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Aims and Scope

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

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

Phlebolymphology is scientifically supported by a prestigious editorial board.

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

Phlebolymphology comprises an editorial, articles on phlebology and lymphology, reviews, and news.

Correspondence

Editorial Manager
Hurrem Pelin YALTIRIK
Servier Affaires Médicales
35, rue de Verdun
92284 Suresnes Cedex, France
Tel: +33 (1) 55 72 38 98
Email: hurrem-pelin.yaltirik@servier.com

Publication Director
Christophe CHARPENTIER
Suresnes, France

Publisher
Les Laboratoires Servier
50, rue Carnot
92284 Suresnes Cedex, France
Tel: +33 (1) 55 72 60 00

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Editorial

Dear Readers,

In this new issue of Phlebolymphology,

Mohamed K. KAMEL *and* ***John BLEBEA (USA)*** *present the anatomic, hemodynamic, and main pathophysiological mechanisms of lower-limb edema formation in patients with chronic venous insuffiency.*

Sarah ONIDA *and* ***Alun H. DAVIES (UK)*** *summarize the existing evidence on long-haul travel and venous thromboembolism, while considering the pathophysiology underlying the development of thrombotic events, factors increasing risk, and what conservative and pharmacological measures can be taken to reduce the venous thromboembolism risk.*

Yuji HOSHINO (Japan) *discuss the management of chronic venous insufficiency patients presenting an axial deep reflux in isolation or combined with iliac vein obstruction.*

The methods of treating varicose veins have been constantly evolving over the past 20 years, leaving a prominent place today for endovenous techniques, with conventional surgery being gradually abandoned. ***Nicolas NEAUME (France)*** *provides an overview on the management of small saphenous vein varices with perspectives from a recent meta-analysis and recommendations.*

Transient premenstrual phlebopathy, is considered to be a particular venous problem in fertile women. ***Yuri T. TSUKANOV*** *and* ***Alexandr NICOLAICHUK (Russia)*** *present the changes in clinical manifestations and biophysical properties of the great saphenous vein in transient premenstrual phlebopathy after 12 months' treatment with micronized purified flavonoid fraction.*

Enjoy reading this issue!

Editorial Manager

Dr H. Pelin Yaltirik

Pathophysiology of edema in patients with chronic venous insufficiency

Mohamed K. KAMEL,
John BLEBEA

Department of Surgery, College of Medicine , Central Michigan University, Saginaw, MI, USA

Abstract

The prevalence of chronic venous insufficiency and its associated health care costs have been greatly underestimated for a long period of time. Many patients suffering from chronic venous insufficiency either present with or have associated lower-limb edema. The main pathophysiological mechanisms of edema formation in such patients include increased capillary hydrostatic pressures secondary to valvular insufficiency or venous obstruction. In addition, there is increased capillary permeability due to associated inflammatory reactions that subsequently lead to leakage of protein-rich fluid into the interstitial space. Such fluid increases the oncotic pressure within the interstitium leading to additional edema formation. This article will review the anatomic, hemodynamic, and pathophysiologic mechanisms of lower-limb edema associated with chronic venous insufficiency. The clinical methods most commonly used to assess the extent and severity of edema formation will also be briefly examined.

Keywords:

chronic venous insufficiency; edema; leg swelling; pathophysiology

Introduction

According to the VEIN-TERM transatlantic interdisciplinary consensus document published in 2009, chronic venous insufficiency (CVI) was defined as "any morphological and functional abnormalities of the venous system of long duration manifested either by symptoms and/or signs indicating the need for investigation and/or care."[1] It was further defined as applying to functional abnormalities of the venous system that resulted in producing moderate to severe edema. Therefore, CVI should be reserved for the description of more advanced disease, beginning with venous edema (C_3), but more commonly in conditions where skin changes (C_4) or ulceration (C_{5-6}) have taken place, as defined in the Clinical, Etiological, Anatomical, and Pathophysiological (CEAP) classification system.[2] Chronic venous disorders are one of the most prevalent, yet greatly underestimated, chronic health disorders in the USA and worldwide. A recent report by the SAGE group estimated that CVI affects approximately 175 million US citizens with an estimated cost of $46 billion annually.[3,4] Worldwide, investigators from the Vein Consult Program prospectively surveyed over 90,000 individuals

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from different continents and found that the prevalence of symptomatic CVI was similar between Western/Eastern Europe (78%/87%), Latin America (88%), the Middle East (85%), and the Far East (87%).[5]

Several population-based epidemiological studies have investigated demographic and clinical factors associated with the development of CVI. Among those, advancing age is one of the most well-established risk factors for the development of CVI. In the Framingham study, Robertson reported that the risk of CVI was 1% for men and 10% for women younger than 30 years, but this increased to 57% and 77% for men and women aged 70 years or older, respectively.[6] With the aging population in the USA and other Western countries, CVI incidence and prevalence are expected to increase even further in the coming years. Sex is another important risk factor. In the San Diego population-based study, Criqui reported that females were twice as likely to develop varicose veins compared with their male counterparts.[7] However, in the Edinburgh vein cross-sectional population survey, which examined chronic venous insufficiency rather than just varicose veins, a higher incidence was found in males.[8] Other previously reported CVI risk factors include pregnancy and a positive family history. A high incidence of CVI was also found to be associated with certain genetic disorders, such as Klippel-Trenaunay syndrome, Von Hippel-Lindau syndrome, and FOXC2 and NOTCH3 abnormalities.[9-12] On the other hand, there is currently no strong evidence showing that smoking, hypertension, obesity, or decreased physical activity are associated with a higher incidence of developing CVI.

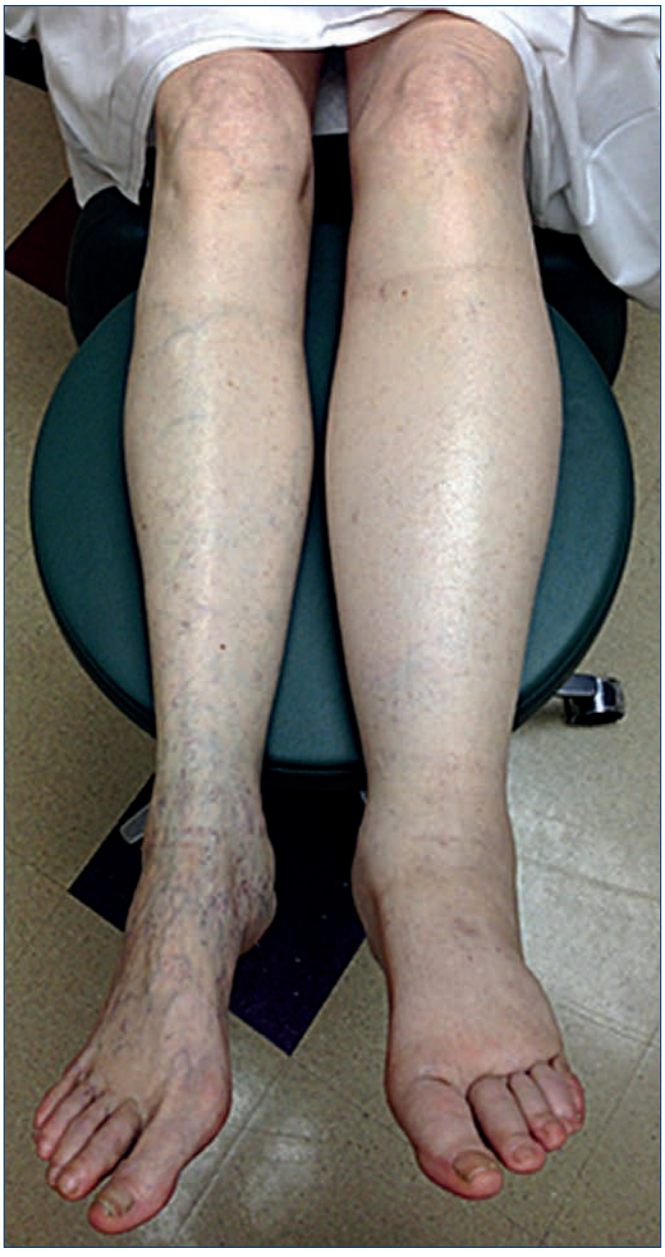

Figure 1. Patient with left leg swelling secondary to chronic venous insufficiency due to proximal iliac vein stenosis.

Edema, defined as the accumulation of fluid in the interstitial space leading to leg swelling, is frequently the first clinical symptom or sign associated with CVI *(Figure 1)*. A multitude of disorders, including cardiac, renal, and hepatic diseases, as well as medications, can induce leg swelling. Lymphedema, in particular, can cause severe and persistent leg edema. However, it has been estimated that CVI-associated edema represents 90% of all lower-limb edema because of the prevalence of venous insufficiency.[13] The different mechanisms of lower-limb edema formation associated with the pathophysiology of CVI will herein be examined.

Anatomic and hemodynamic considerations

The anatomy of the lower extremity venous system can be highly variable among individuals, making the definition of a "normal anatomy" challenging. The International Interdisciplinary Consensus Statement in 2002 was helpful in updating the anatomical nomenclature of the venous system.[14,15] The interplay between the three venous systems of the leg, the deep and superficial systems, and the connecting perforators are important in the hemodynamic changes that occur in disease states. While the deep system accompanying the major arteries of the leg return approximately 80% of the lower-limb venous blood, and the superficial system is associated with visible varicosities and are the ones most subject to therapeutic interventions, it is the more than 150 perforating veins that provide the

collateral pathways for pathologic retrograde flow that can be important in the edema manifestation of CVI.[16] Of these perforators, the most well described and of greatest clinical relevance have been the medial calf perforators involving the posterior tibial veins, but any group of them may be important in the treatment of specific patients.

Under normal physiologic conditions, a unidirectional and cephalad venous blood flow is maintained by a healthy system of venous valves, lower-limb muscular pump compressive action, and negative intra-abdominal and intra-thoracic pressure. During walking, contraction of calf muscles within their fascially enclosed compartments generates an ambulatory pressure gradient between the lower leg and thigh, which leads to displacement of blood in an antigravity direction toward the heart with the assistance of competent valves. This calf pump is most important because it contains the largest venous capacitance within the soleal and gastrocnemius sinusoids and generates the highest pressures. Intramuscular pressures generated in the gastrocnemius and soleus muscles can increase up to 250 mm Hg from 9 mm to 15 mm Hg in their relaxed state.[17] Valvular function, in all three venous systems, is important in the maintenance of antegrade venous flow. It is most helpful that modern ultrasound technology allows us both to directly visualize the valves and quantify their function as exemplified by valve closure times. The initial studies by van Bemmelen et al established a normal value of 0.5 seconds for the valves to close in the superficial system.[18] For the deep system, 1 second or more is suggestive of valvular dysfunction, while 0.35 seconds of reversed flow in combination with a diameter of greater than 3.5 mm is generally accepted as abnormal for leg perforators.[19]

In pathologic states, be it due to prior episodes of deep venous thrombosis or superficial thrombophlebitis, or when there is primary valvular dysfunction, venous reflux with retrograde blood flow takes place. In the deep system, after the initial thrombotic event, intrinsic thrombolysis and recanalization allows for blood flow to resume within the previously occluded vein. However, the inflammatory and fibrotic processes that take place on the valve cusp restrict the movement of the valve leaflets resulting in only a partially mobile leaflet or a completely "frozen valve." In addition, inflammation of the nonvalvular segments of the vein can lead to thickening and calcification in the vein wall. It is unclear to what degree this loss of elasticity and distensibility affects venous flow hemodynamics, but, at a minimum, it must decrease volume flow in those segments because of the diminished luminal diameter. The result of these processes is valvular incompetence and reflux *(Figure 2)*.[20] Dysfunction in venous valves most frequently affects all three venous systems in patients with more advanced CVI, particularly those with CEAP C_6 disease with active ulcers.[21-23] This leads to venous hypertension, which can be quantified by elevated ambulatory pressures in the superficial venous system when measured in the pedal veins.[24] In these circumstances, venous hypertension and the associated increase in hydrostatic capillary pressure leads to edema formation.

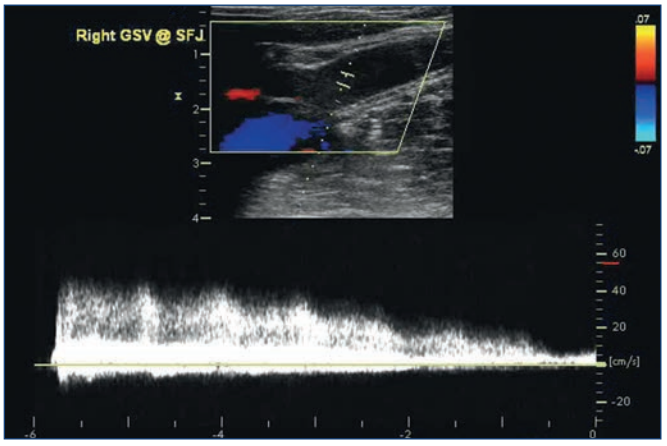

Figure 2. Longitudinal ultrasound image demonstrating six seconds of high volume reflux at the proximal saphenofemoral junction of the great saphenous vein.

Transcapillary fluid balance

In order to have an understanding of the pathophysiology of CVI-associated edema, one should have an appreciation of the basic physiologic principles behind transcapillary fluid exchange. Under physiologic conditions, total interstitial fluid volume is kept fairly constant, even in conditions that lead to large increases in tissue fluid transfer, secondary to the balance between transcapillary filtration and lymphatic outflow. In 1896, the British physiologist Ernest Starling was the first to describe the counteraction between hydrostatic and oncotic forces that act across the semipermeable capillary wall and controls fluid filtration from the intravascular to the extravascular space.[25] Venous hypertension extends into the microcirculation with increased hydrostatic pressure in capillaries that lead to wall remodeling and microvenous valvular insufficiency.[26] There is a secondary enlargement of the capillary bed, excessive transcapillary filtration causing interstitial fluid accumulation with exudation of fibrinogen and proteins into the interstitial space, which later produce the characteristic changes of lipodermatosclerosis.[27] Plasma proteins, mainly albumin, are responsible for the intravascular oncotic pressure. Increased transcapillary

pressures and oncotic attraction with progressive protein accumulation in the interstitial space is thought to be the primary pathophysiologic mechanism in the development of CVI-associated edema.[21,28]

This mechanistic understanding has been further elucidated with details of the molecular basis of this process. Almost a century after Starling, Curry and Michel explained that transcapillary fluid movement reflects an ultrafiltration process through the interpolymer spaces of the glycocalyx layer of the endothelial cells of capillary membranes.[29] In addition, the underlying capillary basement membrane, composed of type IV collagen and laminin, and the adjacent extracellular matrix act as second- and third-order resistance layers opposing fluid movement from the intravascular space to the interstitial space.[30] Initially conceived of as a nonfunctional space, the interstitium contains an extensive extracellular matrix composed of collagen fibrils upon which glycoprotein molecules are attached in a web-like manner. Beyond the contribution of transcapillary pressure and oncotic forces, in inflammatory conditions, such as those seen in CEAP C_{4-6}, this extracellular matrix can physiologically affect transendothelial pressure differences and thus result in increased transcapillary fluid flow with associated edema.[31,32] Any derangements in lymphatic drainage would only exacerbate this problem if the terminal interstitial lymphatic capillaries had a decreased ability to clear proteins and macromolecules from this relatively hyperoncotic environment.

Capillary hydrostatic pressure

Under normal physiologic conditions, the mean hydrostatic capillary pressure is tightly regulated by the balanced changes in precapillary arteriolar and to a lesser extent postcapillary venular resistance (vasoconstriction/vasodilation). This tight balance largely contributes to maintaining a relatively constant interstitial fluid volume by adjusting transcapillary fluid filtration rate. As arteriolar resistance is four times higher than the venular resistance, changes in venular pressure, as seen with venous outflow obstruction or venous valvular insufficiency and secondary hypertension, can have a very profound effect on transcapillary filtration.

Any of a multitude of factors leading to a decrease in venous return from the lower-limb, such as deep venous outflow obstruction, multisystem valvular incompetency, and inadequate lower-limb muscle contraction, can lead to an increase in the ambulatory venous pressure up to 60 mm to 90 mm Hg.[33] With the excess blood volume in both the deep and superficial veins that is associated with venous hypertension, exacerbated by standing and worsening toward the end of the day, venous distension leads to anatomic distortion and progressive valvular incompetence in a vicious circle. As the veins become maximally distended, any further increase in venous blood volume can produce a large increase in intraluminal venous pressure. Associated with this resultant venous hypertension is the associated loss of precapillary arteriolar reflex constriction that is intended to decrease the transmission of the increased venous pressure to the capillary system.[34] This venoarteriolar response (VAR) involves the arterioles constricting to reduce blood flow and normalize the arteriovenous pressure difference in the face of venous hypertension. Several studies have shown that reduction in this VAR contributes significantly in the formation of edema and correlation of CVI clinical severity.[21,35]

Shear stress and inflammation

Another factor that plays a role in the pathophysiology of CVI-associated edema is the reduction in shear stress, which is the tangential force of the blood flow on the endothelial lining of the blood vessel. Shear stress was found to be associated with regenerative functional and morphological changes in endothelial cells as well as release of anti-inflammatory and vasodilatory molecules.[36] However, the reduction in shear stress associated with venous hypertension has been found to be associated with proinflammatory changes in the vein wall and valves. The venous wall inflammatory process leads to gap formation between endothelial cells secondary to endothelial cells' actin/myosin filament contraction. These gaps lead to excess permeability of plasma proteins into the interstitial space, a reduction in oncotic pressure differences between the intra- and extravascular spaces and secondary edema formation.[37]

The combined volume effect of venous hypertension and the reduction in endothelial shear stress causes both endothelial glycocalyx damage and the release of vasoactive substances, such as chemokines, inflammatory mediators, and adhesion molecules (ICAM-1 and E-Selectin). The increased release of the ICAM-1 adhesion molecules leads to increased leukocyte adherence. Due to altered shear stress, leukocytes begin sticking to the vein wall, migrate out of the capillary, and release inflammatory mediators. These mediators trigger local inflammation, which induces further remodeling of the adjacent venous wall and valves

and aggravating the venous hypertension.[38] This response also includes local monocyte and macrophage recruitment with their infiltration into the vein wall and valves.[39] Chronic venous hypertension increases hypoxia-inducible factors leading to increased matrix metalloproteinase (MMP) expression/activity with resultant degradation of extracellular matrix proteins. This inflammatory cascade involving both the venous system and surrounding soft tissues ultimately leads to the classic presentation of lower-limb edema, lipodermatosclerosis, and leg ulcer associated with CVI.[40] Whether such inflammatory responses precede or follow valvular dysfunction and venous incompetency, is not yet conclusively elucidated.[21,41] The combination of these changes contribute to endothelial cell dysfunction and venous wall and valvular damage that result in venous insufficiency.[37]

Assessment of lower-limb edema

Characteristically, CVI-associated edema is pitting in nature and more pronounced after prolonged standing or sitting and at the end of the day. It most commonly involves the lower legs, ankle malleolar area, and less often the foot. The skin may show a whitish discoloration from stretching. In more advanced stages of CVI, leg edema is also associated with more pronounced skin color changes, thickening, and tenderness. The Venous Clinical Severity Score (VCSS) classifies venous edema by asking the patient about the extent of leg edema that is experienced: none, edema limited to the foot and ankle, edema that extends above the ankle, but below the knee, or one that extends to the knee or above.[42] The most commonly used clinical method to assess lower-limb venous edema is the pitting test wherein pressure is applied by the thumb or index finger on the medial surface of the tibia.[43] Severity of leg edema is described according to the pitting depth of the tissue, the time needed for the pit to resolve, and in terms of the extent to which it involves the length of the leg.[44] Although easy to perform, it is an unvalidated and subjective measure of edema and may be uncomfortable for the patient. Other more objective methods that indirectly assess lower-limb edema include measuring the leg circumference at a single point or multiple fixed points using a measuring tape, usually at 3 cm above the ankle or the calf at its largest circumference. The Leg-O-Meter device utilizes a measuring tape attached to a stand, thus ensuring that measurements are taken at the same point at different times.[45] Other more sophisticated methods employing mathematical computations have also been used to estimate lower-leg edema volume. These include the Frustrum method, which assumes that the lower-limb is a truncated cone and utilizes an upper and lower leg circumference as reference points from which the leg volume is calculated.[46] The gold standard for measurement of lower-limb volume is a direct method utilizing volume displacement measurements wherein the leg is immersed in a water-filled container and the volume of displaced water is measured.[47] Several considerations of this technique have been proposed to improve accuracy and reproducibility, including volumeter type, patient/leg/feet positions, as well as room and water temperature.

More recently, potentially less cumbersome imaging modalities have been used to estimate lower-limb volume. In the optoelectronic measurement method, infrared rays are used to measure the lower-limb to produce a three-dimensional image from which the leg volume can be electronically calculated.[48] High-frequency ultrasound imaging has been used to assess dermal thickness associated with CVI edema.[49] Computed tomography has been used to measure lower-limb volume and to localize edema to the different leg compartments.[50] Magnetic resonance imaging has been shown to have good sensitivity in detecting venous lower-limb edema and in differentiating between lymphedema, venous edema, or lipedema *(Figure 3)*.[47] The cost, availability, and associated radiation exposure make CT and MRI less attractive

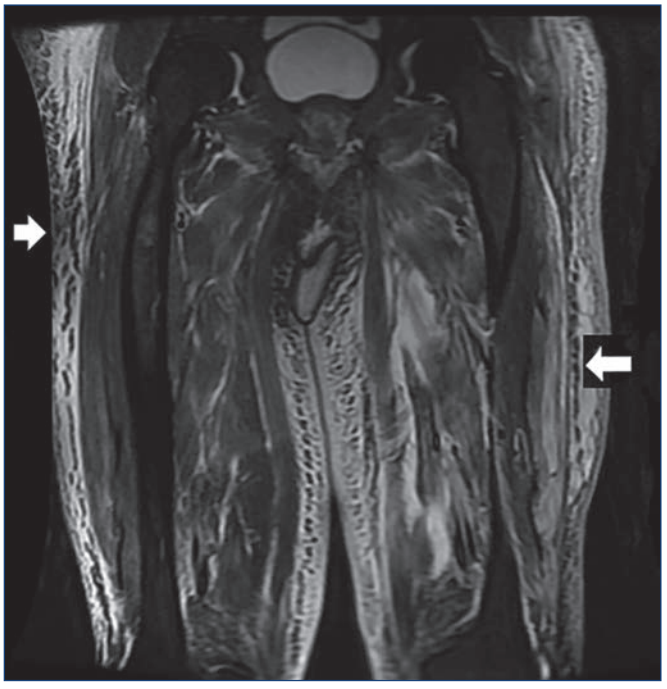

Figure 3. Coronal fat-suppressed T2-weighted magnetic resonance image of the legs demonstrating diffuse subcutaneous edema (white arrows).

modalities. Duplex ultrasound, on the other hand, has a greater appeal because of its wide availability, ease of use, and technical familiarity to phlebologists and other vascular specialists.[51] Rather than just examining the skin, B-mode gray scale ultrasonography with a 15 to 18 MHz linear probe allows direct visualization of anechoic areas representing subcutaneous edema *(Figure 4)*. Suehiro et al have proposed that subcutaneous echogenicity and subcutaneous echo-free space semiquantitation can reflect tissue inflammation and fluid accumulation, respectively *(Figure 5)*.[52] Efforts have been made to quantify the degree of edema, both by a qualitative grading scale as well as, more easily, measuring the greatest depth from the skin which encompasses the edema.

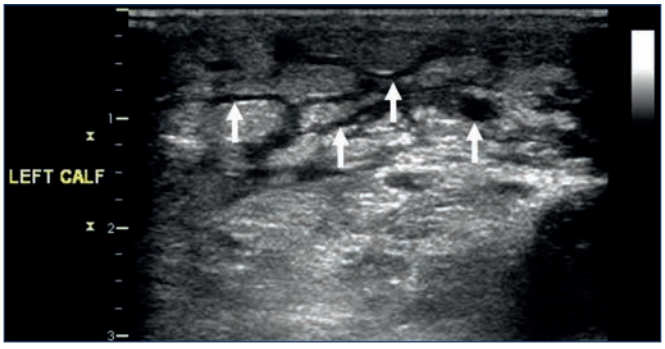

Figure 4. Transverse B-mode ultrasound image of the calf illustrating anechoic areas of edema (arrows).

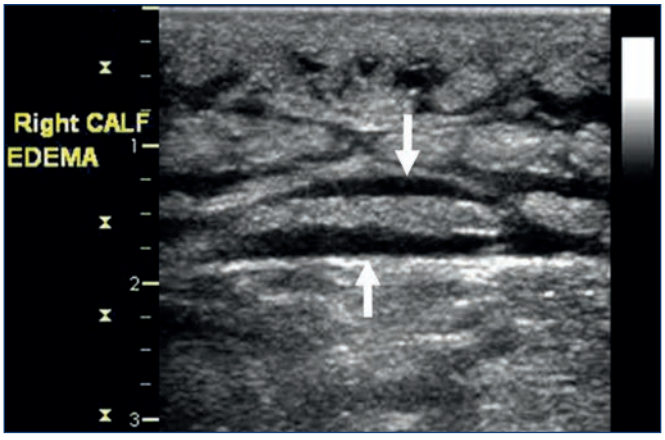

Figure 5. Longitudinal ultrasound image demonstrating horizontally-oriented echo-free spaces (arrows) suggesting more severe edema.

Although these qualitative and quantitative edema measurements are useful for research purposes, they have not yet been accepted for routine clinical care because of the associated additional costs and because clinical interventions have not generally utilized edema as a separate therapeutic outcome end point. However, with the increasing use of venoactive agents, which have been demonstrated to have an anti-edema effect by increasing capillary resistance, improving lymphatic drainage, and reducing capillary filtration, quantitation of leg edema may become more beneficial.[53]

Lower-extremity edema has long been recognized to be associated with chronic venous insufficiency. Similarly, the basic mechanism of valvular insufficiency and secondary venous hypertension leading to leg swelling and pain has been appreciated and compression therapy effectively instituted as usual clinical therapy. More recently, we have had available excellent ultrasound imaging to directly visualize valve movement and quantify reflux times as well as guiding endovascular ablation therapy. The basic hemodynamic principles of transcapillary filtration and oncotic pressure leading to edema have been known for decades. Our understanding of the details of microvascular function, molecular mediators, and inflammatory processes, however, are still at a very basic level. We have a long way to go in discovering the particulars of the intermediary pathways of edema formation and discover more specific targeted drug therapy for its control. This should provide fertile grounds for investigation in the years to come.

Corresponding author
John BLEBEA, MD, MBA, FACS,
Department of Surgery,
College of Medicine,
Central Michigan University,
912 S Washington Ave, Suite #1,
Saginaw, MI, 48601

Email: john.blebea@cmich.edu

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Long-haul travel venous thromboembolism – an update

Sarah ONIDA,
Alun H. DAVIES

Academic Section of Vascular Surgery, Department of Surgery and Cancer, Imperial College London

Abstract

Venous thromboembolism (VTE) describes obstructive presentations of deep venous disease, including deep vein thrombosis and pulmonary embolism, which, together, affect up to half a million people in Europe every year. VTE is also the single, most common cause of preventable hospital-acquired mortality; furthermore, up to 50% of individuals with deep vein thrombosis develop the postthrombotic syndrome, with its significant impact on quality of life and a considerable economic burden. Immobility is amongst the most important recognized risk factors for VTE. Long-haul travel, where individuals are in a forced state of relative immobility for prolonged periods, has been associated with VTE development, notably in the context of the "economy class syndrome." However, the effect of the type and duration of travel, as well as the mechanisms through which long-haul travel increases VTE risk, are poorly characterized. This narrative review aims to summarize the existing evidence on long-haul travel and VTE, with considerations on the pathophysiology underlying the development of thrombotic events, factors increasing risk and what conservative and pharmacological measures can be taken to reduce VTE risk, particularly in the context of planned intervention.

Keywords:

deep venous thrombosis; long-haul travel; superficial venous intervention; surgery; venous thromboembolism

Epidemiology and disease burden

Venous thromboembolism (VTE) is a leading cause of morbidity and mortality worldwide, and it is the single most common cause of hospital-acquired mortality. It is estimated that 10 million cases of VTE occur every year worldwide, although this may be an underestimation of the true prevalence due to the lack of reported VTE events and the presence of subclinical VTEs in patients with sudden deaths.[1]

VTE describes the presence of thrombosis in the deep venous system; this includes deep venous thrombosis (DVT), which, in 30% of individuals, can progress to the development of a pulmonary embolism. Postthrombotic syndrome (PTS) develops in 50% of patients with DVT and is characterized by chronic signs and symptoms of venous insufficiency, including venous claudication, swelling and, in the most severe cases, venous leg ulceration.

VTE is responsible for an estimated $27.2 billion expenditure in the US per annum between actual and preventable costs.[2] This expenditure is due not only

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to the costs of the acute management of VTE and ongoing care for PTS, but also secondary to the lost productivity due to loss of work days, resulting in societal costs. Due to its significant morbidity and mortality, VTE prevention is key, which is performed by providing either pharmacological or mechanical thromboprophylaxis to individuals deemed at risk of developing this condition.

Risk factors

Risk factors for VTE are numerous and can be both innate and acquired. Innate factors include age, male sex (especially in the older population), ethnicity, and the presence of an underlying thrombophilia. Acquired factors include a diagnosis of cancer, the presence of significant comorbidities, a family history of VTE, varicose veins, recent pregnancy, undergoing surgery with immobility, trauma or pelvic/long bone fractures, a critical care admission, obesity, and medications, such as hormone replacement therapy or the oral contraceptive pill.[3]

The relative importance, or weight, of different VTE risk factors has been explored, leading to the development of risk assessment tools that permit assessment of patients based on their risk factors and their risk stratification, guiding VTE prophylaxis. In the UK, the Department of Health risk assessment tool is most commonly used,[4] while, in the US, the Caprini risk assessment tool is often used, particularly in surgical patients[5]; the Padua risk assessment tool is used in medical patients.[6] Immobility features in these risk scoring systems as an important risk factor. The Department of Health tool mentions "significantly reduced mobility for 3 days or more" and "surgery with significant reduction in mobility[6]"; the Caprini risk assessment tool includes "on bed rest or restricted mobility, including a removable leg brace, for less than 72 hours" (1 point additional risk), and "confined to bed for 72 hours or more" (2 point additional risk),[5] while the Padua risk assessment tool mentions "reduced mobility.[6]" However, no tool specifically mentions long-haul travel as an independent risk factor, despite its known association with VTE. This is an important consideration as there is evidence that factors other than immobility can lead to a prothrombotic state, which may be of relevance for patients being admitted to the hospital.

Long-haul travel and VTE

Air travel is now one of the main modes of transportation, with direct flights available for increasingly longer routes. The longest existing flight is the Singapore Airlines service from Singapore to Newark, New Jersey, which has a duration of 19 hours.[7] Long-haul travel is normally defined by flight length greater than 6 hours, although the definition can be variable in the literature; this has also been defined as flight length greater than 4 hours *(Table I)*.

Short-haul flight	<3 hours
Medium-haul flight	3 to 6 hours
Long-haul flight	>6 hours

Table I. Flight length definitions.

From reference 8: McGinley Group. The differences between long-haul & short-haul piloting. https://www.mcginleygroup.co.uk/blog/the-differences-between-longhaul-and-shorthaul-piloting/bp67. Published July 2015.

The 2018 International Air Transport Association (IATA) forecast predicts that, by 2037, air passenger numbers could double to 8.2 billion, which will be associated with a shift in travel toward the Asia-Pacific region, which will drive the largest growth of new passengers *(Figure 1)*,[9] and will likely result in a larger number of individuals travelling on long-haul flights.

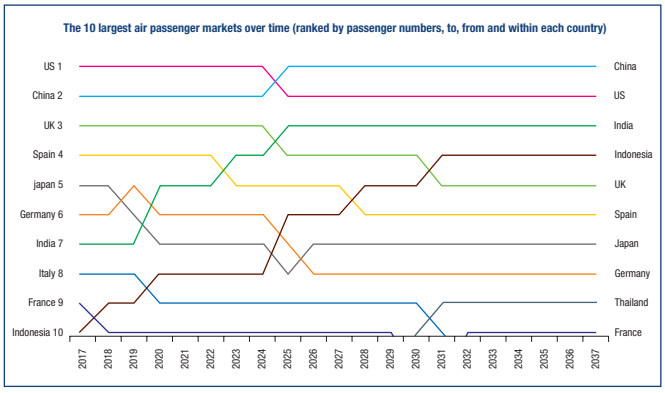

Figure 1. Predicted growth in the 10 largest air passenger markets in the next 20 years.

From reference 9: International Air Transport Association. IATA forecast predicts 8.2 billion air travelers in 2037. Published October 2018.

The first report associating long-haul travel with VTE was by John Homans in 1954, who described the development of a DVT in one of his colleagues travelling from Boston to Caracas on an 8-hour flight.[10] Since then, the relationship between long-haul travel and VTE has been highlighted and often described by the term "economy class syndrome." Numerous airlines have taken measures to reduce this risk by providing passenger advice on how to recognize

risk factors for VTE and suggestions for calf muscle pump exercises aimed at reducing the risk of thrombus formation, though the evidence for this is sparse.[11] The World Health Organization research into global hazards of travel (WHO WRIGHT) project highlighted the research priority of setting up multicenter, international epidemiological, prospective studies to obtain more robust data on the incidence and prevalence of travel-related VTE,[12] with the aim of improving the existing evidence on the subject.

Estimation of travel-related VTE prevalence is challenging for a number of reasons because there is a lack of evidence in the literature, with a limited number of studies that are heterogeneous in nature and with limited patient numbers. Furthermore, although patients with symptomatic VTE may be identified when presenting to health care professionals for assessment, the proportion of subclinical VTE events is likely much higher. It is important to note that prospective study design in this patient population is challenging, requiring duplex ultrasound screening of large numbers of participants undertaking long-haul flights.

Retrospective data has estimated the overall incidence of pulmonary embolism as 0.39 per one million passengers; for flights up to 8 hours, the incidence was 0.25, while, for flights longer than 8 hours, this increased to 1.65 per one million passengers.[13] A meta-analysis exploring the relationship between travel >8 hours and VTE events revealed a relative risk for VTE of 2.8, with an 18% additional risk for each 2-hour increase in travel duration by any mode; interestingly, the increased relative risk for air travel was 26% for every 2 additional hours, suggesting that flying conferred an increased risk of VTE compared with other forms of transportation.[14]

The mechanism for the development of travel-related VTE has been the subject of a number of research studies. Candidate mechanisms include hypobaric hypoxia, immobilization, and stress.[15,16]

Hypobaric hypoxia

Air travel is associated with a hypoxic environment in the context of decreased cabin pressure, which is equivalent to approximately what is found at an altitude of 1524 to 2134 meters. Associated with this is a reduced oxygen partial pressure, with resulting saturations of approximately 93% in healthy individuals, although people with underlying cardiac or respiratory conditions may be affected more severely.[17] Studies have replicated these conditions experimentally, for example, by sampling participants in Antarctica,[18] where hypobaric hypoxia is present due to atmospheric conditions, or by employing hypobaric chambers,[19] with the aim of investigating the role of hypobaric hypoxia in the development of a procoagulant state. These studies have provided evidence that markers of coagulation activation, fibrinolysis, and platelet and endothelial cell activation do not significantly vary between hypobaric and normobaric experimental exposures,[19] including D-dimer, thrombin antithrombin complexes, and prothrombin fragments.[18] It is important to note that patients with a previous history of VTE,[18,19] or testing positive for Factor V Leiden or prothrombin mutations were excluded from these studies,[19] with the aim of isolating the true effect of the experimental conditions on the development of thrombosis.

Conversely, a separate study assessing patients following an 8-hour flight found an increase in prothrombin fragments, thrombin antithrombin complex, and D-dimer; these increases were particularly marked in individuals with a Factor V Leiden mutation who also took oral contraceptives, suggesting that additional factors may increase travel-related VTE risk in addition to hypobaric hypoxia.[20]

Immobilization

Immobilization is one of the most important risk factors for VTE, as evidenced by its inclusion in the risk assessment tools. However, the evidence for this, in the context of travel thrombosis, is unclear, with some studies suggesting that prolonged immobilization does not affect hypercoagulability,[18] while others are demonstrating increased prothrombotic effects. In a study investigating healthy women who underwent 60 days of bed rest, there was no evidence of an activated coagulation system.[18]

Individuals exposed to two sessions of immobilization lasting 8 hours (8-hour flight, 8-hour movie marathon) and one session of regular daily activities lasting 8 hours (each activity separated by at least 2 weeks) did not demonstrate statistically significant increases in procoagulant factors in the blood during immobilization, although the use of the oral contraceptive pill and the presence of a Factor V Leiden mutation increased the levels, particularly after a flight. Therefore, it is likely that immobilization alone is not enough to confer an increased VTE risk in healthy participants, unless other risk factors are present.[20] Despite being typically associated with VTE development, there is no evidence that travelling in economy class confers a higher risk,[21] suggesting that the "economy class syndrome" may be a misnomer.

One of the main drawbacks in the presented literature is that study sizes are limited, ranging from 24 to 73 participants.[18-20] Larger studies have explored other risk factors of relevance in individuals who have developed VTE in the context of long-haul travel.

Additional risk factors

Additional VTE risk factors appear to play an important role in determining who is likely to have an event. In a large study enrolling 568 patients, individuals who had a proven DVT did not have a statistically significant association with a history of air travel >8 hours. However, the presence of any additional single VTE risk factor conferred a statistically significant increase in the odds of developing VTE for travel >3 hours and >8 hours, suggesting that the cumulative effect of increased risk factors in addition to the length of flight can influence the development of a clinically symptomatic VTE.[22] Risk factors included hormonal therapy, surgery, malignancy, immobilization, pregnancy, obesity, previous thrombosis, and significant family history. A further questionnaire-based study identified a dose-dependent effect of flying time on VTE risk, with flights >12 hours associated with an odds ratio (OR) of 2.75 for VTE development, while those of 4 to 8 hours had an OR of 1.81. Interestingly, previous surgery within 28 days conferred the highest increase in risk, with an overall OR >30; when subgrouped by low- (day case or overnight stay), moderate-, and high-risk surgery, OR values were 5.4, 36.6, and 141.7, respectively. Previous VTE (OR, 9) and obesity (OR, 2.7) were other risk factors of importance in increasing VTE risk.[23] The importance of concurrent risk factors in increasing the risk of flight-related VTE was also highlighted by the LONFLIT 1 study (LONg-haul FLIghTs deep vein thrombosis), where only the high-risk VTE group developed thrombotic events (2.8% versus 0% in the low-risk VTE group).[24] A further study identified increased risk in those with repeated flight exposures, with increasing flight duration, in those aged <30, women on oral contraceptives, and participants who were short (<1.65 m), tall (>1.8 m), or overweight (>25 kg/m^2).[25]

VTE risk following long-haul travel

There is evidence that the increase in VTE risk following a long-haul flight can last for a number of weeks. A study recruiting 8755 participants exposed to flights of at least 4 hours or more (defined as long-haul flights) recorded a VTE incidence of 1 event per 4656 long-haul flights, of which 42% occurred in the first 8 weeks following travel, with particularly high rates in the first 2 weeks.[25]

The MEGA study is among the largest cohorts investigating the relationship between VTE and long-haul travel (defined as >4 hours), recruiting 1906 patients with a first episode of venous thrombosis.[26] This study found that travelling increased the odds of developing VTE two-fold, regardless of the mode, with travel by car, bus, or train resulting in a similar risk. Patients with known hypercoagulability, such as Factor V Leiden mutation, obesity, and on the oral contraceptive pill, were at a particularly high risk of developing VTE when traveling by car, bus, or train. Interestingly, an association with height greater than 1.90 meters also conferred an OR of 5 for the development of VTE with any form of travel, while those shorter than 1.60 meters had a 5-fold increase in the risk of developing VTE following air travel. The risk of VTE was highest in the first week, but remained elevated up to 6 weeks posttravel.

In travelers with symptomatic VTEs following international flights from Australia, the reported risk of VTE was 4-fold 2 to 4 weeks following travel, suggesting that the prothrombotic state is maintained.[27]

Measures to reduce VTE

The aforementioned studies have suggested a relationship, which is likely multifactorial and associated with the presence of a number of risk factors, between VTE and long-haul travel. With respect to measures that can be taken to preemptively reduce VTE risk, the LONFLIT studies explored this with duplex ultrasound performed 24 hours following a long-haul flight. LONFLIT 2 evaluated high-risk individuals for VTE; risk factors included a previous history of DVT, reduced mobility, neoplastic disease within the previous 2 years, severe obesity, large varicose veins, and a documented coagulation disorder. Participants were randomized to no thromboprophylaxis (n=422) and mechanical thromboprophylaxis via below-knee compression stockings (n=411, class I or class II). The control group had a VTE prevalence of 4.5%, while the compression stocking group had a prevalence of 0.24%, demonstrating an 18-fold difference.[24] The effectiveness of graduated compression stockings in preventing travel-related VTE has been highlighted by a recent Cochrane review, which evidenced a large reduction is asymptomatic DVT with high-quality evidence and a reduction in leg swelling with low-quality evidence. There was also moderate-quality evidence suggesting that superficial vein thrombosis events were reduced in the compression group. The review could not comment on symptomatic DVT, pulmonary embolism, or

death due to the paucity of these events occurring in the trials included.[28]

LONFLIT 3 explored the use of aspirin versus low-molecular-weight heparin (LMWH) in 300 high-risk patients who were randomized to no thromboprophylaxis, 400 mg of aspirin (duration of 3 days starting 12 hours before the flight), or LMWH (single dose of 1000 IU per body weight delivered 2 to 4 hours before the flight).[29] A substantial proportion of the study population (17%) was lost to follow-up; nonetheless, thrombotic events for the three groups (including superficial and deep vein thrombosis) were 4.8% in the control arm, 3.6% in the aspirin arm, and 0.6% in the LMWH arm. The authors suggested that LMWH dosing as a single intervention prior to a long-haul flight in high-risk patients should be considered. Interestingly, the vast majority of thrombotic events, 85%, were observed in nonaisle seats, suggesting that reduced mobility associated with a seated position may be a contributing factor to the development of thrombotic episodes.

Guidance and relevance to superficial venous intervention

The American College of Chest Physicians Clinical Practice Guidelines for the prevention of VTE in nonsurgical patients quote a relative risk of VTE of 2.8 with long-haul travel; risk factors associated included immobility, sitting in a window seat, obesity, and recent surgery. They advise, with a grade 2C recommendation, frequent ambulation, calf muscle exercises, and sitting in an aisle seat for high-risk, long-haul travelers.[30] Graduated compression stockings delivering pressures of 15 to 30 mm Hg are also recommended with a grade 2C recommendation for high-risk patients, though not for any other travelers. The routine use of pharmacological thromboprophylaxis in all long-haul travelers is not recommended (grade C).

The National Health Service (NHS) website provides advice relating to when patients can fly following an intervention.[31] The range is from 1 to 2 days after keyhole surgery to 10 days following coronary artery bypass grafting or more complicated abdominal surgery. There is no specific information regarding long-haul flights or flying following superficial venous intervention. Minimally invasive superficial venous interventions carry a risk of VTE that is less than 1%[32]; however, there is an association between the presence of varicose veins and the development of VTE, as described in international risk assessment tools.[5] Therefore, this population may be at an increased risk of developing flight-related VTE events. Formal guidance, however, is not available.

Based on the existing evidence, the risk with a short-haul flight may not be significant. For medium- to long-haul flights (4 to 6 hours), however, it may be advisable to delay a superficial venous intervention for at least 2 weeks following air travel, due to reported increased VTE rates.

There is no evidence to provide advice on the timing of travel following superficial venous intervention. Advice should be based on an individual patient's risk factor assessment, bearing in mind travel duration, with consideration of additional mechanical and/or chemical thromboprophylactic measures. Currently, there is no accepted standard regarding routine thromboprophylaxis in the context of superficial venous interventions, although individual units use thromboprophylaxis.[33,34]

Conclusion

This review highlights that VTE prevalence is increased during long-haul travel, but that the increased risk is likely due to a combination of factors, as opposed to travel alone. The risk of VTE is reported to be highest in the first 2 weeks following travel, which must be taken into account when planning an intervention. There is evidence that compression stockings reduce VTE rates in travelers, and targeted pharmacological thromboprophylaxis may be suitable in select high-risk patients.

Further studies are required to clarify the relationship between long-haul travel and VTE in the context of patients with underlying venous disease.

Corresponding author
Professor Alun H. DAVIES,
4th Floor, East Wing Charing Cross Hospital, Fulham Palace Road,
London, W6 8RF, UK

Email: a.h.davies@imperial.ac.uk

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Management of chronic venous insufficiency patients presenting an axial deep reflux in isolation or combined with iliac vein obstruction

Yuji HOSHINO, MD

Section of Vascular Surgery. Fukuoka Sanno Hospital, Japan

Keywords:

chronic venous insufficiency; deep venous incompetence; postthrombotic syndrome; iliac stenting; deep venous surgery

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Abstract

The pathology of chronic deep venous incompetence often involves postthrombotic syndrome, secondary to an episode of deep venous thrombosis. Obstruction of the iliac vein and valve incompetence of the femoral/popliteal veins produce symptoms caused by the resulting chronic venous hypertension in the legs. The clinical symptoms are common symptoms of chronic venous insufficiency: varicose vein formation, swelling of the lower-limbs, heaviness, venous claudication, stasis dermatitis/pigmentation, and ulceration; these are generally severe and refractory in cases of deep venous incompetence. Diagnosis and assessment are based on ultrasonography, similarly to general venous disease. As deep venous incompetence necessitates integrated assessment of the veins of the legs, including the inferior vena cava and iliac veins, assessment requires computed tomography, magnetic resonance imaging, venography, and even endovascular assessment with intravascular ultrasound. The initial approach for patients with chronic venous insufficiency is typically compression therapy, superficial venous surgery, and perforator surgery, which are effective for most patients. When these treatment modalities fail to heal, therapeutic options focus on the deep venous system. Endovascular treatment, such as venous stenting, is indicated for obstructive lesions of the iliac vein, and deep venous reconstructive surgery for valve reflux of the femoral/popliteal vein. Iliac vein stenting has become common in recent years, reportedly yielding the most favorable results.

Introduction

Deep venous intervention has been challenging, as it is performed in only a small number of centers; however, a recent increase in the use of venous stenting has resulted in this therapy becoming more common. Iliac vein stenting is a relatively new method of treatment, but it should be considered as an additional option to conventional compression therapy or common leg vein therapies, such as superficial vein surgery or perforator surgery.

Constructing a proper treatment strategy requires a clear understanding of the pathology, etiology, and knowledge of the indications and limitations of the various therapeutic techniques. With the introduction of new therapeutic methods, it is important to be aware of how these should be combined with conventional therapeutic methods, what methods of examination should be used for assessment, and for what kinds of cases these therapies are indicated. This paper provides an explanation thereof, along with an explanation of the management of patients with chronic venous insufficiency.

Pathology

The main pathology of deep venous incompetence is defined as clinical symptoms caused by venous hypertension due to stenosis/obstruction of the iliac vein as well as valve incompetence of the femoral/popliteal veins.[1-3] However, in patients with severe chronic venous insufficiency, venous reflux involves deep veins as an isolated abnormality in less than 10% of cases, but it is associated with superficial venous insufficiency and/or perforator incompetence in 46% of cases.[1,4] The clinical symptoms of chronic venous insufficiency are classified in the CEAP classification (C_0, no clinical signs; C_1, telangiectasias or reticular veins; C_2, varicose veins; C_3, edema; C_{4a}, pigmentation or eczema; C_{4b}, lipodermatosclerosis or atrophic blanche; C_5, healed venous ulcer; C_6, active venous ulcer).[5] These symptoms can also be caused by superficial venous insufficiency or perforator incompetence in isolation, but deep venous incompetence often presents with more severe clinical symptoms *(Figure 1A)*. deep venous incompetence can also be implicated in the refractory varicose vein postoperative recurrence.

Postthrombotic syndrome

The pathology of postthrombotic syndrome, the main subject of this paper, can cause both iliac venous outflow obstruction and deep venous axial reflux and it is the most common form of deep venous incompetence. The pathology is secondary to an episode of deep venous thrombosis and is caused by a venous thrombus, fibrotic change in the chronic phase of deep venous thrombosis, with stenosis/obstruction of venous drainage and reflux due to venous valve damage causing stasis symptoms.[6] Only 20% to 30% of iliac vein thrombi completely recanalize with anticoagulation therapy alone, while the remaining veins develop obstruction with variable collateralization.[7-9] A fibrotic-changed thrombus may cause narrowing of the intravascular lumen, creating an obstructive lesion *(Figure 1B)*, or form a septum that presents with a honeycomb-like multichannel form in the intravascular lumen *(Figure 1C)*. The venous outflow obstruction causes several paths of collateral circulation to form, resulting

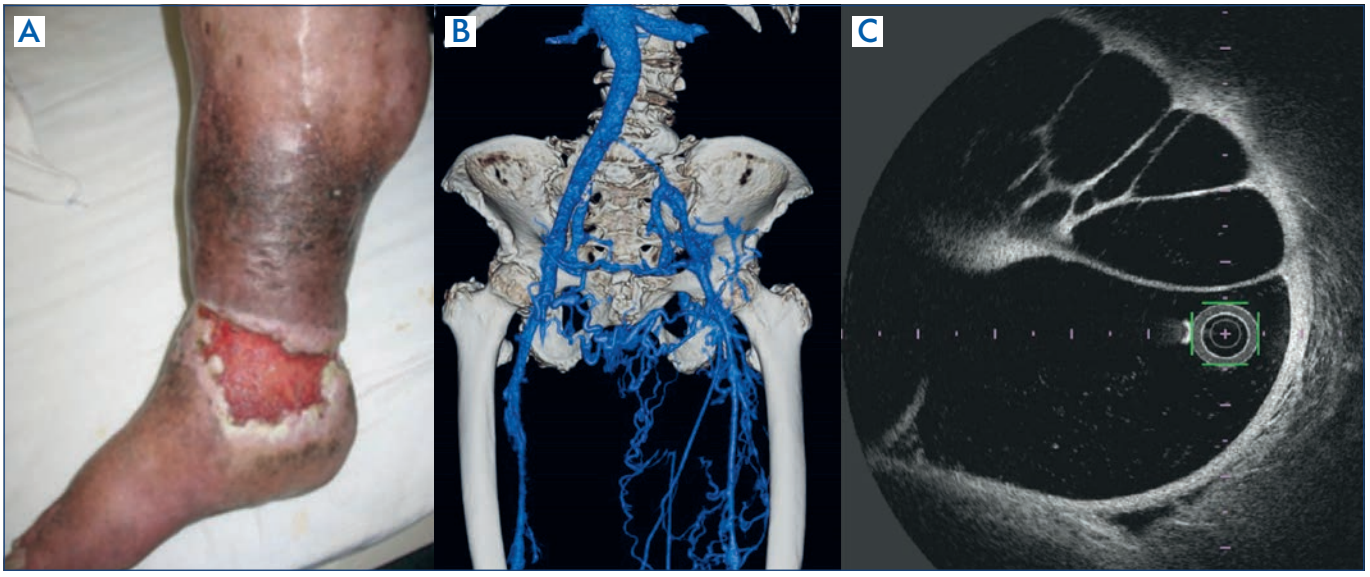

Figure 1. Postthrombotic syndrome.

Panel A. Stasis dermatitis, active ulcer.

Panel B. Computed tomography venography showing the obstruction of the left common iliac vein and the significant developed collateral veins.

Panel C. Optical frequency domain imaging finding of the common iliac vein: intraluminal fibrotic septum (a honeycomb-like multichannel form).

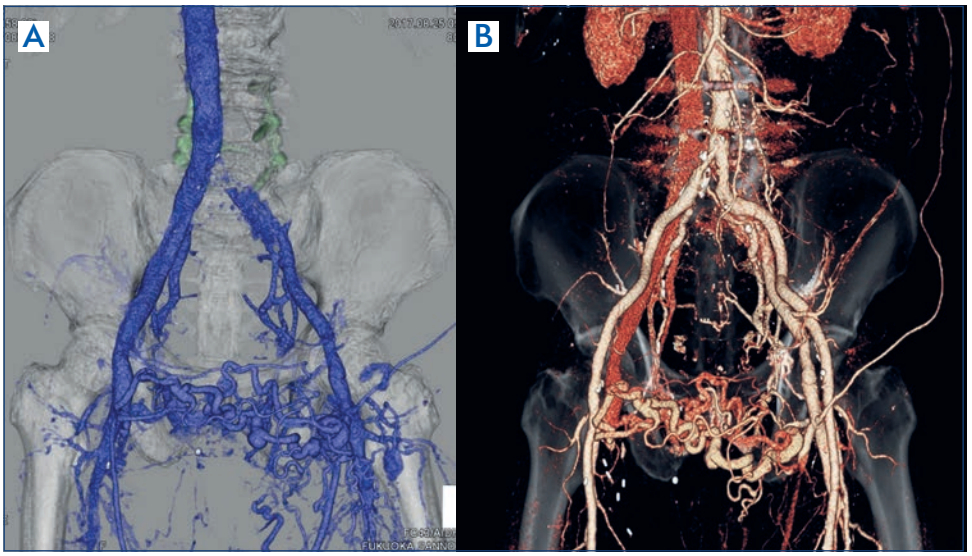

Figure 2. Postthrombotic syndrome.

Panel A. Contrast-enhanced computed tomography (venous phase) left common iliac vein obstruction, much collateral circulation observed.

Panel B. Contrast-enhanced computed tomography (arterial phase); arteriovenous fistula formation at the site of the collateral circulation.

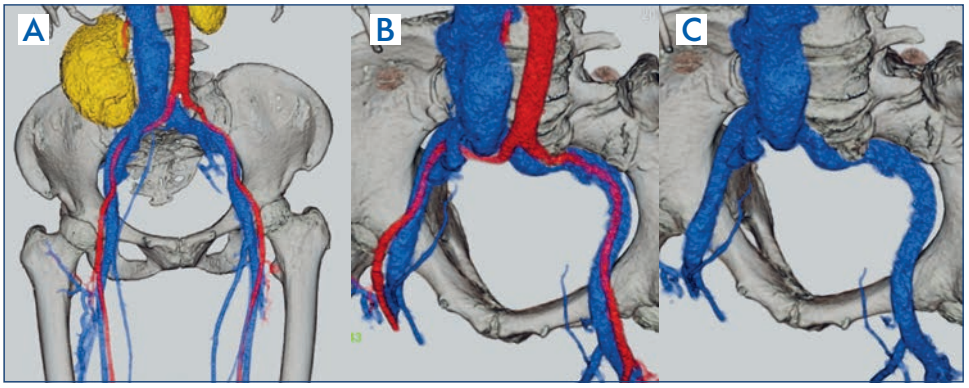

Figure 3. Nonthrombotic iliac vein lesions case: findings from contrast-enhanced computed tomography.

Panels A and B. The left common iliac vein is compressed between the right common iliac artery and the vertebral body.

Panel C. Same computed tomography findings (image with arterial portions subtracted).

in secondary varicosities, which, when reaching the finer venous vessels, results in open arteriovenous channels and formation of arteriovenous fistulae *(Figure 2A and 2B)*. The fibrotic changes also cause valve destruction, resulting in downward venous reflux. Postthrombotic syndrome involves coexisting stenotic/obstructive and regurgitant lesions, and clinical symptoms tend to be especially severe in the presence of obstructions at the iliac vein level and valve incompetence at the femoral vein level. Clinical symptoms include chronic venous insufficiency, as already mentioned, and one known clinical classification is the Villalta scale.[10]

Nonthrombotic iliac vein lesions

Causes of iliac vein stenosis are not limited to thrombi and include being compressed between the iliac artery and a vertebral body, also known as May-Thurner syndrome after aomprehensive reporting from May and Thurner in 1957.[11] Later, Raju et al described the same pathology around 2006 as nonthrombotic iliac vein lesions.[12] The pathology is thought to present with clinical symptoms of chronic venous insufficiency and provoke deep venous thrombosis, as it involves venous outflow obstruction in the legs due to stenosis of the iliac vein. A common, well-known form is stenosis of the portion where the left common iliac vein is compressed between the right common iliac artery and the fifth lumbar vertebra *(Figure 3A-3C)*. Such stenosis, however, is also reportedly often observed in many healthy individuals[13] and the necessity remains a matter of debate.

Less common causes of chronic iliocaval obstruction include tumors, retroperitoneal fibrosis, iatrogenic injury, irradiation, and aneurysms. Primary deep valve incompetence and congenital valve malformation should also be considered as causes of deep venous valve incompetence.

Examination

Assessment points include iliac vein stenosis/obstruction and patency/reflux of the femoral vein, deep femoral vein, and popliteal vein, as well as superficial venous insufficiency and the perforator incompetence.

Ultrasonography

Ultrasonography should be the first examination because it is minimally invasive and provides a high volume of information.

Iliac vein level

The assessment point is whether there are findings of stenosis/obstruction. If a deep location makes direct observation impossible, indirect assessment remains possible by using the respiratory maneuvers or the Valsalva maneuvers. As obstruction of the iliac vein results secondarily in collateral circulation at the saphenofemoral junction, thicken collateral paths at the saphenofemoral junction are regarded as a sign to suspect stenosis/obstruction of the iliac vein.

Femoral/popliteal vein level

Assessing reflux necessitates performing the examination in a standing posture. Venous reflux is assessed by compressing the calf, and is deemed positive if the reflux duration exceeds 1 second.[14] A fibrotic-changed thrombus, also sometimes partially presenting with calcification, are overall highly echogenic *(Figure 4A)*. Patency/reflux of the deep femoral vein can also be assessed, however, in some cases it may be difficult to investigate due to its deep location. Moreover, adequate great saphenous vein reflux can be observed. With postthrombotic syndrome, it is crucial that there are cases of secondary varicosities resulting merely from significant development of the saphenous veins (with no reflux) as collateral circulation due to deep vein occlusion.

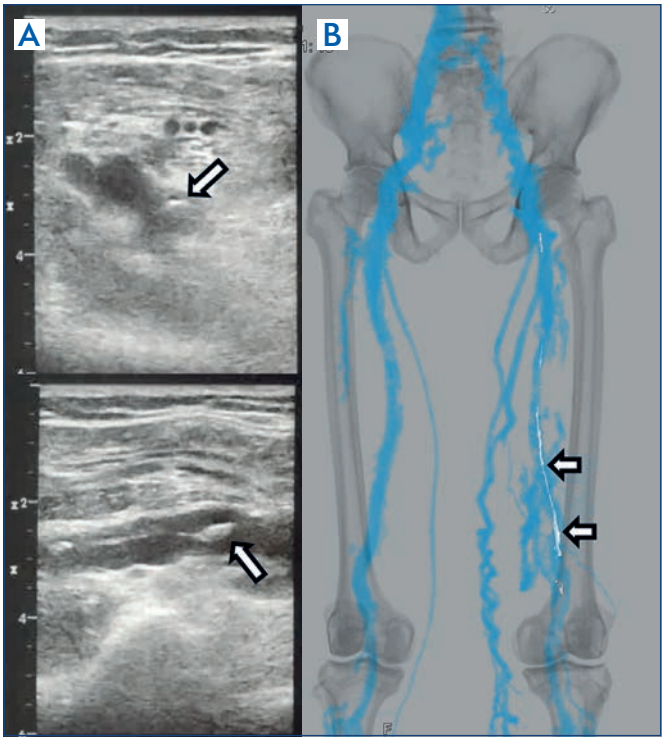

Figure 4. Postthrombotic syndrome.

Panel A. Ultrasound findings: fibrotic changed thrombus of the popliteal vein, with high echogenicity and a portion (arrow) presenting with calcification.

Panel B. Plain computed tomography findings: calcification (arrow) observable in plain computed tomography as well.

Calf vein level

This will mainly be an assessment of incompetent perforators in the legs. Cases of deep venous incompetence caused by postthrombotic syndrome often have posterior tibial perforator incompetence, and thus assessment of incompetent perforators must be centered on this area. As with the great saphenous vein, reflux of the small saphenous vein is also assessed.

Air plethysmography

The leg is completely covered with an air-filled cuff, and volume changes in the leg are recorded as numerical values; this offers a completely noninvasive, quantitative assessment of arteriovenous return function in the legs. However, it is not able to differentiate between superficial venous insufficiency and deep venous incompetence or to assess reflux of an incompetent perforator. Additionally, it is difficult to assess the accurate deep venous incompetence from isolation data because the arterial blood flow rate has a major impact on the data.

Computed tomography and magnetic resonance imaging

Computed tomography and magnetic resonance imaging allow for regional assessments of deep vein stenosis/obstruction, as well as the formation of collateral circulation. Even plain computed tomography (no contrast agent is used) offers a certain degree of assessment of deep vein stenosis/obstruction and the aforementioned venous calcification can also be observed *(Figure 4B)*. Contrast-enhanced computed tomography enables a more detailed assessment of stenosis/obstruction lesions. Offsetting the timing of imaging makes it possible to assess both the arterial phase and the venous phase, with stereoscopic image construction making it possible to build an overall image that is easier to understand *(Figures 1B, 2, and 3)*. It is also possible to assess differential diseases, such as retroperitoneal fibrosis, tumors, congenital venous malformations, and arteriovenous fistulae. Similar assessments can also be made with magnetic resonance imaging; however, for the aforementioned reasons computed tomography is of greater utility.

Venography

Direct imaging of stenotic/obstructive lesions of the iliac vein make it possible to assess lesion sites, check for guide wire passage, and assess the development of collateral circulation. "Pancake-shaped" contrast imaging of stenosis of the iliac vein could potentially be missed with venography alone, hence, stenosis must be assessed from the intravascular lumen by intravascular ultrasound *(Figure 5)*. Not only findings of iliac vein stenosis/obstruction, but also findings of femoral/popliteal vein axial reflux are an important assessment point. To assess femoral/popliteal vein reflux, descending venography is used with the Valsalva maneuver to assess how far the venous reflux descends *(Figure 6)*. One known classification for reflux assessment is the Kistner classification *(Table I)*.[16,17] If deep axial reflux has been observed, assessing valve morphology and checking for their presence or absence enables differentiation as to whether the etiology is postthrombotic syndrome or primary deep valve incompetence, as well as congenital venous valve dysplasia/hypoplasia[1]; it is a crucial examination to perform when deep venous reconstructive surgery is being considered. It is optimal with oblique projection; however, a supine position is also possible. Direct measurement of venous pressure is not of particularly great significance if examination is done in the supine position. Proper valve assessment is not possible if the guide wire or catheter is located inside the femoral vein; therefore, there must be a case-by-case consideration of the ideal puncture site.

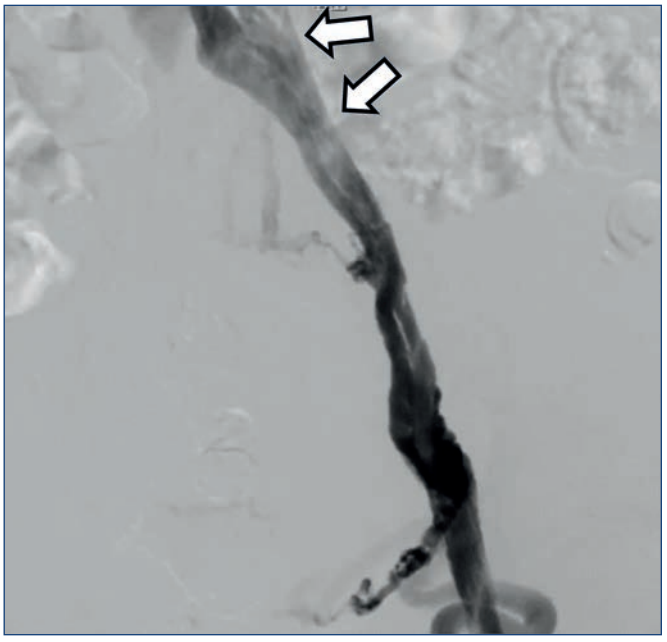

Figure 5. Postthrombotic syndrome.

Ascending venography findings: stenosis at the common iliac vein, with a "pancake" shape at the arrow.

Kistner's classification
Grade 0: No reflux
Grade 1: Reflux of the upper thigh
Grade 2: Reflux in the lower thigh to the popliteal level
Grade 3: Reflux below the popliteal level into the upper calf
Grade 4: Reflux to the ankle

Table I. Kistner classification.

While the abovementioned examinations are crucial, completely asymptomatic cases that still have obstructive findings in the iliac vein and axial reflux findings in the femoral vein are not uncommon. Perrin has noted that, because various examination findings and a patient's clinical symptoms may not be correlated, the decision of performing deep venous interventions should be based not only on examination data, but also on the patient's clinical condition.[4]

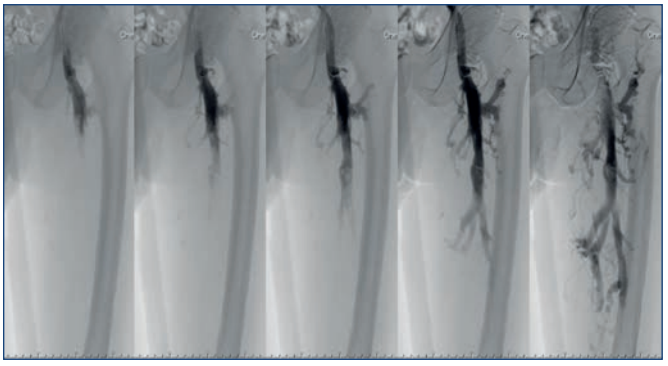

Figure 6. Postthrombotic syndrome.

Descending venography demonstrating axial reflux down to the knee level.

Treatment

Compression therapy

Comparable to compression therapy for ordinary venous diseases, compression therapy with elastic stockings or elastic bandages also lies at the center of treatment for deep venous incompetence. The fundamental role of compression in the treatment of chronic venous insufficiency is well recognized and has been validated

by randomized controlled studies.[18] Intermittent pneumatic compression pumps can also serve as useful auxiliary means.[19] Several symptoms of chronic venous insufficiency improve with rest, elevation of the legs, and utilization of compression therapy. Weight loss, walking exercise, and physical therapy to improve the mobility of the ankle joint are also effective for symptom improvement.[9] The pressure from compression with compressive garments in compression therapy must be higher with deep venous incompetence than with superficial venous insufficiency.[20] Compression therapy is also a technique that must be performed simultaneously with the various treatments described below.

Superficial vein surgery, perforator surgery

Even if deep venous incompetence coexists with superficial venous insufficiency or perforator incompetence, superficial vein surgery and perforator surgery should first be considered. These are both simple, but highly effective techniques. In a randomized controlled trial, superficial venous surgery significantly reduced the 12-month ulcer recurrence rate.[21] In a subgroup analysis of this study, it was shown that superficial venous surgery might improve venous hemodynamics in legs with venous ulceration despite coexistent deep venous reflux.[22] Surgical techniques for superficial venous insufficiency include endovascular ablation, foam sclerotherapy, and stripping. Patency of the femoral vein and popliteal vein is a requirement for performing these treatments. There is still debate on the efficacy of perforator surgery, but surgery on an incompetent perforator has shown favorable results, especially in cases with deep venous incompetence.[22] There have been several techniques for eliminating incompetent perforators including the classic Linton procedure (rarely performed now), subfascial endoscopic perforator surgery, and, recently, perforator ablation and foam sclerotherapy.[23]

Deep venous interventions should be considered if these treatments fail to yield desired results.

Deep venous intervention

Pattern 1: cases of iliac vein obstruction or iliac vein obstruction combined with femoral vein axial reflux

With pattern 1, revascularization of the obstructed iliac vein should be considered, as it is an important venous outflow of the leg veins. An obstructed iliac vein has been previously treated with bypass surgery, as with the Palma-Dale procedure, or surgical revascularization[24]; however, these are currently rarely performed due to poor long-term outcomes. They have been replaced by endovascular therapy in the form of stent placement *(Figure 7)*,[25,26] with many recent reports showing favorable treatment outcomes.[27,28] Despite the absence of objective hemodynamic outcome measures, the clinical efficacy of iliac vein stenting has been proven by alleviation of symptoms, such as pain and swelling, and by the high rate of ulcer healing. Objectively documented swelling is completely alleviated in approximately one-third of limbs and is significantly improved in others. About 50% of patients have complete relief of pain following stenting. Median venous clinical severity and disability scores also significantly improved (8.5 to 2 and 2 to 0, respectively).[29] Despite the presence of untreated axial reflux, approximately half of ulcerated legs will heal, and stay healed for up to 2 years, following iliac vein stenting.[30,31]

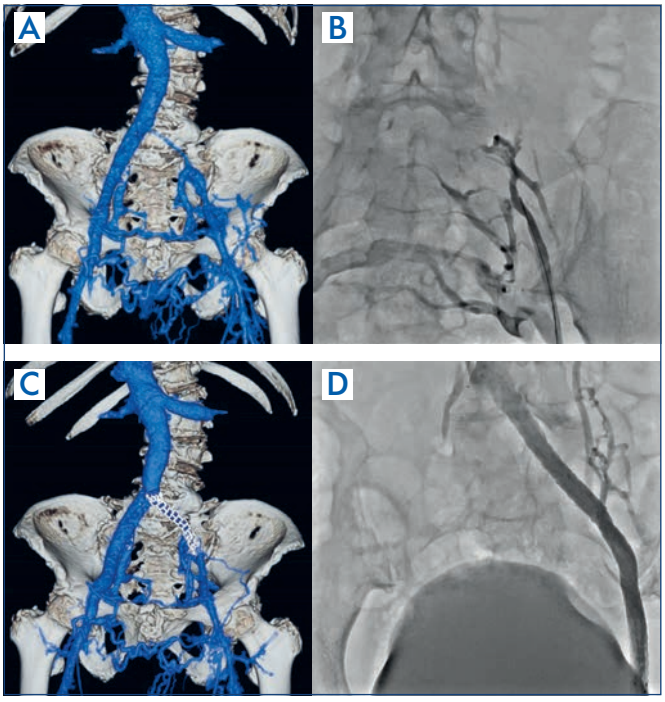

Figure 7. Iliac vein stenting in a postthrombotic syndrome case.

Panel A. Contrast-enhanced computed tomography finding: before stenting.

Panel B. Ascending venography findings: before stenting.

Panel C. Contrast-enhanced computed tomography finding: after stenting.

Panel D. Ascending venography findings: after stenting.

A large diameter stent is used: 14 mm to 16 mm at the common iliac vein, 12 mm to 14 mm at the external iliac vein, and 10 mm to 12 mm at the common femoral vein.[28] Decision for the site of stent placement and the optimal stent size must take into consideration both findings from venography and intravascular ultrasound *(Figure 8)*.

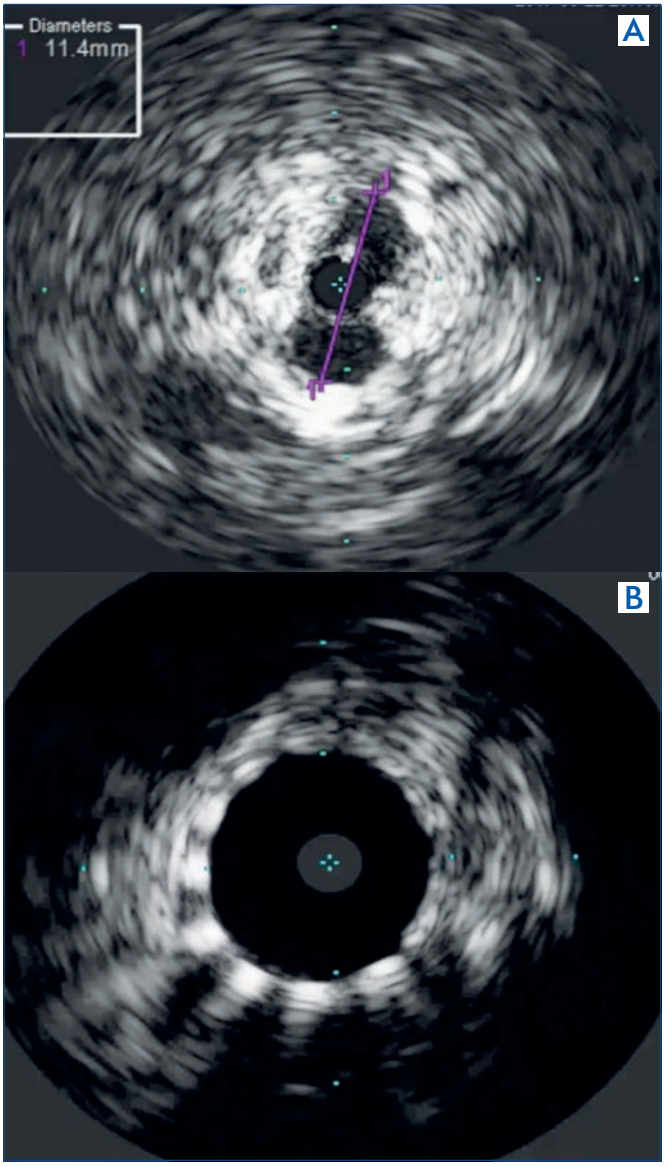

Figure 8. Intravascular ultrasound finding in a postthrombotic syndrome case.

Panel A. Assessment/measurement of stenotic lesion; left common iliac vein before stenting.

Panel B. Examining patency after stenting.

Especially with postthrombotic syndrome, fibrotic changes in the thrombus cause the intravascular lumen to have a honeycomb-like multichannel form, or to be completely obstructed, and thus intravascular ultrasound is very useful because the guide wire can be passed through the correct route. Meissner stated that several technical factors may improve patency including the use of adequately sized stents, the routine use of intravascular ultrasound, stenting all areas of disease, and assuring adequate inflow.[28] It is well known that stent outcomes are poor if there is postthrombotic syndrome areas at the common femoral vein, and the risk of stent occlusion when extending stents across the inguinal ligament reportedly increases 3.8-fold.[27] Femoral endovectomy is also performed at the same time as stenting, while conserving the deep femoral vein, which is recognized as an important inflow.[32]

The mortality rate following venous stenting is zero, with a morbidity rate of 1%. Cumulative secondary patency rates are about 90% at 4 to 6 years, and late occlusions are rare.[29,30] Several patients have been followed for 5 years or more without precipitous deterioration of stent patency or clinical efficacy. However, limbs with postthrombotic syndrome fare significantly worse after stenting than those with nonthrombotic disease (primary, assisted-primary, and secondary cumulative patency rates at 36 months of 65%, 85%, and 88% with postthrombotic syndrome vs 89%, 100% and 100% with nonthrombotic disease).[30,31]

The data regarding the adjunct use of antiplatelet agents and anticoagulants in venous interventions is substantially less robust. Antiplatelet agents are likely most appropriate for patients with nonthrombotic disease, while anticoagulants likely have a greater role in postthrombotic disease, but there is no evidence yet.[28] However, given the absence of evidence supporting their use, long-lasting anticoagulant therapy is regarded as necessary for cases with a previous history of deep venous thrombosis.

Pattern 2: Femoral vein axial reflux in isolation or if symptoms persist after stenting in patients with pattern 1

The treatment aims to surgically repair femoral/popliteal vein reflux. The most common etiology is postthrombotic syndrome (60% to 85% of cases), where the valve is completely or partially damaged by the postthrombotic fibrotic changes. Primary deep valve incompetence is less frequent, where the valve cusps are present, but malfunctioning; the abnormal, free edge of each valve results in valve prolapse, dilatation of the annulus with a widening of the commissures.[1] A very rare cause of reflux is the congenital valve aplasia. Indication for deep venous reconstructive surgery is severe chronic venous insufficiency (C_{4b}-C_6) not controlled by any treatment modality *(Figure 9)* in patients with deep axial reflux (grade 3to 4 according to Kistner classification.[1,4] Various surgeries have previously been performed; the surgical technique is selected in accordance with the etiology and the condition of the valve.

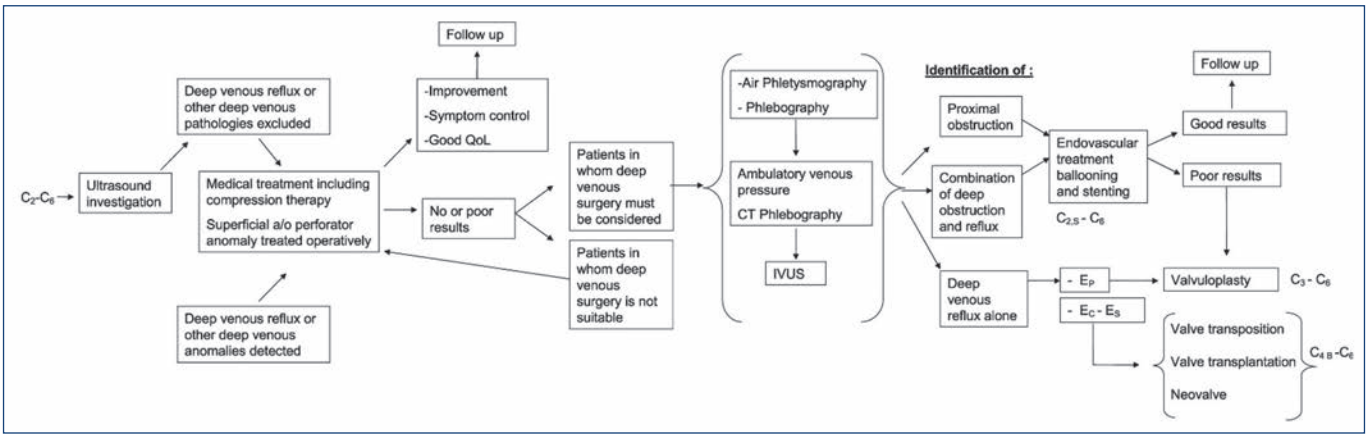

Figure 9. Diagram of the therapeutic strategy for deep vein insufficiency.

From reference 1: Maleti O, Perrin M. Eur J Vasc Endovasc Surg. 2011;41(6):837-848. © 2011, European Society for Vascular Surgery.

Internal valvuloplasty

Known as the "Kistner method," this technique involves making a phlebotomy to expose the incompetent valve to reapproximate the valve leaflets.[33] The whole valve apparatus is visualized, and the advantage is that the cusp can be repaired even with left/right asymmetry. The difficulty, however, is that valve competence cannot be checked before proximal clamp release.

External valvuloplasty

With no phlebotomy, this technique involves transmural suturing of the valve commissure,[34] and, in some cases, an angioscopy may be used *(Figure 10)*. Though there is an advantage in that no phlebotomy is made, the repair is difficult and less precision.

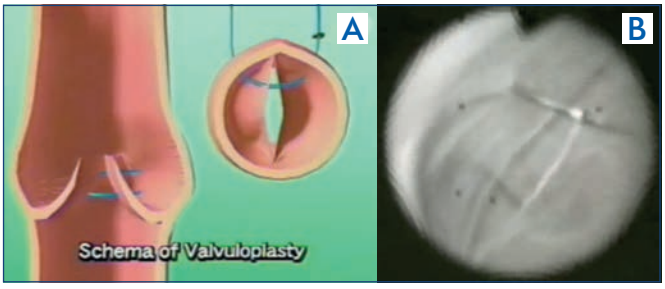

Figure 10. External valvuloplasty.

Panel A. External valvuloplasty schema.

Panel B. Transmural suturing with angioscopic supervision.

External valve banding

The use of an external sleeve of Dacron or PTFE wrapped around the incompetent valve has been applied to correct reflux.[35] Despite an advantageously simple technique, there is a potential risk of vein lumen narrowing. This procedure can be used alone or in association with other reconstructive techniques.

Axillary vein transplant

The principle behind axillary vein transplants consists of inserting a segment of a competent valvulated vein in the incompetent deep venous network.[36] The donor segment can be the axillary vein or brachial vein. However, 40% of axillary veins also have valve incompetence, and there is a high risk of early occlusion.

Femoral vein transposition

If the ipsilateral great saphenous vein or deep femoral vein has a proximal competent valve and adequate caliber, the transfer of a femoral vein distal to the competent valve can be performed *(Figure 11)*.[37] The advantage is that there is no direct action on the valve apparatus.

Neovalve

The neovalve technique is obtained by dissecting the vein wall to create a flap, which is positioned as a monocuspid or bicuspid valve.[38] Since the principle of this procedure is creating a new valve in the deep venous system, this technique can not only be employed for postthrombotic syndrome, but also for primary deep valve incompetence and valve aplasia *(Figure 12)*. The disadvantage of this procedure is that the technique cannot be standardized; it depends on the anatomical condition of the wall and, therefore, the most suitable option is decided only after phlebotomy.

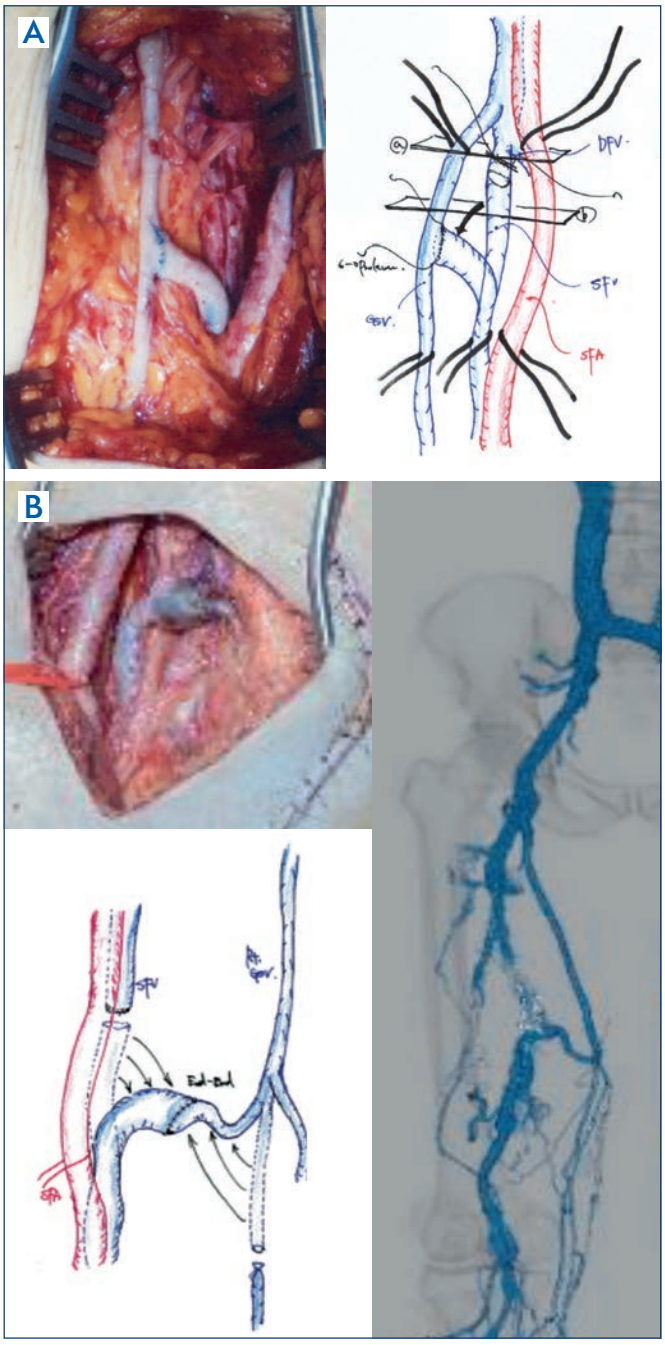

Figure 11. Femoral transposition.

The transfer of a femoral vein distal to the competent valve.

Panel A. Termino-lateral anastomosis of the femoral vein into great saphenous vein (picture and scheme).

Panel B. End-to-end anastomosis of the femoral vein into the great saphenous vein (picture, scheme, and contrast-enhanced computed tomography finding).

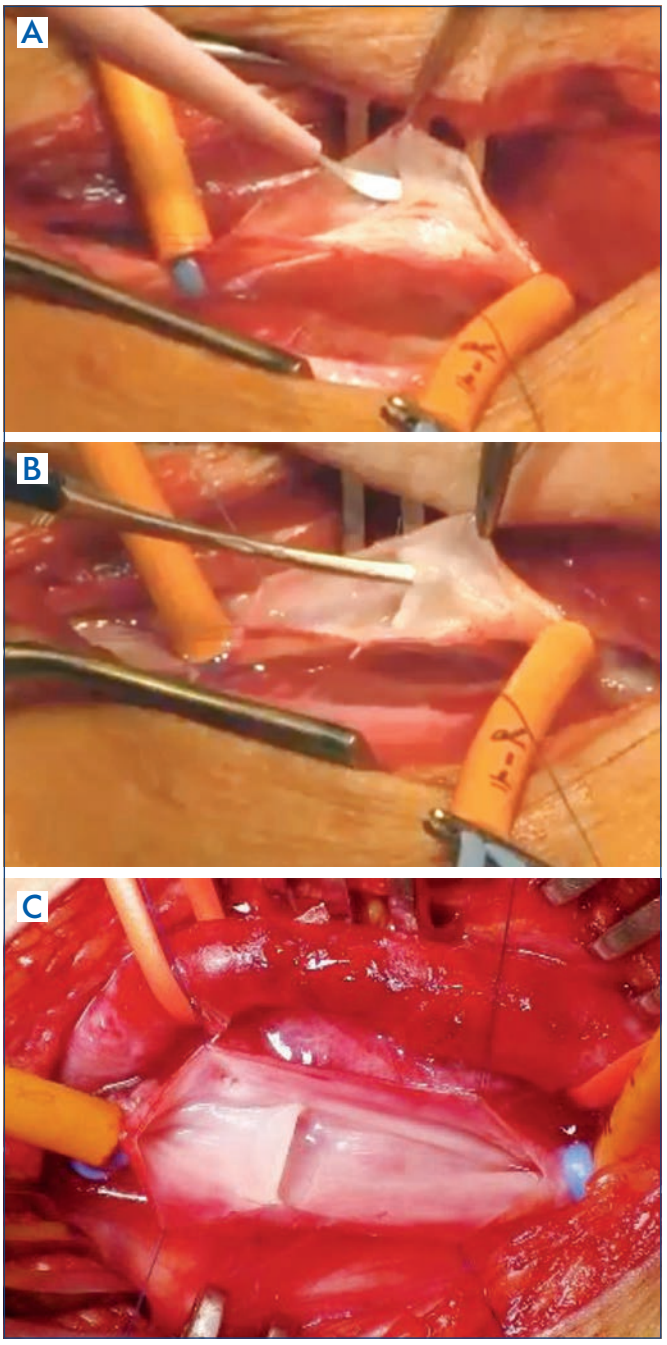

Figure 12. The Neovalve (monocusp).

Panel A. Neovalve in postthrombotic syndrome: partial incision and parietal dissection.

Panel B. Neovalve in postthrombotic syndrome: dissecting the vein wall to create a flap.

Panel C. Neovelve in primary deep valve incompetence.

It is difficult to evaluate the results of deep venous reconstructive surgery and, generally, the outcomes are based on pain relief, absence of ulcer recurrence, and restored valve competence.

In terms of outcomes of valvuloplasty for primary deep valve incompetence, clinical outcome and valve competence generally show an excellent correlation, and the 5-year follow-up surgical success rate has been around 70%.[39-42]

For postthrombotic syndrome, an axillary vein transplant has a clinical outcome of 33% to 82%, with valve competence of 16% to 87%,[40,41,43,44] while, for femoral vein transposition, these figures are 50% to 70% and 40% to 77%, respectively.[39,40,44] The neovalve technique has an 83% ulcer healing rate, with success rates in terms of valve competence of 68% (monocuspid) and 100% (bicuspid).[45]

In cases of primary deep valve incompetence, the recommended technique is internal valvuloplasty for the majority of authors.[39,40,44] In postthrombotic syndrome, the techniques to be used, in order of recommendation, are femoral vein transposition, neovalve, and axillary vein transplant.[1,4] Issues with deep venous reconstructive surgery include the difficulty of the technique, case-by-case differences in the extent of deformation and damage to the valve, differences in technique between a postthrombotic syndrome, a primary deep valve incompetence, or a congenital etiology, and the lack of long-term outcomes data; thus, the procedure is performed only in specialized and highly trained centers.

Conclusion

The severe and refractory clinical symptoms of chronic venous insufficiency are often correlated with deep venous incompetence. With these treatments for chronic venous insufficiency, each of the techniques do not exist on their own, but consideration must also be given to understanding the etiology, hemodynamics, and pathophysiology, and assessing all venous systems to consider the indications for therapy and the timing of treatment. For deep venous interventions, long-term anticoagulant therapy must be considered in most cases. Therefore, the interventions should be decided on only after careful consideration.

Corresponding author
Yuji HOSHINO, MD
Section of Vascular Surgery. Fukuoka Sanno Hospital.
3-6-45, Momochihama, Sawara-ku,
Fukuoka-shi, Fukuoka, Japan. 814-0001

Email: uz0130@hotmail.com

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Management of small saphenous vein varices with perspectives from a recent meta-analysis and recommendations

Nicolas NEAUME

Clinique Pasteur, 45 avenue de Lombez, 31076 Toulouse, France

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Abstract

The methods of treating varicose veins have been constantly evolving over the past 20 years, leaving a prominent place today for endovenous techniques, with conventional surgery being gradually abandoned. The modern treatment of varicose veins of the lower-limbs is performed either by tumescent endovenous thermal techniques (laser, radiofrequency, steam) or by nonthermal nontumescent techniques (ultrasound-guided foam sclerotherapy, glue cyanoacrylate, mechanochemical endovenous ablation). The introduction of minimally invasive endovenous ablation techniques (thermal and nonthermal techniques) are associated with several advantages, including minimally invasive, immediate discharge and ambulation, faster recovery, and less periprocedural morbidity. Based on the literature and recommendations, endovenous thermal ablation should be preferred to surgery and foam sclerotherapy in the treatment of small saphenous vein incompetence. The potential benefits, particularly the reduced risk of nerve damage, might be of considerable clinical importance and may lead to a preference for nonthermal techniques in the future. Extensive data about nonthermal techniques are necessary to improve outcomes and achieve robust evidence.

Introduction

Isolated saphenopopliteal reflux may occur in up to 15% of patients with primary varicose veins.[1] This reflux can be associated with equally significant chronic venous disease (CVD) signs and symptoms compared with great saphenous vein incompetence. Untreated varicose veins may sometimes lead to leg ulcerations, which are difficult to manage. Traditionally, treatment was restricted to surgery or compression therapy. Small saphenous vein surgery is considered more challenging than great saphenous vein surgery and is associated with higher recurrence and postoperative complication rates. Treating the small saphenous vein must be carried out very carefully because the ending is variable, and it is in close proximity to the nerves.

Over the past two decades, the treatment of varicose veins has been revolutionized by the introduction of minimally invasive endovenous ablation techniques (thermal and nonthermal techniques). These procedures are associated with several advantages, including a minimally invasive nature, immediate discharge and ambulation, faster recovery, and less periprocedural morbidity. They seem to have superior anatomical success rates compared with traditional surgical stripping.[2-5]

Surgical anatomy

Many complications of surgical stripping of the small saphenous vein have been described, such as damage to the sural nerve, the tibial nerve, and the fibular nerve. The small saphenous vein drains blood from the external part of the foot and the posterior internal part of the leg. It is a continuation of the external marginal vein that runs along the dorsal side of the foot. At its origin, the main trunk passes below, then behind the external malleolus in the external retromalleolar groove. It then rises vertically and in a median supra-aponeurotic position along the rear of the calf, and is then attached to the sural (sensory) nerve, which must not be damaged during thermal ablation. The sural nerve is an axial nerve formed by sensory branches of the tibial and fibular nerves. The sural accessory nerve emerges from the fibular nerve. At the apex of the calf, the sural nerve and its accessory branch join in a common trunk and accompanies the small saphenous vein down to the ankle.

At the mid-leg point, the small saphenous vein enters the subaponeurotic tunnel of the sural triceps. It then bends slightly, which tends to send it deeper, and the vein continues along its path to the top of the knee joint line. At the knee joint, it bends and forms an anterior concave arch to join the popliteal vein at a level that can vary, or it may even be attached to a subordinate popliteal trunk in the great saphenous vein or the tributaries thereof, in the deep femoral vein, or it may even form a joint trunk with the gastrocnemius veins.

The sciatic nerve, which is located posterior to the thigh, is divided at variable levels, but mostly at the summit of the popliteal fossa. This division is slightly displaced from the longitudinal axis of the limb on the lateral aspect. It is divided into 2 nerves: the tibial nerve and the fibular nerve; it is advisable to stay below this area (by about 15 mm to 20 mm in general) to avoid damaging the nerve during endovenous thermal ablations.

In 15% to 20% of cases, the saphenopopliteal junction is nonexistent. The external saphenous trunk extends to the rear side of the thigh. It then bends inward to join the internal saphenous trunk, or it may run down toward the deep femoral vein.[3,6,7]

Thermal techniques (laser and radiofrequency ablation) have emerged as an effective alternative to open surgery with stripping and high ligation. These methods are nevertheless accompanied by risks and side effects. Compared with open surgical therapy, the risk of damage to peripheral and motor nerves is reduced; however, it still exists as a result of heat exposure and tumescent anesthesia. Nonthermal methods that can be applied without tumescent anesthesia have been introduced as they pose a considerably lower risk of nerve lesions while proving to be effective.[8]

Recommendations for treating the small saphenous vein

International recommendations for endovenous saphenous ablation are heterogeneous, particularly for small saphenous vein treatment *(Table I)*.[9-15] Concerning surgery, the 2011 American Venous Forum guidelines did not mention thermal treatments, but rather surgery, with level 1B evidence. For thermal treatments, the 2011 American Venous Forum guidelines recommend high ligation with invagination stripping with a grade of 1B, the 2012 International Union of Phlebology recommends thermal treatment with a grade of 1A, the 2013 NICE guidelines considered all of the saphenous axes together, without making a specific analysis of the small vs the great saphenous vein, the 2015 ESVS guidelines gave thermal treatments a grade 2B recommendation, and the 2016 AVLS and the 2016 LATAM guidelines gave grade 1B recommendations. In a recent publication, the European College of Phlebology guidelines for truncal ablation reports that, for the treatment of short saphenous reflux, endovenous laser ablation or radiofrequency ablation techniques are recommended in preference to surgery or foam sclerotherapy, assigning a 2A level of evidence.[16] The 2014 Europe and LATAM 2016 guidelines gave sclerotherapy a grade 1A. The other guidelines indicated sclerotherapy treatment, but without a grade of evidence. The guidelines on nonthermal nontumescent techniques consider all of the saphenous axes together, without making a specific analysis of the small vs the great saphenous vein. Since 2016, the AVLS has recommended mechanochemical endovenous ablation

	AVF 2011	UIP 2012	NICE 2013	EUROPE 2014	ESVS 2015	AVLS 2016	LATAM 2016
Surgery	1B	X	Thermal treatment, foam over surgery	X	Thermal treatment over surgery	Thermal treatment over surgery	1C
Thermal treatment (radiofrequency/ laser)	-	1A	Recommended	X	2B	1B	1B
Steam	X	X	X	X	X	X	Need more investigations
Glue	X	X	Under evaluation	X	Need more investigations	X	Need more investigations
MOCA	X	X	Accepted as standard (2016)	X	Need more investigations	2B (Clarivein)	Need more investigations
Sclerotherapy	Thermal treatment over sclerotherapy	X	If thermal treatment unavailable, foam sclerotherapy rather than surgery	1A	Can be an alternative to thermal treatment and surgery.	X	1A

Table I. Guideline recommendations.

The text in red indicated the guidelines are considering just the small saphenous vein. The rest are considering all of the saphenous axis together, without making a specific analysis of the small vs the great saphenous vein. X, no specific recommendation.

with a grade 2B and the NICE accepted the procedure as standard.

Literature

Surgery

Before the past two decades, conventional saphenopopliteal junction ligation with or without stripping of the small saphenous vein has been the standard treatment for varicose veins associated with saphenopopliteal reflux. Small saphenous vein surgery is considered more challenging than great saphenous vein surgery and is associated with higher recurrence and postoperative complication rates. With a conventional surgical procedure, an incision is made in the popliteal fossa, and the small saphenous vein and saphenopopliteal junction are identified. The saphenopopliteal junction is then disconnected and a short segment of the small saphenous vein is either resected or stripped. Treating the small saphenous vein must be carried out very carefully because the ending is variable, and it is in close proximity to the nerves. Generally, a class II stocking is worn for a month.

In their meta-analysis, Boersma et al[2] reported the results of nine articles (surgical treatment of 798 small saphenous veins).[17-25] The surgical procedures were heterogeneous, included ligation and/or disconnection of the saphenopopliteal junction, with or without stripping, and there were anatomical success rates of 24% to 94% over a mean follow-up of 17.3 months. Two studies that randomized patients to either surgery or endovenous laser ablation showed inferior anatomical success rates for surgery.[17,19] Brittenden et al[18] reported data from a study that randomized patients to surgery, endovenous laser ablation, or foam, showing inferior anatomical success rates compared with endovenous laser ablation, but comparable results with foam. Allegra reported long-term anatomical success in 70% of 132 small saphenous veins after 5 years of follow-up.[22] Paresthesia occurred in up to 31% (mean 19.6%) and deep venous thrombosis in 0.7%. In their study, van Groenendael et al[26] compared the treatment of recurrences of 42 small saphenous veins (laser vs surgery) and showed that the incidence of recurrences was not statically significant between the groups. There was a faster recovery following laser ablation (1 day vs 7 days),

and endovenous laser ablation reduced the incidence of sural nerve injury (9% vs 20%).

Ultrasound-guided foam sclerotherapy

In the treatment of small saphenous veins, thermal ablation or surgery are well-established methods. Nevertheless, treatment of saphenous veins by ultrasound-guided foam sclerotherapy could also be an effective and cost-effective treatment option. Sclerotherapy is the targeted chemical ablation of varicose veins by an intravenous injection of a foamed sclerosing drug. The irritant nature of the sclerosant causes inflammation of the endothelium and subendothelium layers of the vein wall, resulting in fibrosis and occlusion of the vein. Traditional foam has been prepared by mixing liquid sclerosant with room air or gas, using the Tessari method or the double syringe method.[27]

Postsclerotherapy compression is not clearly defined, but Hamel Desnos et al[28] found, in a randomized controlled trial, no differences between the compression group and the control group when comparing efficacy, side effects, satisfaction scores, symptoms, and QOL.

In their meta-analysis, Boersma et al[2] reported the results from 6 articles, including 1 randomized controlled trial (foam sclerotherapy treatment of 494 small saphenous veins).[18,29-33] The Tessari method was mostly used to produce foam (liquid-to-air ratio of 1:4 or 1:3); studies were heterogeneous and used polidocanol (1% or 3%) and sodium tetradecyl sulfate (1% or 3%), with a mean anatomical success rate that ranged from 20% to 96%. Only 2 studies described postprocedural complications and deep venous thrombosis was noted in just 1 patient. In a prospective and controlled study, Gillet et al[34] demonstrated a low rate of deep venous thrombosis after foam sclerotherapy of 331 small saphenous veins. Only two (0.6%) deep venous thromboses were observed, both of which were confined to the medial gastrocnemius veins and were reported in symptomatic patients.

Thermal treatments

Endothermal modalities (ie, endovenous laser ablation and radiofrequency ablation) use heat transfer to ablate incompetent venous trunks, with local infiltration of tumescent anesthesia used to protect surrounding structures from heating injury, to induce venous compression, and to limit procedural pain. The small saphenous vein is punctured at mid-calf to reduce the risk of sural nerve injury. When treating the small saphenous vein, the tip is positioned at the point where the small saphenous vein leaves the subfascial space to join the popliteal vein.[16] Despite this, thermal injury may increase the rates of periprocedural pain, skin burns, and nerve injury. Postintervention compression for 1 week is often recommended, but the value and duration of compression is not clearly defined.[35] However, a recent meta-analysis did not reveal any advantage of compression therapy.[36]

Endovenous laser ablation

In endovenous laser ablation, under ultrasound guidance, a bare-tipped or jacketed laser optical fiber is inserted into the vein from a distal point toward the junction, followed by laser activation. The fiber is then slowly withdrawn, and the vein becomes occluded. Boersma et al[2] reported the results of 28 articles, including 4 randomized controlled trials (laser treatment of 2950 small saphenous veins).[17-19,37-61] Studies were heterogeneous regarding energy delivery, wavelengths used (810 nm, 940 nm 980 nm, and 1470 nm), and use of pulsed and continuous modes. In almost all studies, patients underwent additional therapies (phlebectomy, sclerotherapy, and stripping). Anatomical success rates were 81% to 100% and the mean follow-up was 12.5 months (range 0.5 to 48). Deep venous thrombosis was seen in 0.8% of all patients, and postprocedural paresthesia was described in 4.8%. In a randomized controlled trial, Doganci et al[37] showed that the puncture site affects the rate of nerve injury: the rate of paresthesia is significantly lower when the small saphenous vein is cannulated in the mild-calf. Hirokawa et al[62] reported that the rates of pain (0% vs 25.0%) and bruising (7.0% vs 57.1%) were significantly lower in the group that used the 1470-nm laser and the radial 2-ring fiber.

Radiofrequency ablation

In radiofrequency ablation, under ultrasound guidance, a catheter electrode is inserted into the vein and the tip placed close to the junction. When activated, heat generated from the electrode results in closure of the vein. Boersma et al[2] reported the results of nine articles (radiofrequency ablation treatment of 386 small saphenous veins)[63-71] Studies were heterogeneous and used ClosurePlus, ClosureFast, and Celon. The anatomical success after a mean follow-up of 14.3 months ranged from 82% to 100%. Complications were poorly reported, and 5 studies described a mean deep venous thrombosis rate of 1.2% (range, 0% to 8%) and paresthesia was seen in 9.7% (mean). Park et al[65] described paresthesia in 26% of patients, but radiofrequency ablation in some patients in this cohort was performed by proximal ligation and retrograde ablation. Woźniak et al[72] published a comparative analysis of 5-year

outcomes of lower extremity varicose vein therapy (13 small saphenous veins) using monopolar and segmental radiofrequency ablation and reported a 100% occlusion rate and no paresthesia.

Nonthermal nontumescent ablation

Nonthermal techniques, including mechanochemical ablation and cyanoacrylate vein ablation, have been developed with a view to remove the risk of thermal injury. The various techniques of nonthermal ablation can completely avoid the need for tumescent anesthesia, reduce the time of the intervention, per-interventional pain, bruises, and sensory nerve lesions.

Mechanochemical endovenous ablation

Mechanochemical endovenous ablation is a hybrid endovascular procedure that has two components: mechanical abrasion via a special catheter and chemical ablation by injecting foam sclerosant (sodium tetradecyl sulfate or polidocanol). The ClariVein catheter is positioned through a microsheath with the tip of the device 2 cm distal to the saphenopopliteal junction under ultrasound guidance. The mechanical damage to the endothelium is caused by the catheter's rotating element and the chemical damage by the sclerosants.

Witte et al,[73] in a meta-analysis, reported the results of six articles (mechanochemical endovenous ablation of 254 small saphenous veins).[74-79] Two publications (randomized controlled trials) included the same patient population.[76,77] The primary outcome was anatomical success, defined as closure and absence of reflux on duplex ultrasound imaging. The anatomical success rate was 87% (mean) after a follow-up that ranged from 8 to 52 weeks. Studies were heterogeneous and used liquid polidocanol (1.5% or 2%) or liquid sodium tetradecyl sulfate (1.5% or 2%). There was one patient with an injury of the sural nerve after treatment resulting in transient hyperesthesia. This patient already suffered from sensory, sural neuropathy after previous saphenopopliteal junction ligation, which was aggravated by the mechanochemical endovenous ablation. Paresthesia has not been reported specifically for the small saphenous vein.

Glue cyanoacrylate ablation

n-Butyl cyanoacrylate is delivered intravascularly, and it polymerizes when it comes in contact with blood, leading to occlusion of the vessel. In animal models, the cyanoacrylate-treated veins have a granulomatous-type inflammatory response with the presence of giant cells, segmental wall thickening, and fibrosis.[80] The procedure involves using an introducer sheath, a dispensing catheter, and a syringe that is attached to a dispenser gun. The catheter is advanced into the varicose vein under ultrasound guidance. The catheter is placed in specific areas along the varicose vein and the clinician conducts a series of trigger pulls to deliver the medical adhesive. Compression is applied to the leg during the procedure. When treating the small saphenous vein, the catheter tip is positioned 3 cm to 5 cm distal to the saphenopopliteal junction.[81] Compression after cyanoacrylate ablation is not mandatory. Extensive data about small saphenous vein treatment are necessary to improve outcomes and achieve robust evidence.

Eroglu et al,[82] in a randomized controlled trial comparing cyanoacrylate, radiofrequency ablation, and endovenous laser ablation for the treatment of superficial venous incompetence, included 28 small saphenous veins (9 with cyanoacrylate, 3 with radiofrequency ablation, and 16 with endovenous laser ablation) and, at 2 years in any patient undergoing procedures, there were no reported recanalizations, deep venous thromboses, or paresthesia. In the WAVES trial, Gibson et al[83] showed, in 8 small saphenous veins, an anatomical success rate of 100% after a follow-up of 12 months. In their study, Yasim et al[84] treated 11 small saphenous veins and observed, after a mean follow-up of 5.5 months, no recanalizations and no adverse effects.

Safety data

Thromboprophylaxis can be prescribed for high-risk patients (previous venous thromboembolism, documented thrombophilia, obesity, immobilized patients, patients with neoplasm, and older patients). It is recommended to perform duplex ultrasound screening after thermal and nonthermal ablation within 10 days postoperatively, but this is not clearly defined.

Conclusion

In their meta-analysis, Boersma et al[2] reported that ablation techniques (endovenous laser ablation and radiofrequency ablation) were found to present higher pooled anatomic success rates (98.5% and 97.1%, respectively) as compared with surgery (58%) and ultrasound-guided foam sclerotherapy (63.6%). Neurologic complications were also more frequent after surgery than thermal ablation (19.6% vs 4.8% after endovenous laser ablation and 9.7% after radiofrequency ablation). Based on the literature and

recommendations, endovenous thermal ablation should be preferred to surgery and foam sclerotherapy in the treatment of small saphenous vein incompetence. The potential benefits, particularly the reduced risk of nerve damage, might be of considerable clinical importance and may lead to a preference for nonthermal techniques in the future. Extensive data about nonthermal techniques are necessary to improve outcomes and acquire robust evidence. The cost analysis of varicose vein treatments should also be taken into account in future treatment recommendations.

Corresponding author
Nicolas NEAUME
Clinique Pasteur, 45 avenue de Lombez,
31076 Toulouse,
France

Email: nneaume@clinique-pasteur.com

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Changes in clinical manifestations and biophysical properties of the great saphenous vein in transient premenstrual phlebopathy after 12 months' treatment with micronized purified flavonoid fraction

Yuri T. TSUKANOV, PhD,
Aleksandr NICOLAICHUK, MD

Department of Surgery and Urology,
Omsk State Medical University,
Omsk, Russia

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Abstract

Aim. To study clinical manifestations and biophysical properties of the great saphenous vein (GSV) in 42 women with transient premenstrual phlebopathy (TPP) after 12 months of micronized purified flavonoid fraction (MPFF) treatment (1000 mg/day) and to compare GSV diameters measured in 84 legs before 10:00 and after 18:00. In 12 months the number of women with leg heaviness and swelling decreased to 2 (4.8%). The interphase gradient of the circumference (a difference between the circumferences during the secretory and menstrual phases) for the area over the ankle decreased from 6.87 mm to 3.0 mm. During the secretory phase GSV diameter decreased from 6.4 mm to 4.9 mm in the morning and from 7.2 mm to 5.3 mm in the evening. Interphase gradient of GSV diameter (a difference in diameters measured during the secretory and menstrual phases) decreased from 1.2 mm to 0.5 mm in the morning and from 1.1 mm to 0.5 mm in the evening. Only 2 patients out of 18 with an initial evening reflux of 11cm had an evening reflux of not more than 3.5cm. No patients had morning reflux.

Conclusion. Administration of MPFF (1000 mg/day) over 12 months, in the form of intermittent cyclic 15-day courses which started 15 days before menstruation, causes a decrease in leg swelling and elimination of premenstrual leg heaviness in 95.2% of women. It also provides the recovery of GSV diameter along the entire length and a total elimination of premenstrual morning reflux in the secretory phase.

Introduction

Nowadays, functional venous disorders are widespread.[1-3] Transient premenstrual phlebopathy (TPP) is considered to be a particular venous problem in fertile women. Its symptoms include leg heaviness, aching pain, leg swelling, and increased tiredness before menstruation that disappear at the beginning of the menstrual cycle. The reason for such a phenomenon is changes in biophysical properties of the venous wall. In TPP, as well as in transient orthodependent evening phlebopathy, venous tone decreases due to the increased creeping ability of the venous wall. To understand the processes that occur in the venous wall during prolonged orthostatic stress, it is useful to borrow the term "creep" from solid-state physics. In solid-state physics the creep of substances, or after effect, or slowly occurring deformation of a solid body, occurs under the influence of a constant load or stress over time. In settings of prolonged vertical load, it is this creep that can lead to a substantial dilation of the vein lumen.However, an additional clinically significant hormone-induced increase in the expansibility of the venous wall during the secretory phase of the menstrual cycle is thought to be a specific feature of TPP.[4]

In some patients phase venous dilation may be to such an extent that it causes transient premenstrual great saphenous vein (GSV) reflux due to the relative insufficiency of the valves. By contrast with reflux in orthodependent evening phlebopathy, transient premenstrual GSV reflux is registered only during the secretory phase in the morning with minimal orthostatic loading.[4]

TPP treatment can be motivated by a monthly decrease in physical activity and quality of life.[5] Optimistic results of MPFF treatment in premenstrual syndrome[5] and a positive experience with MPFF administration in transient orthodependent evening phlebopathy[6] created a basis for studying clinical and biophysical peculiarities of MPFF treatment effect in TPP. Such a therapy should take into the consideration the fact that a provoking factor – monthly changes in the endocrine profile which are natural in fertile women – cannot be excluded.

Intermittent cyclic 15-day courses of drug administration prescribed only for the second part of the menstrual cycle are considered to be a peculiarity of the proposed treatment protocol.

Aim: to study changes in clinical manifestations and biophysical properties of the great GSV in TPP of the lower-limbs with a 12-month MPFF treatment in a form of intermittent cyclic 15-day courses.

Material and methods

Clinical observation

From 2016 to 2019 a total of 42 women aged from 21 to 40 years (mean age 31.3 ± 8.9) were examined. At the beginning of the study all of them had leg heaviness and swelling which occurred before menstruation and disappeared in the first part of the menstrual cycle.

Inclusion criteria: parous women at their fertile age with a regular menstrual cycle during the last 6 months suffering from leg heaviness and swelling that occur before menstruation and disappears at the beginning of the menstrual cycle with usual daily activity; voluntary informed consent to participate in the study.

Exclusion criteria: regular leg heaviness and swelling which are not associated with the menstrual cycle; chronic venous disease (CVD) C2-C6 (according to the CEAP classification); history of venous thrombosis; lymphedema and lipedema; gynecological disorders; administration of combined oral contraceptive pills (COC); thrombophilia; chronic obstructive pulmonary disease (COPD); extra physical loading.

All women had had 1 to 3 uncomplicated natural births (1.72;95%CI:1.38-1.99). At the beginning of the study their mean body mass index was 25.15 ± 6.13kg/m^2. Their mean height was 164.5 ± 4.42. All patients lived in the city, had an office job, and did not go to fitness classes. All women had daily activity and a traditional night's rest.

Clinical assessment

During their menstrual cycle all women underwent a clinical and instrumental examination twice: at days 1 to 4 (menstrual phase), and 25 to 28 (secretory phase).[7] The intensity of leg heaviness was assessed according to VAS-10.

The circumference of the area over the ankle and of the muscular part of the calf (its upper third) was measured with a measuring tape. The measuring levels were marked on the skin with indelible ink. The measuring levels were also photographed. The previous study showed that in case of no lymphedema and inflammation the changing increase of the calf volume (first of all its muscular part) within 24 hours is mostly caused by regional venous hypervolemia.[8]

To evaluate the influence of estrogens and progesterone during the secretory phase of the menstrual cycle on changings of the limb circumference, the interphase gradient of the circumference (IGC) was calculated; this is a difference between the circumferences during the secretory and menstrual phases.[4]

Duplex ultrasound scanning

Duplex ultrasound scanning (DUS) of the veins was performed according to the international protocol.[9] After a traditional examination, morning and evening DUS results (obtained before 10:00 and after 18:00 during the menstrual (1 to 4 days) and secretory (25 to 28 days) phases were obtained, to study the reaction of the GSV to a prolonged orthostatic loading.[7]

According to the previous study, in TTP all trunk veins cyclically dilate during the secretory phase; however, this happens to a greater extent with the GSV.[4] Therefore, the present research is aimed at monitoring GSV. Its diameter was measured at 1 cm from the saphenofemoral junction (including the GSV reflux zone if any). To have an identical projection of the repeated scanning (in the morning and in the evening during the menstrual and secretory phases before during and after the treatment) in the case of complex leg geometry, the sensor was put in the area with a minimal distance from the skin to the vein in the proximal part of the reflux. This area was marked on the skin with indelible ink and then photographed as well.

The diameters of veins were measured by the same physician with the patient in the upright position with normal breathing, at room temperature.

To identify the pathophysiological GSV features, two calculated values were used. The first constituted the difference in vein diameters measured during the secretory and menstrual phases (interphase gradient of the diameter–IGD). This value allowed assessment of hormonal effects on the vein. The second was the difference in vein diameters measured in the morning and in the evening during the secretory and menstrual phases (orthostatic gradient of "evening-morning" diameter–OGD "evening-morning"). This value aided understanding of the GSV reaction to long orthostatic loading.[10]

These values integrally characterize the biophysical properties of the vein. The first evaluates the change in the expansibility under the hormonal influence during the secretory phase. The second demonstrates the degree of the creeping ability of the vein, being the value of its gradual expansion at long vertical loading.[4]

GSV reflux was defined as retrograde flow of >0.5 sec. duration[9,11] after a Valsalva maneuver and manual compression and decompression of the distal limb.

Considering the fact that the lesion at phlebopathy is usually of a bilateral nature, the study included GSVs in 84 legs.

Treatment

All patients had a 12-month MPFF monotherapy in the form of intermittent cyclic 15-day courses which started 15 days before menstruation. The dose of the drug was 1000 mg once a day.

The effectiveness of this protocol was assessed by comparing the results of the examination performed before and after the 3rd and the 12th month of treatment.

The assessment of quality of life during the secretory phase was done according to the CIVIQ-2 basing on pain and physical, social, and psychological factors.[12]

The safety and tolerability of the drug was studied with active identification of possible digestive complaints, and allergic and other manifestations, as well as general tolerability and significant laboratory safety tests (hematology, medical biochemistry, urinalysis).

The statistical analysis was performed using the nonparametric Wilcoxon test. The value $P<0.5$ was considered statistically significant. The mean values were determined with the 95%CI.

Results

In 3 months the number of women with leg heaviness during the secretory phase decreased from 42(100%) to 4(9.5%). The intensity of leg heaviness in those women who still had it also decreased from 5.2(95%DI:4.7-5.7) to 0.3 (95%DI:0.0-0.6) ($P<0.0001$) according to VAS-10 scale. In 12 months the number of women with such a complaint decreased to 2(4.8%), and the intensity in those who still felt heavy legs decreased to 0.1(95%DI:0.0-0.2) ($P<0.0001$) according to VAS-10 scale.

In 3 months IGC for the area over the ankle decreased ($P=0.000004$) from 6.87 mm (95%DI,6.31-7.35) to 3.3

mm (95%DI,2.9-3.6); for the muscular part of the calf it also reduced (*P*=0.000004) from 9.7 mm (95%DI,9.1-10.2) to 2.6 mm (95%DI,2.2-3.0). In 12 months IGC for the area over the ankle decreased (*P*=0.000004) to 3.0 mm(95%DI,2.8-3.3); for the muscular part of the calf it also reduced (*P*=0.000004) to 2.4 mm (95%DI,2.1-3.0) *(Figure 1)*.

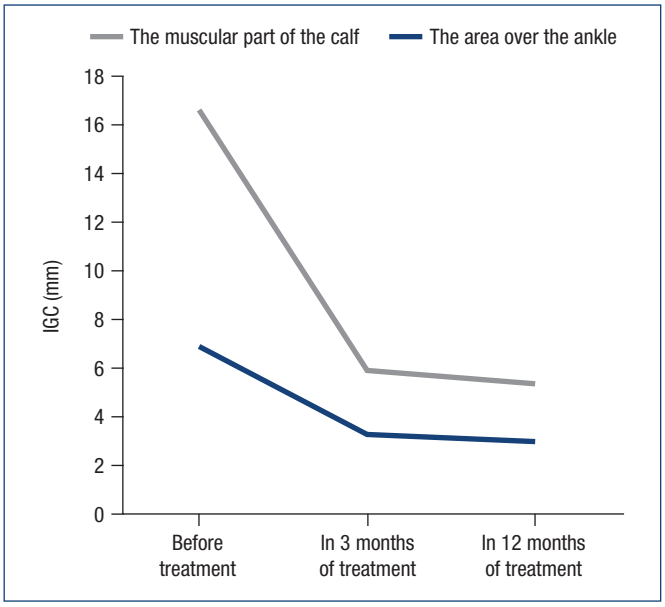

Figure 1. Dynamics of the interphase gradient of the circumference of the limbs during treatment.

IGC – the interphase gradient of the circumference (cm)

Clinical manifestations of phlebopathy during the secretory phase completely disappeared; moreover, one also noted the decrease in the diameter of GSV(n=84) *(Table I)*. In 3 months of treatment GSV diameter in the groin during the secretory phase reduced from 6.4 mm to 5.0 mm in the morning and from 7.2 mm to 5.4 mm in the evening; OGD also reduced from 0.85 mm to 0.4 mm. A positive effect of MPFF treatment on the expansibility of the venous wall was registered as well: in the morning the IGD of GSV in the groin decreased from 1.2 mm to 0.2 mm, and in the evening from 1.1 mm to 0.2 mm.

In 12 months a further decrease of GSV diameter and the stabilization of biophysical values were noted *(Table I, Figures 2 and 3)*. During the secretory phase GSV diameter in the groin decreased to 4.9 mm in the morning and to 5.3 mm in the evening; OGD value constituted 0.4 mm. A positive effect of MPFF treatment on the expansibility of the venous wall was registered as well: in the morning IGD of GSV in the groin decreased to 0.5 mm, and in the evening–to 0.5 mm.

	Phase of the menstrual cycle	Time of the day	Before treatment	3 months of treatment	12 months of treatment	*P*-level (before and after 12 months of treatment)
GSV in the groin (mm)	Menstrual phase	morning	5.2 5.10-5.30	4.8 4.73-4.87	4.4 4.33-4.49	0.000001
		evening	6.1 5.96–6.14	5.2 5.13-5.28	4.7 4.67-4.83	0.000001
		OGD	0.85 0.70 – 1.00	0.4 0.35-0.45	0.3 0.31-0.37	0.000001
	Secretory phase	morning	6.4 6.29-6.58	5,0 4.96-5.08	4,9 4.83-5.00	
		evening	7.2 7.08-7.28	5.4 5.37-5.49	5.3 5.22-5.34	0.000001
		OGD	0.8 0.58-0.94	0.4 0.37-0.44	0.4 0.39-0.42	0.000001
	IGD	morning	1.2 1.02-1.45	0.2 0.18-0.27	0.5 0.48-0.54	0.000001
		evening	1.1 1.02-1.25	0.2 0.19 -0.26	0.5 0.48-0.60	0.000001

Table I. Great saphenous vein in the groin in transient premenstrual phlebopathy during treatment with micronized purified flavonoid fraction in the form of intermittent cyclic 15-day courses in the second part of the menstrual cycle (n=84).

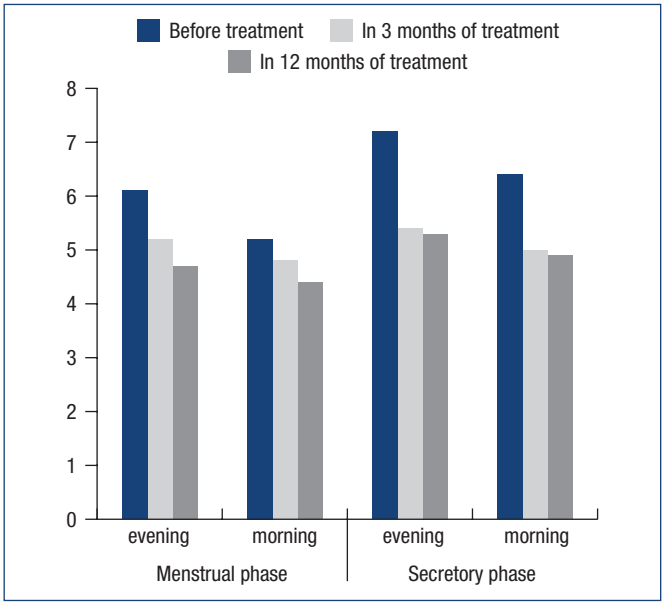

Figure 2. Changes in great saphenous vein (GSV) diameter in the groin during the menstrual and secretory phases with micronized purified flavonoid fraction treatment.

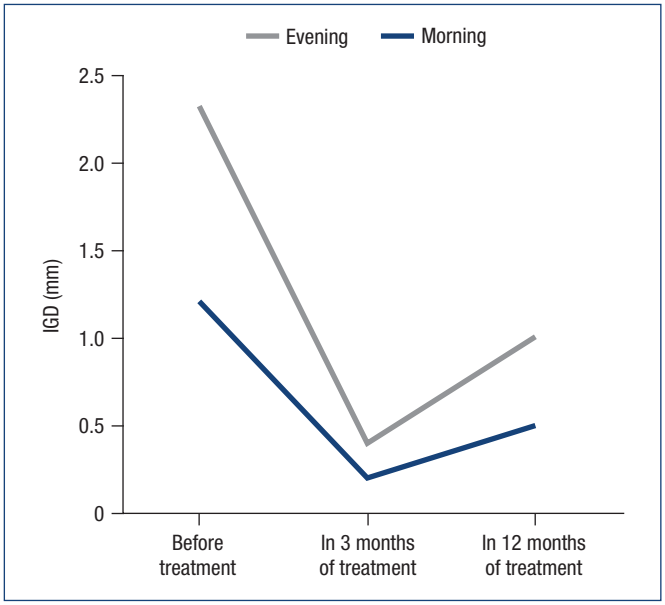

Figure 3. Dynamics of the interphase gradient of great saphenous vein (GSV) diameter in the groin during treatment. IGD – the interphase gradient of the diameter of GSV (the difference in vein diameters measured during the secretory and menstrual phases)

	Phase of the menstrual cycle	Time of the day	Before treatment	3 months of treatment	12 months of treatment	*P*-level (before and after 12 months of treatment)
GSV in the relux zone (mm)	Menstrual phase	morning	5.2 5.10-5.30	4.8 4.61-4.91	4.5 4.36-4.64	0.000196
		evening	6.0 5.93-6.14	5.2 5.02-5.40	4.8 4.69-4.95	0.000196
		OGD	0.8 0.68-0.98	0.5 0.43-0.60	0.3 0.26-0.38	0.000293
	Secretory phase	morning	6.4 6.29-6.58	5.1 4.94-5.25	5.0 4.88-5.18	0.000196
		evening	7.2 7.08-7.28	5.4 5.24-5.53	5.4 5.26-5.54	0.000196
		OGD	0.8 0.58-0.94	0.3 0.24-0.35	0.4 0.32-0.42	0.002865
	IGD	morning	1.23 1.02-1.45	0.3 0.28-0.38	0.5 0.42-0.64	0.000419
		evening	1.2 1.02-1.28	0.2 0.03-0.30	0.6 0.45-0.68	0.000629

Table II. Great saphenous vein in the reflux zone in transient menstrual phlebopathy during treatment with micronized purified flavonoid fraction in the form of intermittent cyclic 15-day courses in the second part of the menstrual cycle (n=18).

The GSV reflux zone also showed significant results (n=18) *(Table II)*. In 3 months of treatment GSV diameter during the secretory phase reduced from 6.4 mm to 5.1 mm in the morning and from 7.2 mm to 5.4 mm in the evening. A significant reduction of IGD in the reflux zone was registered as well: from 1.2 mm to 0.3 mm in the morning and from 1.2 mm to 0.2 mm in the evening. In 12 months GSV diameter reduced to 5.0 mm in the morning and to 5.4 mm in the evening; IGD in the morning and in the evening constituted 0.5 mm and 0.6 mm.

Initially during the menstrual phase GSV reflux was absent in all women. During the secretory phase 18 women (42.9%) had an evening reflux of 11.8 cm (95%DI:9.9 -13.7 cm). Of these, 17 patients had a morning reflux of 9.9 cm (95%DI: 5.9-7,8 cm) as well. In all cases it was unilateral and had a segmental nature,[13] located in the upper and middle thirds of the thigh.

In 3 months of MPFF treatment no patients had GSV reflux in the morning during the secretory phase; moreover, the number of women with an evening reflux decreased to 6 (14.3). In 12 months of treatment only 2 patients had an evening reflux of not more than 3.5 cm (95%DI:3-6 cm).

Figure 4 shows the initial level of patients' quality of life (QL) and their levels at 3 and 12 months of treatment. The levels were measured with CIVIQ-2.[12] The total score decreased initially from 43.4 (95%DI:41.0-45.8) to 16.5 (95%DI:14.3-18.6) and further to 13.5 (95%DI:12.1-14,8) (*P*=0.000001).

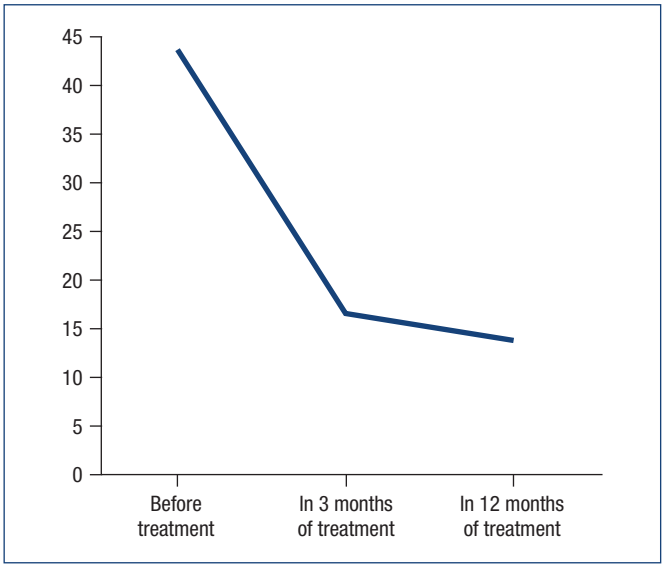

Figure 4. Dynamics of total scores during the secretory phase according to CIVIQ-2 in patients with transient premenstrual phlebopathy during treatment.

Side effects

Any effects that can be considered as side effects were noted only in one patient (2.38%). She complained of a mild epigastric burning and gastralgias during the first week of the drug administration. They disappeared spontaneously, did not renew, and did not require drug withholding. In 12 months any significant changings in cardiac rate and blood pressure, as well as any side effects connected with MPFF administration were not registered. Drug tolerability was of a high level. In 12 months of treatment there were no allergic reactions to the drug. Patient compliance during the whole study was 100%.

Discussion

Earlier we discovered that the decrease in the venous tone at TTP is provoked by changes in two biophysical properties of the venous wall. In TPP, as well as at transient orthodependent evening phlebopathy, creeping ability of the venous wall increases in cases of long orthostatic loading. However, an additional clinically significant hormone-induced increase in the expansibility of the veins during the secretory phase is supposed to be a specific feature of TPP. Such a phase venous dilation is accompanied and followed by premenstrual complaints and symptoms.[4] This fact gives an explanation of why the treatment should be provided only during the secretory phase.

Positive results of MPFF administration in the form of intermittent cyclic courses during the second part of the menstrual cycle proved the correctness of theoretical grounds. In 12 months MPFF treatment eliminated premenstrual leg heaviness in 95.2% of women and significantly decreased premenstrual swelling in 100% of cases.

Values before and after treatment showed significant changes in GSV diameter and proved GSV tone recovery during both secretory and menstrual phases. The dynamics of IGD of GSV clearly demonstrated a possibility to stop the development of hormone-induced venous expansibility with a help of medication. At the same time, venous tone recovery occurred to an extent where transient premenstrual GSV reflux was totally eliminated, and GSV diameter in this zone was equal to that in the groin. As a result, patients' quality of life during the secretory phase improved significantly.

The proposed protocol of treatment based on the study of changes in biophysical properties of veins during the menstrual cycle is completely suitable for the described pathology which occurs due to a long fertility period in women.

It is of note that a decrease in both total dose of the drug and the duration of its continuous administration helped to solve the stated medical problem. This also minimized the risk of side effects, with compliance of 100%.

With a broader understanding of the pathology, which consists of systemic lesions of the venous wall, the results

of a 12-month treatment with MPFF were not surprising. With MPFF treatment, venous tone was increased due to the modulation of noradrenergic signaling through the reduced norepinephrine metabolism.[14,15]

The treatment method proposed in the study differs from a traditional prescription of the drug due to its intermittent cyclic courses connected with the period of maximum progesterone aggression. Such a theoretical background and the chosen treatment guidelines seem to be correct, given that the examined women experienced both subjective and objective improvements.

Administration of MPFF (1000 mg/day) over 12 months in the form of intermittent cyclic 15-day courses in the second part of the menstrual cycle was proven to be safe and well-tolerated.

Conclusion

Detailed analysis of biophysical processes in veins at TPP during the menstrual cycle allowed a change in the prescription methods for phlebotropic drugs.

Administration of MPFF (1000 mg/day) over 12 months in the form of intermittent cyclic 15-day courses starting 15 days before menstruation brings about a significant decrease of leg swelling and elimination of premenstrual leg heaviness in 95.2% of women suffering from TPP, and improves patient's quality of life.

The proposed treatment over 12 months also provides the recovery of GSV diameter along its entire length in menstrual and secretory phases, and a total elimination of a transient premenstrual morning reflux in secretory phase due to a reduction of hormone-induced expansibility of veins

Corresponding author
Yuri T. TSUKANOV, PhD
Department of Surgical Diseases,
Omsk State Medical University,
Omsk, 644099,
Russia

Email: yutsoukanov@mail.ru

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