable reasons for satisfaction:

- The previous two patients (1 and 2) are improving, we continue to be impressed by their ability to perform



their own care themselves (*Figure 14*). They made an extensor to make it easier to put on the medical compression stockings. We will show them how to put on several bandages, one over the other, to obtain stronger and more inelastic compression, and so more effective reduction of lymphedema (*Figure 15*).<sup>12</sup>

In the thirty-year-old patient (Patient 3, *Figure 11*), the ulcer healed but lymphedema of the foot worsened (*Figure 16*). The reason seemed obvious to us: the bandage had covered the ulcer zone but not the foot. This patient was to return to the consultation every day during our stay, but we never saw him again.



**Figure 14.** April 2010, the same patient's legs, (Patient 1) ie, after a year and half of self-care.



**Figure 15.** Wrapping of three 20 mm Hg elastic stockings, ie about 60 mm Hg.



**Figure 16.** Patient 3 - April 2010: The 40 cm<sup>2</sup> wound has healed, but lymphedema has markedly progressed.

The first two patients took it upon themselves to explain to other patients how important it is to comply with treatment. In our absence they took care of other young patients who had the same problem: oral explanations, care, bandages, and distribution of a document they themselves had written. In no time at all, they became specialists in reduction of elephantiasis, an unforeseen and major event. Consequently, Dr Sidi suggested the principle of making them head the dispensary.

In the midst of our medical and political concerns, and in temperatures of 40°C in the shade, we were nevertheless able to attend to other areas of interest to Contacts: contacts with schools (*Figure 17*), contests to collect



**Figure 17.** Contact with teachers to give them school supplies and to ask what they need.



plastic bags strewn in large numbers in streets, fields, and even in the schools (*Figure 18*), help teaching reading and writing in the evening for the youngest children.



*Figure 18. Collection of plastic bags by school children.*

### Videoconference monitoring: The unimaginable happens

As before, videoconferencing was used every Wednesday. In May, the use of a 3G key improved image and sound quality. We understood that the actions of our youthful assistants continued to increase. By going through the city, other young people with the disease were discovered. They made every effort to convince them of the need to be treated by wrapping using several bandages and stockings. We receive photos of these new patients regularly. What a success! Without asking for anything, they are doing remarkable work.

As soon as the building has been renovated, we will make certain they are recruited, with a salary reserved for the best nurses. This rehabilitation project seems imminent, because as of the end of July, the Burkinabé Kontacts was officially recognized. Authorization from the Burkina Faso Ministry of Health to practice medicine has yet to be obtained, as has an official document allocating to us this old maternity building.

### Future missions

September 2010: Launch of building renovation. The Skype phone system may be adequate, but closer supervision seems preferable.

November 2010: Departure of a group of vascular specialist doctors and surgeons to continue our initiatives

(the number is not limited; for information see [www.kontacts.org](http://www.kontacts.org)).

September 2011: Planned departure just after the UIP Congress in Prague.

Other trips are planned but will depend on budgets and donations received (pharmaceutical firms, private persons or sponsors). Donations are not used to pay for airline tickets but to pay for our actions in the field. No money is given. Each paid action is detailed in an invoice: the entire accounting system is transparent (see Web site for additional information).

To finish this section and to catch a glimpse of the future, according to what was said by the Ambassador of Burkina Faso in France, his Excellency Luc Tiao, if completion of this first dispensary is a success, many other centers could be built in Burkina Faso. We will make use of what has been done in India to fight this scourge ([www.filariajournal.com](http://www.filariajournal.com)) and information given by the Global Alliance to Eliminate Lymphatic Filariasis which indicates that Burkina Faso is one of the countries of Africa which best fights for eradication of lymphatic filariasis.<sup>13,14</sup> The mission of these healthcare centers will be identical: *To restore hope to abandoned young people and to rehabilitate them socially, educationally, and occupationally. In a word to restore their freedom. We have much work to do.*

## IN CONCLUSION

Lymphatic filariasis continues to affect millions of people worldwide. One of its results is the occurrence of lower limb lymphedema which can assume massive proportions, whence the term elephantiasis. Our humanitarian aid missions have enabled us to discover this terrible disease, and to make every effort to treat it so as to prevent the worst possible treatment, amputation. The basic treatment for reduction of elephantiasis is compression therapy, which we have used to good effect several times. The most unbelievable event in this medical adventure was that some patients spontaneously managed fellow sufferers. What satisfaction!

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# Recent Guidelines in Chronic Venous Disease: the place of Daflon 500 mg

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This article addresses some of the newer guidelines, the purpose of which is to help clinicians manage patients with chronic venous disease (CVD) of the lower extremities.

**What is chronic venous disease?** CVD covers a full spectrum of venous conditions ranging from telangiectasias to the ultimate complications (venous ulcers). Symptoms are commonly associated with signs of CVD.

Venous symptoms are defined as tingling, aching, burning, pain, muscle cramps, swelling, sensations of throbbing or heaviness, itching skin, restless legs, leg tiredness and/or fatigue, which may be exacerbated during the course of the day or by heat, but relieved with leg rest or elevation or both.<sup>1</sup> Venous signs are visible manifestations of CVD, which include dilated veins (telangiectasias, reticular veins, varicose veins), leg edema, skin changes, and ulcers, as described in the clinical, etiology, anatomy, pathophysiology (CEAP) classification.<sup>2</sup>

**A common language is needed before building guidelines in CVD:** It should first be stressed that no consensus on guidelines is possible without the use of a common language. A leap forward was made recently thanks to a common terminology on venous anatomy,<sup>3</sup> the CEAP classification proposed by the ad hoc committee of the AVF in 1994 and subsequently adopted worldwide as a basis for improved patient description<sup>2,4</sup> a consensus on terminology related to CVD to avoid misunderstanding and lack of precision in publications. The VEIN TERM consensus document provides the definition of 33 widely used clinical venous terms and was published in J Vasc Surg 2009 under the aegis of the main American and European Scientific Societies (AVF, ACP, EVF, UIP, IUA, SVS).<sup>1</sup>

The CEAP classification includes a clinical assessment (C), an etiologic assessment of the patient's disease (E), an anatomic assessment of location of the pathology (A), and the pathophysiologic basis for the underlying disease (P). It provides a broad-based, objective, anatomic, and physiologic basis for classification of venous disease. This is why CEAP has improved standardization, communication, decision making, and reporting of venous disease.

**Keywords:**

Chronic venous disease, MPFF, guidelines

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**Understanding the pathophysiology of a disease state is essential for effective treatment.** Results from studies that demonstrate treatment efficacy lead to guideline recommendations.

Ambulatory venous hypertension is the hemodynamic disease which is related to all symptoms and signs of CVD, the underlying components of venous hypertension being failure of the calf muscle pump, venous valvular incompetence, and luminal obstruction.<sup>5</sup>

After prolonged standing, venous pressure in the foot is approximately 90 mm Hg in both a patient with incompetent venous valves and a person with a normal leg. In CVD patients, ambulatory venous pressures remain high in the lower limbs during walking (more than 40 mm Hg in the present example), when normally these pressures should fall (to 30 mm Hg). Due to valve incompetence, venous refill time at APG is shorter in CVD patients than in healthy individuals.<sup>5</sup> When venous pressures in the leg reach higher-than-normal levels and remain elevated for prolonged periods, a progressive increase in skin damage occurs. Nicolaides reported that nearly all patients with exercising venous pressures of >90 mm Hg experienced venous ulceration.<sup>6</sup>

The apparently simple concept of venous hypertension being responsible for CVD lies in the complex cellular and molecular processes set in motion by abnormal venous hemodynamics.

What initiates the inflammatory events in venous valves and walls is not yet clear. It is likely that venous hypertension and subsequent stasis lead to vein distension which in turn allows venous flow reversal and areas of low shear stress. Even in the absence of reflux, endothelial cells which are exposed to flow reversal become activated, together with leukocytes which are activated by low shear stress. The leukocyte-endothelial interaction initiates and maintains inflammation.<sup>5</sup>

When leukocytes are activated as a result of venous hypertension, they produce adhesion molecules which bind to intracellular adhesion molecules at the endothelial surface. This permits endothelial cell adhesion of leukocytes and initiates their migration through the vessel wall into the extravascular tissues, leading to degranulation and release of proteolytic enzymes [such as matrix metalloproteinases (MMPs),

tissue inhibitors of MMPs (TIMPs), and transforming growth factor beta (TGF- $\beta_1$ )]<sup>7,8</sup>

## THE CONSEQUENCES OF INFLAMMATION IN CHRONIC VENOUS DISEASE

Morphologic changes in venous valves occur. With prolonged pressure-induced inflammation, valve remodeling and damage occur as a result of leukocyte infiltration into valve leaflets, and reflux appears.

The production of MMPs and in greater proportion of TIMPs leads to the accumulation of extracellular matrix material. In addition, increased production of TGF- $\beta_1$  stimulates collagen synthesis and further increases production of TIMPs. The sum of these events results in the structural and hypertrophic changes in venous wall that typify patients with varicose veins.<sup>9</sup>

An early event in CVD is the elevation of endothelial permeability with opening of leakage sites between endothelial cells. As a result of such microvascular permeability, extravasation of water and water soluble nutrients leads to edema.<sup>10</sup> In a further step, the extravasation of red cells leads to the hyperpigmentation of skin in lipodermatosclerosis.

Fluid transport through the lymphatic vasculature completes the body's circulatory loop. The lymphatic vessels maintain tissue homeostasis and compensate for capillary leakage by absorption of extravasated interstitial fluid.<sup>11</sup> In the case of intense blood capillary leakage, the lymphatic capacity of drainage is insufficient to absorb excess fluid and macromolecules. This adds to the formation of venous edema, which spares the toes, unlike lymphatic edema.

## PHARMACOLOGICAL TREATMENT OF CHRONIC VENOUS DISEASE

A number of venoactive drugs (VADs) of plant or synthetic origin are available for the treatment of the symptoms of CVD, as illustrated in *Table I*.<sup>12</sup>

What are the mechanisms at work in pharmacological treatment of CVD by VADs?<sup>13</sup>

Most VADs increase venous tone, and thereby reduce venous distensibility and stasis.

Group	Substance	Origin	Dosage	Number of doses/day
Alpha-benzopyrones	Coumarin	Melilot ( <i>Melilotus officinalis</i> ) Woodruff ( <i>Asperula odorata</i> )	90 combined with troxerutin (540)	3
Gamma-benzopyrones (flavonoids)	Diosmin	Citrus spp. ( <i>Sophora japonica</i> )	300-600	1 or 2
	Micronized purified flavonoid fraction (MPFF)	<i>Rutaceae aurantiae</i>	1000	1 or 2
	Rutin and rutosides	<i>Sophora japonica</i>	1000	1 or 2
	O-( $\beta$ -Hydroxyethyl)-rutosides (troxerutin, HR)	<i>Eucalyptus</i> spp. <i>Fagopyrum esculentum</i>		
Saponins	Escin	Horse chestnut ( <i>Aesculus hippocastanum</i> L)	Initially 120, then 60	3
	Ruscus extract	Butcher's broom ( <i>Ruscus aculeatus</i> )	2 to 3 tablets	2 to 3
Other plant extracts	Anthocyanins	Bilberry ( <i>Vaccinium myrtillus</i> )	116	2
	Proanthocyanidins (oligomers)	Maritime pine ( <i>Pinus maritimus</i> ) Grape pips ( <i>Vitis vinifera</i> )	100 to 300 300 to 360	1 to 3 3
	Extracts of Ginkgo	Ginkgo biloba	2 sachets (extracts of Ginkgo, heptaminol, and troxerutin)	2
Synthetic products	Calcium dobesilate	Synthetic	1000 to 1500	2 to 3
	Benzaron	Synthetic	400 to 600	2 to 3
	Naftazon	Synthetic	30	1

Table I: Classification of the main venoactive drugs. Adapted from Ramelet et al, 2008<sup>12</sup>

Beneficial effects on capillary abnormal permeability have been demonstrated for almost all VADs.

Only 3 VADs have been shown to improve lymphatic drainage.

Only one available VAD has documented evidence of its ability to attenuate the effects of various mediators of the inflammatory cascade, particularly leukocyte-endothelial interactions, which are important in many aspects of the disease (Figure 1).

The mechanism of the beneficial effects of VADs on venous tone have been studied and published for micronized purified flavonoid fraction (MPFF)<sup>14,15</sup> and ruscus extracts.<sup>16</sup> These 2 VADs appear to increase venous tone by prolonging the vasoconstrictor effect of

noradrenaline on the vein wall. This increases the venous return and reduces venous pressure in patients suffering from CVD.

The improvement of abnormal permeability has been described for VADs, while evidence of increased lymphatic flow is available for only 3.<sup>17-19</sup>

Among available drugs able to block leukocyte adhesion to the venous valves and wall and thereby stop venous inflammation very early in the disease process, only MPFF so far has been studied in detail. In an animal model of venous hypertension, MPFF delayed the development of reflux and suppressed damage to the valve structures by decreasing the interaction between leukocytes and endothelial cells.<sup>20</sup>



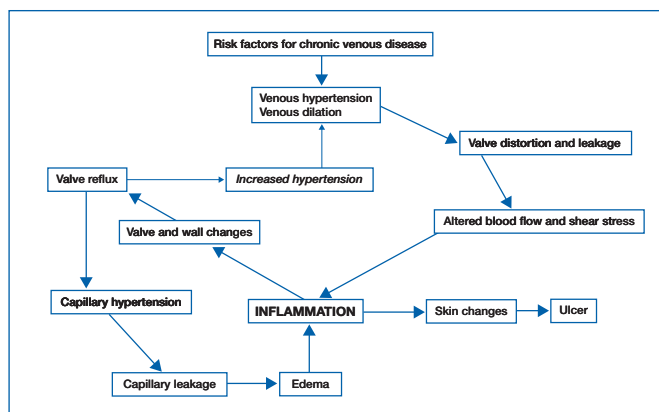


Figure 1. The vicious circle of venous hypertension/venous inflammation. Adapted from Bergan et al, 2006<sup>5</sup>

## A NEW GRADING SYSTEM FOR CHRONIC VENOUS DISEASE GUIDELINES

Many grading systems are available in guidelines (Figure 2).

### Cochrane reviews:

In a recent Cochrane review on VADs, randomized, double-blind, placebo-controlled trials (RCTs) were classified as level A (low risk of bias), level B (moderate risk of bias), or level C (high risk of bias). Special emphasis was placed on the method of randomization, the conditions of blinding, and the inclusion of an intention-to-treat analysis. The effect of treatment with VADs was estimated using relative risk (RR), with its corresponding 95% confidence interval (CI), by applying a random effects statistical model used in meta-analyses. The presence of statistically significant heterogeneity was also established. In the presence of heterogeneity, the results had to be interpreted carefully.

A total of 10 Cochrane reviews of CVD have been published since 2000;<sup>21-30</sup> 2 are on VADs.<sup>21,22</sup>

Significant and homogeneous results were found for most VADs in terms of edema reduction, decrease in restless legs syndrome, and improvement in trophic disorders.<sup>21</sup> Some VADS performed better than others in improving venous disorders, while the review on HCSE did not use the same methodology and consequently cannot be compared with the review on other VADs.<sup>21</sup>

### European guidelines

In European guidelines, studies are usually classified as: grade A (at least two RCTs with large sample sizes, meta-



Figure 2. European and US guidelines that have considered the drug treatment of chronic venous disease in recent years.

analyses combining homogeneous results), grade B (RCTs with small sample size, single RCT), or grade C (other controlled trials, nonrandomized controlled trials).<sup>13</sup>

Two of these guidelines deal with VADs. The article of Ramelet et al in *Clinical Hemorrhology and Microcirculation* represents the proceedings of the International Medical Consensus Meeting held in Siena on "Veno-active drugs in the management of symptoms of chronic venous disease".<sup>31</sup> Eighty-three publications on the effects of VADS on venous symptoms were analyzed.

International guidelines on the management of CVD, published in *International Angiology*,<sup>13</sup> used the same grading system as that of the Siena experts except for meta-analyses which were grade B. Outcomes included not only symptoms but also edema and venous ulcer healing. In all, 128 publications on VADs were analyzed in this document.

According to these two recent guidelines on VADs, and because of the consistency of the evidence,<sup>13,31</sup> a grade A was assigned to 2 VADs: MPFF (Daflon 500 mg), and HR-oxerutins for their effects on symptoms, edema, and skin changes (summarized in Table I).

### American guidelines

The method of determining the strength and quality of the recommendations in American guidelines deserves mention. Recommendations are generally accompanied by a number, which refers to the *strength* of the recommendation, and a letter, which refers to the *quality of the evidence* supporting the recommendation. Recent

guidelines for venous disease have used two levels for the strength of their recommendations depending mainly on the benefits/risks ratio: Grade 1 for strong and Grade 2 for weak. They further indicate that statements accompanied by a Grade 1 level are “recommendations” and statements accompanied by a Grade 2 level are “suggestions.”<sup>32</sup>

The quality of evidence upon which the strength of the recommendation is based ranges from “A” for high quality, which is consistent evidence from randomized trials, to “B” for moderate quality, which is evidence from nonrandomized trials or inconsistent evidence from randomized trials. Level “C” is low quality, which is suggestive evidence from nonrandomized trials, observational reports, or expert opinion. Writing committees are increasingly aware of the cost of care and patient values and preferences, as are physicians. These are also considered in the strength of recommendation.

Two guidelines on venous diseases used this system:

- American College of Chest Physicians Evidence-Based Practice Guidelines (8<sup>th</sup> edition) published in 2008 in Chest, which included a section on the treatment of venous leg ulcers in patients with venous thromboembolic disease that reviews the evidence for therapies added to conventional compression.<sup>33</sup>
- the second is the latest edition (3<sup>rd</sup>) of the Handbook of Venous Disorders, Guidelines of the American Venous Forum.<sup>34</sup>

Acceleration of the healing of venous leg ulcers has been demonstrated by several double-blind studies using MPFF (Daflon 500 mg) in combination with compression. This was confirmed in 2005 by a meta-analysis of 5 trials with MPFF as an adjunct to standard compression treatment in 723 patients in class C6 according to the CEAP classification.<sup>35</sup>

On the basis of this review, the author of the chapter devoted to “drug treatment of varicose veins, venous edema, and ulcers” of the latest edition (3<sup>rd</sup> edition) of the Handbook of Venous Disorders, Guidelines of the American Venous Forum, assigned VADs a grade 2B in the improvement of symptoms and edema associated with chronic venous disease. In the same chapter, only MPFF (Daflon 500 mg) was quoted in the pharmacological treatment of venous ulcer. The use of MPFF in combination with compression in long-standing or large venous ulcers of primary etiology was recommended (Grade 1B).<sup>34</sup>

The recent ACCP guidelines stated that MPFF should be added to compression (Grade 2B) in patients with persistent venous ulcers of secondary etiology.<sup>33</sup>

In summary and based on the quality of evidence, it is possible to propose a strong recommendation, based on evidence of moderate quality, for the use of MPFF and rutosides in symptoms and edema.

HCSE and *Ruscus* extracts have also proven effective against CVD-related symptoms and lower limb edema, although the volume and quality of evidence is less than for the previous two drugs (2C).

Calcium dobesilate has been associated with a potential safety concern relating to rare cases of agranulocytosis. Guidelines writers have considered it is only possible to give a weak recommendation for its use, given the uncertainty over the balance between benefits and harms (2B).

There is evidence from a meta-analysis of RCTs that MPFF is effective in the healing of venous ulcers. In the absence of important safety concerns, its use in this indication can be given a strong recommendation in primary ulcers (1B) and a weak one in secondary ulcers (2B).

## UPDATING GUIDELINES IN CVD

An update of the “guidelines for testing drugs for CVD” is needed that will allow the pharmaceutical industry investing the necessary resources to perform large and definitive clinical trials that could improve the recommendations, which are useful for clinicians and organizations involved in decision making in this important field of CVD. Such guidelines could:

Reiterate the basic principles that should prevail when reporting from (and setting up) any RCT, using the Consolidated Standards of Reporting Trials (CONSORT) statement,<sup>36</sup> as for meta-analyses with the QUORUM checklist.<sup>37</sup>

Describe comprehensively patients at selection in a study, using the advanced CEAP classification.<sup>4</sup>  
Promote the use of validated tools to assess symptoms, edema, and venous leg ulcer, and have a consensus on end-points.<sup>38</sup>

Encourage the adoption of a simple and universally understood system of grading.<sup>34</sup>

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# Lymphatic system dysfunction in pediatric populations

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## SUMMARY

Lymphatic system dysfunction in children has many presentations and syndromes and may affect all parts of the body. It can be classified according to the type of abnormality present as dysplasia of the lymphatics (LAD I), dysplasia of the lymph nodes (LAD II), or dysplasia of the lymphatics and lymph nodes (LAAD). Lymphatic dysplasias can be clinically represented by peripheral lymphedema alone or be associated with more and complex dysfunction in different locations, eg, intestinal lymph vessels, thoracic duct, and others. Primary lymphedema has for many years been the least understood form of lymphedema, but exploration of the underlying genetic causes of certain types of primary lymphedema is helping researchers identify and understand previously unrecognized syndromes. Carefully searching for lymphatic dysplasia in these patients, and if indicated in their relatives, as well as establishing the exact nature of the lymphatic dysplasia means that most cases of lymphatic dysfunction can now be diagnosed. This paper summarizes current knowledge on the recognition and classification of lymphatic system dysfunction in pediatric populations, with a focus on primary lymphedema.

## INTRODUCTION

A broad spectrum of inherited and acquired diseases is characterized by an impaired ability of the lymphatic system to collect and transport fluid. The most easily recognizable feature of lymphatic vessel incompetence is the presence of tissue swelling, lymphedema, which arises as a consequence of insufficient lymph transport. It is important for healthcare practitioners to be aware of signs and symptoms that may be precursors to the clinical diagnosis of lymphedema as not only is the efficient drainage of interstitial fluid from the capillary beds essential to prevent edema, but it also allows pathogenic material, from infections and injuries, to pass into the lymphatic system where it can be effectively trapped. Earlier detection and treatment of lymphedema means that more can be done to prevent its progression.

### Keywords:

lymphedema, tissue fluid, subcutaneous tissue, manual drainage, pneumatic compression

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## STRUCTURE AND FUNCTION OF THE LYMPHATIC SYSTEM

Vertebrates have developed a sophisticated system of recognition, rescue, integration, and transport of macromolecules and pathogenic material suspended in water. Located between the interstitial space and the deep jugular-subclavian venous system, this multipurpose system links the interstitial and intravascular space, returning fluids, solutes, and proteins filtered from the capillaries back to the systemic circulation. It has three major functions: removal of tissue fluid, production of immune cells, and absorption and transport of fatty acids and lipid-soluble vitamins to the circulatory system. To achieve this task the lymphatic system has a complex network of vessels throughout the body. In two clearly defined circuits, lymphatic channels from the upper right side of the body converge to form the right lymphatic duct, which empties into the confluence of the right internal jugular and subclavian vein, and lymphatic channels from the remainder of the body drain via Pecquet's cistern (cisterna chyli) into the thoracic duct, which empties into the left internal jugular vein at its confluence with the left subclavian vein.<sup>1</sup>

All tissues of the body are continuously bathed in interstitial fluid. As the blood supplies nutrients and important metabolites to cells via the interstitial fluid and collects cellular waste products, the composition of the interstitial fluid continually changes. Approximately 90% of the interstitial fluid returns to the blood via the venous capillaries, but the remaining fluid, which also contains larger protein molecules unable to diffuse across the venous capillary walls as well as white blood cells, dead cells, bacterial debris, infected substances, enters the lymphatic system.<sup>1</sup> The loss of this fluid (in adults, approximately 1-2 liters/day) would rapidly become life-threatening if the lymphatic system did not function properly.

The smallest lymphatic vessels are the lymph capillaries, which begin in the tissue spaces as pre-capillaries.<sup>2</sup> The wall of the pre-lymph capillary is composed of a single layer of overlapping endothelial cells with no basal membrane. When interstitial fluid volume and pressure increase, largely as a result of hydrostatic and colloidal osmotic pressure gradients, the space expands and the overlapping borders of the endothelial cells separate to allow unidirectional flow of fluid into the lymphatic capillaries and prevent backflow of lymph into the

interstitial space.<sup>3</sup> The lymphatic capillaries do not have valves, so lymph flows in the direction of lower pressure. This process creates a flow gradient for lymph from the interstitium into the lower pressure lymphatic capillaries and subsequently into the larger precollector and collector lymph vessels. Its functional unit is the lymphangion, surrounded by a spiral of muscle, which contracts when the lymphangion has expanded to a certain level, pumping the lymph from one lymphangion to the next. In addition, a system of one-way valves only allows the lymph to flow in one direction. Unlike the cardiovascular system, the lymphatic system is not closed and has no central pump. Lymph movement occurs despite low pressure due to the action of peristalsis, valves, and compression during contraction of adjacent skeletal muscle.

The lymphatic system plays an integral role in the immune functions of the body and is the first line of defense against disease. Approximately 500-600 lymph nodes occur along the entire length of the lymphatic system and are organized in groups that drain specific regions of the body.<sup>1</sup> Their primary role is to filter, concentrate, and purify the lymph fluid. The nodes produce macrophages and lymphocytes, and cytokines, which form part of the body's immune defense system. Lymphocytes are produced by stem cells in the bone marrow and then migrate to either the thymus or bone marrow (the primary lymphoid organs) where they mature into T-lymphocytes or B-lymphocytes, respectively. After maturation, both B- and T-lymphocytes circulate in the lymph and accumulate in secondary lymphoid organs including the splenic parenchyma, lymph nodes, and accessory lymphoid tissue (including the tonsils, adenoids, and Peyer's patches).

The lymphatic system is also involved in the absorption and transport of fat to the circulatory system.<sup>1</sup> Lymph vessels in the lining of the gastrointestinal tract absorb fats from food. Lymph draining from intestinal cells appears milky because of the fat globules that have been absorbed and is known as chyle. A malfunction of this part of the lymphatic system can result in serious malnutrition as a result of protein-losing enteropathy.

## THE ETIOLOGY OF LYMPHEDEMA

An excess of interstitial fluid does not necessarily mean a malfunction of the lymphatic system as it is designed to

cope with varying loads. Lymphedema only occurs when there is failure of lymph drainage as a result of lymph transport capacity falling below normal. In this situation, the normal volume of interstitial fluid formation exceeds the rate of lymphatic return, resulting in the accumulation of high-molecular-weight proteins in the interstitium. The high oncotic pressure in the interstitium favors the accumulation of additional water, which exacerbates the lymphedema. Eventually cell damage occurs because of the increase in interstitial pressure, disturbed cell nutrition, and transport of metabolites. Lymphedema of the extremities is clinically evident, but it is less widely recognized that lymphedema may also result in intracellular edema causing parenchymal cell lesions, which may appear in any organ drained by the lymphatics (hydrops). The two main classifications of lymphedema are primary and secondary.

### Primary lymphedema

Primary lymphedema is due to an inherent defect within the lymphatic tissue itself and usually manifests as aplasia, hypoplasia, hyperplasia, and dysplasia of lymph tissue (lymph vessels and nodes), which results in the presence of abnormally high levels of proteins and tissue fluids in the interstitial space.<sup>4</sup> Figures 1 to 4 illustrate examples of lower and upper limb lymphedema in infants. Primary lymphedema is usually further subdivided into three forms depending on age at presentation: congenital lymphedema (clinically evident at birth), lymphedema praecox (becomes clinically evident after birth, usually during puberty, and before age 35 years), and lymphedema tarda or Meige disease (becomes clinically evident after 35 years of age). These



**Figure 1.** Primary lymphedema in both feet in an infant,



**Figure 2.** The Stemmer sign, and pitting test. Newborn with primary lymphedema.



**Figure 3.** Primary lymphedema in both legs in an infant.



**Figure 4.** Primary lymphedema in one upper limb in an infant.

conditions often occur sporadically with no family history, and most frequently involve the lower extremities. All three forms of primary lymphedema are thought to originate from a developmental abnormality that is present, but not always clinically evident, at birth.

### Secondary lymphedema

When the cause of lymphedema is attributed to trauma, infection, or surgical removal of lymph nodes, it is

referred to as secondary or acquired lymphedema. In pediatric populations, secondary lymphedema is mainly caused by inflammatory or traumatic lymphatic injuries. Congenital causes include amniotic band (constriction band) syndrome,<sup>5</sup> hair tourniquet syndrome,<sup>6</sup> truncular venous hypertension because of intrinsic or extrinsic venous dysplasias or prenatal thrombosis. Obstructive mechanisms (pelvic tumor, compressive lymph flow disturbances) are less frequent than in the adult population. Noncongenital causes include parasitosis, drugs and pharmacological treatment, podoconiosis,<sup>7</sup> and trauma. In the tropics, secondary lymphedema in children is most frequently caused by lymphatic filariasis, the most common cause of lymphedema worldwide, which affects an estimated 120 million people.<sup>8</sup> The disease is caused by infection with the mosquito-borne parasites *Wuchereria bancrofti*, *Brugia malayi*, *Mansonella*, and others. These live and reproduce in the lymphatic system causing progressive dysfunction and obstruction at the nodal level, resulting in lymphedema.<sup>9</sup> Infection is concentrated in the tropics and does not account for the majority of cases of lymphedema seen in temperate zones. Other parasites causing infections that reside in the lymphatic system include *Onchocerca volvulus* (river blindness) and *Schistosoma haematobium* (bilharzia).

## CLASSIFICATION OF LYMPHATIC SYSTEM DYSFUNCTION

Whether it is congenital or acquired, lymphatic system dysfunction can be classified according to the type of dysplasia present as follows: lymphangiodysplasia—dysplasia of the lymphatics (LAD I); lymphadenodysplasia—lymph node dysplasia (LAD II); or lymphangiadenodysplasia—dysplasia of the lymphatics and lymph nodes (LAAD).<sup>10-12</sup> The classification is similar to that of the International Society for the Study of Vascular Anomalies (ISSVA), which classifies the congenital lymphatic dysplasias as truncal or extratruncal, depending on the embryonic stage at which the defect was produced.<sup>13</sup> LAD I dysplasias include agenesis, hypoplasia, disvalvulation, avalvulation, aganglionosis (angioneurosis), lymphangiectasia, lymphangiomatosis, and lymphangiomiomatosis. LAD II dysplasias include hypoplasia, hyperplasia, agenesis, peripheral, central, and global fibrosis, lymphangiomatosis, and intranodal vascular hamartomatosis. Mixed or combined vascular/lymphatic anomalies and malformation

syndromes and conditions include the Turner, Noonan, Klippel-Trenaunay-Weber, and Klippel-Trenaunay-Servelle syndromes, Gorham Stout Haferkamp Syndrome, Proteos Syndrome and others.

Using the above classification, a total of 21 causes of dysplasia can be identified. These form the basis of nearly 100 syndromes that are recorded in detail by the Online Mendelian Inheritance in Man (OMIM), the London Dysmorphology Database, the Human Cytogenetic Database, and others.<sup>14</sup> Genetic defects are associated with three well-known syndromes.<sup>15</sup> Milroy's disease is a congenital form of primary lymphedema with autosomal dominant inheritance accounting for 2% of primary lymphedema cases. The syndrome is associated with dysfunctional initial lymphatics (hypoplasia of the capillaries) and a failure of absorption of interstitial fluid. Mutations in the *VEGFR-3* gene on chromosome 5 are responsible.<sup>16</sup> Lymphedema-distichiasis syndrome is associated with lymphatic valve failure giving rise to lymph reflux. This disorder is characterized by distichiasis (a double row of eyelashes) with facial edema at birth and bilateral lower limb lymphedema at puberty. Other features include congenital heart defects and varicose veins.<sup>17</sup> This autosomal dominant condition is attributable to a mutation in *FOXC2*.<sup>18</sup> Finally, mutations in the transcription factor *SOX18* have been identified in recessive and dominant forms of hypotrichosis-lymphedema-telangiectasia syndrome.<sup>19</sup> Lymphedema may be present at birth, or may not be evident during the early years of life, despite the presence of vessel impairment.<sup>12</sup> The severity of the lymphedema may be classified according to the clinical features and degree of limb volume from subclinical lymphedema (Grade 0) to fibrotic tissue with skin changes (Grade III).<sup>20</sup> Primary lymphedema Grade 0 is not generally diagnosed in pediatric patients. Regardless of the type of primary lymphedema, the underlying causes (LAD I, LAD II, LAAD) are likely to be the same, which has important implications for treatment, as the sooner treatment is initiated the better the possible outcome is likely to be.

Primary lymphedema encompasses a diverse spectrum of human disease. In addition to the LAD I, LAD II, and LAAD dysplasias, it is associated with endothelial dysfunction, and at least 22 combined syndromes, including the combined angiodysplastic syndromes, linking it to at least 120 different diseases. Less well-known examples amongst these include aortic



coarctation, cleft palate, lissencephaly, yellow nail syndrome,<sup>21</sup> distichiasis,<sup>22</sup> and Turner or Noonan syndrome. The latter is associated with an unknown percentage of primary lymphedema, lymphangiectasias, and external fistulas of the lymph vessels.<sup>23</sup> Many of these syndromes are not easily recognized as they are infrequently encountered and can be confused with other disorders. The diagnosis of lymphedema therefore requires careful attention to patient risk factors and specific findings on physical examination. Adequate evaluation of primary lymphedema is required to determine the underlying cause, eg, too few initial lymphatics, collectors too few or too small, collectors too many or too large, too few lymph nodes or malformed lymph nodes, problem with abdominal lymphatics or thoracic duct. All patients with primary lymphedema should undergo genetic analysis to register and gather data on families with lymphedema.<sup>24,25</sup> DNA technology allows researchers to perform linkage analysis. By comparing the DNA samples of members with and without lymphedema, they are able to trace which chromosome is involved, and the location of the specific gene on the chromosome, which has important implications for future research.

## HISTOPATHOLOGICAL FINDINGS

As the lymphatic system is distributed throughout the human body, lymphatic system dysfunction is implicated in a wide variety of syndromes and diseases both local and systemic.

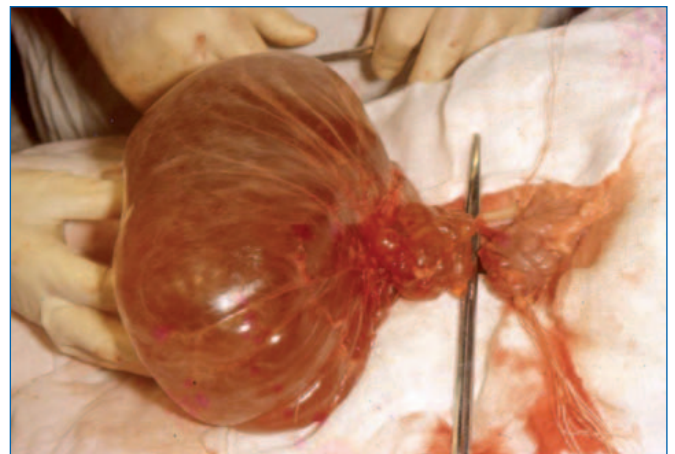
### Lymphangiectasia

Lymphangiectasia is a condition in which the lymphatics are dilated and is frequently associated with lymphedema. Dilated lymphatics are under increased pressure and leak lymph into the surrounding tissue spaces probably through small fistulas. However, not all lymphatic fistulas are due to lymphangiectasias. Cysts that result from lymphatic capillary dilatation (lymphangiomatosis) can also be a cause and may or may not be associated with edema. Pathologically lymphangiomatosis shows multifocal lymphatic dilations, but does not show the localized proliferation of anastomosing lymphatic channels.

### Lymphangioma

A lymphangioma is an abnormal collection of dilated lymphatics that are isolated from the normal lymphatic

system. Congenital forms are thought to occur because the embryonic lymph sacs have not connected correctly with the lymphatic system and are not associated with lymphedema. When acquired, lymphangiomas arise from endothelialization of trauma-induced lymphoceles and may be associated with lymphedema. A variety of lymphangiomas exist, including uni- or multilocular, and macro- or microcystic, based on the size of the lymphatic spaces within the malformation (*Figure 5*, *Figure 6*). They are usually classified into two major groups based on the depth and size of the abnormal lymph vessels. The superficial vesicles are called lymphangioma circumscriptum. The more deep-seated group includes cavernous lymphangioma (cystic hygroma).<sup>26</sup> Lymphangioma can occur in any region of the body in which there is lymphatic drainage. The single most common site of cystic occurrence is in the neck



**Figure 5.** Mesenteric macrocystic, multicystic lymphangioma with chylous vessels.



**Figure 6.** Macrocystic mesenteric lymphangioma.





**Figure 7.** *Lymphangiomatosis in a volvulated greater omentum.*

(Figure 7). An uncommon, but possible, site is the muscles and bones (eg, phantom bone disease or bone disappearing syndrome—Gorham-Stout syndrome). Combined hemolymphangiomas may also occur, as may combined vascular syndromes, eg, with hemangiomas and risk of malignization—Gorham-Stout-Haferkamp syndrome. Lymphangiomas are a form of angiodysplasia; they have a normal endothelium and therefore cannot be classified as tumoral. Histology of these lesions demonstrates no proliferative component.

### **Lymphangiomatosis**

Lymphangiomatosis is a condition where a lymphangioma is not present in a single localized mass, but in a widespread or multifocal manner. It is often wrongly diagnosed as lymphangioma circumscriptum, but this term describes lymphangioma of thin-walled capillaries. Lymphangiomatosis is frequently associated with other lymphatic-related abnormalities and usually involves multiple organs. The histology of lymphangiomatosis resembles a lymphangioma (Figure 8, Figure 9), but can appear to infiltrate tissues, and may be confused with more aggressive lesions. Intramuscular lymphangiomatosis has not been described, but at this level, phlebo-angiomatosis forms are frequent.<sup>27,28</sup>

### **Lymph reflux**

Another manifestation of lymphatic dysfunction is systemic lymph reflux, which occurs in both primary and secondary lymphatic dysfunction. The backflow of chyle from the intestines can occur in many areas of the body as a result of abnormalities of the abdominal lymphatics



**Figure 8.** *Latero-cervical, macrocystic, unilocular lymphangioma in a pediatric patient.*



**Figure 9.** *Lymphangiomatosis on a tongue in a pediatric patient.*

or the thoracic duct. When it leaks into the gut it may lead to lymphedema of the intestinal wall and a generalized swelling of the body as well as protein-losing enteropathy.

## AREAS OF ONGOING RESEARCH

### Angiodysplastic syndromes

Disorders associated with the transport capacity of the lymphatic system (true lymphedema) such as lymphangiomas, lymphangiectasis, and lymph-angiomas are well described. However, lymphatic dysfunction can also occur because of an overload of the lymphatics, eg, as a result of infection or cardiac failure, and sometimes a combination of both types of dysfunction can be observed. More research is needed into lymphatic malformations that have mixed vascular system involvement comprising lymphatic and venous and/or arterial vessels in association with chronic venous hypertension and insufficiency.<sup>29</sup> Examples of conditions in which lymphedema is a prominent feature include the



**Figure 10.** Skin with hemangioma, phlebectasias, and lymphangiectasia in a patient with Klippel-Trenaunay-Servelle syndrome.



**Figure 11.** Phlebography findings from a patient with Klippel-Trenaunay-Servelle syndrome illustrating persistent vena marginalis (embryonic saphena externa, Ayas or Albanese vein) confluent to the common femoral vein, with severe hypoplasia of the superficial femoral vein.

osteohypertrophic syndromes (hemangiomatosis and varicose veins), Klippel-Trenaunay-Weber syndrome (precapillary arteriovenous shunts and secondary venous hypertension),<sup>30</sup> Klippel-Trenaunay-Servelle syndrome (primary deep venous dysplasia and venous hypertension (Figure 10, Figure 11),<sup>30</sup> F.P. Weber syndrome (macro-arteriovenous shunts and secondary venous hypertension), cirroid aneurysm (multiple macro-arteriovenous shunts and hemangioma), Proteus syndrome,<sup>31</sup> and other syndromes with primary deep venous dysplasias. In all the above hypertension of the regional lymph system is probably secondary.

### Secondary lymphatic organ dysfunction

Further work is also required on dysfunctions related to the secondary lymphatic organs in relation to immunocompetence. Such research requires a multidisciplinary approach and must be analyzed in the context of multisystem functions in which the lymphatic system is a key player.

## CONCLUSIONS

In the past the lymphatic system has played a minor role in traditional pediatric medicine. Although rare, it is now recognized that primary lymphedema is the result of a spectrum of lymphatic disorders. It may be uncomplicated or complicated by other associated disorders of the vascular system. However, with a multidisciplinary team approach, most of these dysfunctions can be diagnosed clinically.



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# Treatment of vulvar and perineal varicose veins

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## SUMMARY

Vulvar varicose veins occur in 10% of pregnant women, generally during month 5 of a second pregnancy. Anatomically, the vulvar veins have communicating branches and anastomoses between the pelvic wall and the veins of internal organs, between the internal and external iliac venous system, and with the circulation of the medial aspect of the thigh via the perineal veins. Vulvar varices are not caused by an increase in circulatory volume during pregnancy, but by increased levels of estrogen and progesterone. Vulvar veins are the target of these hormones.

Out of embarrassment, women rarely mention vulvar veins and they are not adequately sought in the physical examination with the woman in the standing position during month 6 of pregnancy and the first month post partum. Most often they are asymptomatic. Pain, pruritus, dyspareunia, and discomfort during walking are possible during pregnancy. Thrombosis and bleeding are rare. Treatment is symptomatic during pregnancy and curative during the post-partum period.

Most often, vulvar varices disappear a month after delivery. Small residual, asymptomatic varices are seen again 1 year later. Large or symptomatic varices are managed with curative therapy. Sclerotherapy is the preferred method because it is very effective on thin-walled varices.

## INTRODUCTION

Vulvar varices are found on the labia majora and minora. Usually, they develop during month 5 of a second pregnancy. They occur in 10% of pregnant women. Out of embarrassment, women rarely mention vulvar veins, which in addition are not adequately sought in the physical examination with the woman in the standing position during month 6 of pregnancy and the first month after delivery. Pain, pruritus, dyspareunia, and discomfort during walking are possible during pregnancy. Thrombosis and bleeding are rare. Treatment is symptomatic during pregnancy, and curative during the post-partum period.

### Keywords:

vulvar varices, pregnancy, perineal varices.

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In this article, we will not discuss perineal varices in men or after crosssectomy (extended saphenofemoral or saphenopopliteal junction ligation), pelvic varices, hemorrhoids, or superficial gluteal varices.

## REVIEW OF ANATOMY

The new anatomical terminology refers to the pudendal veins (pudenda: external genital organs). The vulvar or vulvovaginal veins are drained anteriorly by the external pudendal veins, below by the perineal veins, and posteriorly by the internal pudendal veins. The external pudendal veins empty into the saphenofemoral junction and depend on the external iliac system, the perineal veins into the crural trunk of the long saphenous vein, and the internal pudendal veins into the internal iliac vein (Figure 1).

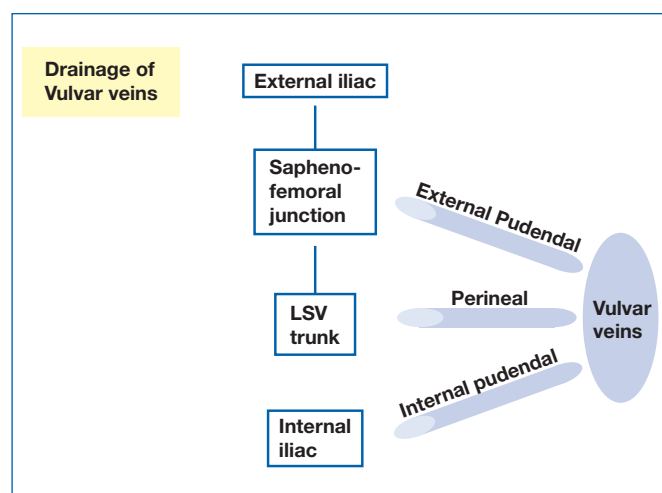


Figure 1. Review of anatomy: drainage of vulvar veins.

The saphenofemoral junction is a crossroads which, from inward to outward, receives the external pudendal veins, the superficial dorsal vein of the clitoris, the suprapubic vein, the superficial epigastric vein, the superficial abdominal cutaneous vein, and the superficial circumflex iliac vein. Above, there is an anastomosis between the vulvar veins and the pelvic veins (uterovaginal and ovarian veins).

Thus, the vulvar veins have communicating branches and anastomoses between the pelvic wall veins and the veins of internal organ, between the internal and external iliac system, and with the circulation of the medial aspect of the thigh via the perineal veins

(Figure 2). According to some authors, two sites of leakage may be more common in multiparous women: 1/4 perforating labial vein at the union of the posterior and the anterior 3/4 of the labia majora and the perforating vein in the inguinal canal.<sup>1,2</sup>

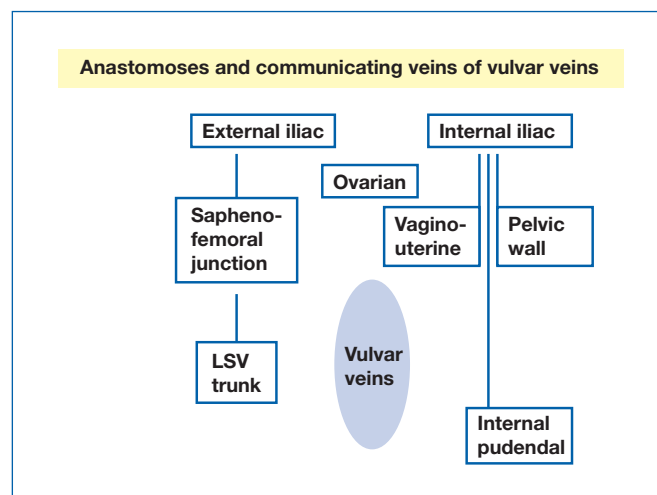


Figure 2. Review of anatomy: communicating veins of vulvar veins.

## STRUCTURE AND PATHOPHYSIOLOGY

Vulvar veins have a thin wall which contains many elastic fibers and few muscle fibers, and hormonal receptors. Vulvar varices do not appear to be caused by pelvic compression or overload. In fact, death of the fetus in utero results in regression of varices and large uterine fibroids do not lead to the development of varices. Similarly, such varices are not caused by the increased circulatory volume of pregnancy, but by increased levels estrogen and progesterone. Thus, vulvar veins are the target organ for these hormones. It should be kept in mind that pregnancy is a risk factor for venous thrombosis.

## CLINICAL PRESENTATION

Vulvar varices occur in about 10% of pregnant women. They are rare during a first pregnancy and generally develop during month 5 of a second pregnancy. The risk increases with the number of pregnancies.<sup>3-5</sup> Their incidence is underestimated for 3 reasons:

1. Women are embarrassed to talk about them,



in case of a complication or to look for leakage sites. Assessment of varicose veins and venous mapping are then performed in the adjacent areas such as the thigh, groin, mons veneris, suprapubic area, the gluteal area, and the abdominopelvic cavity (*Figure 4*).

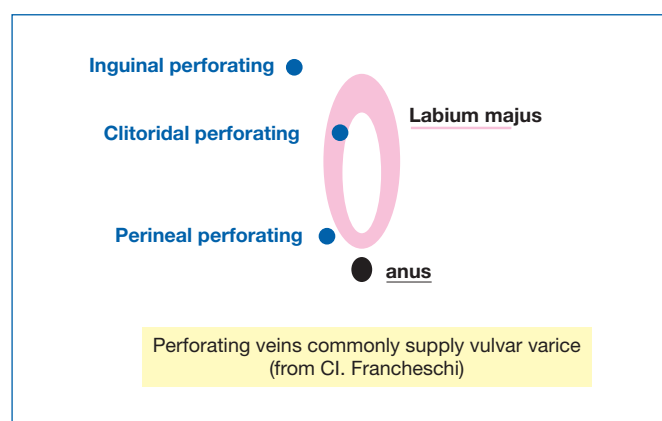
Doppler sonography is the preferred method of investigation.<sup>10-13</sup>

**During pregnancy** Doppler sonography is requested in cases of :

1. Early-onset vulvar varices (first two months of a first pregnancy), to look for a malformation.
2. Unilateral vulvar varices (malformation, left iliac thrombosis).
3. Superficial thrombosis of a vulvar varicose vein, to look for deep vein thrombosis.

**Outside of pregnancy**, Doppler sonography is requested for:

1. Pre-treatment mapping with screening to detect a leakage point between the vulvar varices and the abdominopelvic cavity. Two findings seem to be more common in multiparous women: the perforating inguinal vein and the perforating labial vein at the union of the posterior 1/4 and the anterior 3/4 of the labium majus.<sup>1,2</sup> (*Figure 4*)
2. To rule out a Palma-like suprapubic transverse venous network, which can develop following an iliac thrombosis.
3. To explore the saphenofemoral junction and the long saphenous vein even after stripping of the saphenous vein, because recurrence of varicose veins in the lower limbs is frequent during the post-partum period.<sup>14</sup>



**Figure 4.** The diagnosis of vulvar varices is clinical.

4. To explore the abdominopelvic cavity. In fact, perineal and inguinal varices can be evidence of elevated pelvic pressure. Two investigations are differentiated: transparietal and endovaginal.<sup>15-18</sup>.

### Angio-CT scan

This investigation is requested if pelvic congestion syndrome is associated with vulvar varices. The contrast medium progressively opacifies the uterine and ovarian veins by retrograde approach during the arterial phase. Abnormal venous flow can be found as well as tortuous and dilated veins.

### Magnetic resonance angiography

This is a method of investigation recently used to evaluate ovarian venous reflux.<sup>19</sup>

### Selective venography

This is the reference method because it provides comprehensive information on whether vulvar varices are associated with pelvic congestion syndrome. It is invasive as it involves venipuncture, catheterization, injection of iodine, and irradiation. It can visualize the leakage points during Valsalva maneuvers between the abdominopelvic cavity and the lower limbs, passing through the veins of the groin or the perineum.<sup>20,21</sup>

## TREATMENT

Treatment is symptomatic during pregnancy, and curative afterward if the varices persist.

### 1. During pregnancy

It is sometimes useful to refer the patient to a vascular specialist who is very familiar with the subject, to relieve the patient's anxiety. Pruritus is treated by bathing with a foaming solution without soap, and then a water-based zinc oxide paste. Pain and heaviness are treated with high-dose phlebotonic agents.<sup>22</sup>

Lower-limb compression therapy is systematic in this varicose vein context. Use is made of class 2 calf-high stockings over which are placed class 2 thigh-high stockings. This is equivalent to a class 4 compression of the foot and calf and class 2 of the thigh. This combination is easier to place than class 3 or 4 articles.

As for superficial venous thromboses of the lower limbs, there is an increasing trend to prescribe low-molecular-weight heparin at prophylactic dosage for vulvar thromboses, during the second and third trimesters of pregnancy, and for a short duration (5 days). This provides prophylaxis of deep vein thrombosis, is analgesic within 24 to 48 hours, and lyses the clot. Thrombectomy is thus avoided.

It should be remembered that pregnancy is a risk factor for venous thrombosis.

Bleeding requires compression therapy.

Sclerotherapy is always possible during pregnancy. It does not carry any particular risks either for the woman or the fetus. It is rarely performed because its beneficial results are uncertain in an unfavorable hormonal context.

## 2. After pregnancy

A month after delivery, vulvar varices most often have disappeared. Small, asymptomatic residual varices are seen again after 1 year. Large or symptomatic varices are managed with curative therapy. Sclerotherapy is the preferred method because it is very effective on these thin-walled varices. It is administered most often in a very superficial varicose vein blister under visual control using a very fine gauge needle (30G1/2) and a liquid sclerosing product. Sclerosing foamy products are more thrombogenic and are not indicated here.

The dose used is 1 cc of 0.5% or 1% Aetoxisclerol; or 0.33% or 0.5%. Trombovar.

Varices in the groin or the mons veneris can be treated with echosclerosis. Care should be taken to avoid the external pudendal artery for which an accidental injection produces disastrous lesions in the vascular area downstream. Identification with the duplex color technique, by greatly increasing gains in the future area of injection, is essential to keeping in mind that "what is not seen exists."<sup>5-23</sup>

Phlebectomy remains possible for perineal varices,<sup>24</sup> but is little performed because of the good results obtained with sclerotherapy. The same holds true for ligation of the labial or marginal perforating veins with the patient in the lithotomy position after identification by sonography.

## DISCUSSION

When vulvar or perineal varices exist together with pelvic congestion syndrome, we consider that it is preferable to start treatment using a sclerosing solution administered by injection and under visual control of varices in the crotch. After this simple-to-administer treatment, we observe the disappearance of the vulvar or perineal varicose vein and are often surprised to learn that the patient reports a marked decrease in symptoms of pelvic congestion. Conversely, patients who undergo embolization of pelvic varices continue to present with vulvar and perineal varices.<sup>25-27</sup>

Hemodynamic logic dictates that a high reflux should be treated first. In this regard, our experience seems to favor sclerotherapy, which is not expensive, is simple and confined to the crotch area, as first-line therapy. Currently, we do not have a randomized trial to assess results.

## CONCLUSION

Vulvar varices develop during month 5 of a second pregnancy. Their frequency is underestimated. Screening to detect them with the patient standing is desirable at month 6 of pregnancy and 1 month after delivery. During pregnancy, Doppler sonography is justified by early occurrence of such varices at the start of a first pregnancy, by their unilateral presentation, and by a thrombosis. If these varices persist after delivery, a visit to a vascular specialist is desirable and treatment with sclerotherapy is almost always possible.



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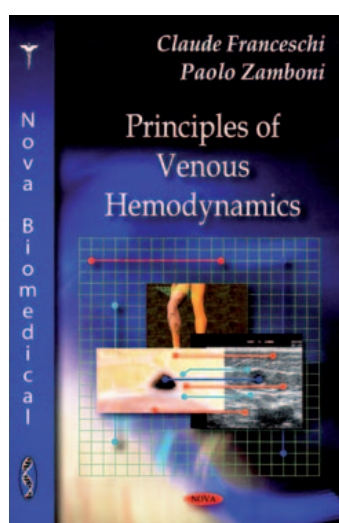
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## Book review

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PRINCIPLES OF VENOUS HEMODYNAMICS. FRANCESCHI C, ZAMBONI P (EDITS). NOVA BIOMEDICAL BOOKS.2009. NEW YORK.  
ISBN 978-1-606692-485-3



This 200-page hardback book in glazed paper is divided into 12 chapters, with a total of 284 references, and is prefaced by both E. Rabe, the current President of the Union Internationale de Phlébologie (UIP), and N. Morrison, the elected President of the next UIP Meeting.

For readers unaware of the CHIVA procedure (in French “*cure Conservatrice et Hémodynamique de l’Insuffisance Veineuse en Ambulatoire*—Ambulatory Conservative Hemodynamic Management of Varicose Veins), this book will be quite a surprise both in terms of the terminology used and the concept of varicose vein treatment.

CHIVA was first described by Franceschi in 1988<sup>1</sup> and West European phlebologists are accustomed to the specific terms it uses, as Shunt 0, I, II, III, and IV, venous networks N1, 2, 3, 4, etc., as well as the hemodynamic principles, given that many publications on CHIVA have been published, mostly in European journals.<sup>2-13</sup>

The first chapter is devoted to the physical principles of venous hemodynamics, a reminder of the correlation between pressure and energy and their influence on venous flow according to Castelli’s flow, Bernoulli’s principle, and Venturi effects.

The second chapter is very informative on ultrasound data and introduces the next one on venous compartments and their hierarchical order of emptying in accordance with the five phases initiated by the muscular pump in a healthy individual.

Chapters 4, 5, and 6 deal with pathophysiological mechanisms in chronic venous insufficiency\* and develop the shunt concept, including pelvic shunts, which demands careful attention from the uninitiated. Happily, many figures and diagrams illustrate the different types or modalities of the “private circulation” or venous shunts according to CHIVA terminology. Understanding of this classification is crucial before reading the subsequent chapters.



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\*Chronic venous insufficiency as used by the author is not the appropriate term as there is a consensus to limit its use to C<sub>3</sub> to C<sub>6</sub>\* patients, according to the VEIN-TERM consensus.<sup>14</sup>

Chapter 7 states the CHIVA goal strategy in detail:

- First, preservation of the superficial venous capital as a possible arterial substitute when treating coronary or peripheral arterial disease.
- Second, conservation of saphenous trunks ensures better drainage of the superficial compartment tissues.

Many examples of treatment are displayed according to the various patterns of varicose veins evaluated by careful preoperative duplex investigation.

Chapter 8 describes methods of measuring hemodynamic parameters and what specific information they provide. Chapter 9 entitled “How to perform a duplex mapping” (before CHIVA) is crucial reading if this procedure is to be used properly. The chapter includes 41 color figures as detailed illustrations of clinical cases.

Chapter 10 is illustrated by 46 figures and describes the technical procedures to be performed according to the identified pathophysiological patterns: high ligation, tributary disconnection, hook phlebectomy, etc.

The penultimate chapter presents the results of CHIVA, including clinical findings, duplex scanning results, and health-related quality of life assessment. The last chapter revisits the problem of so-called incompetent perforators.

The purpose of this book review is not to formulate an opinion of the value and effectiveness of the CHIVA procedure, but to provide information on Franceschi and Zamboni's book. Nevertheless, I would say that whether or not you are a CHIVA supporter or user you will, like me, learn a lot on varicose veins by reading it.

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# Report from the EVF meeting

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## A SNAPSHOT FROM THE 11TH ANNUAL MEETING OF THE EUROPEAN VENOUS FORUM (Antwerp, Belgium)

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It was my privilege to serve as the first president at the 2000 inaugural European Venous Forum (EVF) meeting held in Lyon. Ten years later it seems logical to take stock of the present state of the EVF by analyzing the Antwerp congress. First of all in terms of the number of attendees. Attendance has increased from 160 founding members in Lyon to 320 in Belgium. More impressive is the number of participating countries: 38 in total this year covering the five continents.

Quality remains the EVF's main criterion for presentations, which explains why just 29 papers were selected from the 85 submitted. From the beginning the EVF board decided that the time devoted to discussion should be equal to the presentation time, and this rule remains both crucial and fruitful.

To go back to the Antwerp meeting, which was remarkably organized by Marianne de Maeseneer—the first woman president of the EVF, the sessions were divided into 5 topics: clinical and basic research, deep venous problems, endovenous treatment of varicose veins, socioeconomic implications of chronic venous disease, and short miscellaneous venous subjects. Preceding the EVF paper sessions, the 7th North Sea meeting organized by the Benelux Society of Phlebology was devoted to long-term follow-up after varicose vein treatment, followed by 2 other topics selected by the EVF committee: prevention of venous thromboembolism in 2010 and its treatment. All 3 were high-quality sessions. Between the selected papers we had, as usual, invited presentations, including those of the winners of the American Venous Forum and EVF traveling fellowship. Following a lovely musical intermezzo, the meeting ended with the presentation of the EVF prizes.

To summarize, this was an outstanding EVF vintage.







# Instructions for authors

## AIM AND SCOPE

**Phlebology** is a quarterly peer-reviewed publication that aims to provide clinicians with updated information on every aspect of the venous and lymphatic disorders: epidemiology, pathophysiology, diagnosis, management, and basic science. Articles are usually in the form of review articles on timely topics with a broad update of recent developments and their clinical applications.

## GENERAL INSTRUCTIONS

Articles should discuss a topic of current interest, outline current knowledge of the subject treated, give personal views and also analyze the different opinions regarding the topic discussed, and be up to date on the latest literature data.

The text should be 3000-5000 words, not including references, tables, figures. Illustrations are strongly encouraged. All texts should be submitted in English.

**Submission:** Manuscripts may be submitted by e-mail<sup>1</sup>, double-spaced, 8 to 16 typed. All pages should be numbered. All corresponding authors should supply a portrait photograph for inclusion at the end of the article. This may be sent by e-mail, provided the resolution of the file is at least 300 dpi.

**Title page:** The title page should include a title, the full names of all the authors, the highest academic degrees of all authors (in country-of-origin language), affiliations (names of department[s] and institution[s] at the time the work was done), a short running title (no more than 50 letters and spaces), 5 to 10 keywords, the corresponding author's complete mailing address, telephone, fax, and e-mail, and acknowledgments.

**Abstract:** A 150-word abstract should be provided for all articles. The editorial department will edit abstracts that are too short or too long.

**Text:** Abbreviations should be used sparingly and expanded at first mention. The style of titles and subtitles should be consistent throughout the text. The editorial department reserves the right to add, modify, or delete headings if necessary. *Phlebology* uses SI units and generic names of drugs.

## REFERENCES

**Citation in text:** All references should be cited in the text and numbered consecutively using superscript Arabic numerals.

**Reference list:** Presentation of the references should be based on the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. *Ann Intern Med.* 1997;126:36-47 ("Vancouver style"). The author-date system of citation is not acceptable. "In press" references should be avoided. In the bibliography, titles of journals should be abbreviated according to *Index Medicus*. All authors should be listed for up to six authors; if there are more, only the first three should be listed, followed by "et al." Where necessary, references will be styled by the editorial department to *Phlebology* copyediting requirements. Authors bear total responsibility for the accuracy and completeness of all references and for correct text citation.

## Examples of style for references

**Journal article:** Sessa C, Perrin M, Porcu P, et al. Popliteal venous aneurysms. A two-center experience with 21 cases and review of the literature. *Int J Angiol.* 2000;9:164-170.

**Article in a supplement:** Sansilvestri-Morel P, Rupin A, Badier-Commander C, et al. Chronic venous insufficiency: dysregulation of collagen synthesis. *Angiology.* 2003;(suppl 1):S13-S18.

**Chapter in a book:** Coleridge Smith PD. The drug treatment of chronic venous insufficiency and venous ulceration. In: Gloviczki P, Yao JST, eds. *Handbook of Venous Disorders: Guidelines of the American Venous Forum.* 2nd ed. London, UK: Arnold; 2001:309-321.

**Web-based material:** Nicolaides AN. Investigation of chronic venous insufficiency: a consensus statement. American Heart Association, 2000. Available at: <http://www.circulationaha.org>. Accessed October 17, 2005.

**Presentation at a conference:** Jantet G. Epidemiological results of the RELIEF study across different continents. Paper presented at: 15th World Congress of the Union Internationale de Phlébologie; October 2-7, 2005; Rio de Janeiro, Brazil.

## FIGURES AND TABLES

Figures should be of good quality or professionally prepared, with the proper orientation indicated when necessary (eg, "top" or "left"), and be identified by Arabic numerals, eg, *Figure 2*. Tables should be identified by roman numerals. Provide each table and figure on a separate sheet. Legends must be provided with all illustrations, including expansion of all abbreviations used (even if they are already defined in the text). All figures and tables should be numbered and cited in the text.

## PHOTOGRAPHIC ILLUSTRATIONS

Illustrations in color are encouraged.

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## Congress and conference calendar

DATES	CONGRESS	COUNTRY	CITY
21-22 January 2011	63 <sup>èmes</sup> JOURNEES INTERNATIONALES FRANCOPHONES D'ANGEOLOGIE 3 <sup>èmes</sup> RENCONTRES NATIONALES DES GROUPES DE TRAVAIL DE LA SFA 10 <sup>ème</sup> REUNION DU RESEAU FRANCOPHONE VASCULAIRE LES 1001 FACETTES DE L'ANGEOLOGIE EN 2011	France	Paris
21-22 January 2011	3rd Panhellenic Congress of Phlebology & 2nd Annual Meeting of the Balkan Venous Forum, Hotel Crowne Plaza, Athens	Greece	Athens
27-29 January 2001	CONTROVERSIES & UPDATES IN VASCULAR SURGERY	France	Paris
29 January 2011	THE COURSE OF THE SOCIETY OF PHLEBOCTOMY	Romania	Bucharest
4-5 February 2011	4th ANNUAL CONFERENCE OF THE VENOUS ASSOCIATION OF INDIA	India	Chandigarh
10-13 February 2011	AFROCHAP-V 5th CONGRESS OF N. AFRICAN 1 MIDDLE EAST CHAPTER INTERNATIONAL UNION OF ANGIOLOGY	Egypt	Sharm El-Sheikh
23-26 February 2011	XXXVI Angiological Days 2011 with International Participation	Czech Republic	Praha
16-18 March 2011	45th MEETING OF THE FRENCH COLLEGE OF VASCULAR PATHOLOGY (CFPV)	France	Paris
30 March - 3 April 2011	XV. CONGRESS OF SLOVAK SOCIETY OF VASCULAR SURGERY WITH INTERNATIONAL PARTICIPATION	Slovak Republic	Jasná, High Tatras
April 2011	MEETING OF THE CANADIAN SOCIETY OF PHLEBOLOGY	Canada	
7-9 April 2011	SPANISH PHLEBOLOGY CHAPTER (CEF)	Spain	Granada

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DATES	CONGRESS	COUNTRY	CITY
8 April 2011	1ST CROATIAN CHRONIC VENOUS DISEASE PREVENTION DAY	Croatia	Zagreb
20-23 April 2011	INTERNACIONAL CONGRESS OF ENDOVASCULAR PROCEDURES (CICE)	Brazil	São Paulo
21-22 April 2011	UKRAINIAN PHLEBOLOGICAL CONGRESS 'SUKHAREV'S READINGS'	Ukraine	Irpen', Kiev region
3-6 May 2011	25TH NATIONAL CONGRESS OF SURGERY	Romania	Cluj Napoca
13-14 May 2011	7TH EUROPEAN SYMPOSIUM OF VASCULAR BIOMATERIALS (ESVB 2011) - NEW ENDOVASCULAR TECHNOLOGIES - FROM BENCH TEST TO CLINICAL PRACTICE	France	Strasbourg
20 May 2011	SPRING CONGRESS OF THE SWISS SOCIETY OF PHLEBOLOGY: SCLEROTHERAPY FROM A TO Z...	Switzerland	Lausanne
20-22 May 2011	6TH INTERNATIONAL COURSE / ULTRASOUND GUIDED ENDOVENOUS LASER / RF TREATMENT OF VARICOSE VEINS, SEMINAR AND HANDS-ON COURSE	Slovenia	Oto ec
2-4 June 2011	57TH CONGRESS OF THE SPANISH SOCIETY OF ANGIOLOGY AND VASCULAR SURGERY	Spain	Valladolid
2-4 June 2011	NATIONAL CONGRESS OF THE ROMANIAN SOCIETY OF ANGIOLOGY AND VASCULAR SURGERY	Romania	Cluj - Napoca
24-25 June 2011	XI ANNUAL CONGRESS OF THE PORTUGUESE SOCIETY OF ANGIOLOGY AND VASCULAR SURGERY	Portugal	Viseu
June 2011	MEETING OF THE FRENCH SOCIETY OF PHLEBOLOGY	France	Lyon
1-3 July 2011	12TH ANNUAL MEETING OF THE EUROPEAN VENOUS FORUM (EVF)	Slovenia	Ljubljana
1-5 July 2012	XXV WORLD CONGRESS OF THE INTERNATIONAL UNION OF ANGIOLOGY	Czech Republic	Praha



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**Micronized** purified flavonoid fraction

## A unique action at the core of chronic venous disease

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Micronized, purified flavonoid fraction 500 mg:

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50 mg. **Therapeutic proper-**

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tion of Daflon 500 mg increases its gastrointestinal absorp-

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pathic chronic venous insufficiency of the lower limbs with the following

symptoms: heavy legs; pain; nocturnal cramps. Treatment of hemorrhoids and

acute hemorrhoidal attacks. **Side effects:** Some cases of minor gastrointestinal and

autonomic disorders have been reported, but these never required cessation of treatment.

**Drug interactions:** None. **Precautions:** *Pregnancy:* experimental studies in animals have not

demonstrated any teratogenic effects, and no harmful effects have been reported in man to date. *Lac-*

*tation:* in the absence of data concerning the diffusion into breast milk, breast-feeding is not rec-

ommended during treatment. **Contraindications:** None. **Dosage and administration:** *In venous dis-*

*ease:* 2 tablets daily. *In acute hemorrhoidal attacks:* the dosage can be increased to up to 6 tablets

daily. As prescribing information may vary from country to country, please refer to the complete data

sheet supplied in your country.

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Daflon 500 mg (MPFF) is also registered under various trade names, including: Detralex,

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1 - Ramelet AA, Clin Hemorheol Microcir. 2005;33:309-319. 2 - Nicolaidis A, Int Ang. 2008;27:1-60.



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