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Dear Readers,

Jean Francois Uhl from Paris (France) undertakes the challenge of explaining venous embryogenesis of the lower limbs. In fact, most referenced studies in phlebology (Lewis, Hochstetter, etc) relate not to humans, but to other mammals, and even to birds or reptiles. After an interesting review of the techniques of embryological studies, Dr Uhl provides an updated summary of current knowledge on the development of leg veins. Moreover, he illustrates the text with his original, magnificent, and time-consuming 3D reconstructions. Finally, Dr Uhl describes the close relationship between embryology and clinically relevant vascular malformations.

In his paper, Stefano Ricci from Rome (Italy) reviews current knowledge on the anatomy of foot veins. Starting from anatomy (and ultrasound anatomy), Dr Ricci sheds light on the complex mechanisms of the venous foot pump and how this pump connects with the more proximal pumps of the anterior and posterior leg. Moreover, he highlights the possible implications of functional abnormalities in this “chain of pumps,” paying particular attention to the phlebologist’s point of view. When should a dilated vein on the dorsum of the foot be considered varicose, and therefore, treated? And how should it be treated? What are the causes and significance of corona phlebectatica? Do primary varicose veins of the foot exist?

Sergey G. Gravilov and colleagues from Moscow (Russia) report on a selected group of 85 women with pelvic pain and lower limb varicose veins, treated with micrized purified flavonoid fraction for 8 weeks. Pelvic pain (self-assessed using a visual analog scale) was significantly reduced in all women during the period of administration. Pelvic pain soon recurred in women with evidence of pelvic varices. In turn, pain was still reduced after 14 weeks in women with only leg varicose veins. In conclusion, the authors suggest the need for long-term administration of micrized purified flavonoid fraction in women with pelvic varices, especially in those “wishing for a future pregnancy or reluctant to undergo surgery.”

Jean-Luc Gillet from Bourgoin-Jallieu (France) reviews the evidence, or lack thereof, for the correct treatment of superficial vein thrombosis. Once considered a benign disease or a common complication of varicose veins, superficial vein thrombosis is currently included among the venous thromboembolic diseases because of the frequent concurrence of deep vein thrombosis and pulmonary embolism. Although long-term anticoagulant treatment was recently proposed, Dr Gillet points out that the guidelines assign such treatment a low-grade recommendation. He concludes that further research is needed to define subgroups of patients with a higher incidence of deep vein thrombosis or pulmonary embolism, in whom long-term anticoagulation may be warranted.

Bo Eklöf from Lund (Sweden) critically analyzes an excellent paper by Malas et al on the effectiveness of surgery of superficial veins in ulcerated patients. Curiously, Malas et al report that “adding superficial vein ligation and stripping to compression did not improve the wound healing rate,” whereas Dr Eklof considers that “ablation is suggested for ulcer healing due to weak evidence; while for the prevention of recurrence, ablation is recommended due to stronger evidence.” More prospective studies are surely needed!

Jerry G. Ninia from NY (USA) comments on an important article by Asbeutah et al showing that cyclic morphological and functional changes occur in the leg veins of women. These consist of a significant increase in vein diameter and in valve closure times. Dr Ninia describes the relationship between these venous changes and cyclic hormonal variations.

Finally, Paolo Prandoni from Italy analyzes for Phlebolymphology readers the randomized study of Haig et al on residual rates of reflux and obstruction after catheter-directed thrombolysis. Dr Prandoni shows how the results of this study and others are strongly suggestive of the protective role of early restoration of vein patency in preventing postthrombotic syndrome.

Enjoy reading this issue!

Alberto Caggiatti
Focus on venous embryogenesis of the human lower limbs

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Abstract
Embryogenesis of the venous system is a complex phenomenon that is not fully understood. In spite of the studies done by Born, Hochstetter, and Lewis, we do not know the precise chain of events leading to vasculogenesis of the venous network in humans. Yet, this is an important topic in order to improve our anatomical knowledge, which is of the highest interest in clinical practice. A good knowledge of anatomy is mandatory to perform in-depth assessments of chronic venous disorders by ultrasound mapping. Understanding venous embryology is also crucial to investigate and treat congenital venous malformations. Further research projects, particularly using new techniques of 3D modeling combined with immunolabeling of the anatomical structures (computer-assisted anatomical dissection) will contribute precious data regarding the onset and maturation of the human embryo’s vessels, as well as providing data on the relationship between veins and nerves.

Introduction
Today, human embryology is one of the main topics in biomedical research.\(^1\) Several 3D atlases of the human embryo have been produced using the Carnegie embryo collection (National Museum of Health and Medicine, Washington, D.C., USA) and the Kyoto collection (Congenital Anomaly Research Center, Kyoto, Japan).\(^2\) The Visual Human Embryo with digital serial sections of human embryos from the Carnegie embryo collection illustrates the major stages of human embryonic development.\(^3,4\) The Kyoto human embryo collection\(^5\) is an example of computerized 3D modeling of human embryos by MRI, presented according to the Carnegie stages. However, today, to our knowledge, there have been no studies describing the different steps of development and the precise human anatomy of the venous system of the lower limbs, due to the lack of direct observation.

The aim of this paper is to focus on the updated knowledge about venous embryogenesis of the lower limbs and to discuss the interest of a new research technique for 3D modeling of human embryos—computer-assisted anatomical
dissection (CAAD). A better understanding of embryology, and therefore venous anatomy, is of the highest interest for the clinical practice in phlebology and vascular medicine (Figure 1).

**Historical References**

The Scandinavian method of Bamm was created in 1883 to build 3D reconstructions of embryos. It is based on the enlargement of serial anatomical slices, displayed on a tablet of colored wax. In 1893, Hochstetter also made huge progress on the embryogenesis of amniotes. However, the most innovative results were shown by Lewis in 1906 in the rabbit. In addition, the works of Bokova (1970) and Gilbert (1990) are also noteworthy.

Since then, several works on the Hox genes have brought about a revolution in our knowledge of limb organogenesis. Hox genes control the positional information, spatial orientation, morphogen gradients, and cellular differentiation. Molecular models and growth factors also condition the limb’s development. Finally, vasculogenesis is also tightly related to the skeleton formation.

**Development of the Human Embryo and Lower Limbs**

The human embryo development can be divided into three main stages: (i) embryogenesis occurs between postovulatory weeks 0 and 4; (ii) organogenesis between postovulatory weeks 4 and 8 (Figure 2); and (iii) the fetal period between week 9 and birth.
the density of vessels in those locations, particularly in the marginal venous network. The toes appear at stage 20 (50 days; 18 mm) and the limb’s development ends at stage 23 (56 days; 30 mm).

**Classic “Basic” Knowledge about Venous Embryogenesis**

**The early stages of development**
The “primitive veins” were described by Lewis after observations made in the rabbit (Figure 4). Lower limb buds appear toward the end of day 10 during rabbit embryonic development. Starting on day 14, Lewis observed a concentration of the venous network at the caudal and distal aspect of the limb bud, which is called the marginal vein. This drains into a primitive fibular vein, then into an ischiatic and posterior cardinal vein (Carnegie stage 1). On day 17, he observed that the fibular vein became the main vein, while the lateral marginal vein disappears (Carnegie stage 2). At about 3 weeks of development (Carnegie stage 3), he noticed the existence of an anastomotic branch originating from the sciatic vein and connecting to a new vessel, the femoral vein. The latter forms the final deep venous system, while the sciatic vein disappears.

![Figure 4. The primitive veins at week 5.](image)

Note that the veins of the primitive limb are fed by the umbilical vein (containing oxygenated blood); the blood flux goes from the root to the extremity of the limb (black arrows). Therefore, the veins appear first. The arteries then drain the blood back from the limb (red arrows).

Abbreviations: 1, primitive marginal vein; 2, primitive fibular vein; 3, primitive axial vein; 4, primitive ischiatic vein; 5, primitive anterior tibial vein; Um, umbilical vein.

**Theory of angio-guiding nerves**

Later (after week 6), the arrangement of the venous network could be explained by the theory of the angio-guiding nerves proposed by Gilliot. The nerves appear at 6 weeks (embryo size, 18 mm; Carnegie stage 19; Figure 5). The axons and Schwann cells secrete a vascular endothelial growth factor (VEGF). It has a 2-fold role: (i) to attract the vascular plexuses to the vicinity of the nerves; and (ii) to induce their arterial, venous, or lymphatic specialization. The ephrin family (B2-B4) plays an important role in the differentiation of primitive endothelial cells.

**Fetal period**

After postovulatory week 8, known as the fetal period, the venous plexuses along the three nerves condense and mature (Figure 6).

![Figure 5. Growth of the three angio-guiding nerves at week 6.](image)

Abbreviations: 1, primitive marginal vein; 2, primitive fibular vein; 3, primitive axial vein; 5, primitive anterior tibial vein; 6, intergemellar vein (vein of the sural nerve); A, axial (sciatic); C, popliteal crossroad; Cau, caudal (small sciatic); Cr, cranial (femoral); F, femoral plexus; purple, caudalplexus; S, sural nerve.

Data about the early stages are from small mammals and need to be confirmed by direct observations in human embryos. Angio-guiding nerves are just a hypothesis that is based on extensive anatomical observations in adults, but has not yet been confirmed in embryos.
Today’s Hypotheses and Proposals for the Steps of Venous Embryogenesis

Our knowledge is reduced to several hypotheses, which need to be confirmed by further direct observations and 3D reconstructions of human embryos (Figures 7 and 8):

- The lower limb bud first appears at 33 days (embryo size, 6 mm; Carnegie stage 15). The vascular layout is then reduced to a peripheral undifferentiated venous network, which is located subcutaneously and secondary to a central artery.

- Around week 5 (37 days; embryo size; 8 to 11 mm; Carnegie stage 16), the primitive veins emerge. A thickening appears at the distal and caudal aspect of the bud due to the migration of endothelial cells, and explains the location of the first veins of the limb.

![Figure 8. Summary of the fetal period of development (after week 8).](image)

The primitive veins are colored in purple. Notice that the fetus (weeks 9 to 15) commonly has a big axial vein while the femoral vein is smaller and plexus shaped. Later, the axial vein becomes a small arcade along the sciatic nerve, and the femoral vein becomes the main trunk of the thigh in the majority of cases at birth, commonly with a collateral canal.

Abbreviations: 3, fibular veins; 4, arch of the SSV; 5, great saphenous vein; 7, anterior tibial veins; 8, SSV; 9, posterior tibial; 10, femoral vein; 11, axial vein; 12, epigastric vein; 13, thigh extension of SSV; 14, deep femoral vein; 15, obturator vein; 16, hypogastric vein; 17, external iliac vein; 18, inferior gluteal vein; cc, collateral canal; P, perforating branches of the femoral vein; POW, postovulatory week; sna, axial arcade along the sciatic nerve; SSV, small saphenous vein.

![Figure 7. Summary of the organogenesis period of an embryo’s development (postovulatory weeks (POW) 4 to 8; Carnegie stages 15 to 23).](image)

At week 4 (Carnegie stage 15), the reticular phase starts where the central artery (a) and superficial venous plexus (v) develop.

At week 5 (Carnegie stage 16), the primitive veins (marginal [1,2]; fibular [3]; and axial [4]), umbilical vein (5), posterior cardinal vein (6), anterior tibial vein (7), and small saphenous vein (SSV [8]) appear.

At week 6 (Carnegie stage 19), the three angio-guiding nerves (axial [sciatic; a]; cranial [femoral; b]; and caudal [small sciatic; c]) appear.

At week 7 to 8 (Carnegie stage 23), the following appear: marginal vein (1); fibular vein (3); axial vein (4); umbilical vein (5); anterior tibial vein (7); small saphenous vein (8); posterior tibial vein (9); femoropopliteal axis (10); deep femoral vein (11); epigastric vein (12); cranial extension of the SSV (13); great saphenous vein (14); arch of the SSV (A).

Note the direction of blood circulation coming from the umbilical vein: from the root to the extremities of the veins (black arrows), and then circulated back by the arteries (red arrows).

which are located superficially and are called the marginal venous sinus.

- The oxygenated blood comes from the placenta by the umbilical vein joining the posterior cardinal vein. It then reaches the root of the limb by the primitive ischiatic vein, feeds the primitive fibular vein, and finally, forms the lateral marginal vein located at the caudal aspect of the bud. The distal part of the marginal vein will form the “primitive small saphenous vein,” the very first vein present in the adult to appear in the embryo. At that time, the nerves do not exist. The blood goes back to the root of the primitive limb by the arteries. (Figure 7, left).

- Around week 6 (47 days; embryo size, 16 to 18 mm; Carnegie stage 19), the three angio-guiding nerves appear and quickly grow along the limb bud. This
will initiate the development of the deep venous system and the great saphenous vein. In fact, due to the secretion of VEGF by the Schwann cells, the three angio-guiding nerves will attract the undifferentiated vascular plexuses and induce their maturation into veins, arteries, and lymphatics. These three angio-guiding nerves are: (i) axially, the sciatic nerve; (ii) cranially, the femoral nerve; and (iii) caudally, the small sciatic nerve.

- Around week 7 to 8, the three venous plexuses of the lower limb grow and mature along the three angio-guiding nerves. Along the sciatic (axial) nerve, the primitive axial vein becomes a huge vein and joins the deep femoral vein upwards. At this time, this is the main venous trunk of the thigh, but it will regress to become a small arcade in the majority of adults. Along the femoral (cranial) nerve from the cranial plexus, the great saphenous vein appears together with the femoral vein, which connects upward with the ischiatic vein to form the iliac vein. Downward, the anastomosis with the axial plexus will give birth to the popliteal crossroad. Along the caudal nerve (small sciatic), the caudal plexus forms the distal part of the small saphenous vein (SSV) below the knee and the cranial extension of the SSV at the thigh level. A possible anastomosis with the axial plexus will lead to SSV termination into the popliteal axis (saphenous popliteal junction or French “crosse”). Of note, around weeks 6 to 8, there is a medial rotation of the limb, where the cranial aspect of the limb becomes medial and the caudal aspect becomes lateral.

- At the end of the 12th week, organogenesis is finished and the venous anatomy is similar to an adult. However, some remodeling of the venous axis will occur, particularly at the femoral level. The axial vein, which is a large vein, will become a small arcade along the sciatic nerve, while the femoral vein commonly reduces to a thin network along the femoral nerve and will become the main venous axis of the thigh in 90% of the cases in adults.

- After 12 weeks, remodeling of the subcutaneous part of the superficial venous system (reticulum network) will lead to its definitive anatomy at birth. The venous valves appear and are closely related to the hemodynamic patterns of the anatomical arrangement, and thus, the blood circulation.

CAAD: A New Technique to Build 3D Models Depicting the Main Steps of Venous Embryogenesis

CAAD was first used by Yucel and Baskin to identify the penis nerves.²⁹ Our laboratory then published several papers showing the benefit of CAAD for the studies of the male and female uretra2⁰,²¹ and intrapelvic innervation.²² We recently dedicated the CAAD technique to the 3D reconstruction of the embryo’s limbs.²³ Briefly, the principle of this technique is to make thin horizontal slices of the limbs. After digitalization and alignment of the slices, a different staining is used, in particular, proteins S-100 and D2-40 are stained to recognize the nerves and vessels, respectively. An example is shown in Figure 9 with the reconstruction of a big axial vein at the thigh.

Figure 9. Immune markers for nerves and vessels in a 13-week-old fetus.

Panel A. A 3D reconstructed limb showing a big axial vein along the sciatic nerve, while the femoral vein is reduced to a small plexus-shaped network located inside the femoral canal with its companions the femoral artery and femoral nerve. Slices of a 13-week-old fetus stained for nerve-specific immune markers (slice A with protein S-100; Panel B) and vessel-specific immune markers (slice B with D2-40; Panel C) using the CAAD technique.

Abbreviations: 1. sciatic nerve; 2. femoral nerve; 3. femoral vein; 4. femoral artery; a. axial vein; CAD: computer-assisted anatomical dissection; f. fibula; f. femur; t. tibia.

The first results of these 3D reconstructed limbs were recently obtained from three embryos at postovulatory weeks 13 to 15 (discussed in the following section and illustrated in Figures 10 and 11), but it is a work in progress as detailed data about the earlier stages are still lacking.
Clinical Applications of Embryogenesis

Anatomical variations of the femoral vein
Three types of anatomical variations of the femoral vein have been observed in 12% of adults (Figure 12). If the large primitive “axial vein” of the embryo persists, then either an axiofemoral trunk (unitruncular layout, 3%) or axiofemoral vein (bitruncular layout, 9%) is found in adults. Most commonly, a modal layout (88%) will be found in the adult’s anatomy; the primitive axial vein becomes hypotrophic and reduced to a small arcade. The main vein of the thigh is a femoral vein inside the femoral canal.

Figure 10: Three-dimensional reconstruction of a 14-week-old fetus (right lower limb). Medial view (Panel A), inferior view without muscles (Panel B), and inferior view with muscles (Panel C).
Abbreviations Panel A: 1, sciatic nerve; 2, axial vein; 3, femoral vein and artery; 4, great saphenous vein; 5, tibial nerve; 6, small saphenous vein; 7, sural nerve; 8, tibial nerve; 9, medial plantar nerve; 10, lateral plantar nerve.
Abbreviations Panels B and C: 1, posterior tibial artery and two veins; 2, vastus medialis muscle; 3, semimembranosus muscle; 4, rectus femoris muscle; 5, lateral gastrocnemius muscle; 6, soleus muscle; 7, long tibular muscle; 8, tibialis anterior muscle; 9, extensor hallucis longus.
Figure 10B has been reproduced from reference 6: Kurobe et al. Surg Radiol Anat. 2015;37:231-238. © 2014, Springer Verlag France.

Figure 11: Three-dimensional reconstruction of a 15-week-old fetal right lower limb without (Panel A) and with muscles (Panel B).
Abbreviations: 1, sciatic nerve; 2, axial vein; 3, femoral vein and artery; 4, great saphenous vein; 5, saphenous nerve; 6, small saphenous vein; 7, sural nerve; 8, tibial nerve; 9, tibial nerve; 10, medial plantar nerve; 11, posterior tibial artery and two veins; 12, tendon of the halluc flexor longus; 13, flexor digitorum longus; 14, posterior tibial tendon; 15, tendons of peroneous longus and brevis.

Figure 12: Anatomical variations of the femoral vein occur in 12% of adults.
If the primitive “axial vein” of the embryo persists, either an axiofemoral trunk (unitruncular layout, 3%) or an axiofemoral vein (bitruncular layout, 9%) can be found in adults. In the modal layout (88%), the primitive axial vein becomes hypotrophic and reduced to a small arcade.
Abbreviations: AF, axiofemoral vein; AFT, axiofemoral trunk; cc, collateral canal; CF, common femoral vein; DV, deep femoral vein; FV, femoral vein; IG, inferior gluteal vein; P2, second perforator vein; P3, third perforator vein; SNA, sciatic nerve arcade.
Venous Embryogenesis in a Nutshell

The *primitive venous system* of the lower limb appears between weeks 5 and 6 of the embryo’s development. The marginal vein and the small saphenous vein appear superficially. They come from the primitive ischiatic vein, then the axial system, and then from the primitive fibular vein.

The *second stage* occurs between weeks 7 and 8, after the apparition of the nerves (end of week 6) by maturation of the three plexuses along the angio-guiding nerves; the femoral vein, the great saphenous vein, and the posterior tibial veins appear. The anastomosis between the three plexuses also forms the popliteal crossroad, the saphenous popliteal junction, and the Giacomini vein.

Anatomy of the lateral network of the leg and fibular perforators in the adult

A thin marginal venous network of the leg, commonly seen in adults, is a remnant of the primitive marginal vein. Just like in the embryo, it is connected to the fibular veins by several fibular perforators, as is nicely shown in Figure 13.

Figure 13. Remnant of marginal vein and fibular perforators in an adult.

Anatomical dissection after latex injection in the left leg (lateral view after resection of the fibula bone). Notice the alignment of the fibular perforator veins connecting the thin marginal network to the fibular veins at specified locations (10, 14, 17, and 22 cm from the apex of the lateral malleolus).

Abbreviations: 1, dorsal foot network connected to the anterior tibial perforators; 2, lateral marginal network connected to the fibular veins; 3, calcaneus perforator vein; 4, Achilean vein joining the small saphenous vein.
Conclusion

Understanding embryogenesis is important mostly in terms of clinical applications: it improves our anatomical knowledge about the venous system and is particularly useful to perform a venous mapping for all CVD patients. Embryology is also essential for the diagnosis and management of congenital vascular malformations (CVM). As explained in the Hamburg classification of CVM,\(^2\) the severity of the malformations is related to the stage of the embryo's development when they occur: (i) before week 4, they provide severe "extratruncular" malformations; (ii) between week 4 and 8, they are responsible for less severe "truncular" malformations; and (iii) after the organogenesis period (week 8), simple anatomical variations will occur.
FURTHER READING: RECONSTRUCTION-TYPE BORN:

a. Peter K. Rekonstruktions methoden. Greifswald, Germany; 1922.
g. Lewis WH. The use of guide planes and plaster of paris for reconstructions from serial sections: some points on reconstruction. Anat Rec. 1915;9:719-729.
The venous system of the foot: anatomy, physiology, and clinical aspects

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Abstract
Venous return from the foot is worthy of interest for both research and clinical purposes. This review summarizes the available knowledge of venous return from the foot with a special focus on research and clinical implications. The anatomy and physiology of venous return are described with an emphasis on the differences between standing and walking and the interplay between the venous systems of both the foot and the calf. Selected conditions of clinical interest are discussed and mechanistically interpreted, including the distinctive localization of leg ulcers, the corona phlebitectatica, the possible independence of dilatation of the veins of the foot from refluxing varices, and the arteriovenous fistulae of the foot. From this perspective, the practice of using a postoperative lower-leg bandage is also discussed.

Little attention has been devoted to the veins of the foot: surgeons begin the saphenectomy where the foot ends and echographists do not extend their exploration distally to the malleolus. Even anatomists have been more interested in the arteries of the foot, rather than the veins, as demonstrated by the more detailed description of arteries in anatomical tables. Finally, experts in hemodynamics focus on the calf to explain the mechanism of the limb pump, leaving the blood in the foot “undrained.” However, as shown in the present bibliography, a few well-conducted classic studies have clarified the anatomical and functional characteristics of venous circulation in the foot, although some areas of uncertainty still exist.

The main concepts concerning the anatomy and physiology of venous return from the foot will be revisited in this article, followed by observations of clinical interest and hypotheses for research and daily practice.

Anatomy
In 1968, Kuster et al provided the most complete description of the veins of the foot, describing five systems: (i) the superficial veins of the sole (also known as
Lejars’ venous plexus); (ii) the deep veins of the sole; (iii) the superficial dorsal plexus; (iv) the marginal veins and dorsal venous arch; and (v) the perforating system.

i. The superficial veins of the sole (Lejars’ venous plexus), once considered the most important impulse for venous return, is a net of tiny veins with limited clinical interest (Figure 1).

ii. The deep veins of the sole are the most interesting from a functional point of view.

o The deep plantar venous arch runs from the proximal end of the first interosseous space to the base of the fifth metatarsal and accompanies the deep plantar arterial arch, which receives the deep metatarsal veins and surrounding muscular veins (Figure 2). The deep plantar venous arch measures ≈9 cm (range, 5 to 14 cm) according to Binns and Pho and ≈48 mm according to Corley, with an average external diameter of 5 mm. In 8 out of 10 foot dissections, 2 deep plantar venous arches were identified, which is often referred to as being doubled. A single, constant, and proximally oriented valve has been described.

o The medial plantar vein is a thin and short vein (≈5 cm long according to UhI et al., ≈12 cm according to Binns and Pho, and ≈38 mm according to Corley) that is usually doubled, with a few proximally oriented valves. It runs along the medial border of the sole from the medial end of the plantar arch to the medial malleolus to form the posterior tibial veins after the confluence with the lateral plantar vein. The medial plantar vein receives blood from the adjacent muscles, i.e., the abductor hallucis, the flexor digitorum brevis, and the plantar quadratus muscle.

o The lateral plantar vein (length between 80 mm and 84 mm) is curved, constantly doubled, and large (2 mm) with fusiform dilatations (resembling the gastrocnemius sinuses), and it is located between the two muscle layers of the sole of the foot (i.e., quadratus plantae and abductor hallucis). Proximally directed valves are present in the lateral plantar vein. The lateral plantar artery lies between the two parts of this vein, which are interconnected an average of three times. The lateral plantar vein is in continuity with the lateral end of the plantar venous arch and runs back across the sole to join the medial vein at the calcaneal confluent, forming the posterior tibial veins. It receives blood from the lateral marginal vein, the calcaneal veins, and the veins in the adjacent large plantar muscles.

In the deep plantar system, doubled veins have been constantly observed with the corresponding arteries. The vessels are surrounded by connective tissue and this arrangement facilitates venous compression by the artery, serving as a localized pumping action. Furthermore, while performing
cadaveric dissections, Corley found a consistent presence of an evident secondary arch either located deep in the quadratus plantae or as part of a more complex network of deep interconnections. This could represent a potential blood reservoir explaining the interindividual differences in venous outflow recorded during muscular activity.

iii. The superficial dorsal plexus may be clinically important because it is in continuity with the superficial veins of the leg and ankle and may be involved in varicose dilatation of the superficial veins. These veins are very superficial (limited to the fat layer), well visible (esthetically demanding), and contiguous with the cutaneous nerves (easily encountered during foot phlebectomies).

iv. The marginal veins and the dorsal arch are separated from the superficial dorsal plexus by a relatively strong connective fascia (corresponding to the fascia covering the great saphenous vein and the small saphenous vein all over the limb); thus, the superficial network of the dorsum runs separately over these veins in a distinct layer (Figure 3 and 4). The dorsal arch lies over the proximal ends of the metatarsal bones and is the origin of the marginal veins, receiving the dorsal metatarsal veins and several perforating veins. The medial marginal vein arises from the perforator of the first metatarsal interspace and is contiguous with the great saphenous vein. It receives several perforators from the plantar veins that are important from a functional point of view. The lateral marginal vein ends in the short saphenous vein, which receives important perforators from the deep plantar veins.

v. The perforating system is the most distinctive system of the foot because these veins are valveless or contain valves oriented from deep to superficial veins. According to Uhl et al.:5

- The perforator of the first metatarsal interspace generally has a large diameter without valves and connects the dorsal venous arch with the deep plantar system, and as a consequence, it is the true starting point of all venous networks in the foot. It accompanies the dorsalis pedis artery.

- The medial marginal perforators, which open into the medial marginal vein, differentiate into plantar veins (ie, malleolar, navicular, and cuneiform veins) and dorsal veins (ie, anterior tibial vein).

- Consistently, the lateral marginal perforators-the calcaneal and cuboidal veins-join the lateral marginal vein at the perimalleolar plexus.

Figure 3. Marginal veins and their superficial network.

The marginal veins, connected anteriorly by the anterior arch vein (Panel A), are the origin of the two saphenous veins, and are similarly situated under the superficial fascia. The superficial network of the dorsum of the foot is in continuity with the superficial network of the anterior leg (Panel B).

Figure 4. Superficial network of the dorsum (longitudinal) is clearly visible with a duplex scan.

The network runs independently over an arch vein (transversal), which is separated by the superficial fascia.

Venomuscular Pumps

The energy needed for venous blood to overcome the hydrostatic pressure, which is generated by the distance between the heart and the leg in standing subjects, in a dynamic state, is created by multiple myofascial compartments that are separate yet integrated, act like muscle pump units, and are known as the venomuscular pumps (VMP). The composition of VMPs includes the following: (i) the venous foot pump; (ii) the distal and proximal calf pumps; (iii) the thigh pump; and (iv) the abdominal pump. The contraction and relaxation of the skeletal muscles surrounding the veins impress volume and pressure variations to the venous blood, while the flow direction is controlled by the valvular arrangements.

The position of each deep venous valvular act will determine the pump output. A tract located inside the muscle creates very effective ejection systems (gastrocnemius, soleus). At the soleus and gastrocnemius sites, the veins are numerous and arranged in a spiral shape due to the longitudinal excursion amplitude of the muscles between contraction and relaxation (volumetric pump). Extramuscular tracts are subjected to compression over tough surfaces, i.e., bone or aponeuroses, by the close muscles; therefore, they have a lower, though still satisfactory, efficiency (distal calf pump or peristaltic pump). This is the case for the posterior deep compartment veins (posterior tibial veins and peroneal veins) and the anterior external compartment veins (anterior tibial veins), which have a rectilinear organization, as the containing muscles lean against the bones and have a limited shortening during contraction.

The superficial venous network is only indirectly affected by the VMPs through aspiration during muscle relaxation or diastole; there is an exception for the venous foot pump where the superficial veins may be directly filled, which is in contrast with the deep veins.

Proximal calf muscle pump

The most active pump of the lower limb is the one due to the sural and gastrocnemius muscles: these muscles are rich in venous sinuses that are strongly squeezed during the impulse phase of the step, when pressure exceeds 200 mm Hg and calf volume decreases by 80%.

When the calf muscles contract, the pressure rises in all veins of the lower limb, and the increase is three times greater in muscle than in superficial veins. During muscle contraction (systole), the strong pressure gradient between the deep calf veins and the popliteal vein causes a rapid eflux of blood from the calf to the thigh (Figure 5). Venous pressure exceeds the intramuscular pressure in calf compartments in most of the step phases, but competent venous valves prevent retrograde flow. On subsequent muscle relaxation (diastole), venous pressure falls below the pressure at rest. The fall is greater in the deep veins, less in the superficial veins, and negligible in the popliteal vein. In this phase, perforator veins allow blood to flow from the superficial to the deep veins, while competent valves prevent backflow from the popliteal to the deep calf veins.

![Figure 5. Mechanism of action for the distal calf pump.](image)

Panel A. Muscles (M) are unsheathed by common fascia (f) and veins within the same compartment. Contraction of the calf muscles, as in plantar flexion of the ankle joint during walking (bottom), expels blood into the proximal collecting vein. During relaxation (top), the blood is drained from the superficial veins (SV) into the deep veins (DV) in addition to the arterial inflow; thereby preparing for the subsequent ejection. V, venous valve. Panel B. Distal calf pump: upon 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. Panel C. The venous foot pump: upon weight bearing, the tarsometatarsal joints are extended and the tarsal arch is flattened. Thus, the veins are stretched, causing them to eject their content of blood.

Image courtesy of E. Stranden.
Distal calf “piston” pump
In contrast with conventional descriptions, there are two pumping systems in the calf, a proximal (gastrocnemius/soleus) and a distal system. The distal one is activated by dorsiflexion of the ankle (Figure 5), i.e., when the calf muscles are stretched and their distal parts descend within the fascial sheath. This movement acts like a piston, which expels venous blood in a proximal direction. The pump mechanism has been documented by ultrasound Doppler measurements of venous blood flow and is supported by compartment pressure measurements.

Venous foot pump
According to Browse et al., the force required to overcome the pressure of the blood column within the venous system of the lower legs exceeds that generated within the muscular compartments of the calf during motion. For Gardner and Fox, the plantar venous plexus could overcome this pressure. Located within the plantar surface of the foot, the plantar venous plexus is submitted to high-pressure compression during ambulation, possibly constituting a mechanism for driving the venous outflow from the leg (Figure 6). During the gait process, the plantar plexus is able to overcome the pressure of the blood column within the deep venous system of the calf. It squeezes a small volume (20 to 30 mL) but the pumping mechanism is very effective; it works by voiding chambers distal to their axis and without a proximal valve, but closed distally in a cul-de-sac formation (C. Franceschi, unpublished data).

Figure 6. Phlebogram of the lateral plantar veins with a dilated middle portion that acts like a reservoir.
Panel A. Nonweight bearing. Panel B. Weight bearing, which empties the venous foot pump into the calf.


The venous foot pump, in fact, is activated by the compression caused by either body weight or plantar muscle contractions during each step. According to the anatomical disposition, the site of the pump may be identified in the lateral plantar veins, whose middle portion is dilated and acts as a reservoir with a volume of 20 to 30 mL (Figure 6). The ratio of the diameter of the posterior tibial veins when compared with the diameter of the posterior tibial veins is 1.91:1, which creates a bellows-type effect to rapidly increase the velocity of flow within the posterior tibial veins. The distal part of the pump is a sort of “suction pole” coming from the highly vascularized toes and the large metatarsal perforator vein that drains the superficial network of the medial marginal vein. The posterior part, at the calcaneal confluent, corresponds to an “ejection pole,” which empties directly into the posterior tibial veins.

During a walking exercise, the foot is in contact with the ground 60% of the time and remains off the ground 40% of the time. The foot architecture is designed so that weight bearing takes place almost entirely on the ball of the foot, the heel, and the lateral part of the plantar surface of the foot. The medial part remains pressure free; thus, the plantar veins, which are located here, are protected from direct pressure, except in subjects with flat feet.

The pumping mechanism has been explained as follows. The plantar veins are connected like a bowstring between the base of the fourth metatarsal and the medial malleolus. Upon weight bearing, the tarso-metatarsal joints are extended and the tarsal arch is flattened. Thus, stretching makes the veins eject their content of blood. Successively, upon heel strike, weight bearing on the forefoot with dorsiflexion of the toes makes the muscles of the sole contract, resulting in compression of the pump in the musculotendinous plane (Figure 7). There is no difference
between the venous volume elicited by weight bearing and by toe curls. It is still not clear why both of these mechanisms produce the same effect or which mechanism is dominant; however, these two different venous foot pumps would be active at slightly different points in the phase of the gait cycle and both are likely active during the stance phase. Probably the muscle contraction pump is a memory of the preplantar phase in ontogenesis (ie, suspended or immersed life) in the absence of plantar support. Finally, in the suspension phase, pump filling is allowed.

During normal walking, the three vein-pumping systems (foot, proximal calf, and distal calf pumps) are synchronized to form a complete network both in series and in parallel, which promote venous return. Even moderate muscular movements of the legs, while in a seated position, may activate the pumping mechanism, and significantly reduce mean distal vein pressure.

Although synchronized with the calf pumps, the outflow from the footplexus is independent of the proximal calf muscle contraction. This is possible because the proximal calf pump and the venous foot pump work “in parallel,” ie, voiding their volumes separately into the main duct (popliteal vein) and not “in series,” ie, emptying in the same longitudinal duct in succession. This arrangement allows for an independent behavior of the two stronger pumps.

**Venous foot pump voiding**

Considering the three main deep veins of the leg, (ie, anterior, posterior, and peroneal veins, which are all doubled, with frequent interduplication connections), during venous foot pump activity (weight bearing and flexion of the first toe) the prevalent flow is directed into the posterior tibial veins. The posterior tibial vein is doubled with a deeper vein that is parallel to a more superficial vein. The more superficial vein originates from the medial planter vein, whereas the deeper vein originates from the lateral plantar vein.

The peroneal vein is doubled and drains the lateral aspect of the foot surrounding the calcaneal confluent and the ankle, passing upward and posteriorly through the calf, as well as passing posteriorly and medially to the fibula. The peroneal veins may receive the soleus veins at midcalf, creating an independent pump.

The anterior tibial vein is doubled and drains the blood from the dorsum of the foot starting from the perforator of the first metatarsal interspace and running up the anterior compartment, lateral to the tibia, and close to the interosseous membrane that connects the tibia and fibula. At the knee, the junction of the tibia and fibula, the vessels penetrate the interosseous membrane and enter the posterior compartment of the leg. Just below the knee, the four anterior and posterior tibial veins join with the two peroneal veins to become the large popliteal vein.

Video phlebography investigations confirmed that the preferential outflow of the pump is the posterior tibial vein, which is in direct continuity with the venous foot pump. The peroneal and anterior tibial veins share the same alternative outflow paths as the saphenous vein (through the malleolar perforators).

Mechanical compression of the plantar venous plexus produced a mean peak velocity of \(123 \pm 71 \text{ cm/sec}\) in the posterior tibial veins, \(29 \pm 26 \text{ cm/sec}\) in the peroneal veins, and \(24 \pm 14 \text{ cm/sec}\) in the anterior tibial veins.

Consequently, each volumetric pump is anatomically independent (although with multiple connections) and connected in parallel with the final formation of the popliteal vein. However, the venous foot pump has a supplementary way of emptying through the saphenous vein, possibly by being fed from the medial marginal vein (ie, the dorsal perforator that communicates with the anterior tibial vein) and the malleolar perforator vein, which is connected to the calcaneal confluent.
This event is indirectly demonstrated by the studies of Strand et al that showed greater ambulatory pressure reduction in the dorsal foot vein (behaving like deep foot veins) than in the saphenous vein of the calf (mean, 25 mm Hg) during exercise, suggesting that a part of the ejected volume goes via the great saphenous vein. In another more recent study by Neglén and Raju, the drop in venous pressure in the dorsal foot is significantly more marked compared with both the popliteal vein and great saphenous vein at all levels (Figure 8). The recovery time is significantly increased in the long saphenous vein compared with the deep vein, and it is then further prolonged in the dorsal foot vein, proving that the three veins hydraulically behave as separate compartments. As the measurements are made distally to the calf pump, this indicates that the venous foot pump is the “engine” of the distal blood return. This may explain why signs and symptoms of chronic venous insufficiency occur with normal ambulatory venous pressures in the dorsal foot. The channel with the lower gradient will be favored in any occasion, depending on the muscular activity, temperature, position, overflow, and/or obstruction.

Gait
At the beginning of a step, the distal calf pump is activated. This process is initiated by dorsiflexion of the foot as the leg is lifted to take a step. The anterior compartment muscles contract, dorsiflect the foot, and empty its veins (ie, the anterior tibial veins). Dorsiflexion passively stretches the Achilles tendon and empties blood from the lower portions of the peroneal and posterior tibial veins. As the foot strikes the ground, weight bearing activates the second phase: the above-described venous foot pumps. Plantar flexion initiates the third phase as the foot comes up on its toes: the muscles of the posterior compartments, particularly the gastrocnemius and soleus muscles, contract, and then empty the proximal venous reservoir. Plantar flexion also tenses and shortens the Achilles tendon, which maintains pressure on the distal portion of the calf muscle pump.

More detail regarding dorsiflexion of the ankle (passive or active) is provided in Figure 9. The bulk of the calf muscle descends within the fascial sheath and expels blood in the distal veins like a piston, which provides space to the blood coming from the venous foot pump (due to weight bearing).

<table>
<thead>
<tr>
<th>A</th>
<th>Dorsal V</th>
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<tr>
<td>B</td>
<td>Deep V</td>
</tr>
<tr>
<td>C</td>
<td>GSV</td>
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**Figure 8. Lower leg venous pressure tracings.**

The dorsal foot (Panel A), popliteal (Panel B), and great saphenous (Panel C) venous pressure tracings simultaneously recorded 5 to 7 cm above the ankles during 10 toe stands in a patient with no reflux or obstruction. The right set of curves is a magnification of the left set.

Abbreviations: GSV, great saphenous vein; V, vein.
which will prevalently feed the posterior tibial veins. The proximal calf pump and venous foot pump act “in series,” ie, in succession on the same axis. If the deep veins are not emptied regularly, the venous foot pump finds resistance to expel the blood in the deep veins; thereby, creating a favorable gradient. The proximal pump, on the other hand, is strong and can empty a high (although variable) volume of blood in the popliteal vein, even in the absence of a favorable gradient, and it works “in parallel” with the more distal complexes (ie, the systems working separately on variable volumes at independent pressures).

The distal leg pump may become insufficient, ie, unable to void the blood volume coming from the perforators during diastole, due to a reflux or functional overflow (excess of volume) or an organic or functional obstruction (excess of pressure). In this instance, the venous foot pump will redirect the blood in the alternative direction, that is, from the saphenous veins (marginal veins at the foot) through the perforators, which are normally valveless.

Many of the records by Pegum and Fegan were generated by cannulation of deep and superficial veins through an incision at the first interosseous space and show that when the pressure in the deep veins rose to exceed the superficial pressure, the superficial pressure also began to rise, although to a lesser extent.24 This suggests that pressure in the deep veins of the sole was being transmitted to the superficial veins (dorsal venous arch) by the perforating veins along the pressure gradient. This finding is consistent with the deep layer of the superficial fascia of the foot, which also supports the dorsal venous arch against this pressure (similar to, but stronger than, the saphenous fascia).

Blood from the lateral side of the foot and ankle is not drained in an upward direction by the saphenous veins, but downward through the intermetatarsal veins that feed the lateral plantar vein, ie, the venous foot pump “reservoir.” These veins are all interconnected by the rich net of vessels around the ankle joint. The high number of perforators in the foot and the absence of an oriented valvular system are the most interesting aspects and the anatomical basis of the venous foot pump. They allow a rapid filling of the reservoir, draining of the deep and superficial network, and they make possible, in alternative outflow channels, the ejection of a volume of blood greater than could be achieved in a closed system.24 The saphenous veins of the distal calf are able to transfer the blood received from the venous foot pump in the deep veins via the valvular perforating veins during the diastole (relaxation) of surrounding muscles, when the gradient is favorable.
Clinical Considerations

As a consequence of these observations, some clinical events could be related to the venous foot pump’s work against venous overload of the more proximal sections of the limb, as in most chronic venous insufficiency (CVI) situations. The pressure increase, due to the proximal obstacle (functional or organic) on the main duct, charges the collateral veins and activates shunts with a subsequently possible dilatation. This mechanism may overestimate the increased flow resistance and be fully compensatory. However, even if full compensation is achieved, the valvular system may become insufficient, thereby causing an inefficient action of the VMPs, and consequently, a functional obstruction, generating a short circuit.

Corona phlebitica

Corona phlebitica has been described as a fan-shaped cluster of small, dilated veins radiating down from the soleus perforator area over the medial side of the ankle and foot corresponding to C3 of the clinical, etiological, anatomical, pathophysiological (CEAP) classification (Figure 10). The Society for Vascular Surgery and the American Venous Forum consider it an early sign of advanced venous disease.

![Figure 10. Corona phlebitica paraplantaris in the absence of venous insufficiency.](image)

In the Phlebolymphological Guidelines of the Italian College of Phlebology, the corona phlebitica paraplantaris (also known as malleolar or ankle flares) is, by definition, due to the telangiectatic dilatation of intradermic veins at the medial (more frequent) and lateral sides of the foot. This is sometimes considered a sign of venous hypertension at an advanced stage of CVI; however, it may also be present independently, i.e., in the case of diffuse telangiectasias. Either definition or significance is uncertain. The dilatation of the superficial network of the skin of the foot could be explained as a hypertensive state due to an initially normal activity of the venous foot pump associated with events leading to a slowing of the blood flow in the deep veins, such as for chronic hypomobility (long periods of sitting, obesity, laziness), to the use of the wrong shoes, to age-related progressive inactivity, which is not necessarily in association with CVI. The association with CVI could be casual, or alternatively, the venous hypertension could enhance an already present tendency.

Skin lesions

Venous ulcers, lipodermatosclerosis, and pigmentation are typical skin manifestations of venous hypertension during CVI (Figure 11). Such signs typically appear in the medial supramalleolar area, regularly sparing the foot skin, with limited exceptions. An explanation may be that many patients with CVI have normal venous value pressure in the foot, as shown in 1986 by Strandén et al.

This lesion’s location is probably due to the relative “hemodynamic weakness” of the supramalleolar area, containing perforators that act as reentry ways for superficial reflux, but missing a strong pumping mechanism.

![Figure 11. Supramalleolar ulcer associated with lipodermatosclerosis and skin pigmentation.](image)
Indeed, the distal calf pump, generates a pressure that is much lower than the pumping energy of the venous foot pump (distally) and the sural-gastrocnemius pump (proximally).

When submitted to reentry flow due to saphenous incompetence, hypertension may be aggravated by pressure peaks generated at every step by the venous foot pump that radiates upward. Skin lesions could then be the result of the conflict between the venous overflow due to the refluxing volume reentering the distal calf perforators and the active “kicks” coming from below. Similar effects could take place when venous hypertension is due to impairment of the deep veins (postthrombotic syndrome).

Postexercise pressure, percentage of pressure drop, and recovery times are widely different in the deep veins, long saphenous veins, and dorsal foot veins, indicating that the three veins hydraulically behave as separate compartments. This may explain why signs and symptoms of chronic venous insufficiency occur with normal ambulatory venous pressures in the dorsal foot.23

Varices of the foot
Varices of the foot, often present in patients with varicose veins, have a peculiar behavior (Figure 12). Although the most distal part of the leg undergoes the strongest hydrostatic pressure, usually these varices appear late in the progression of the disease, and interestingly, they often do not seem to be directly involved in the reflux pathways, as if they were “suspended varices.” Indeed, the most important reentry perforators are located more proximally; the dilated veins of the foot are connected to foot perforators and may sometimes, but not always, communicate with the reflux pathway.

These varices might result from the action of the plantar pump “against” a system submitted to hypertension, particularly the deep veins, which are involved in the reentry of the refluxing volume. The strong venous foot pump would empty into the more compliant superficial network, developing varicose dilatations of the foot, which are connected with, but functionally unrelated to, the shunt circuit. Interestingly, dilatations of the foot veins almost exclusively involve the superficial network, which is unprotected by the superficial fascia, and spares the saphenous-type veins (ie, the marginal veins), which are sheltered by the superficial fascia (Figure 4) and are particularly robust in the foot.49

Is compression necessary for the foot?
Posturgery compression of the limb is mandatory, especially when treatment is partly based on phlebectomy of varicosities (under local anesthesia). The compression by selective pads provides hemostasis and allows the patient to walk immediately after the procedure. It also improves venous return and provides an analgesic effect.

With 40 years of experience in this practice, one of the authors observed that excluding the foot from the compression does not result in distal swelling and congestion. Naturally, this is possible only in C2 (of the CEAP classification) patients with a normal deep venous system, without edema, and who are actively walking (like most of our patients), and when the foot and distal limb are not involved in varices. Furthermore, the compression must be inelastic, which only acts during muscle activity and not at rest, and must involve the gastrocnemius area. It works like a “Perthes test.” Limited swelling may be present in the morning when rising from bed and disappears soon after the subject begins to walk. Inelastic compression of the leg allows the patient to wear normal shoes, conceal the surgical procedure, wash the foot, and is more comfortable.

Of the 183 phlebectomies (associated with or without great saphenous vein exclusion) performed from September 2010 to June 2011 at our institution, about half (90) of the feet
were not given compression and did not show any notable inconveniences.\textsuperscript{28} According to this concept, a similar “suspended compression” may be used in cases of knee joint inflammatory swelling for decongestive and analgesic purposes, provided that the patient is able to actively walk. The same experience is made by athletes and sportmen wearing compression sleeves in limited areas of the limb. Furthermore, a new stocking has been commercialized, which provides more compression at the upper calf than at the ankle, producing a “progressive” compression as opposed to the traditional “regressive” one.\textsuperscript{29}

According to Gardner, “If function can be maintained, encircling bandages limited to the proximal limb are permissible—as long they are not excessively tight—since the venomuscular pump are able to overcome resistances in excess of 150 mm Hg.”\textsuperscript{30}

\textbf{Arteriovenous fistulae}

Yoshida et al\textsuperscript{30} suggests, using a potential method to identify spontaneous arteriovenous fistulae, that arteriovenous fistulae occur between the plantar artery and the dorsal venous arch. These fistulae are activated when the foot is heated, eg, using a 38°C to 40°C footbath for 5 minutes, and can be visualized by duplex ultrasonography employing a 12 MHz transducer. Arteriovenous shunts (Sucquet-Hoyer canals) are present in the skin of toes, fingers, ears, and nose with thermoregulating functions. In fact, during vasodilation induced by heat, even vigorous walking movements fail to reduce the mean venous pressure below 0 mm Hg. However, when in the comfort zone, far less activity is required to effect such a reduction. Finally, when cool, even normal involuntary postural movements will reduce venous pressure to 50 mm Hg.\textsuperscript{31}

While arteriovenous fistulae have been reported as a potential contributtor to the development of thigh and calf varices,\textsuperscript{32} no information is available on the clinical relevance of arteriovenous fistulae of the feet. The hemodynamic role of these fistulae would be worthy of clarification, especially in the presence of varices of the lower leg or foot.

\textbf{Conclusion}

The pathophysiological and clinical conditions summarized here show that venous return from the foot is more than a gait-activated sponge and could be hemodynamically more important than has been previously considered. However, the incomplete knowledge of the physiopathology of venous return from the foot univocally hinders defining the relationship between dysfunction and clinical consequences. Some clinical aspects of venous pathology (eg, ulcer localization, corona phlebectatica, and venous dilatations) could be explained by a conflicting mechanism between the venous foot pump and the more proximal leg pumps, rather than a generic venous pump insufficiency. More thorough anatomy/physiology knowledge of the venous system of the foot could even enhance new methods of compression treatment (ie, “progressive” stockings).\textsuperscript{3}

\begin{figure}[h]
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\caption{Stefano RICCI, Ambulatorio Fieboligico, Rome, Italy. Email: varicci@tiscali.it}
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Micronized Purified Flavonoid Fraction in the treatment of pelvic pain associated with pelvic varicose veins

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Leninskii Prospekt, Moscow, Russia

Abstract

Aim: To evaluate the benefit of micronized purified flavonoid fraction (MPFF) in women suffering from chronic pelvic pain associated with pelvic varicose veins (PVV) and possible gonad varicose veins (GVV).

Methods: Consecutive women consulting for pelvic pain lasting more than 6 months, where a differential diagnosis of PVV had been made and possible concomitant diseases ruled out, were included in the study. Selected patients received MPFF treatment: 1000 mg a day for 8 weeks. Pelvic pain was self-assessed weekly using a visual analogue scale (VAS) during the 8 weeks of MPFF treatment and for 14 weeks after treatment was stopped. Imaging investigations using transvaginal ultrasound angioscan (USAS) and emission computer tomography (ECT) were repeated at 8 weeks, then at 6, 12, 36, and 60 months.

Results: A total of 85 women aged 28±4.6 years, of which 65 were in the PVV group and 20 in the PVV+GVV group, were enrolled in the study between 2000 and 2010. From weeks 2 to 4 of MPFF treatment, a reduction in pelvic pain was seen in either group. While a continuous pain decrease was reported by the PVV patients up to week 8 of treatment, there was no additional pain reduction in the PVV+GVV group. Over the 14 weeks following MPFF treatment, pelvic pain intensity was increased back to the pretreatment level in the PVV+GVV group, but was eliminated in the PVV group. In the latter group, the diameter of the PVVs did not significantly change over the long term (up to 60 months) as illustrated by USAS, and pelvic venous congestion declined as shown by ECT, reflecting a stabilization of the disease course.

Conclusion: In the present study, an 8-week MPFF treatment, 1000 mg up to 2000 mg per day, in women with isolated PVV, relieved them from their chronic pelvic pain in the short and long term. In patients with combined PVV and GVV, MPFF did not eliminate pain. However, MPFF may be used in women who wish a future pregnancy or in those reluctant to undergo surgery. ECT of the pelvic veins

Keywords:
micronized purified flavonoid fraction, pelvic pain, pelvic varicose vein
is a reliable method for monitoring the efficacy of treatment or progression of the disease thanks to quantitative assessment of the degree of pelvic vein congestion.

Introduction
Millions of women may suffer from chronic pelvic pain at some time in their life and the frequency may be as high as 39%.

The association with pelvic varicose veins (PW) was first documented in 1949. Severe and chronic pelvic pain often results from the presence of ovarian varicose veins and PW, reflecting chronic venous disorders in the pelvic veins. The compression of the left ovarian vein, the left renal vein, or the common iliac vein may also cause pelvic varices and pain.

Clinical practice has shown that only one-third of patients with PW need surgical treatment. The rest require conservative therapy, and the use of venoactive drugs has the most justification with regard to the pathogenesis and underpinnings of this pathology.

Research objective
The aim of our research was to evaluate the benefit of a pharmacological treatment with micronized purified flavonoid fraction (MPFF) in women suffering from chronic pelvic pain associated with PW and possible gonadal varicose veins (GW).

Materials and methods
Consecutive women consulting the S.I. Spasokukotskii Faculty Surgery Clinic for pelvic pain lasting greater than 6 months, where differential diagnosis of PW had been made and other possible causes had been ruled out, were included in the study. The diagnosis of PW was made on clinical presentation (pelvic pain, coital and postcoital pain, menstrual cycle disturbances, and dysuria), and was confirmed by imaging investigation on transvaginal ultrasound angioscan (USAS) and emission computer tomography (ECT) of the pelvic veins. Among the inclusion criteria was the absence of concomitant diseases. A bimanual pelvic examination by a urologist must reveal tenderness without induration or masses that could suspect another condition. An ultrasound investigation was systematically performed by a gynecologist to uncover pathological causes, such as endometriosis, adhesions, interstitial cystitis, and irritable bowel syndrome.

Once selected, the participants were further divided into 2 groups depending on the findings at investigation: (i) those with isolated dilation of pelvic venous plexus without any deterioration of the vulvar or ovarian veins (PVW group); and (ii) the others with more extended pelvic vein damage, combining both PVW and GW (PVW+GW group). Both groups underwent a conservative treatment with MPFF, at least 1000 mg per day for 8 weeks, with the goal of assessing the extent of pelvic vein damage, such that a conservative treatment could be efficient.

The primary end points were:

- Reduction or even elimination of the chronic pelvic pain on a 10-cm visual analogue scale (VAS) during MPFF treatment.
- Reduction in or absence of blood deposits in the pelvic venous plexus on ECT, reflecting a diminution of the pelvic venous congestion that could be assessed by a coefficient of pelvic venous congestion (CPVC), during MPFF treatment.

The long-term results (or secondary end points) were:

- Reduction in pelvic pain on VAS.
- Reduction in pelvic vein diameter on transvaginal USAS.
- Diminution of the CPVC.
- Amelioration of the associated symptoms (coital pain, dyspareunia, menstrual pain, and dysuria).

Every week during the 8 weeks of MPFF treatment, and then during the 14-week follow-up after treatment (until week 22), the patients self-assessed their pelvic pain on VAS. Imaging investigations (ie, USAS, ECT) were repeated at different times during the study: 8 weeks, then at 6, 12, 36, 48, and 60 months.

Results
A total of 85 women were enrolled in the study between 2000 and 2010. The age ranged from 18 to 43 years, with an average of 28±4.6 years. The clinical picture of the disease was characterized by the presence of chronic pelvic pain in 100%, coital and postcoital pain in 72%, menstrual cycle disturbances in 42%, and dysuria in 34% of the enrolled women. A total of 65 women had PW in isolation, and 20 presented with both GW and PW.
During MPFF treatment (baseline to week 8)

Pelvic pain measurement on VAS

We noticed that the starting MPFF dose of 1000 mg/day relieved most of the women, right from the first month, in both groups (58 women; 50 in the PVW group and 8 in the PVW+GW group), but was insufficient to relieve the 27 remaining patients from their pelvic pain. In “nonrespondent” women (15 in the PVW group and 12 in the PVW+GW group), we had to increase the MPFF dosage up to 2000 mg/day after 1 month.

From weeks 2 to 4 of treatment, a reduction in pelvic pain was seen in either group (PVW and PVW+GW) at the dosage of MPFF 1000 mg/day. From weeks 5 to 8 of MPFF treatment, the dose increase achieved a continuous pelvic pain decrease in the PVW group. There was no additional pain reduction in the PVW+GW group despite the dose increase (Figure 1).

![Figure 1. Assessment of pelvic venous pain.](image)

Assessment of pelvic venous pain on a 10-cm VAS during an 8-week MPFF treatment in patients with pelvic vein dilation in isolated PVW and with associated PVW and GW.

Abbreviations: GW, gonadal varicose veins; MPFF, micronized purified flavonoid fraction; PVW, pelvic varicose veins; VAS, visual analog scale.

Pelvic venous congestion on ECT

In the 65 PVW patients who were all relieved from pelvic pain with MPFF treatment (with VAS≤1) as evidenced in Figure 1, the comparison of ECG imaging at baseline and at week 8 of treatment showed a decline in the level of labeled erythrocytes in the venous plexus of the pelvis (Figure 2), together with a drop in the CPVC from 1.6±0.4 at baseline to 1.0±0.02 at week 8 (P<0.05).

In contrast, patients presenting with PVW+GW did not report a complete elimination of pelvic pain after 8 weeks of MPFF treatment, even though they felt an improvement. This was confirmed by an absence of any significant changes on

![Figure 2. ECT assessment of pelvic veins before and after MPFF treatment.](image)

ECT of the pelvic veins at baseline (Panel A) and after an 8-week MPFF treatment (Panel B) in a patient with pelvic vein dilation in isolated PVW. Deposit of labeled erythrocytes in the uterine venous plexus is indicated by the arrows.

Abbreviations: ECT, emission computer tomography; MPFF, micronized purified flavonoid fraction; PVW, pelvic varicose veins.
ECG imaging. A surgery of ovarian veins was proposed to these women and was accepted by 12 of the 20 women.

After MPFF treatment (week 9 to week 22)
Patients in the PW group who self-assessed their pain during the 14 weeks following MPFF treatment (week 9 to week 22) were almost relieved of their pelvic pain in the long term. Contrarily, those who belonged to the group with more extended PW (PVV+GWV group) reported an increase in pelvic pain that reached the pre-MPFF treatment level within the 10 weeks that followed the treatment (Figure 3).

Long-term readministration of MPFF
Over the 60 months of observation of patients with PV in isolation (PVV group), additional courses of MPFF therapy were undertaken using the previously recommended dose and duration. A total of 8 patients were excluded for the long-term observation due to concomitant pathology that occurred in the meantime: 4 women developed endometriosis; 2, vulvar varicose veins; 1, an adhesive process; and 1, acute cystitis. Of the 57 PW women who followed several, long-term treatment courses, 7 took MPFF for preventive purposes and the others only when the symptoms reoccurred (pelvic pain, dyspareunia, coital and postcoital pain, etc).

Table 1 summarizes the number of MPFF-treatment courses undertaken by 57 PW women at the different times of the study. Of note, the number of courses per year usually did not exceed 3, and the duration of administration ranged from 2 to 3.2 months.

Long-term pelvic pain measurement
Over a 60-month period, pelvic pain scores in PW patients were maintained around 1 cm according to the VAS assessment, with an increase at 36 and 48 months, corresponding to noncompliance with MPFF treatment in some patients. The PVV+GWV group of patients remained with a high level of pelvic pain similar to that before MPFF treatment despite a drop in pain from VAS 8 cm to VAS 4 cm after a 2-month MPFF treatment (1000 mg/day) was seen. The patients’ flow diagram is summarized in Figure 5.

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<td>Duration of MPFF</td>
<td>2</td>
<td>2</td>
<td>3.2±0.4</td>
<td>2.6±0.3</td>
<td>2.3±0.4</td>
</tr>
<tr>
<td>administration in months</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Table 1. Number of courses and duration of MPFF treatment in 57 patients with pelvic vein dilation in isolated PV only over a 60-month observation period.

Abbreviations: MPFF, micronized purified flavonoid fraction; PV, pelvic varicose veins.
Figure 5. Patients flow-diagram.

Abbreviations: CPVC, coefficient of pelvic venous congestion; ECT, emission computer tomography; GVV, gonadal varicose vein; Mo, month; MPFF, microneedles purified flavonoid fraction; pts, patients; PVV, pelvic varicose vein; VAS, visual analogue scale; W, week.
Pelvic venous congestion on ECT

In PVV patients who were all relieved from pelvic pain and congestion of the pelvis with MPFF treatment (Figure 1 and Figure 2), the comparison of ECT imaging at baseline, and at 6, 12, 36, and 60 months showed results similar to 8 weeks post-MPFF treatment: the level of labeled erythrocytes in the venous plexus of the pelvis declined (Table II) and the CPVC remained at a low level (1.3±0.1) even at the 60-month follow-up.

Pelvic vein diameter on transvaginal USAS

The diameter of PVV did not significantly change over the long term, reflecting a stabilization of the disease course with MPFF treatment (Table III).

Side effects

Over a 60-month follow-up period with iterative MPFF treatments, no side effects were noted, except a few manifestations of gastric dyspepsia, which disappeared after a short time (2 to 3 days) when the drug was withdrawn and did not recur.

Conclusion

In the present study, an 8-week MPFF treatment, 1000 or 2000 mg per day, in women with isolated PVV, relieved them from their chronic pelvic pain. In the long term (up to 60 months), iterative MPFF treatments of an average of three 3-month courses helped to eliminate pelvic pain in these PVV patients. In patients with combined PVV and GWV, MPFF treatment failed to eliminate pelvic pain. However, MPFF may be used in women who wish a future pregnancy or in those reluctant to undergo surgery. ECT of the pelvic veins is a reliable method of monitoring the efficacy of treatment or progression of the disease thanks to quantitative assessment of the degree of pelvic vein congestion.

Table II. Results of ECT in 57 patients with pelvic dilation in isolated PVV assessed using the CPVC.

*P≤0.05 compared with baseline.

<table>
<thead>
<tr>
<th>Study time in months (mo)</th>
<th>Coefficient of pelvic venous congestion (CPVC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1.6±0.40</td>
</tr>
<tr>
<td>6 mo</td>
<td>1.1±0.20</td>
</tr>
<tr>
<td>12 mo</td>
<td>1.0±0.30</td>
</tr>
<tr>
<td>36 mo</td>
<td>1.2±0.08</td>
</tr>
<tr>
<td>60 mo</td>
<td>1.3±0.10</td>
</tr>
</tbody>
</table>

Table III. Results of transvaginal USAS in 57 patients with pelvic dilation in isolated PVV using the diameter of the pelvic vein.

*P=NS compared with baseline.

<table>
<thead>
<tr>
<th>Study time in months (mo)</th>
<th>Pelvic vein diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3.2±0.40</td>
</tr>
<tr>
<td>6 mo</td>
<td>3.4±0.12</td>
</tr>
<tr>
<td>12 mo</td>
<td>3.7±0.09</td>
</tr>
<tr>
<td>36 mo</td>
<td>3.6±0.15</td>
</tr>
<tr>
<td>60 mo</td>
<td>3.5±0.07</td>
</tr>
</tbody>
</table>

Abbreviations: CPVC, coefficient of pelvic vein congestion; ECT, emission computer tomography; PVV, pelvic varicose veins.

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REFERENCES


Management of superficial vein thrombosis of the lower limbs: update and current recommendations

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Abstract

Initially, superficial vein thrombosis (SVT) was considered a benign disease or a common complication of varicose veins. Recent studies have shown the potential severity of SVT and defined its place within the venous thromboembolic (VTE) diseases, along with deep vein thrombosis (DVT) and pulmonary embolism (PE). A concomitant DVT was identified in 25% to 30% of patients at presentation and a PE in 4% to 7% of patients. Subsequent VTE were reported in 3 to 20% of patients, depending on the follow-up duration. Until recently, numerous anticoagulant strategies have been tested, with no clearly demonstrated clinical benefit. However, the recent CALISTO study (Comparision of Arixtra in lower Limb Superficial vein Thrombosis with placebo) validated an anticoagulant therapy protocol based on fondaparinux, 2.5 mg daily for 45 days, resulting in updated recommendations for the management of SVT. This article will present an update on the management of lower-leg SVT and the current recommendations and guidelines. Briefly, all patients with SVT should have a bilateral duplex scan to confirm the diagnosis of SVT, determine the precise location and extent of the SVT, and diagnose or rule out the presence of a DVT. For patients with symptomatic SVT at least 5 cm in length, it is recommended to prescribe a prophylactic dose of fondaparinux or low-molecular-weight heparin for 45 days over no anticoagulation (Grade 2B), and when the cost of treatment with fondaparinux is acceptable, it is recommended to use fondaparinux 2.5 mg daily vs low-molecular-weight heparin (Grade 2C). However, the recommendations and guidelines have assigned these treatments with a low grade, and questions remain about SVT management. Some risk factors for subsequently developing a VTE have been identified, but further research is needed to define subgroups of patients with a higher incidence of a VTE after an SVT.

Introduction

Superficial vein thrombosis (SVT) has been considered a benign disease or common complication of varicose veins; however, recent studies have shown
their potential severity and defined their place within the venous thromboembolic (VTE) diseases, along with deep vein thrombosis (DVT) and pulmonary embolism (PE).

Anticoagulant therapy is widely used today instead of nonsteroidal anti-inflammatory drugs (NSAID), which were commonly used until the last decade. A recent study has, for the first time, validated a therapeutic protocol. However, questions remain concerning SWT management: (i) is anticoagulant therapy required to treat all patients with SWT of the lower limbs?; (ii) should prophylactic or therapeutic doses be used?; (iii) what is the recommended treatment duration?; (iv) should the management be the same for SWT occurring in varicose veins and non-varicose veins?; (v) can the risk factors of VTE complications after SWT be predicted?; and (vi) is surgery still indicated for the management of an acute SWT?

This article will present the rationale behind the update for the management of SWTs of the legs and the current recommendations and guidelines.

**Incidence of superficial vein thrombosis of the lower limbs**

SVT is considered a common disease, but the actual incidence in the adult population remains unknown. A recent study, conducted in France, showed that the annual diagnosis rate was 0.6%. It was higher in women and increased with advancing age regardless of gender. Surprisingly, the annual diagnosis rate of SVT was lower than expected and lower than the annual diagnosis rate of DVT (about half that of DVT). According to another French study, which was conducted with comparable methods, the annual incidence of a lower limb DVT and PE was 1.24% and 0.6%, respectively.

**Superficial vein thrombosis with concomitant deep vein thrombosis at presentation**

The POST (Prospective Observational Superficial Thrombophlebitis) and OPTIMEV studies (OPTimisation de l’Interrogatoire dans l’évaluation du risque thrombo-Embolique Veineux), two large observational and epidemiological studies, recently published essential data on SWT. A total of 844 patients with SWT of the legs were analyzed in the POST study and a DVT or PE was identified in 25% of patients with SWT at presentation and a proximal DVT was diagnosed in 9.7% of the patients. We must emphasize that DVT was not contiguous with SWT in 41.9% of patients with DVT. A total of 788 patients with SWT were enrolled in the OPTIMEV study where an SWT was associated with a DVT at inclusion in 29% of patients, with distal DVT occurring in 59.5% of these patients (128/215; the exact location of DVT was missing in 12 patients).

These data confirm previous studies showing that DVT was associated with SWT in 23% to 36% of patients and show coherence among the different studies (Table 1). Table 1. Superficial vein thrombosis with concomitant deep vein thrombosis at presentation.

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients with DVT (n) / patients with SWT (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutter et al.⁴ 1991</td>
<td>53 / 186 (28.5%)</td>
</tr>
<tr>
<td>Barrellier⁷ 1993</td>
<td>38 / 105 (36%)</td>
</tr>
<tr>
<td>Jørgensen et al.⁸ 1993</td>
<td>10 / 14 (22.7%)</td>
</tr>
<tr>
<td>Bilancini and Lucchi⁹ 1999</td>
<td>25 / 106 (23.6%)</td>
</tr>
<tr>
<td>Gillet et al.¹⁰ 2001</td>
<td>32 / 100 (32%)</td>
</tr>
<tr>
<td>Decousus et al.¹ⁱ 2010</td>
<td>210 / 844 (24.9%) (DVT and/or PE)</td>
</tr>
<tr>
<td>Galanaud et al.¹² 2011</td>
<td>227 / 788 (28%)</td>
</tr>
<tr>
<td>Frappé et al.¹³ 2014</td>
<td>42 / 171 (24.6%)</td>
</tr>
</tbody>
</table>

Table 1. Superficial vein thrombosis with concomitant deep vein thrombosis at presentation.

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; SWT, superficial vein thrombosis.

**Superficial vein thrombosis associated with pulmonary embolism at presentation**

At inclusion, symptomatic PE was diagnosed in 3.9% and 6.9% of patients in the POST and OPTIMEV studies, respectively. However, SWT with PE, but without DVT, accounted for only 2.2% of all SWTs with DVT or PE. These data corroborate findings from previous studies (Table 2). Table 2. Superficial vein thrombosis with concurrent pulmonary embolism at presentation.

In practice, a duplex scanning examination is mandatory in patients with SWT to confirm the diagnosis (Figure 1), determine the precise location and extent of the SWT, and diagnose the presence of a DVT.
Table II. Superficial vein thrombosis with concomitant pulmonary embolism at presentation.

Abbreviations: PE, pulmonary embolism; SVT, superficial vein thrombosis.

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients with PE (n) / patients with SVT (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutter et al.⁶ 1991</td>
<td>8 / 186 (4%)</td>
</tr>
<tr>
<td>Barrellie⁷ 1993</td>
<td>14 / 105 (13.3%)</td>
</tr>
<tr>
<td>Bilancini and Lucchi.⁸ 1999</td>
<td>2 / 106 (1.9%)</td>
</tr>
<tr>
<td>Gillet et al.⁹ 2001</td>
<td>3 / 100 (3%)</td>
</tr>
<tr>
<td>Decousus et al.¹⁰ 2010</td>
<td>33 / 844 (3.9%)</td>
</tr>
<tr>
<td>Galanaud et al.¹¹ 2011</td>
<td>54 / 788 (6.9%)</td>
</tr>
<tr>
<td>Frappé et al.¹² 2014</td>
<td>8 / 171 (4.7%)</td>
</tr>
</tbody>
</table>

Outcome and venous thromboembolic recurrence

In the literature, the rate of thromboembolic recurrence ranges from 3% to 20% depending on the duration of the follow-up. In a personal study,¹³ we reported the occurrence of symptomatic VTEs in 16.4% of patients with isolated SVT, with a mean follow-up of 14.5 months. The VTE events included DVT (31%), PE (6%), another SVT in a different saphenous system (37.5%), and a recurrent SVT in the same saphenous system (25%).

In the POST study,⁴ 8.3% of patients with an isolated SVT at inclusion developed at least 1 symptomatic VTE event at 3 months (symptomatic DVT, 2.8%; symptomatic PE, 0.5%; symptomatic extension of SVT, 3.3%; and symptomatic recurrence of SVT, 1.9%). In the OPTIMEV study,⁵ 3% of patients with an isolated SVT and 5.4% of patients with an SVT associated with DVT at presentation, developed a VTE at 3 months; the rate of VTEs was 12.5% at the 3-year follow-up. In the study by Dewar and Panphier,⁴ a symptomatic DVT occurred in 4% of the patients with an isolated SVT at a 6-month follow-up.

These epidemiological findings show the potential severity of SVT. They should no longer be considered a benign condition. Consequently, their place has now been clearly defined within the VTE diseases.

Risk factors for developing a thromboembolic event

A multivariate analysis of the POST study⁴ identified male sex, history of DVT or PE, previous cancer, and no varicose veins as risk factors for a symptomatic VTE at 3 months, including recurrence or extension of the SVT. In the STENOX study (Superficial Thrombophlebitis treated by Enoxaparin),¹⁵ history of a VTE (DVT or PE), male sex, and severe chronic venous insufficiency were identified as independent predictive factors for a VTE at 3 months. Only severe chronic venous insufficiency was an independent predictive factor for DVT or PE. In a pooled analysis of the POST and OPTIMEV studies,¹⁶ Galanaud et al showed that male sex, cancer, personal history of VTE, and saphenofemoral or saphenopopliteal involvement significantly increased the risk of a subsequent VTE or DVT/PE in a univariate analysis. In multivariate analyses, only male sex significantly increased the risk of a subsequent VTE or a DVT/PE recurrence. For cancer and a personal history of VTE, the adjusted hazard ratios were only slightly

Recommendation

Clinical examinations may underestimate the real extent of SVTs and do not provide information on the status of the deep venous system. Therefore, it is mandatory to perform an extensive color duplex ultrasound scan of both the superficial and deep venous system.¹¹²
below the level of statistical significance (P=0.06 for both), suggesting that, for these factors, the study merely lacked sufficient statistical power.

In the STEFLUX study (Superficial Thromboembolism FLUXum), being having a body mass index (BMI) between 25 and 30 kg/m² and a composite of a previous SVT and/or VTE and/or family history of VTE were identified as significant independent risk factors for a VTE event (composite of symptomatic and asymptomatic DVT, PE, and SVT recurrence or extension).

Vein status
Varicose vein status has been reported to influence the risk of exhibiting DVT at presentation. In the POST⁴ and OPTIMEV studies,⁵ SVTs occurring in a non–varicose vein (NW-SVT) were more often associated with a concomitant DVT or PE than SVTs occurring in a varicose vein (W-SVT). Similar findings were reported by Gorty et al.¹⁸

At the 3-month follow-up in the OPTIMEV study, isolated NW-SVT was not associated with a higher risk of adverse outcomes (i.e., death, VTE recurrence, and bleeding). Isolated NW-SVT had a higher association with symptomatic DVT or PE recurrence (2.7% vs 0.6%), but this result did not reach statistical significance (P=0.07).

In the POST study, the absence of varicose veins was identified as a risk factor for the subsequent development of a symptomatic VTE in patients with an isolated symptomatic SVT at presentation (P=0.049). In the STEFLUX study,¹⁷ the absence of varicose veins was a risk factor for VTE (P=0.004) after the treatment with low-molecular-weight heparin was stopped.

In the placebo group of the CALISTO study (Comparison of Aristra in lower Limb Superficial vein ThromboSis with placebo),¹³ thromboembolic complications occurred more often when the great saphenous vein (GSV), was extended to within 10 cm of the saphenofemoral junction (SFJ), involved veins above the knee, and in patients with a history of VTE.

Venous stasis is the primary mechanism of SVT in patients with varicose veins. Inflammation may play an essential role in thrombus formation in patients without varicose veins; thereby, conferring a higher risk for a more clinically serious thromboembolism. Screening for thrombophilia is not recommended for the routine management of patients with NW-SVT, although data from the literature showed that thrombophilia was frequent in this situation. In a personal prospective study,¹⁰ we identified thrombophilia in 50% of patients with NW-SVT, while only 15% of the patients with W-SVT had thrombophilia. In another prospective study involving 42 patients with NW-SVT,¹⁹ we identified thrombophilia in 20 (47.6%) patients. The most common thrombophilia was due to the heterozygous factor V Leiden mutation. In a study involving 63 patients with isolated NW-SVT,²⁰ Martinelli et al identified thrombophilia in 30% of patients. Screening for thrombophilia is advisable, after exclusion of an occult cancer, especially for patients with thrombus progression despite appropriate anticoagulant therapy.¹¹,²¹

Treatment of superficial vein thrombosis
Treatment of SVT has always been a controversial topic. Great variations in the treatment are reported, especially regarding anticoagulant therapy. The POST study,⁴ which was carried out in France between March 2005 and October 2006, provided interesting information regarding SVT treatment. A total of 634 patients had an isolated SVT at inclusion. Information about the treatment they received during the 3-month observation period was available for 597 patients, with 90.5% of patients having received one or more anticoagulant drugs. Of the patients receiving anticoagulant therapy, 63% received therapeutic doses, 36.7% prophylactic doses, and 16.8% vitamin K antagonists. Treatment duration was highly variable. A total of 472% of patients received a topical NSAID, 8.2% an oral NSAID, and 10% had venous surgery (stripping or high-ligation).

These data showed the necessity of clarifying the role of anticoagulant therapy in SVT management. The use of anticoagulant therapy in patients presenting with an SVT was first reported in 1962 by Zollinger et al,²² after observing the occurrence of a PE, which was fatal in 34 (10.1%) of a series of 335 patients with an SVT. Until recently, although numerous anticoagulant strategies had been tested, including unfractionated heparin or low-molecular-weight heparin, at prophylactic or therapeutic doses for various durations, none had clearly demonstrated any clinical benefit.

The STENOX study,²³ was a randomized double-blind trial involving 427 patients, comparing low-molecular-weight heparin (enoxaparin at therapeutic and prophylactic
doses) with NSAID and placebo. Patients were treated for 10 days, with a 3-month follow-up. At 10 days, there were more VTEs in the placebo group (P<0.01) than the other groups, but at 3 months there was no difference, suggesting that the 10-day treatment period was too short. The VESALIO study \textsuperscript{24} compared therapeutic vs prophylactic doses of nadroparin in 163 patients with an isolated SVT in the GSV, and patients were treated for 1 month. At the 3-month follow-up, the results were similar in both groups (7.2% and 8.6% occurrence of a VTE, respectively; P=0.7), showing no benefit of the therapeutic dosage. A "catch-up" or rebound phenomenon was observed during the follow-up, as many VTEs were reported, especially in the group of patients treated with the therapeutic dosage. A "catch-up" phenomenon was also observed after discontinuing low-molecular-weight heparin treatment after 1 month in the STEFLUX study.\textsuperscript{25} These findings, like those of the STENOX trial, plead for the choice of prophylactic doses of low-molecular-weight heparin in SVT. The occurrence of the majority of VTEs during the 2 and 3 months after discontinuing treatment with low-molecular-weight heparin in the group receiving therapeutic doses, once again highlights the issue of the optimal duration of anticoagulant therapy.

The randomized, double-blind CALISTO study\textsuperscript{1} compared fondaparinux 2.5 mg daily for 45 days with placebo in 3002 patients with an isolated symptomatic lower limb SVT that was at least 5 cm in length. The main exclusion criteria were treatment for cancer within the previous 6 months, DVT or PE within the previous 6 months, SVT located within 3 cm of the SFJ, and severe renal insufficiency (creatinine clearance <30 mL/min).

According to Decousus et al.,\textsuperscript{26} the 2.5 mg dose of fondaparinux was selected on the idea that a prophylactic dose would be sufficient to treat patients with SVT. In addition, this dose was shown to be more effective in preventing VTEs after major orthopedic surgery than a prophylactic dose of low-molecular-weight heparin, and as effective as the therapeutic dose of low-molecular-weight heparin in patients with acute coronary syndromes, suggesting that 2.5 mg fondaparinux would match the 2008 American College of Chest Physicians (ACCP) recommendations\textsuperscript{27} that advocate the use of either prophylactic or intermediate doses of low-molecular-weight heparin to treat patients with SVT. The duration of 45 days was chosen because a treatment period of 30 days or less might be too short, as most symptomatic VTEs occur after treatment discontinuation. The primary efficacy outcome was a composite of death from any cause, a symptomatic PE, a symptomatic DVT, a symptomatic extension to the SFJ, or a symptomatic recurrence of SVT at day 47. There was a 77-day follow-up period for the patients.

The primary efficacy outcome occurred in 0.9% of patients in the fondaparinux group and 5.9% in the placebo group (P<0.001). The incidence of each component of the primary efficacy outcome was significantly reduced in the fondaparinux group as compared with the placebo group, except for death (0.1% in both groups). The rate of PE or DVT was 85% lower in the fondaparinux group.

Unlike previous studies with low-molecular-weight heparin, and using shorter courses of treatment, similar risk reductions were seen at day 77, 1 month after discontinuing fondaparinux. Based on the results from the CALISTO study, fondaparinux was granted European market authorization for treatment of isolated SVT and the ACCP guidelines were updated.\textsuperscript{28}

### 2012 ACCP guidelines

In patients with SVT of the lower limb that are at least 5 cm in length, section 8.1.1 of the 2012 ACCP guidelines suggest using a prophylactic dose of fondaparinux or low-molecular-weight heparin for 45 days vs no anticoagulation (Grade 2B).\textsuperscript{28} In patients with superficial vein thrombosis who are treated with anticoagulation, section 8.1.2 of the guidelines suggest using fondaparinux 2.5 mg daily over a prophylactic dose of low-molecular-weight heparin (Grade 2C).

### 2012 ACCP guidelines

It is interesting to notice the change of recommendations from the 2008 ACCP guidelines.\textsuperscript{27} However, we must take into account that they are low-grade recommendations (Grade 2B or 2C).

In the update of the Cochrane Database Systematic Review on “Treatment for superficial thrombophlebitis of the leg,”\textsuperscript{29,30} Di Nisio et al reached the same conclusions. This review was based on the analysis of 30 randomized controlled trials involving 6507 participants with SVT of the legs. The authors’ conclude that a prophylactic dose of fondaparinux, given for 6 weeks, appears to be a valid therapeutic option for SVT of the legs. The evidence on oral treatments, topical treatment, or surgery is too limited and does not provide information for use in clinical practice.
about the effects of these treatments in terms of VTE and SVT progression.

**Surgery versus anticoagulant therapy**

A review of studies comparing surgery with anticoagulant therapy does not show any benefit for surgical treatment. The rates of SVT progression were similar while the incidence of VTE and complications were higher with surgery. Lozano et al showed no difference between surgery and enoxaparin for 4 weeks.32

**Recommendations**

Surgery is no better than low-molecular-weight heparin treatment (low level of evidence).11 The extension of the SVT at the SFJ or the saphenopopliteal junction (SPI) is a serious condition, with a high risk of extension into the femoral or popliteal vein and embolization (Figures 2 and 3).33

When the thrombus is close to the SFJ or SPI, low-molecular-weight heparin at therapeutic doses or surgery (ligation) are both acceptable options depending on the patient’s characteristics and the treating physician’s preference (low level of evidence).11

**American Venous Forum guidelines**

The guidelines of the American Venous Forum34 are very similar to the previous recommendations because, for a saphenous vein thrombophlebitis within 1 cm of the SFJ or SPI, they suggest using high ligation with or without saphenous vein stripping to avoid extension into the deep venous system and embolization. Anticoagulation is an acceptable alternative therapy (Grade 2B).

In practice, most experts recommend treating patients with SVT extended at the SFJ or SPI with anticoagulant therapy at therapeutic doses for 3 months.

**Conclusion**

SVT should no longer be considered a benign disease. Recent epidemiological studies, which have included a large number of patients, have shown the potential severity of SVTs and have clearly defined their place within the VTE diseases. A concomitant DVT was identified in 25% to 30% of patients at presentation and a PE in 4% to 7% of patients. Consequently, all patients with SVT should have bilateral duplex scanning to confirm the diagnosis of SVT, determine the precise location and extent of the SVT, and diagnose or rule out the presence of a DVT. Today, SVT management has changed, with anticoagulant therapy being widely used instead of NSAIDs. Until the recent CALESTO study, no anticoagulant protocol had demonstrated a clear clinical benefit. The recommendations were updated after the CALESTO study validated the anticoagulant therapy protocol based on fondaparinux 2.5 mg daily for
45 days. For patients with a symptomatic SVT of the legs at least 5 cm in length, a prophylactic dose of fondaparinux or low-molecular-weight heparin for 45 days is recommended over anticoagulation (Grade 2B). When the cost of treatment with fondaparinux is acceptable, using fondaparinux 2.5 mg daily over a prophylactic dose of low-molecular-weight heparin is recommended (Grade 2C). However, the recommendations and guidelines are of a low grade, and questions remain concerning SVT management. Some risk factors for subsequently developing a VTE have been identified, but further research is needed to clearly define subgroups of patients with a higher incidence of VTE after SVT.

REFERENCES


Comparative effectiveness of surgical interventions aimed at treating underlying venous pathology in patients with chronic venous ulcer


This review was contracted by the US Agency for Health Care Research and Quality (AHRQ) for the Johns Hopkins Evidence-based Practice Center. Two key questions were developed:

1. For patients with a chronic venous ulcer (CVU), what are the benefits and harms of surgical procedures?

2. For patients with a CVU, what are the comparative benefits and harms of different surgical procedures for a given type of venous reflux and obstruction?

A systematic review was conducted and 10,646 citations were identified, of which, 22 studies were included. Six randomized controlled trials (RCTs) compared a surgical procedure with compression. Adding superficial vein ligation and stripping to compression did not improve wound healing rate. However, the recurrence rate was reduced by 50% when surgery corrected the underlying superficial venous pathology (ie, a moderate-to-high strength of evidence according to the AHRQ criteria). Adding subfascial endoscopic perforator surgery (SEPS) and superficial vein surgery to compression did not improve the healing rate of CVU or reduce the recurrence rate, except for medial and large ulcers. There was insufficient evidence on the surgical treatment of CVUs secondary to deep venous reflux and venous obstruction. Their ability to draw conclusions on the best surgical techniques was limited due to poorly designed and executed studies, with no uniformity of treatment methods, follow-up, or reporting, and a lack of randomization. The authors concluded that RCTs for the endovenous procedures currently used for treating CVUs are needed.

Comments

The Society for Vascular Surgery (SVS) and the American Venous Forum (AVF) published their clinical practice guidelines for the management of CVUs in the Journal of Vascular Surgery as a supplement to the August 2014 issue. This is a 59-page document with 547 references that is based on two systematic reviews and meta-analyses from the Knowledge and Evaluation Research Unit at the Mayo Clinic under the leadership of Mohammad Hassan Murad. It contains 5 guidelines on compression and 17 guidelines on operative/endovascular management.
Guideline 6.1: superficial venous reflux and active venous ulcer—ulcer healing

In a patient with a venous leg ulcer (CL) and incompetent superficial veins with axial reflux directed to the bed of the ulcer, we suggest ablation of the incompetent veins in addition to standard compression therapy to improve ulcer healing (Grade, 2; level of evidence, C). In guideline 6.2, on prevention of recurrence in the same clinical situation, the same management is recommended (Grade, 1; level of evidence, B). For ulcer healing, ablation is suggested due to weak evidence (C), while for the prevention of recurrence, ablation is recommended due to stronger evidence (B). In the SVS/AVF guidelines, there is a stronger opinion for active treatment than in this reviewed paper. The ESCHAR trial (Effect of Surgery and Compression on Healing And Recurrence) has led to a very nihilistic attitude toward an aggressive management of CVUs: “Patients with open venous ulcers do not benefit from treatment of superficial reflux.” At the recent VEITHsymposium in New York in November 2014, Manjit Gohel from Cambridge, UK, one of the main investigators of the ESCHAR trial, stated that there is unequivocal evidence that treating superficial reflux is beneficial in patients with venous ulceration, and he pointed out several weaknesses of the trial:

- One-quarter of procedures were saphenofemoral junction or saphenopopliteal junction ligation alone.
- A total of 20% of patients randomized to surgery refused an operation.
- The study was not powered to assess ulcer healing.

He reported that a new study is ongoing in the UK: EVRA study (Early Venous Reflux Ablation). This is a randomized clinical trial to compare early vs delayed endovenous treatment of superficial venous reflux in patients with CVU and 500 patients will be included. In the surgical arm, ablation will be performed within 2 weeks after diagnosis; in the compression arm, surgery will be performed after healing of the ulcer.

I hope that the outcome of this RCT will provide the evidence for an aggressive early management of patients with chronic venous ulcers.

**REFERENCES**


Changes in the diameter and valve closure time of leg veins across the menstrual cycle


This article presents an evaluation of a specific cohort of young, nulliparous women with duplex ultrasound of the lower extremities at various stages of the menstrual cycle. The study was comprised of an evaluation of 106 limbs in 53 women with homogeneity in their demographic makeup. They lacked, for the most part, any of the classic risk factors for the development of chronic venous deficiency and were all classified as class 0 (no venous disease) on the 7-point clinical, etiologic, anatomic and pathophysiologic (CEAP) scale.

The study showed that the differences in vein diameter and valve closure times (using B-mode and color-flow imaging, as well as pulsed Doppler spectral analysis of the deep and superficial venous systems) were statistically significant across the different stages of the menstrual cycle. The authors correctly point out that estrogen levels peak at mid-cycle ovulation and decrease slightly during the second half of the menstrual cycle. Progesterone levels, however, remain low until mid-cycle ovulation, peak in the mid-secretory (luteal) phase, and drop precipitously prior to the onset of menstrual flow (Figure 1). In fact, this phenomenon is so well known in the gynecological community that the onset of menses is synonymous with “progesterone withdrawal.”

Approximate concentrations of pituitary and ovarian hormones during the menstrual cycle

![Diagram of hormone concentrations](image)

Figure 1. Approximate concentrations of pituitary and ovarian hormones during the menstrual cycle.

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone.
The sex hormone progesterone, a smooth muscle relaxant, plays a vital role during gestation by allowing the smooth muscle of the gravid uterus to grow to accommodate the enlarging and developing fetus. One could argue, as the late Professor John Bergan often did in conversations with me, that progesterone is potentially “poison” for the venous system. I've been of the opinion that stimulation of progesterone receptors of the vein wall in the later part of the menstrual cycle contributes to some of the leg discomfort associated with the premenstrual period—a so-called “luteal phase vasodilation syndrome.”1 Along with other somatic complaints and cognitive symptoms, these characteristics are well established in the gynecological literature and are often collectively referred to as the “premenstrual syndrome (PMS).”2 This study is another step in objectively identifying some of the physiological changes associated with the luteal phase. However, the study did not describe any associated symptoms in the participants.

The authors discuss how an ideal study would include following these participants over 10 to 20 years. As discussed, a study design of this type may well be impractical. For example, two identical twin sisters may share the same genetic risk profile for the development of venous disease. However, one twin may have several pregnancies and children, use oral contraceptives, and engage in an occupation requiring prolonged sitting or standing, while the other twin may be nulliparous, use barrier contraceptives, and work in a profession not requiring prolonged sitting or standing.

More studies of this nature are required to determine how the physiological changes associated with the menstrual cycle can contribute to the physical complaints associated with the luteal phase, as well as the development of the full spectrum of venous disease. Contemporary phlebology practice requires a collaborative approach to such studies, drawing on the expertise of phlebologists, interventional radiologists, gynecologists, and others who care for female patients.

REFERENCES


Residual rates of reflux and obstruction and their correlation to post-thrombotic syndrome in a randomized study on catheter-directed thrombolysis for deep vein thrombosis.


**Catheter-directed thrombolysis, venous abnormalities, and postthrombotic syndrome**

Despite appropriate anticoagulant therapy, at least 1 of every 2 to 3 patients with proximal deep vein thrombosis (DVT) of the lower extremities will develop (severe) postthrombotic sequelae (PTS). Among parameters that have been found to be associated with an increased risk of PTS are venous thrombosis of the common femoral or iliac vein, obesity, previous ipsilateral DVT, older age, and female sex.\(^1\)\(^2\) By contrast, the role played by the development of venous reflux and/or the longstanding persistence of venous obstruction is controversial.\(^1\)\(^2\) Accordingly, whether, and to what extent, the earlier restoration of vein patency has the potential to reduce the incidence of late manifestations after an episode of DVT is uncertain.

Recently, the results of the CaVenT study (Catheter-directed Venous Thrombolysis in acute iliofemoral vein thrombosis), the first randomized controlled trial to address the value of catheter-directed thrombolysis (CDT) for reducing the incidence of PTS in 209 consecutive patients with iliofemoral DVT, have been published.\(^3\) The CaVenT study showed a statistically significant 15% reduction in PTS development after 24 months in patients treated with additional CDT compared with those allocated to anticoagulation alone. Iliofemoral patency after 6 months was more often regained in the CDT group and patency after 24 months correlated with the remaining thrombus load after completed CDT treatment. Severe or clinically relevant bleeding complications developed in 8% of patients allocated to CDT and 0% of patients receiving heparin alone.\(^3\)

Very recently, the authors of the CaVenT study assessed whether regained venous patency and development of deep venous reflux differed between patients treated with additional CDT and those receiving standard treatment alone.\(^4\) All 189 patients available for long-term investigation underwent ultrasonography and air plethysmography after 6 and 24 months to evaluate venous reflux and patency. There was an absolute risk reduction in venous reflux of 12% after 6 months and 16.5% after 24 months in the CDT arm when compared with controls. Correspondingly, venous patency was regained in 18.5% more patients after 6 months and 15% more patients after 24 months compared with controls. Both the reduction in venous reflux and the increase in venous patency were statistically significant. Independent of treatment allocation, patients with fully recanalized and competent deep veins at 6-months had a 40.5% absolute risk reduction of developing PTS compared with patients with an abnormal vein assessment.\(^4\)
The findings of this well-designed and properly executed study have two potential implications. On one hand, they provide compelling evidence to support the so-called “open vein hypothesis” in other words, quality venous reflux and lack of patency as powerful and independent predictors of PTS. On the other hand, they suggest that early recanalization of the obstructed veins, at least in patients with iliofemoral thrombosis, has the potential to protect against the development of PTS manifestations.

This aim was achieved 20 years ago with intravenous infusion of either streptokinase or urokinase. Then, this strategy has gradually been replaced by direct infusion of a plasminogen activator into the thrombus using ultrasound-guided access to the deep venous system and fluoroscopic positioning of the catheter into the thrombus. Avoiding systemic infusion has resulted in fewer major bleeding complications, and direct infusion of the lytic agent has been associated with improved efficacy.

Is CDT the future of DVT treatment? Recently, the results of a large observational study that included patients with a principal discharge diagnosis of proximal or caval DVT from 2005 to 2010 in the US have been published. Patients treated with CDT plus anticoagulation were compared with patients treated with anticoagulation alone. Propensity scores were used to construct 2 matched groups, each containing 3594 patients, for a comparative outcomes analysis. While in-hospital mortality was not significantly different between the CDT and the anticoagulation groups, the rates of blood transfusion were found to be significantly higher in patients receiving CDT, as was the incidence of pulmonary embolism, intracranial hemorrhage, and vena cava filter placement. Are these complications a price to be paid for the prevention of PTS? I do not think so. In a scenario where novel direct oral anticoagulants are increasingly streamlining the treatment of venous thromboembolism due to the simplicity of use, coupled with an attractive benefit-to-risk ratio for all of the patient’s presentation and location of thrombosis, the use of CDT raises concerns. At best, CDT requires the identification of a highly selected group of patients who are reputed to carry an unusually high risk of late complications while having a low hemorrhagic risk.

REFERENCES


### Congress and conference calendar

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