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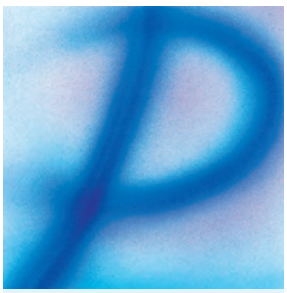

Phlebolymphology

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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.

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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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Correspondent:

Servier Affaires Médicales - 35, rue de Verdun - 92284 Suresnes Cedex - France
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Editorial

Dear Readers,

In this new issue of Phlebolymphology, ***Jorge H. Ulloa, Daniel Guerra, Luis G. Cadavid, Diego Fajardo, and Rubén Villarreal*** *(Colombia) present the results of the Vein Act Program of Colombia. This program is an international, observational, prospective, multicenter survey that is endorsed by the European Venous Forum. The survey assessed patient compliance with nonoperative treatments and their effects on the symptoms of chronic venous disorders.*

As there is a rapid growth in the number of interventions with venous stenting, ***William Marston*** *(USA) describes an initial classification system for venous outflow obstruction with recommendations to improve this system, which requires prospective validation, in order to fill the void that currently exists.*

Lourdes Reina Gutierrez *(Spain) provides an overview of the methods for preventing complications and side effects of sclerotherapy of the lower limb veins with respect to the guidelines and international recommendations.*

Philippe Lemasle *(France) highlights the importance of obtaining a definition of venous obstruction in a common, consensual, and international language to avoid possible therapeutic ambiguity in practice.*

Byong-Boong Lee *(USA) discusses the contemporary concepts regarding the management of chronic lymphedema, which encompass a broad range of currently available treatment options both old and new.*

Enjoy reading this issue!

Editorial Manager

Dr. H. Pelin Yaltirik

Nonoperative approach for symptomatic patients with chronic venous disease: results from the VEIN Act program

Jorge H. ULLOA[1];
Daniel GUERRA[2];
Luis G. CADAVID[3];
Diego FAJARDO[4];
Rubén VILLARREAL[5];
Gabriel BAYONA[6];
Adelma Sofia HOYOS[7];
Giovanni GARCIA[8]

[1]*Professor of Vascular Surgery, Universidad de los Andes, Hospital Universitario Fundación Santa Fe de Bogotá, Colombia*

[2]*Research Fellow in Vascular Surgery, Universidad de los Andes, Hospital Universitario Fundación Santa Fe de Bogotá, Bogotá, Colombia*

[3]*Chief of Vascular Surgery, Clínica del Rosario, Medellín, Colombia*

[4]*Chief of Vascular Surgery, Clinica Imbanaco, Cali, Colombia*

[5]*Chief of Vascular Surgery, Clínica del Caribe, Barranquilla, Colombia*

[6]*Vascular Surgeon, Bogota, Colombia*

[7]*Vascular Surgeon, Centro medico Imbanaco, Cali, Colombia*

[8]*Vascular Surgeon, Antioquia University, Medellin, Colombia*

Keywords:

chronic venous disease; leg pain; micronized purified flavonoid fraction; MPFF; symptoms; venoactive drugs

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Abstract

In patients with chronic venous disease (CVD), there is a variety of symptomatic manifestations, as well as a variety of treatment options available to manage the disease and alleviate the symptoms. Evidence shows that patients benefit from pharmacologic treatment and lifestyle advice to improve quality of life, symptom severity, and ulcer healing. High-quality studies have shown that venoactive drugs, such as micronized purified flavonoid fraction (MPFF) and other flavonoids, are essential tools for healing ulcers and controlling edema. The VEIN Act program served as a worldwide collaboration to study patients with symptomatic CVD (clinical, etiological, anatomical, and pathophysiological (CEAP) classes C_0 to C_6), where medical therapy was offered at the initial office visit. End points of interest included symptom relief after 3 months of noninterventional therapy with venoactive drugs, educational and lifestyle advice, and the use of compression stockings. The results showed that symptoms, including leg heaviness, pain, swelling, and cramps, decreased 3 to 4 points on the visual analog scale at the follow-up visit. Overall patient satisfaction was also recorded, with 72% of patients reporting being "very" or "extremely" satisfied with therapy. These results suggest that, by combining pharmacologic interventions with MPFF, education, and compression stockings, a considerable group of patients can achieve an improvement in their symptoms.

Introduction

Chronic venous insufficiency has a clear impact on a patient's quality of life; symptomatic chronic venous disease (CVD) is characterized by complaints ranging from telangiectasias and occasional itching to pain, severe swelling, ruptured varicose veins, and ulceration.[1] Costs associated with the treatment of venous ulcers carries an undeniable burden to health care systems worldwide.[2]

A molecular pathway explaining the manifestations of CVD has been proposed by several authors.[3] Inflammatory pathways on the venous endothelium, which are activated by unknown triggers, promote leukocyte infiltration and activation, wall

deterioration, and capillary leakage. This proinflammatory microenvironment damages the subcutaneous cellular tissue, skin, and nerves on both the dermis and the vein wall.[4,5] Understanding these pharmacological pathways leads to a more effective treatment of CVD by means of venoactive drugs (VADs) and compression stockings.[2,6] Definitive treatment usually involves a vascular intervention, but, for a significant subset of patients, symptom relief can be achieved gradually after the first consultation and by using nonsurgical therapies.[2,6,7] These therapies include, but are not limited to, the use of compression stockings or elastic bandages, oral and/or topical VADs, exercise, postural recommendations, and skin hydration.

We focused this study on patients with symptomatic CVD in which medical therapy was offered at the initial office visit. End points of interest included symptom relief and an improvement in quality of life after 3 months of noninterventional therapy.

Methods

The VEIN Act program was a multicenter prospective observational study with participation from institutions from Colombia, Central America, the Caribbean, and Europe. It included adult patients with at least one symptom or sign attributable to venous insufficiency who consulted a general practitioner or vascular surgeon participating in the study between March 2016 and April 2017. The main complaint was lower limb pain. At the initial office visit, the physician prescribed a nonoperative treatment and scheduled the patient for a second visit 2 to 3 months later.

	General practitioners	Vascular surgeons
Number of physicians	69	44
Number of patients	1570	1460
• Lost to follow-up	8	31
• V0 • V1	March 2013 September 2015	January 2016 March 2017
Time gap between V0 and V1	60 days	91 days
Time gap between V0 and V1 in women and men	*P*=NS	

Table I. Distribution of patients between physician groups. Abbreviations: V0, initial office visit; V1, follow-up visit.

Patients were classified according to the clinical, etiological, anatomical, and pathophysiological (CEAP) system (using only the clinical "C" grading).[1] At the follow-up visit, the physician recorded treatment compliance and changes in symptoms and quality of life using a survey *(Table I)*.

At the follow-up visit, the physicians evaluated the effectiveness of treating the symptoms. Criteria for this aspect included symptom relief, quality of life, and overall patient satisfaction. Tools used to measure these aspects included a visual analog scale (VAS) and a quality of life questionnaire to track self-reported symptoms.

Results

A total of 44 vascular surgeons, 69 general practitioners, and 3030 patients participated in this study. Patient characteristics are presented in *Table II*.

	General practitioners	Vascular surgeons
Women	80%	86%
Men	20%	14%
Mean age (years)	58.7±14.5	55.9±15.3
BMI (kg/m^2)	26.92±4.24	26.02±5.02
Previous consultation for leg problems	29%	37%
Previous treatment for leg problems	22%	36%

Table II. Patient characteristics between physician groups. Abbreviations: BMI, body mass index.

The initial office visit results

Most patients were female and had mild-to-moderate disease, with 22% classified as C_1, 31% C_2, and 24% C_3 *(Figure 1)*. Body mass index (BMI) showed an overweight population with an average BMI around 26 kg/m^2. Of the patients visiting a general practitioner or a vascular surgeon, 22% or 36%, respectively, had already received treatment for leg problems. The severity and type of symptoms were also comparable between patients from both groups. Heaviness and pain in the lower extremities were the most frequently reported symptoms with severity approximating 6 and 7 on the VAS, respectively *(Figures 2 and 3)*. The frequency of symptoms showed a tendency to be "regular all day" for most subjects *(Figure 4)*. Vascular surgeons tended to prescribe compression therapy more

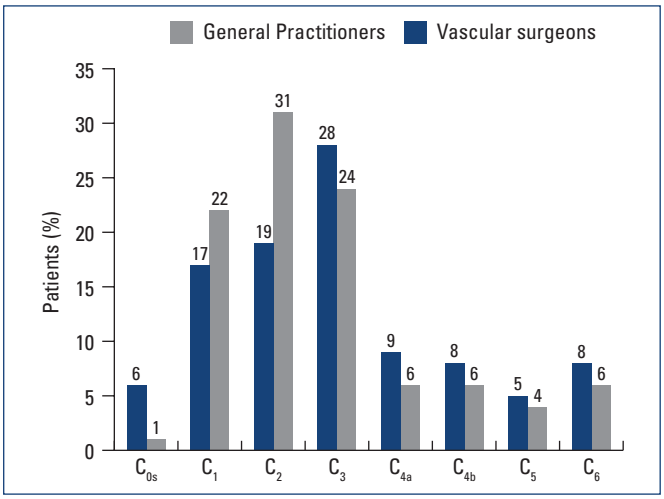

Figure 1. CEAP classification according to clinical severity.
Abbreviations: CEAP, clinical, etiological, anatomical, and pathophysiological.

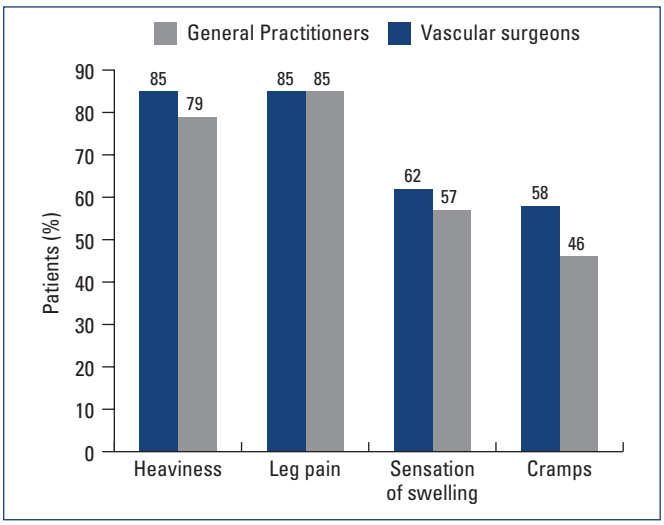

Figure 2. Patient-reported symptoms at the initial office visit.

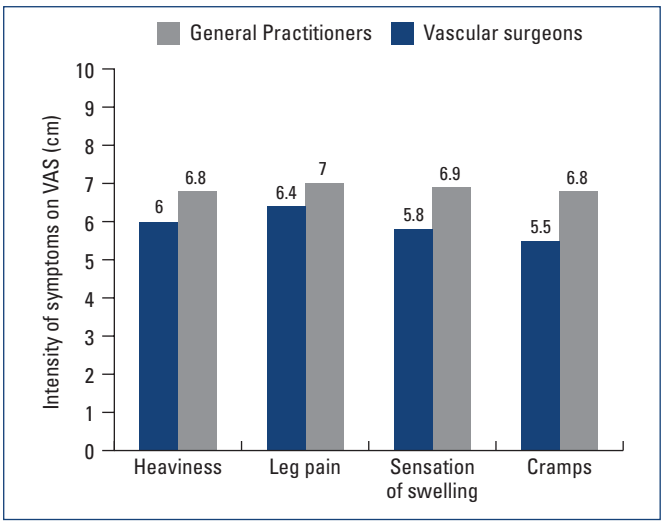

Figure 3. Severity of symptoms at the initial office visit according to the visual analog scale.
Abbreviations: VAS, visual analog scale.

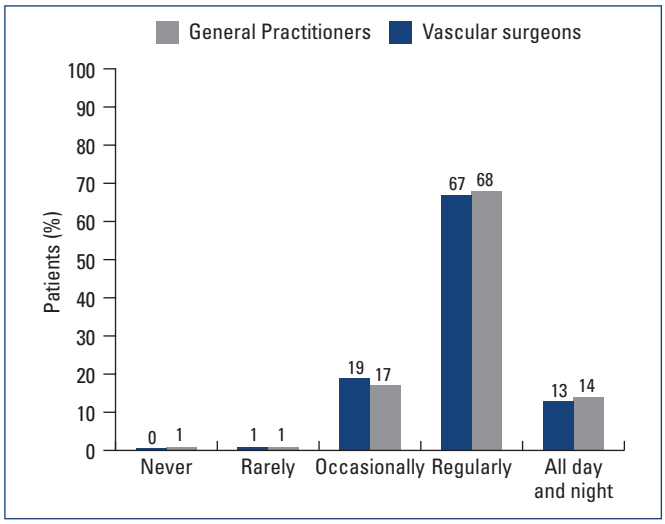

Figure 4. Frequency of symptoms reported by patients.

often than did general practitioners (58% vs 49%) and fewer nonsteroidal anti-inflammatory drugs (NSAIDs).

Follow-up visit results

At the follow-up visit, both symptom relief and severity had improved with nonoperative management in both the general practitioner and vascular surgeon groups. General practitioners tended to provide more lifestyle advice to their patients and achieve a better effect on leg swelling than did vascular surgeons *(Table III)*. Patient satisfaction

Conservative treatments		
	General practitioners	Vascular surgeons
VADs	99%	97%
Lifestyle advice	94%	79%
Compression therapy	49%	58%
NSAIDs	16%	4%
Combination of conservative treatment	95.3% Advice + VADs = 41.3% Advice + VADs + compression = 36% Advice + VADs + compression + Pkd = 9.8% VADs + compression = 5.0%	83% Advice + VADs + compression = 48.3% Advice + VADs = 24.3% VADs + compression = 5.0% Advice + VADs + compression + Pkd = 3.9%

Table III. Treatments prescribed at the initial office visit by general practitioners and vascular surgeons.
Abbreviations: NSAID, nonsteroidal anti-inflammatory drugs; VAD, venoactive drug.

at the follow-up visit was similar in both groups; 47% and 25% of the patients in the general practitioner group were either "very satisfied" or "extremely satisfied" with their results, respectively, and 48% and 24% of the patients in the vascular surgeon group were either "very satisfied" or "extremely satisfied," respectively *(Figures 5 and 6)*.

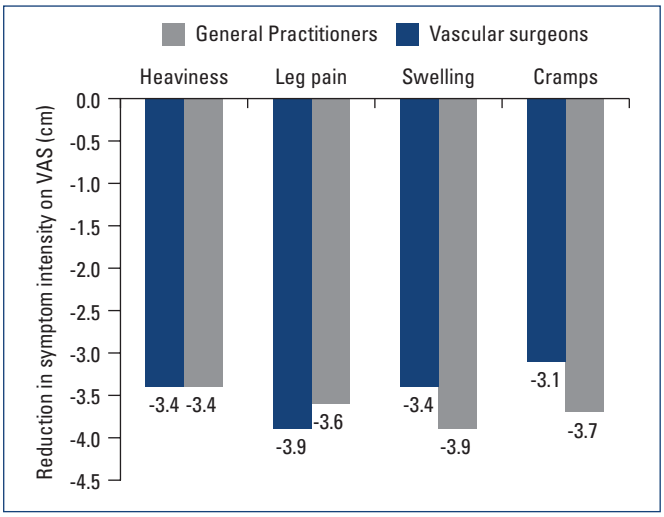

Figure 5. Average symptomatic improvement at the follow-up visit.
Abbreviations: VAS, visual analog scale.

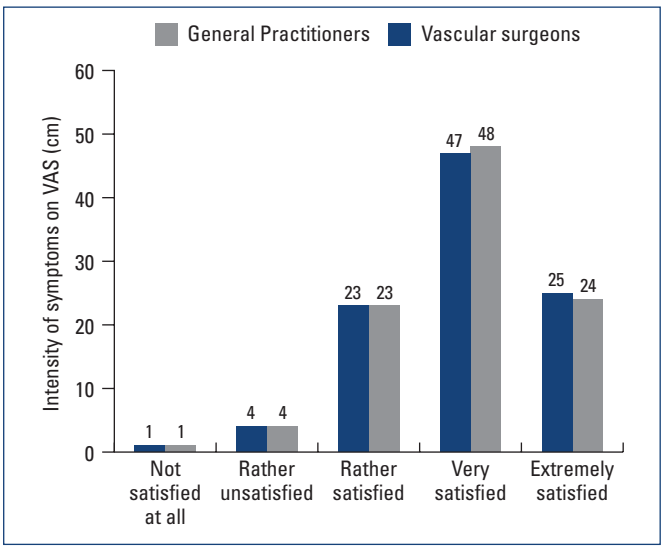

Figure 6. Patient satisfaction at the follow-up visit.

Discussion

The findings from the VEIN Act program suggest a reproducible trend of symptom improvement and satisfaction with MPFF treatment for complaints attributed to CVD. In both groups, physicians had a positive feedback from their patients, who expressed relief from pain, heaviness, swelling, and cramps.

Participants of the VEIN Act program had overall beneficial results after the visit with their general practitioner or vascular surgeon. Prescribing habits varied between general practitioners and vascular surgeons concerning analgesics, compression stockings, and time spent educating the patient. The main habit that remained constant was the prescription of MPFF. It could be inferred that vascular surgeons have more knowledge of the mechanics and formulation of compression stocking; thus, they prescribed them more often. Concerning symptom relief, the results were comparable between the two groups, except for swelling, where there was a slight between-group difference at the follow-up visit.

In the design of our study, there was no standardized way of measuring edema or swelling; the physician was free to choose from clinical observation or objective quantification of edema using a measuring tape, the latter being more frequent during visits with a vascular surgeon. Overall, patient satisfaction and symptom relief remained favorable.

The results of the program are in accordance with literature suggesting that a combination of physical and pharmacological interventions positively affect CVD symptoms.[2,6] Immunopathological and molecular data show that alterations to the vein wall are responsible for the array of CVD symptoms, and these alterations serve as targets for pharmacological interventions.[5,8-10] It is for this reason that patients received MPFF, as it has anti-inflammatory, antioxidant, and phlebotonic properties. Compression stockings, on the other hand, serve as a support for the weakened vein wall and thus help reduce permeability[11]; it is clear that compression stockings could serve a key purpose in healing leg ulcers.[7] Combining these strategies with the knowledge of CVD pathophysiology is indeed a wise practice.

The role of MPFF alone or combined with other interventions has been studied, showing medically relevant results.[12-15] According to moderate-quality evidence and high-level recommendation, VADs, such as MPFF, reduce edema and ankle circumference.[16] Other studies, as summarized by Scallon et al, showed that more venous leg ulcers were healed in patients using MPFF and compression stockings than in the control groups (risk reduction, 1.36; 95% CI, 1.07-1.74).[17] Data from the VEIN Act program are also in accordance with an analysis of studies with low

heterogeneity, demonstrating improvements in edema, trophic disorders, and restless legs, when comparing MPFF with placebo.[15,16]

The effectiveness of treating symptoms seems to be equally important at all stages of the disease.[18] In the 2002 RELIEF study (Reflux assEssment and quaLity of llfe improvEment with micronized Flavonoids), there was significant symptom relief with MFPP for patients classified as C_0 to C_4.[19] Patients at the early stages of the disease, even with no signs of obstruction or reflux, are frequently encountered in primary care and represent a population in which VADs, stockings, and activity play a major role.[11] Patients with mild disease also benefit from noninterventional treatment for symptom relief. MPFF and other flavonoids, such as red vine leaf extract, have demonstrated a significant reduction in edema, swelling, and pain, as demonstrated by Rabe et al in a double-blind, placebo-controlled trial on patients classified as C_3 and C_{4a}.[20]

We consider that having no control of the groups and interventions is a limitation of the VEIN Act program because the results cannot be attributed to a single intervention, but to the multitherapeutic approach. On the other hand, our sample was diverse and large, showing that a complete set of interventions, including education, lifestyle modifications, and pharmacological and physical interventions seems to be the optimal way to treat CVD. We also reckon that the results from the VEIN Act program will be reproducible in other scenarios, which should be taken into consideration for applications elsewhere.

Conclusion

Symptom relief from complaints attributed to CVD is achievable in a considerable group of patients by combining pharmacological interventions, such as MPFF, education, and the use of compression stockings. When formulating a treatment plan, it is crucial both to understand the pathophysiology of CVD and to learn how to treat this deleterious process. The VEIN Act program serves as guidance on how to intervene in CVD in an ambulatory setting.

Corresponding author
Jorge H. ULLOA, MD, FACS,
Professor of Vascular Surgery, Universidad de los Andes, Hospital Universitario Fundacion Santa Fe de Bogota,
Cra 9 # 116-20, Cons. 910,
Bogota, Colombia

Email: cirugiavascular@yahoo.com

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Critical need for an iliofemoral venous obstruction classification system

William A. MARSTON

Division of Vascular Surgery, Department of Surgery, University of North Carolina School of Medicine, Chapel Hill, NC, USA

Keywords:

chronic venous insufficiency; May-Thurner syndrome; postthrombotic syndrome; venous obstruction; venous stenting

Abstract

Intervention with venous stenting is experiencing a rapid growth due to advances in medical technology and increased awareness of the clinical relevance of the importance of deep venous obstruction. As this field begins to mature, stents specifically designed for the venous system are now available with more being tested in clinical trials. It is becoming clear that the anatomy and variety of venous obstruction is diverse, with the traditional May-Thurner syndrome comprising only a fraction of the cases of venous obstruction seen in clinical practice. Obstruction may occur anywhere in the femoral, common femoral, and iliac systems, as well as the inferior vena cava and may be due to a previous venous thrombosis or extrinsic causes. It is clear that this variety of etiology and extent of involvement will require diverse interventional strategies to achieve maximal patient benefit. In order to identify the anatomy and severity of venous obstruction better, a classification system analogous to those used to describe arterial obstruction is urgently required. A carefully constructed and validated system will facilitate the comparison of clinical strategies or venous devices for specific types of venous obstruction, yielding better outcomes for specific patient cohorts. An initial classification system for venous outflow obstruction is described with recommendations to improve this system, which requires prospective validation, in order to fill the void that currently exists.

Critical need for an iliofemoral venous obstruction classification system

The vast majority of therapies used for diseases of the venous system are designed to treat the incompetence of the superficial and/or perforator veins in the lower extremity. The goal of these therapies is to eliminate abnormal reflux in these veins by removing or closing the offending veins to prevent blood from flowing in both directions in these channels. It is then rerouted into other superficial veins, or, more likely, the deep system to return to the heart. Until 10 to 15 years ago, only a few venous specialists addressed disease of the deep venous system using valve repair methods or valve transplants to improve venous function in the

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deep system. Unfortunately, in postthrombotic cases, valve repair was typically not possible and valve transplants often were not useful if significant obstruction persisted in the postthrombotic state. No corrective treatments were available for patients with severe postthrombotic symptoms due to venous outflow obstruction.

Interventions designed to correct venous dysfunction in the superficial and perforator systems are often effective in eliminating symptoms for patients with chronic venous disease particularly in clinical, etiological, anatomical, and pathophysiological (CEAP) clinical classes C_1 to C_3. However, in classes C_4 to C_6, patients are more frequently affected by deep venous insufficiency or the combination of deep and superficial disease. In a study of C_6 limbs, nearly 70% of patients were identified as having significant disease of the deep venous system.[1] In the absence of effective therapies for deep venous insufficiency and related obstruction, it is clear that only a minority of patients with advanced venous disease are able to undergo corrective treatment to eliminate venous hypertension and return the venous system to a normal hemodynamic state.

As device technology designed for coronary intervention made its way to the peripheral vascular system, pioneers began to experiment with the use of intravascular devices in the venous system. Based on the trailblazing work of Raju, Neglen, and others, it was demonstrated to be feasible to treat many patients with venous obstruction in the deep system with significant improvement in symptoms.[2-4]

The understanding of the importance of venous obstructive disease and its impact on venous hemodynamics and clinical symptoms and signs has dramatically increased in the past decade. It has been recognized that severe obstruction of the iliac veins and/or vena cava may result in debilitating lower extremity symptoms and/or signs, including chronic pain, edema, and venous claudication, occasionally leading to intractable ulceration.[4] Compression therapy, the standard therapy for chronic venous insufficiency, is poorly tolerated by some patients with iliocaval venous obstruction. The limb with outflow obstruction swells with physical activity due to the increased blood flow associated with exercise, and high strength compression in this situation may cause increased pain with ambulation. Patients often remove compression due to the increased discomfort and they are subsequently branded as noncompliant patients. Yet, without other therapeutic options, symptoms persist and ulcers do not heal. Patients with chronic nonhealing venous leg ulcers that have not responded to extended compression therapy have a high incidence of iliocaval venous obstruction, which was shown to be present in nearly 40% of recalcitrant C_6 patients.[5]

In their classic report, May and Thurner described the anatomy of the aortic bifurcation and inferior vena cava confluence and the resultant compression of the left iliac vein in 22% of the cadavers they studied.[6] Subsequently, it has been recognized that compression of the iliocaval outflow tract can occur at multiple locations, including the hypogastric origin and the inguinal ligament, among others.[7,8] Patients experience symptoms from anatomic compression alone (primary obstruction) and may also develop postthrombotic obstruction after iliac or caval deep vein thrombosis (secondary obstruction).

Neglen and Raju's publication on a large series of patients with iliocaval venous obstruction who were treated with percutaneous stenting demonstrated that the iliac veins and inferior vena cava could be successfully reopened, even in patients with veins that had been occluded for years.[2] This pioneering study, combined with the availability of improved devices for recanalization and intervention, has led to a rapid increase in the number of procedures performed for the treatment of iliocaval venous obstruction. However, as this procedural area matures, fundamental questions concerning when and how to intervene on patients to maximize the benefits must be answered. Currently, there is no strong evidence available to determine when obstruction of the venous system is the source of limb symptoms and/or signs and should undergo intervention. Given that the normal anatomy at the iliac confluence often creates compression of the iliac veins,[9] pathologic compression must be differentiated from compression that is unlikely to cause significant symptoms and/or signs. Physiologic testing with ultrasound and/or plethysmography have not been able to provide answers to this highly sensitive and specific question.[10,11] Pressure gradients, which are helpful in arterial obstruction, are less reliable in the venous system. Fundamentally, it is difficult to obtain venous hemodynamics in the ambulatory state, and the measurement of venous parameters in the resting state may not be reflective of the situation during exercise.

In a recent publication on deep venous diagnostic methods, Gagne et al studied patients before and after venous intervention with venography and intravascular ultrasound.[12] They then correlated the percentage of the reduction area of the iliac venous lumen with symptom improvement after intervention as defined by the venous

clinical severity score. A greater than 4-point reduction in the venous clinical severity score after intervention was defined as an indicator of clinically meaningful improvement. Measurements made by intravascular ultrasound were significantly better than venography as a predictor of clinical improvement. The best overall predictor of clinical improvement with intervention was a baseline intravascular ultrasound measurement of the area of stenosis that was >54% *(Figure 1)*. However, in the subset of patients with a nonthrombotic iliac obstruction, intravascular ultrasound measurements of the diameter stenosis were more predictive than area measurements, with a value of >61% that was the most predictive of clinical improvement with venous stenting. While this information is useful and begins to provide some data to indicate which patients are more likely to benefit from an intervention, other critical pieces of information, such as the length of the diseased vein or the presence of multifocal areas of stenosis were not evaluated. These and other factors have been found to be important in assessing the need for intervention in the arterial system and are likely to have an impact on the venous system as well.

Patients with iliocaval venous obstruction develop varying anatomical changes in the venous system. In some cases, obstruction involves only a short segment of the common iliac vein, where the contralateral iliac artery crosses over, leading to stenosis of the underlying vein *(Figure 2)*. In other situations, the entire venous system from the common femoral vein through the vena cava is occluded *(Figure 3)*. When considering methods of intervention to treat these problems, it is obvious that the diverse anatomy of venous obstruction may require different tools and strategies to optimize results. If we are to compare results between treatment strategies, we should be sure that we are comparing cases with similar levels of complexity, as is currently done in the evaluation of interventional treatments of arterial and aneurysmal disease.

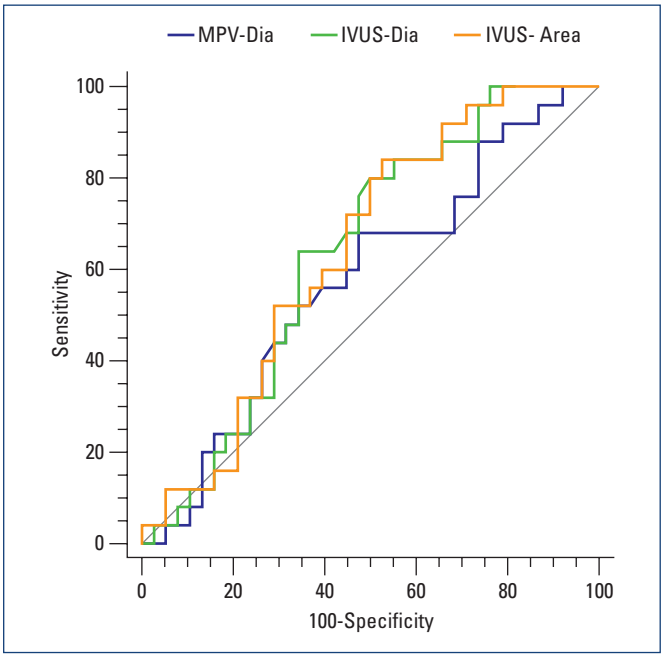


Figure 1. Receiver operating characteristic curve plotting baseline venographic and intravascular ultrasound measurements of anatomic degree of stenosis against change in the revised venous clinical severity score 6 months after stenting (n=64).

Abbreviations: IVUS-Area, intravascular ultrasound area reduction measurement; IVUS-Dia, intravascular ultrasound diameter measurement; MPV-Dia, multiplanar venographic diameter measurement.

From reference 12: Gagne PJ et al. J Vasc Surg Venous Lymphat Disord. *2018;6(1):48-56. © 2018, the Society for Vascular Surger.*

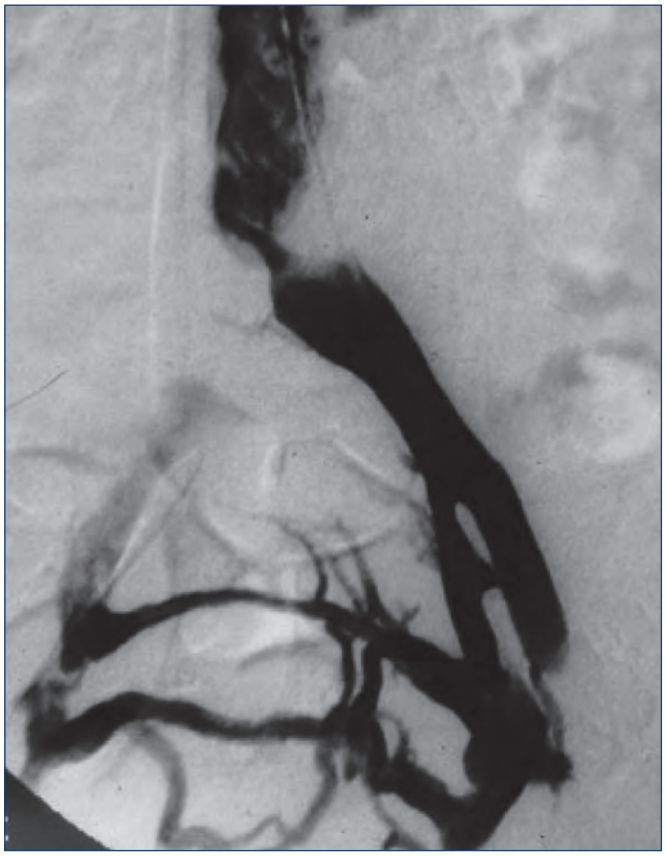


Figure 2. Venogram of localized compression of the left iliac vein at the confluence into the inferior vena cava with collateralization to the contralateral iliac vein.

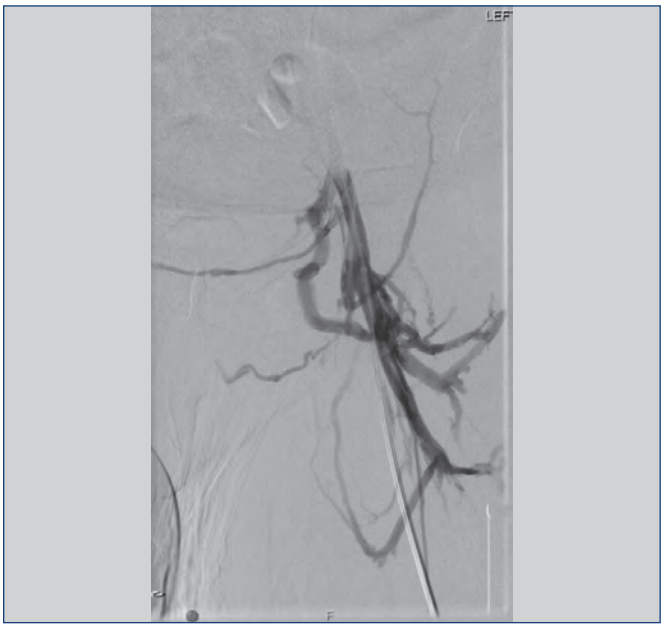


Figure 3. Venogram indicating complete occlusion of the external iliac vein.

Venous stent development

Currently, the stainless steel self-expanding Wallstent (Boston Scientific Corporation) is the most commonly used stent for iliocaval venous interventions in the US, which is primarily because there are few commercially available stents in the 16 to 22 mm diameter size required for this situation. The Wallstent, initially designed over 20 years ago for biliary interventions, has specific characteristics, including flexibility and fracture resistance, in addition to large diameters that suit it well for some situations encountered in the venous system. However, it also has shortcomings, including a lack of strength at the ends of the stent that may lead to failure to resist compression when placed at the iliac confluence, and significant foreshortening at deployment that make it difficult to implant the stent exactly where desired. Despite these shortcomings, the results reported with this device by numerous investigators have been favorable.[2,13] In particular, results in the treatment of patients with nonthrombotic iliocaval obstruction have been excellent. In postthrombotic cases, there is a significantly higher rate of stent occlusion, but secondary patencies have been acceptable over time as reported by Neglen et al.[2]

In the last decade, as interest in deep venous intervention has grown, multiple medical device manufacturers have developed stents designed specifically for the venous system *(Figure 4)*. Several are CE Mark approved and in use in Europe, while ongoing clinical trials in the US are now nearing completion *(Table I)*. There is great interest in the performance of these venous stents to determine how they will compare with the Wallstent. However, when considering the design of any stent, there are significant engineering tradeoffs that must be considered, such that it is unlikely that any one design will be the best solution for all

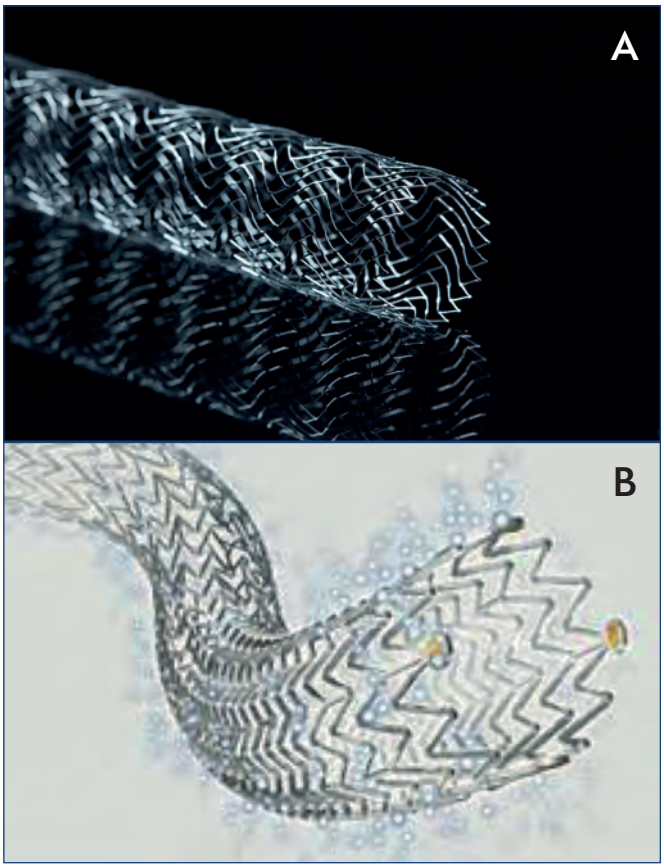


Figure 4. Stents engineered for the venous system nearing completion in clinical trials in the US include the Vici venous stent (Panel A) and Zilver Vena venous stent (Panel B).

Stents in clinical trials in the US	Stents with CE mark approval in Europe
Venovo venous stent (Bard Peripheral Vascular, Inc)	Venovo venous stent
Vici venous system (Veniti, Inc)	Vici venous system and Vici Verto system
Zilver Vena (Cook Medical)	Zilver Vena venous stent
Abre Venous (Medtronic)	Abre Venous (Medtronic)
	sinus-Obliquus (optimed GmbH)
	sinus-Venous (optimed GmbH)
	sinus XL and XL-Flex (optimed GmbH)

Table I. Current status of venous-specific stents.

types of venous disease. There are numerous different stents designed to treat diseases of the arterial system, including self-expanding or balloon-expandable, bare-metal or covered, stainless steel, nitinol alloy, cobalt alloy, and others. The development of biodegradable materials is ongoing, and all of the above may be combined with drug-eluting strategies to improve performance. At the core of this variety in stent development is the understanding that different clinical situations require different device strategies to obtain the best results. For instance, treating an ostial renal artery lesion would require a completely different device strategy than a midpopliteal artery lesion. Fortunately, the arterial device industry has matured to provide specific solutions for the diverse variety of pathology encountered.

In the treatment of venous obstructive disease, the situation is similar. Given the variability of the anatomic distribution and extent of the disease, one venous stent design is not likely to suit all situations encountered by the venous interventionalist. A stent that performs well in a non-thrombotic patient with localized compression at the iliac vein confluence may not be ideal for a postthrombotic patient with chronic total occlusion of the external and common iliac veins. It is important that we compare outcomes with devices in specific anatomic situations to determine which venous devices will perform best for individual patients with iliocaval venous obstruction. A detailed system for the description of the anatomic obstruction of the deep venous system that defines the variety of disease types encountered in the care of these patients is essential to facilitate these comparisons. Likewise, detailed information concerning the hemodynamic impact of venous obstruction will improve our ability to determine which patients would benefit from intervention and the best methods of intervention.

Classifying disease severity

As interventional therapies for the arterial system have evolved, it has become apparent that the extent and severity of disease affecting the artery involved closely related outcomes. The TransAtlantic InterSociety Consensus (TASC) criteria and subsequent TASC II criteria were developed to classify arterial disease severity and provide a framework for clinicians to study the technical success of interventions and the long-term success of a treatment plan.[14] Currently, no anatomic classification scheme has been validated for use in the treatment of diseases of the deep venous system. Neglen et al compared outcomes between patients with postthrombotic iliocaval venous obstruction and patients with nonthrombotic iliocaval venous obstruction. They found that postthrombotic patients experienced significantly higher rates of stent occlusion during follow-up.[2] The same authors also reported that lower patency rates may be due to the presence of disease in the femoral and profunda femoral veins in postthrombotic patients compromising inflow into the iliac venous segments.[15]

However, separating patients based simply on whether or not they have a history of prior deep vein thrombosis is only a start and is prone to inaccuracies. There is great variety in the extent of deep vein thrombosis burden, with some patients having a focal involvement in the affected limb and others having an extensive involvement. In addition, while some postthrombotic patients are left with significant obstruction of vessels throughout the affected limb, others have extensive thrombus lysis leaving minimal residual obstruction. A classification system based on anatomic findings prior to the intervention, similar to the TASC arterial system would improve our ability to predict results from intervention and compare technical and device aspects of intervention to define best practices and improve patient outcomes.

A group of venous interventionalists created an initial classification system, like the TASC criteria for iliac arterial disease, that included four types of iliocaval venous obstruction based on the extent of venous involvement and the severity of obstruction *(Table II)*.[16] In this system, a patient with stenosis of a single venous segment in the outflow tract

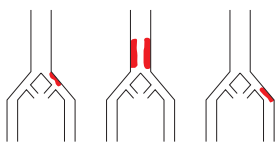
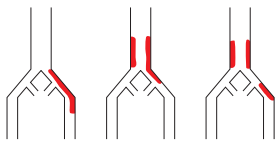
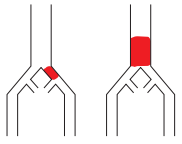
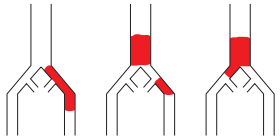
Classification type	Disease characteristics	Examples
Type I	Single-segment stenosis	
Type II	Multiple-segment stenosis	
Type III	Single-segment occlusion	
Type IV	Multiple-segment occlusion	

Table II. Iliocaval venous obstruction classification system.

(common femoral vein, external iliac vein, common iliac vein, or inferior vena cava) was defined as type I. Those with multiple segments identified with stenosis (defined as >50% narrowing) were assigned to type II. A single segment with complete occlusion was defined as type III, whereas multiple segments of occlusion were categorized as type IV.

This initial classification system was tested in a retrospective study of patients with iliocaval venous obstruction undergoing an intervention at two vascular centers.[16] While it is likely that intravascular ultrasound is the most accurate way to perform venous classification as long as imaging of the venous system from the femoral vein to the suprarenal inferior vena cava was performed, a variety of diagnostic methods were used in this initial effort. Computed tomography venography and magnetic resonance venography are acceptable tests, if the venous contrast is well timed to image the system and identify areas of significant obstruction.[9] This assessment allows classification to be performed before intervention to counsel patients better and choose an interventional strategy. A total of 120 patients were identified as having clinically significant iliocaval venous obstruction and an intervention was attempted, of which 42% were in the type I group, and the remainder were evenly distributed between types II, III, and IV. Technical success in reestablishing unobstructed venous outflow was achieved more often in types I and II than in types III and IV (P=0.003) *(Table III)*. Iliocaval patency was measured at 6 months postintervention and showed significantly better results in types I and II than in types III and IV (P=0.02) *(Table III)*. The classification system seemed to provide additional predictive information regarding the classification of nonthrombotic or postthrombotic disease, as patients with postthrombotic disease who were type I had better outcomes than type IV postthrombotic cases.

Type	Number of patients	Procedural success	Early failure rate (within 6 months)
I	51	50/51 (98%)	4/51 (7.8%)
II	23	23/23 (100%)	1/23 (4.3%)
III	16	13/16 (81.3%)	2/16 (12.5%)
IV	30	24/30 (80%)	8/30 (26.7%)

Table III. Initial technical success and early failure rate by anatomic type.

This initial report supports the belief that a well-designed and validated classification system for iliocaval venous obstruction cases could appropriately identify the expected risk and outcomes for the spectrum of disease encountered in this growing area of intervention. Just as the TASC system has done for arterial interventions, varying treatment strategies can be compared for specific types of disease and the outcomes that follow, ensuring that similar types and severities of disease are involved in the comparison. Inevitably, the venous space will evolve as the arterial space did before it and, hopefully, have not one, but multiple venous stents of varying design that may be used when their design characteristics yield the best results. Other devices specific to the venous system would also benefit from the use of an iliocaval venous obstruction classification system to facilitate clinical studies.

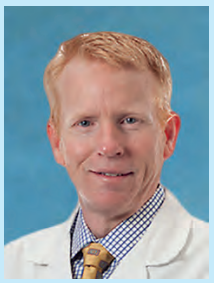
This novel classification system is likely to be too simple to adequately capture all of the key predictors of outcomes associated with intervention for iliocaval venous obstruction. The presence of inferior vena cava filters associated with caval occlusion, as well as the presence of bilateral disease and a history of prior stenting may all have a significant bearing on outcomes. Previous reports have also suggested that inflow into the iliac venous segments, hypercoagulability, and compliance with anticoagulation treatment regimens are also important predictors of outcome after venous stenting.[15,17] A well-developed classification system should capture all of the anatomical factors affecting outcomes to provide the best predictive information to guide treatment and device development.

Significant challenges exist in defining and validating a classification system for the venous system. The absence of widespread use of validated physiological tests for the venous system that characterize venous hemodynamics in patients with obstruction leads to challenges in outcome reporting in this area. Symptom improvement is often subjective and may depend, in some cases, on other conditions that coexist with chronic venous disease. Likewise, it is challenging to determine the severity of inflow obstruction in the venous system. While duplex ultrasound and computed tomography or magnetic resonance imaging can provide an anatomical picture of where the femoral and profunda femoral veins are obstructed, they do not provide specific information on the overall inflow these systems provide into the iliac outflow tract. Validated measures of inflow and overall hemodynamics are available in the arterial system, which allow precise comparisons to be made between various treatment strategies. These measures are needed for the venous system to facilitate a better characterization of the severity of disease and improvement resulting from interventions.

Conclusion

The treatment of deep venous obstruction is currently experiencing phenomenal growth as physicians discover the capability that intervention offers to improve patient symptoms and heal recalcitrant wounds. However, this growing field has yet to define successfully those patients who can benefit the most from these procedures. It appears clear that a multinational consensus of venous specialists is needed to create and validate a classification system to facilitate patient counseling, device development, and the selection of the most appropriate treatment strategies for specific types of disease. As information from ongoing clinical trials in venous stenting becomes available, the generated data may be useful in further defining and validating this type of system. Further use in a prospective manner would be required to determine its relevance to clinical practice.

A final, and potentially the most important, possibility is the ability to relate the extent of disease to symptom improvement after an iliocaval venous obstruction intervention. In many areas of vascular disease management, such as carotid disease or lower extremity peripheral arterial disease, the severity of the disease has been related to the benefit of the intervention. Patients with less severe disease are less often offered an intervention due to a relative lack of benefit from an intervention in these categories of disease. A classification system for venous disease that relates to the type of anatomic disease to symptom improvement after an intervention may provide meaningful information on the improvement in the quality of life that can be expected after a venous intervention. As utilization of venous interventions in this area increases, it is critical that we develop precise information to determine the necessity and guide for the optimal performance of these interventions.



Corresponding author
William A. Marston MD,
George J. Johnson Jr Distinguished Professor of Surgery, Department of Surgery, University of North Carolina School of Medicine, 3029 Burnett Womack Building, CB #7212, USA

Email: william_marston@med.unc.edu

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How to prevent complications and side effects from sclerotherapy of the lower limb veins

Lourdes REINA GUTIÉRREZ

Head of Department of Vascular Surgery, Hospital Central de la Cruz Roja, Madrid, Spain

Keywords:

complications; foam; prevention; recommendations; sclerotherapy; side effects; varicose vein

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Abstract

Sclerotherapy is an effective and safe treatment when used by trained and careful hands. Bad results are usually the consequence of an inappropriate use or indication. The best treatment is prevention; however good technique, satisfactory imaging, general precautions, and compliance with posttreatment instructions may prevent some adverse events. Sclerotherapy must be practiced according to the rules of good practice, which is governed by guidelines and international recommendations.

Introduction

If performed properly, sclerotherapy is an efficient treatment method with a low incidence of complications,[1-5] but some complications can be vital emergencies. The European guidelines for sclerotherapy in chronic venous disorders recommend considering certain adverse events after sclerotherapy *(Table I)*.[4-8] While foam sclerosants does not cause new or different complications vs liquid sclerotherapy, it changes their relative incidence.[4] Most adverse effects are minor and inconsequential, such as local injection site pain, urticaria, itching, erythema, and bruising. Other common, but usually self-limiting, side effects include cutaneous hyperpigmentation and telangiectatic matting, or blisters or folliculitis caused by compression postsclerotherapy. Significant and relatively rare complications include systemic life-threatening reactions, anaphylaxis, thromboembolism, cerebrovascular events, tissue necrosis, edema of the injected extremity, and nerve damage.[4-8]

Adverse effects may be due to the pharmacological properties of the sclerosants, the gas used to produce the foam, the technique of foam production, the injection technique, or postsclerotherapy treatments. Concurrent medical problems, intake of drugs or supplements, and lack of compliance with recommendations are other contributing factors that may also significantly influence the onset of complications.[6,9]

Designation	Incidence	
*****Very common	≥10%	
****Common	≥1% - <10%	
***Uncommon	≥0.1% - <1%	
**Rare	≥0.01% - 0.1%	
*Very rare and isolated cases	<0.01%	
	Frequency	
Type of adverse event	**With liquid**	**With foam**
Severe complications[1]		
Anaphylaxis	**Isolated cases*	**Isolated cases*
Large tissue necrosis	**Isolated cases*	**Isolated cases*
Stroke and TIA	**Isolated cases*	**Isolated cases*
Distal DVT (mostly muscular)	***Rare*	****Uncommon*
Proximal DVT	**Very rare*	**Very rare*
Pulmonary embolism	**Isolated cases*	**Isolated cases*
Motor nerve injury	**Isolated cases*	**Isolated cases*
Benign complications		
Visual disturbances	**Very rare*	****Uncommon*
Headaches and migraines	**Very rare*	****Uncommon*
Sensory nerve injury	**Not reported*	***Rare*
Chest tightness	**Very rare*	**Very rare*
Dry cough	**Very rare*	**Very rare*
Superficial phlebitis	*Unclear*[2]	*Unclear*[2]
Skin reaction (local allergy)	**Very rare*	**Very rare*
Matting	*****Common*	*****Common*
Residual pigmentation	*****Common*	*****Common*
Skin necrosis (minimal)	***Rare*	**Very rare*
Embolia cutis medicamentosa	**Very rare*	**Very rare*

Table I. Complications observed in a prospective French registry of 12 173 sclerotherapy sessions.

Abbreviations: DVT, deep vein thrombosis.

From reference 4: Guex JJ et al. Dermatol Surg. *2005;31(2):123-128. © 2005, Blackwell Publishing Ltd.*

In order to prevent complications, the European guidelines provide several absolute and relative contraindications to sclerotherapy (grade 1C). Absolute contraindications include known allergies to the sclerosants, acute deep vein thrombosis or a pulmonary embolism, local infection in the area of sclerotherapy or a severe generalized infection, long-lasting immobility and confinement to bed, and, for foam sclerotherapy, the presence of a right-to-left shunt (eg, symptoms of a patent foramen ovale). Relative contraindications (individual benefit-risk assessment is mandatory) include pregnancy, breast feeding, severe peripheral arterial occlusive disease, poor general health, strong predisposition to allergies, high thromboembolic risk (eg, history of thromboembolic events, known severe thrombophilia, hypercoagulation state, and active cancer), acute superficial thrombosis, and, for foam sclerotherapy, neurological disturbances, including migraines, following a previous foam sclerotherapy procedure.

This article reviews the methods for preventing sclerotherapy complications.

Major complications

Systemic allergic reaction and anaphylaxis

Systemic allergic reactions caused by sclerotherapy treatment occur very rarely. Local or generalized skin reactions, such as urticaria, are much more frequent (around 0.6%) than systemic involvement, and true anaphylaxis is an extremely rare complication constituting an emergency.[9-13] These reactions are unpredictable. Currently, no available methods can identify the individuals who are predisposed to these reactions, meaning that such adverse reactions cannot be prevented. Patients who have undergone multiple previous treatments with liquid sclerosants, those developing postsclerotherapy generalized urticaria, patients with mastocytosis, chronic urticaria, or other urticarial conditions may be at a higher risk.[6] Since the risk increases with repeated exposures to the antigen, it is best to always be prepared for these reactions.[9] Foam sclerosants are associated with a lower incidence of hypersensitivity reactions compared with liquid sclerosants due to an exposure below the required minimum allergenic dose.[10]

Tissue necrosis and cutaneous necrosis

Tissue necrosis most commonly presents as an ulcer, but it can result in extensive loss of tissue *(Figure 1)*. Cutaneous necrosis may occur with the injection of any sclerosant, even under ideal circumstances, and it does not necessarily represent a physician error. Fortunately, its occurrence is rare and usually of limited sequelae.[9] Cutaneous necrosis can occur weeks after the initial insult, and is often associated with pain, localized inflammation, and edema. A bright erythema or a prolonged blanching, also described as porcelain-white appearance, may be seen immediately after injection. Pain can be immediate or delayed. Dermal sloughing starts 24 to 72 hours after the ischemic event and the dermis can turn pale or dusky.

Skin necrosis has been described after a paravenous injection of sclerosants in higher concentrations, after

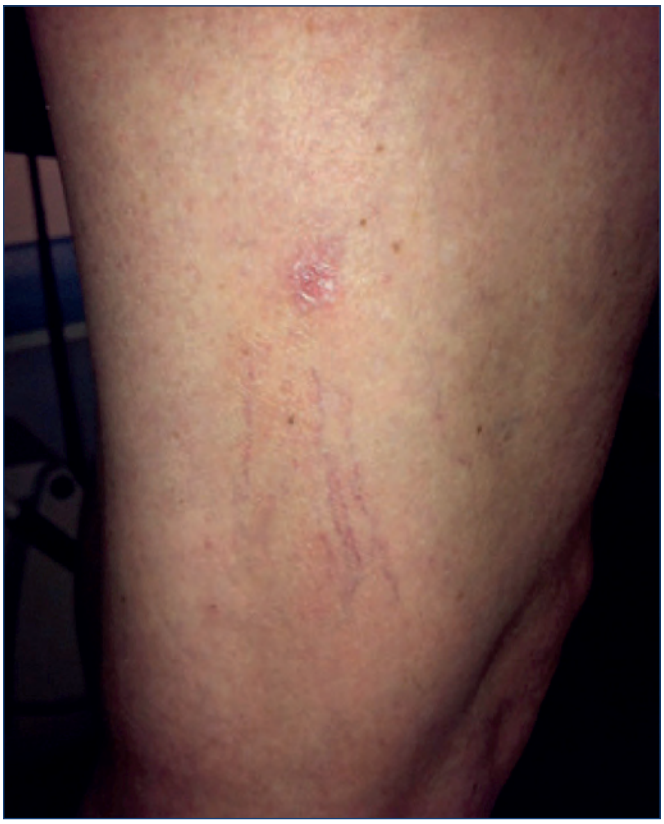

Figure 1. Cutaneous necrosis.

injection into a dermal arteriole or an arteriole feeding into a telangiectatic or varicose vein, or after reactive vasospasm of the vessels or venoarterial reflex vasospasm.[7,8,14-20] Some classes of sclerosants, such as the chemical irritants and osmotic agents, are more likely to cause tissue necrosis following extravasation.[14] The main mechanism leading to tissue necrosis following the use of detergents is arterial occlusion, which may be caused by an inadvertent intra-arterial injection or a venoarterial reflex vasospasm.[6,15-20] Passage of the sclerosant into the arterial circulation may be mediated by open cutaneous arteriovenous shunts.[15-20] Venoarterial reflex vasospasm may result from a high-speed or high-pressure injection in small caliber veins, which leads to the rapid dilation of the target vein and vasospasm of the associated arteries. Venoarterial reflex vasospasm clinically presents with prolonged blanching of the skin a few centimeters away from the site of injection, followed by cyanosis and reactive erythema. Prolonged arterial vasospasm may result in tissue infarction and subsequent necrosis.[15-20]

Prevention

To prevent cutaneous necrosis, a careful and methodical technique must be used: (i) stop injecting if there is a feeling of resistance, if a bleb or wheal forms, or if prolonged blanching occurs; (ii) use the lowest volume and weakest concentration of sclerosant; (iii) avoid using rapid and high pressure injections, especially in telangiectasia and reticular veins, keeping in mind that smaller syringes produce greater pressure; and (iv) use ultrasound-guided sclerotherapy for the deeper reticular veins. These recommendation are classified as grade 1C according to the European guidelines.[7,8] An indirect injection and an injection with a transilluminator can help avoid intra-arterial injections or extravasation *(Figures 2 and 3)*.

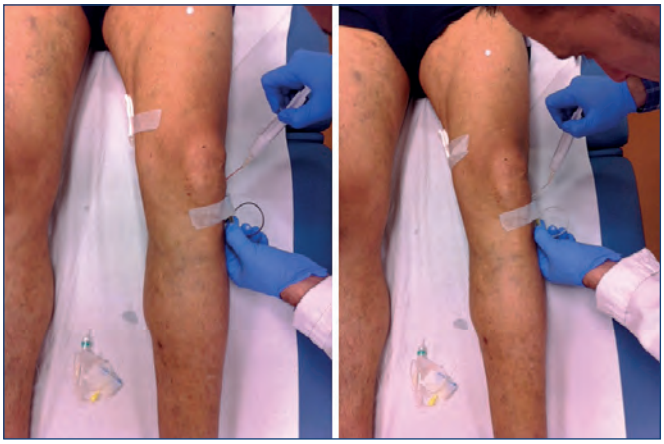

Figure 2. Indirect injection helps avoid intra-arterial injection or extravasation.

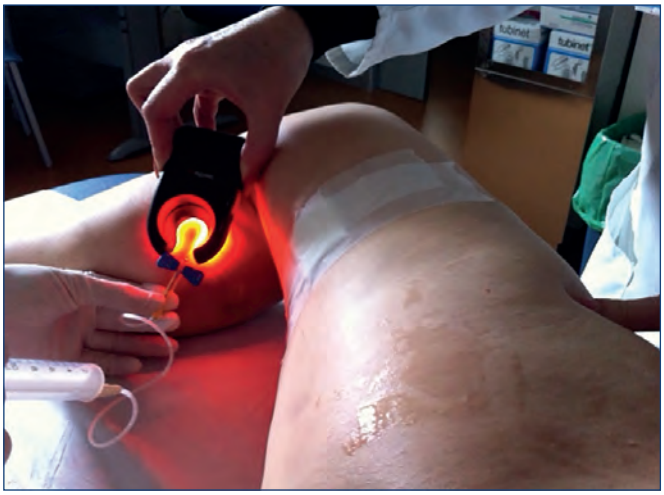

Figure 3. Injection with a transilluminator helps avoid extravasation and treat the underlying reflux, preventing a matting appearance.

Large tissue necrosis: inadvertent intra-arterial injection

Direct arterial/arteriolar injection is exceptionally rare. In fact, less than 70 cases have been described to date,[14,17,23-27] and most of them have occurred after an injection in the ankle region and in the perforating veins above the medial ankle. Other risk areas include the cross-section of

the small saphenous vein *(Figure 4)* and the cross-section of the great saphenous vein. Several cases have involved arterioles of the medial thigh.[23-27] Historically, the medial malleolar region was the most common site for intra-arterial injections,[19,26] which may relate to direct-vision sclerotherapy in these regions, targeting the posterior tibial artery in a relatively superficial position. Larger arteries, such as the femoral or popliteal artery are fortunately less frequently targeted.[27] Likely, target vessels include subcutaneous arterioles, such as those accompanying perforating veins in the medial thigh, the superficial sural artery in the posterior calf, and previously undetected arteriovenous shunts or malformations.[14,17] Arterial collaterals masquerading as varicose veins may pose a significant risk.[28] Ultrasound guidance has helped minimize the occurrence of this catastrophic event, which most frequently results in limb amputation (52.5%).[12,23]

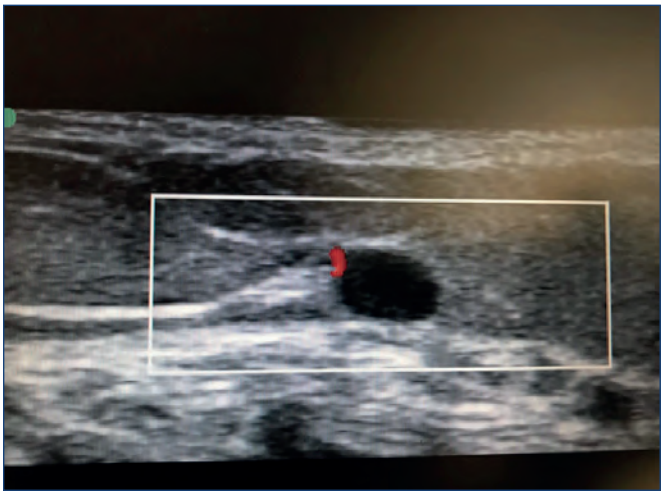

Figure 4. Satellite artery close to the small saphenous vein.

The extent of cutaneous necrosis is usually related to the site of injection and the amount of solution injected, and ranges from mild-to-severe necrosis of the skin, subcutaneous tissue, and muscle. This complication can follow direct-vision sclerotherapy, ultrasound-guided sclerotherapy, and even catheter-directed sclerotherapy. Theoretically, visualization of the arteries and veins with duplex-assisted sclerotherapy should negate this risk; however, a number of arterial ulcerations have occurred with this technique. Thus, no technique is completely free from this complication. Sodium tetradecyl sulfate has been more frequently implicated in this complication, accounting for 65% of cases vs 11% with polidocanol.[23] High concentrations of sodium tetradecyl sulfate can interact with blood to precipitate an insoluble complex of fibrinogen and Apo lipoprotein B[29] and induces platelets to release serotonin, a potent vasoconstrictor, which may contribute to a more prolonged occlusion.[25] Other cases reported have involved polidocanol. Both liquid and foam formats have comparable rates of tissue ischemia[25,26]; hence, practitioners should exercise caution when administering both agents and when using either format.

Intra-arterial injection commonly presents with severe sudden pain at the site of injection that propagates along the artery distribution. Pain can happen quickly or progress over several hours. In rare cases, patients have no complaints of pain and demonstrate only a mild, sharply demarcated erythema that becomes dusky and cyanotic after a few hours.[23]

Prevention

A strong personal experience and a careful ultrasound-guided technique may reduce the risk of this catastrophic complication *(Figure 5)*.[23] The European guidelines show that the risk of intra-arterial injection can be minimized using ultrasound guidance with adequate imaging and identification of arteries in close proximity to the target veins. The guidelines recommend using ultrasound guidance for both foam and liquid sclerotherapy when the target vein is not visible or palpable (grade 1C).[7,8]

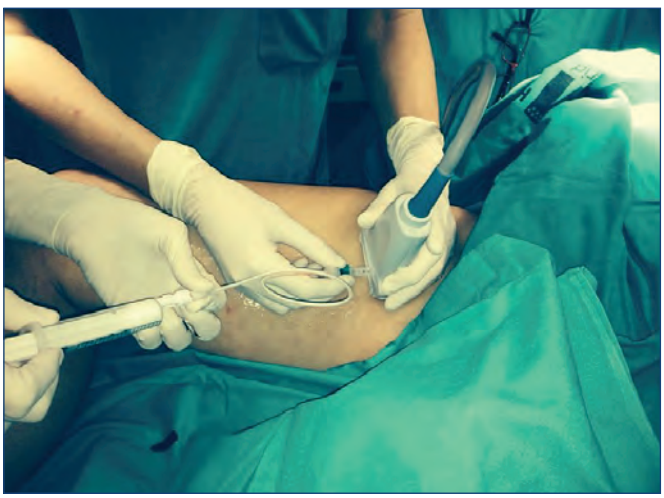

Figure 5. Ultrasound-guided sclerotherapy treatment helps avoid intra-arterial injection.

Neurological complications

The overall frequency of neurological complications of sclerotherapy is around 0% to 2%[30,31]; the complication include transient events, such as visual disturbances and migraine, as well as ischemic events, such as transient ischemic attacks and stroke, which is an event occurring at a much lower frequency. These complications can result

either from a paradoxical clot or from a gas embolism. The most consistent risk factors include a patent foramen ovale or another cardiopulmonary right-to-left shunt.[12] The etiology of neurological symptoms following sclerotherapy is currently unknown.

Transient neurologic events: visual disturbances and migraines

A systematic review found that visual disturbances may occur in up to 14% of patients undergoing foam sclerotherapy,[32] but a recent systematic review found the overall incidence to be around 1.4%.[31] The clinical presentation of these visual disturbances is similar to a classic migraine (with aura).[32] Patients presented with a headache alone, isolated visual disturbances in the form of a scotoma or blurred vision, headache combined with visual disturbances, and chest pressure that was either isolated or combined with blurred vision or a scotoma.[4,5] Transient neurologic events may be observed after any kind of sclerotherapy, although they occur more frequently after foam sclerotherapy and after treatment of reticular and spider veins.[4,5,7,8,32] A session of sclerotherapy for telangiectasia lasts much longer than for a session for varicose veins, and, during this time, the foam can change into liquid with large bubbles.[4] All cases spontaneously regressed without aftereffects.

A patent foramen ovale or another right-to-left shunt, which is present in approximately 30% of the general population,[33] might be one etiological factor because the pulmonary filter is short-circuited, which allows foam bubbles or endothelin-1 (ET-1) to be released from the injected vessel[34] to enter the arterial circulation.[30,32,34,36,37] Gillet et al hypothesized that ET-1 reaches the cerebral cortex and induces cortical spreading and triggers a migraine.[32] Frullini et al believes that ET-1 provokes a vasospasm, which is the key to understanding migraines, chest tightness, retinal transient ischemia, and neurological ischemia.[34,35] There is no clear evidence of a relationship between bubbles and visual or neurological disturbances[7,8,36-38]; however, bubbles are known to cause vasospasms and may trigger migraine-type symptoms and other general transient effects, such as chest tightness.[36] Other factors, such as bubble load, treatment parameters, and patient factors, may also be important.[36]

Ischemic events: transient ischemic attacks and stroke

The presence of a right-to-left shunt, particularly a patent foramen ovale, is the most consistent risk factor in patients with ischemic neurologic events (transient ischemic attacks and stroke).[30] There are only a few published reports of transient ischemic attacks following sclerotherapy,[30] and all reported cases were associated with a right-to-left shunt, had an immediate onset, and followed the use of air-based foam sclerosants. It has been suggested that a right-to-left shunt might allow foam bubbles to enter the arterial circulation.[30,36-38]

Stroke is a very rare, but significant, complication of sclerotherapy.[30,39-42,44] Ma et al reported two cases of stroke following 4059 foam procedures in a 6-year period, ie, an incidence rate of 0.01%.[41] Parsi reviewed 13 cases of stroke occurring after sclerotherapy published after 1994[30]; 4 cases occurred after liquid sclerotherapy and 9 after foam sclerotherapy, where 3 patients had a partial recovery, while the others had a complete recovery. Cases with an immediate onset following foam sclerotherapy were due to a paradoxical gas embolism,[30,39-42,44] while cases with a delayed onset of a few days were due to a paradoxical clot embolism.[30,41,42] The mechanism of infarction in a paradoxical gas embolism may be either due to direct physical occlusion of the intracranial arteries by gas bubbles or due to a bubble-induced vasospasm that activates the coagulation system to cause a secondary thrombotic occlusion.[30,41] No gas or clot embolism could be demonstrated in 5 of the 13 patients with stroke reviewed (idiopathic and other causes).[30,41] The release of cell-derived sclerosant byproducts may play a crucial role in the pathogenesis of neurological and other complications of sclerotherapy.[30,34,35,45] Finally, a coincidental event due to general causes of stroke should be considered.[30]

A venous gas embolism presents with dyspnea, continuous cough, hypotension, dizziness, and substernal chest pain. A "mill wheel" murmur may be produced by movement of bubbles in the right ventricle.[36] A coronary artery embolism can present with chest tightness and pain, coronary artery spasm, ischemia, arrhythmias, and myocardial infarction. A cerebral gas embolism can present with confusion, focal neurological symptoms, and stroke.[30,39-42,44]

Prevention

To prevent neurological complications, the following recommendations should be taken into account:

1. Assess the patient for a history of cardiac abnormalities or migraine.
2. Limit the use of foam to large varicose veins, otherwise use a liquid sclerosant for reticular and spider veins.[46]
3. Prepare the foam using the Tessari method to form the smallest bubbles possible and use the foam within

90 seconds, as bubble coalescence is swift and the stability of sclerosing foam is not great.[7,8,46]

4. Limit the volume of foam to 10 mL per session.[7,8,30,46,47] Technical modifications, such as CO_2 or CO_2 / O_2 foams and Varisolve® polidocanol foam, may allow a larger volume to be injected *(Figure 6)*.[46]

5. Minimize the bubble load to reduce the passage of the sclerosant into the deep veins through perforating veins and the saphenous junction[7,8,30,32] by using multiple low-volume injections[48] and injecting only the necessary volume of foam under ultrasound guidance until the target vein is filled.[30] Catheterization of the target vein combined with perivenous anesthesia reduces the volume required to achieve vessel closure.[49] Sclerotherapy must be administered in a proximal to distal sequence targeting the larger veins and the most proximal sources of reflux first.[9,30,36]

6. Keep the patient supine for 5 minutes after the injection and avoid having the patient sit or stand up immediately after the procedure *(Figure 7)* because the risk of a paradoxical gas embolism increases in the sitting position.[30,50]

7. Avoid manually compressing the saphenous junctions during foam sclerotherapy,[30] as this can cause boluses of foam to be released into the central circulation when the pressure is released.[51] There have been two published reported cases of a stroke after sclerotherapy.[30]

Figure 6. Physiologic gases can be employed at increased risk of neurologic events.

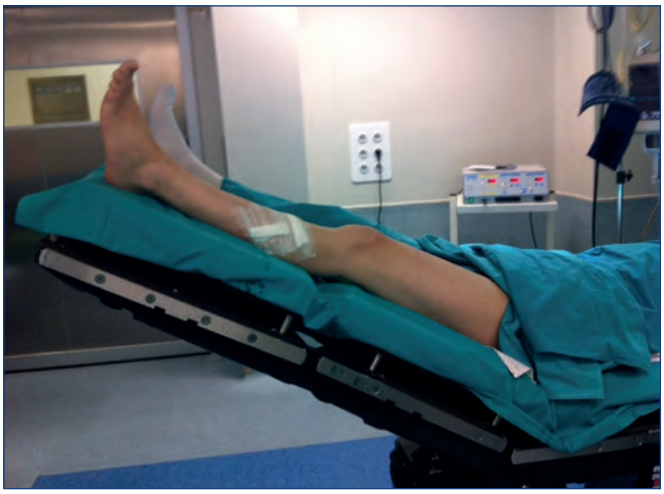

Figure 7. Keep patients supine for 10 minutes after injection and avoid having the patient sit or stand up immediately after the procedure.

Figure 8. Compression stockings should be applied by the medical staff at the end of the procedure to prevent a Valsalva maneuver.

8. Avoid movements that lead to a Valsalva maneuver during or after the procedures, because this would open a patent foramen ovale or another right-to-left shunt, which is why compression stockings should be applied by the medical staff at the end of the procedure *(Figure 8)*.[30]

9. A preliminary screening for a patent foramen ovale or a right-to-left shunt is not necessary.[7,8]

10. Reduce initial volumes and consider using physiologic gases for those patients at an increased risk of neurologic side effects, such as those with a previous classic migraine (with aura) and those with a known patent foramen ovale.[46,52-54]

11. Patients with a past history of cryptogenic stroke or a history of recurrent classic migraines (with aura) have

a higher risk of neurological adverse events and may benefit from preoperative screening and percutaneous closure of a patent foramen ovale.[12,30] However, closure procedures are not risk-free,[55] and the long-term benefits of a patent foramen ovale closure in sclerotherapy patients is unknown.[30]

12. Use only liquid sclerosing agents or recommend another kind of treatment for patients with a known symptomatic right-to-left shunt as this is an absolute contraindication for foam sclerotherapy (recommendation grade 1C in the European guidelines).[8,46]

For patients who have experienced neurological symptoms, including migraines after a previous sclerotherapy session, the European guidelines recommend: (i) the patient should remain lying down for a longer period of time (grade 2C); (ii) avoid injecting large volumes of foam or perform liquid sclerotherapy (grade 2C), although the liquid can also occasionally cause neurologic sequelae in susceptible patients; (iii) the patient should avoid performing a Valsalva maneuver in the early period after the injection (grade 2C); and (iv) on a case-by-case basis, a risk-benefit assessment should be performed based on the particular indication (grade 2C).[7,8]

Patients with a suspected venous gas embolism should be immediately placed in a left lateral decubitus position to reduce entry into the pulmonary arteries and a possible subsequent right ventricular outflow obstruction.[36]

Venous thromboembolism

Severe deep vein thrombosis, proximal or extensive, is rare. The vast majority of reported deep vein thrombosis cases are localized to the lower legs. The overall frequency of deep vein thrombosis is <1%[31,56]; however, the incidence is possibly higher as a significant number of procedural deep vein thrombosis may be silent (most reports only include symptomatic cases). The incidence of symptomatic deep vein thrombosis is 0.02% to 0.6%[4,31,56] and the incidence with a duplex ultrasonography follow-up is 1.07% to 3.2%.[1,4,5,47,57-59] Most of the cases detected by duplex ultrasonography during routine follow-up were asymptomatic.[1,4,5,47,57-59] Medial gastrocnemius vein thrombosis is a complication that is more commonly associated with foam sclerotherapy of the small saphenous vein than with the great saphenous vein, likely due to the anatomy of the small saphenous vein.[59]

Pulmonary embolisms occur very rarely after sclerotherapy. In the study by Gillet,[5] only 1 case of pulmonary embolism was reported out of 1025 patients. In a French registry of 12 173 procedures, no cases of pulmonary embolism were reported.[4] There is no data regarding the incidence of postoperative silent pulmonary embolisms. Research on the effects of sclerotherapy on coagulation has shown contradictory findings.[29,45,59-64] To date, no obvious prothrombotic effect has been demonstrated.[9]

Prevention

The use of larger volumes of sclerosants, particularly foam, increases the risk of a thrombosis.[57,65] Treatments that might influence the risk of deep vein occlusion have been reviewed, and using large total volumes of foam (>10 mL) was identified as a risk factor.[57,65] Myers et al showed that varicose veins >5 mm and small saphenous vein treatment were risk factors for deep vein thrombosis.[47] He recommends limiting the volume of foam to 1.5 to 2 mL during sclerotherapy of the small saphenous vein.[65] The European guidelines recommend avoiding injections near the saphenous junction and perforating veins, if possible, to prevent foam from entering the deep venous system.[7,8]

To prevent venous thromboembolic complications, the follow recommendations should be taken into account:

1. Use a maximum of 10 mL of foam per session in routine cases (grade 2B). Higher foam volumes can be applied according to an individual risk-benefit assessment (grade 2C)[7,8]; however, using large total volumes of foam (>10 mL) was identified as a risk factor for deep vein thrombosis.[57,65]

2. Limit the quantity of sclerosing solution to 0.5 to 1 mL per injection, as multiple small-dose injections using a low volume of foam can reduce the passage of sclerosant foam into the deep veins and decrease venous thromboembolic complications.[48,65] In vitro studies by Parsi[30] and Watkins[66] have shown that the action of sodium tetradecyl sulfate is inhibited by blood proteins and approximately 0.5 to 1 mL of whole blood deactivates 1 mL of 3% sodium tetradecyl sulfate.

3. Implement immediate ambulation after sclerotherapy treatment. Venous stasis is the most likely mechanism for deep vein thrombosis after sclerotherapy. Prolonged immobilization and long-distance travel in the first week after sclerotherapy may increase the risk of a venous thromboembolism (grade 1C).[7,8]

4. Apply compression using compression stockings or bandages after sclerotherapy (grade 2C).[7,8] The critical time for thrombus formation in sclerotherapy-

treated vessels is approximately 9 hours posttreatment. Some authors suggest that compression stockings or bandages are the most beneficial during the night after sclerotherapy treatment and during other periods of relative vascular stasis when an intravascular thrombus is being formed,[9] but there is no evidence to support this idea.

5. Elevate the extremity to 30 degrees and implement immediate ambulation or calf movement with full dorsiflexion of the ankle to empty the deep leg veins, including the muscular and soleal sinuses, as this promotes rapid dilution of the solution from the injected area to decrease the risk of thromboembolic events.[9] While this is a common practice in sclerotherapy treatment, it is not supported with any evidence.

6. Use pharmacological thromboprophylaxis in line with current guidelines/recommendations (grade 1C) *(Figure 9)*, implement physical prophylaxis (compression, movement) (grade 1C) *(Figure 10)*, avoid injecting large volumes of foam (grade 1C), decide on a case-by-case basis (benefit-risk assessment) on the particular indication (grade 1C) in patients with risk factors for a venous thromboembolism (eg, high foam volume, overweight, immobility, older age, hormonal treatments, a history or a previous venous thromboembolism event or thrombophilia).[7,8,67-70]

7. It is not recommended to perform routine investigations for the presence of thrombophilia factors in the coagulation system (Grade 1C).[7,8]

A study by Hamel-Desnos et al[67] suggests that, in the three most common forms of thrombophilia (ie, patients with a Factor V Leiden mutation, a prothrombin 20210A mutation, high levels of Factor VIII, or a combination), sclerotherapy, in combination with thromboprophylaxis, can be performed safely.[67] The volumes used in this study were low. The authors recommend that the risk-benefit balance should be assessed for each patient. Thrombophilia with a significantly elevated relative risk of a venous thromboembolism or thrombophilia is a contraindication for sclerotherapy. In patients with thrombophilia and an elevated or moderate relative risk who are on long-term oral anticoagulation, sclerotherapy may be given without using low-molecular-weight heparin; however, if these patients are not on oral anticoagulation, then 7 days of low-molecular-weight heparin should be used. In patients with thrombophilia and a moderate relative risk who are

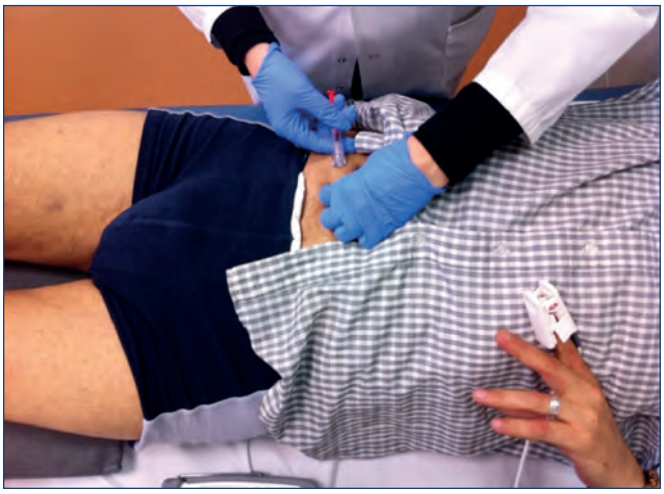

Figure 9. Pharmacological thromboprophylaxis in patients with a high risk of venous thromboembolism.

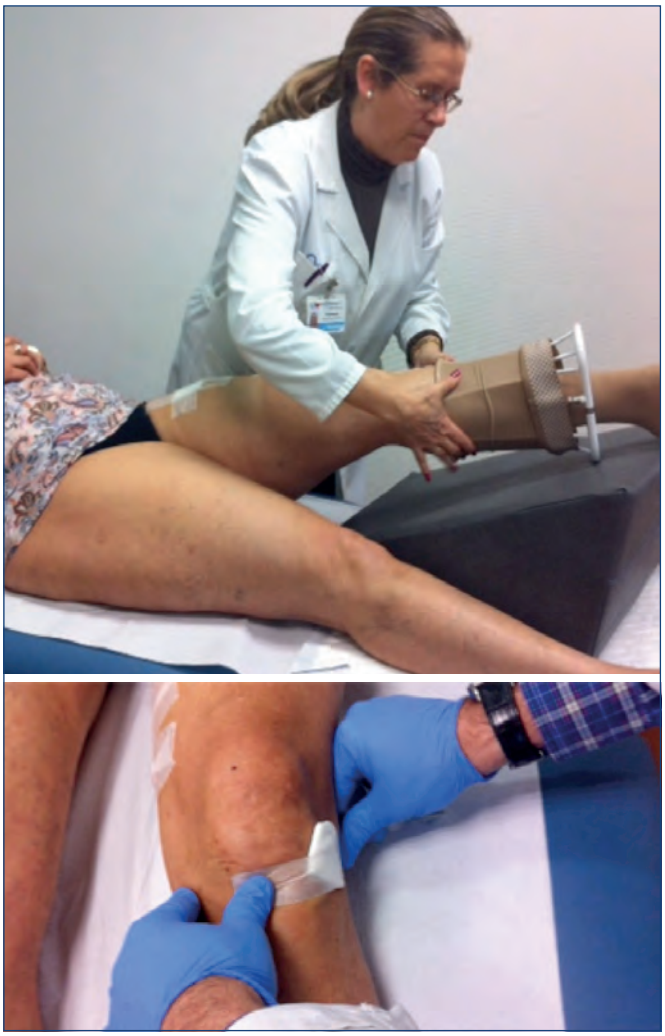

Figure 10 Medical compression systems have anti-inflammatory effects, decrease chronic venous hypertension, and help resolve intravascular coagula.

Physical prophylaxis (compression, movement) is recommended to prevent a venous thromboembolism.

not on oral anticoagulants, low-molecular-weight heparin should be given for 1 to 7 days, depending on the clinical context and medical history.[67]

Gillet et al showed that, when compared with younger patients, sclerotherapy using low volumes of sclerosant in older patients was not associated with a higher risk of side effects, no specific complications, or need for special precautions.[68]

Superficial venous thrombosis

The definition of phlebitis after sclerotherapy in the literature is controversial. It is more a part of the treatment process than a complication, and it is considered an adverse event if there is an extension beyond the treated area or an excessive inflammatory reaction.[7,8] It is difficult to classify as normal or abnormal when there is either an abnormal extension along the vein or an excessive inflammatory reaction. Venous sclerosis (collagen deposition, which results in scar formation), venous thrombosis (intravascular fibrin clot formation), and venous thrombophlebitis (clot formation accompanied by an inflammatory infiltrate) are histologically separate entities that cannot always be clinically or monographically differentiated. Hence, the incidence depends on individual understandings, meaning that the real frequency is unknown (range, 0% to 45.8%; mean, 4.7%).[4,6-8,31] Thrombophlebitis is a complication that should not be taken lightly. If untreated, the inflammation and clot may spread through the perforating veins to the deep venous system. Patients with superficial venous thrombosis have a 5% to 40% chance of developing a deep vein thrombosis.[71]

Prevention

The cause of thrombophlebitis is related in part to the treatment technique as well as to a lack of adequate postsclerotherapy treatment with adequate compression and frequent ambulation *(Figure 10)*.[9] According to Goldman, a decreased incidence of superficial thrombophlebitis may result from a greater degree and length of compression used after sclerotherapy.[9] An inadequate degree or length of compression results in excessive intravascular thrombosis. Perivenous inflammation is observed only in the part of the limb not covered by a compression dressing. Thus, to prevent or minimize the development of postsclerosis thrombosis, compression pads and hosiery should be applied over the entire leg and not just over the treated veins.[9]

However, even when appropriate compression is used, thrombosis and perivascular inflammation may still occur. Ascending phlebitis in the small saphenous vein or its long tributaries, starting at the upper edge of the compression stocking, is relatively common. Here, the sclerosing action continues up the abnormal vessel (even beyond what apparently is the extent of the abnormality). It is thought that the sclerosing solution destroys damaged endothelium to a greater extent than normal endothelium.[9] Therefore, the placement of a foam pad extending above the compression stocking or bandage to create a gradual transition of pressure from a compressed to a noncompressed vein may provide a safety margin, as well as prevent damage to the vein by an abrupt cut-off of the pressure.[9]

Nerve injury

Sclerotherapy using liquid or foam sclerosants is associated with both sensory and motor nerve damage that is usually transient. The incidence is very rare (0.02%) with paresthesia and dysesthesia as the main presenting complaints.[72] Due to their close proximity to the veins, the saphenous and sural nerves may be inadvertently injected during sclerotherapy. Injection into a nerve is reportedly very painful and, if continued, may cause anesthesia and sometimes a permanent interruption in nerve function. Occasionally, a patient complains of an area of paresthesia probably caused by perivascular inflammation extending from the sclerosed vein to adjacent superficial sensory nerves.[9]

Prevention

Nerves are readily visualized on most modern ultrasound systems and inadvertent damage can be mostly avoided *(Figure 11)*.

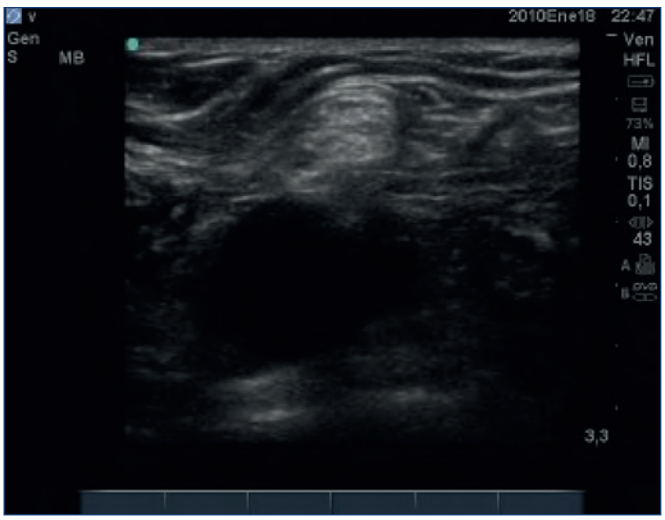

Figure 11. Nerves are readily visualized on most modern ultrasound systems and inadvertent damage can be mostly avoided.

Temporary swelling: edema and lymphedema

The incidence of lower limb edema following sclerotherapy is estimated to be ≈0.5%, but it is rarely reported, meaning that it is probably underestimated.[73] This complication is possibly more frequent following obliteration of the small saphenous vein due to the contiguity of this vein with the superficial lymphatic vessels. Localized lymph stasis may occur due to sclerotherapy-induced chemical phlebitis. Extensive sclerotherapy may result in transient lymph stasis in predisposed patients, such as those with latent congenital lymphatic system abnormalities.[6] Edema may also be due to deep vein occlusion (thrombosis or sclerosis). Extensive sclerotherapy of superficial incompetent veins followed by occlusion of small segments of the deep veins in the lower limb, such as the posterior tibial or peroneal veins, may also contribute to the edema. In some patients, the etiology is multifactorial and involves a combination of obesity, lack of exercise, concomitant drugs, such as calcium channel blockers, and a lack of compliance with the use of compression stockings.[6]

Prevention

This complication may be minimized by using careful techniques to avoid phlebitis and deep vein occlusion. Perivascular inflammation must be limited. Ankle edema occurs much less frequently if the sclerosing solution is limited to 1 mL per ankle. Adequate postoperative compression is important in reducing edema and phlebitis in general *(Figure 9)*.[6,9,74] One study compared the use of postsclerotherapy graduated compression for a period of 3 days to 3 weeks. In the 10 patients analyzed, 0% reported complaints of edema when the stockings were worn for 3 weeks, 40% of patients who did not wear posttreatment compression stockings had edema, 30% had edema if the stockings were only worn for 3 days, and 20% complained of ankle/pedal edema if the stockings were worn for 1 week.[74] Topical application of a potent corticosteroid cream, lotion, or gel is useful.[9]

Minor complications

Telangiectatic matting

Telangiectatic matting is the proliferation of new vessels (<0.2 mm) in the area of a sclerosed vein; they typically appear 4 to 6 weeks after sclerotherapy treatment *(Figure 12)*,[75] and is predominantly seen in women, even though it can also occur in men.[75] The most common location is on the inner and outer thighs, near the knees and calves. Unfortunately, even in the most expert of hands, telangiectatic matting may affect one-third of the patients undergoing sclerotherapy, and usually resolves spontaneously in 3 to 12 months.[76] In many cases, inadequate or no treatment of the underlying reflux is the cause of telangiectatic matting,[77,78] which is especially true when there is underlying saphenous reflux, reticular veins, or when the telangiectasias have been injected directly.[77,78]

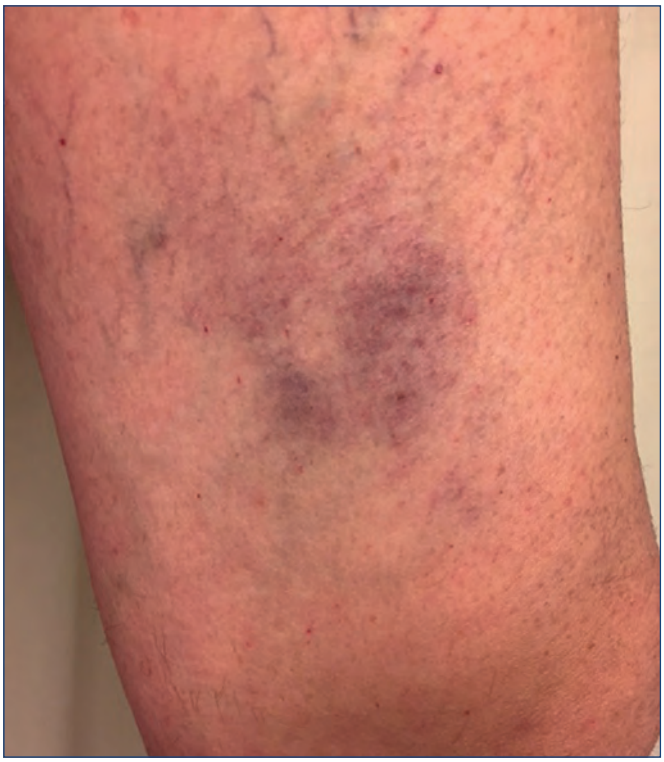

Figure 12. Matting after direct sclerotherapy of reticular veins and telangiectasias in the presence of an underlying saphenous reflux.

The precise cause of telangiectatic matting remains unknown; however, its development is attributed to a reactive inflammatory or angiogenic mechanism and is more prevalent with high concentrations or volume of sclerosant or high infusion pressures that can result in inflammation or excessive vein obstruction with subsequent angiogenesis.[77,78] Telangiectatic matting is more likely to occur when an increased infusion pressure is used, which results in blanching of the entire capillary network of the skin.[75] Patient risk factors include excessive body weight, female sex, hormonal treatments with estrogens, a longer duration of spider veins, and a family history of telangiectasia.[75,77,78]

Prevention

Efforts to minimize telangiectatic matting are especially important because treatment efforts other than waiting often

are not successful. Assess for risk factors prior to treatment. Avoid inadequate treatment of the underlying reflux *(Figure 3)*, use the lowest concentration and volume of the chosen sclerosant that will effectively obliterate the vein, and use the lowest pressure to deliver the sclerosant to minimize excessive vessel injury. When a patient who is taking exogenous estrogen demonstrates a tendency toward telangiectatic matting, consider temporarily stopping the estrogen treatment during the treatment period.[75]

Residual pigmentation

Postsclerotherapy hyperpigmentation refers to the appearance and persistence of pigmentation along the course of a treated vein *(Figure 13)*. Pigmentation occurs in 10% to 30% of patients in the short term, usually appears within 3 to 4 weeks after sclerotherapy, and can last from 6 to 12 months, despite attempts at therapy.[9] Although spontaneous resolution occurs in 70% of patients at 6 months, pigmentation may persist longer than 1 year in up to 10% of patients.[5,9,77] Hyperpigmentation is usually due to a combination of both melanin and hemosiderin pigment deposits secondary to direct hemosiderin deposition, a postinflammatory processes, or a combination of the two. The red blood cells extravasate after rupture of treated vessels or perivenulitis. The red blood cell dies and the hemoglobin is released into the dermis and is degraded into hemosiderin.[8,9]

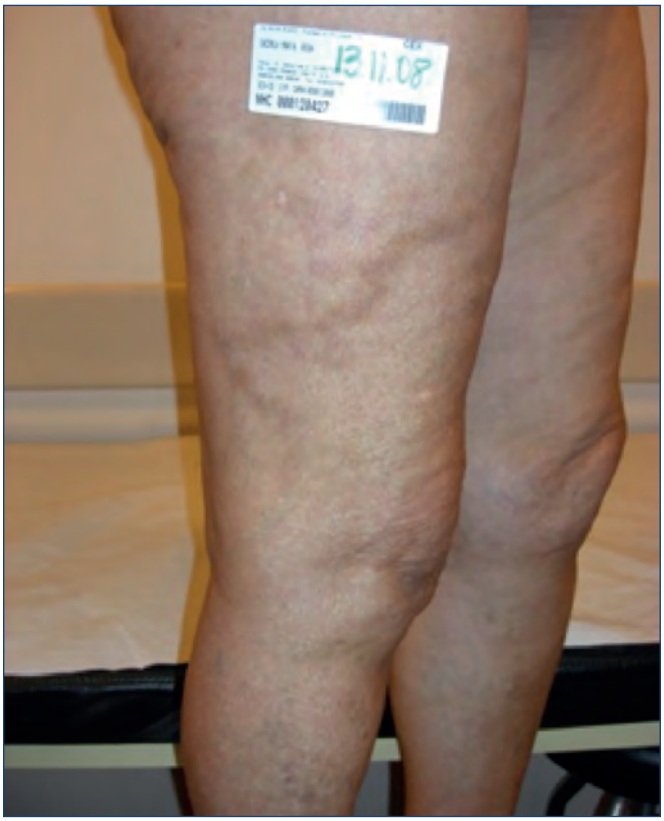

Figure 13. Persisting pigmentation along the course of a treated vein within 3 to 4 weeks after sclerotherapy.

There is a direct correlation between the incidence of hyperpigmentation and the more concentrated strength or volume of any given sclerosant, however, the incidence varies between the three most commonly used agents.[75] A retrospective review showed that there was no difference in the degree or severity of hyperpigmentation between foam and liquid sclerosants.[77] A small randomized clinical trial showed there was no difference in hyperpigmentation between sodium tetradecyl sulfate and polidocanol.[79] In general, the incidence of hyperpigmentation is higher when treating larger (>1 mm), superficial, and fragile vessels.[79]

The risk factors that may play a role are a high serum ferritin level, treatment with minocycline, and an intense sun exposure during the treatment process.[8,9,80] While there is no general agreement on whether certain skin types are more prone to hyperpigmentation, some authors report a more frequent hyperpigmentation in patients with dark skin and dark hair.[4]

Prevention

To minimize the risk of developing hyperpigmentation, sclerotherapy should minimize the risk of vessel rupture and red blood cell extravasation and limit endothelial necrosis with its resulting diapedesis of red blood cells by: (i) using a meticulous injection technique[2]; (ii) avoiding excessive injection pressures by using bigger syringes; (iii) selecting the appropriate solution type, concentration, and dosage in relation to the size and morphology of the vessels to be treated; (iv) using correct therapeutic strategies and tactics, treating areas of venous reflux in a proximal-to-distal manner, and eliminating feeder sources first; (v) aspirating intravascular microthrombi *(Figure 14)*; (vi) prescribing adequate compression therapy *(Figure 10)*.[8,9,79]

Postsclerotherapy hyperpigmentation tends to be more common with greater amounts of intravascular coagula. Persistent thrombi are thought to produce a subacute perivenulitis that favors extravasation of red blood cells.[8] The European guidelines[8,80] recommend that intravascular clots should be removed by needle aspiration or stab incision and coagulum expression as soon as possible to reduce the incidence of hyperpigmentation (grade 1C) *(Figure 14)*. Removal of the retained coagulum immediately relieves tenderness and inflammation and may help prevent discoloration.[6,80] Microthrombi and larger volumes

of intravascular coagulum can be evacuated by puncture with a 16- or 18-gauge needle (depending on the vessel size) and manually expressed or aspired.[81] Intervention is recommended within 2 to 4 weeks postsclerotherapy.

Compression stockings minimize the amount of intravascular coagulum, and they have anti-inflammatory effects, decrease chronic venous hypertension, and help resolve the intravascular coagula; therefore, they are an important part of posttreatment care *(Figure 10)*.[8] Two randomized clinical trials that compared how compression vs no compression affected the side effects after sclerotherapy (eg, hyperpigmentation, bruising, migraines, and edema) showed no difference in the treatment of telangiectasia, reticular veins,[82] or saphenous veins[83]; however, the evidence is poor. Nonrandomized studies have shown that compression decreases the side effects from sclerotherapy of telangiectasia and reticular veins.[74,84,85]

Prevention

Preventing the formation of postsclerotherapy-related ecchymosis would theoretically prevent postinflammatory hyperpigmentation by avoiding dermal hemosiderin deposition. Although *Arnica montana* is routinely used by many surgeons to prevent perioperative bruising, the efficacy of this homeopathic product has not been scientifically proven.[9] Several authors have recommended that patients should avoid taking iron supplements during the course of treatment and for 1 month after treatment.[9,86] Izzo et al recommended that patients stop taking drugs that interfere with hemostasis, which eventually lead to bleeding (NSAID, antithrombotic) and drugs and cosmetics that can potentially increase pigmentation (tetracycline, chloroquine, suntan lotion, dyes, bergamot oil).[80] European guidelines recommend avoiding UV exposure for the first 2 weeks after sclerotherapy.[7,8,80] For high-risk patients, consider another type of treatment or take more rigorous preventive measures.

Intravascular coagulum

Intravascular coagulum refers to the common occurrence of palpable intravascular coagulum in a treated vessel, that appears 1 to 6 weeks after sclerotherapy *(Figure 14)*. The intravascular thrombus tends to remain liquefied. In a systematic review of four randomized controlled trials of foam sclerotherapy, the frequency of retained coagulum ranged from 7.8% to 55.1%.[31] Intravascular coagulum occurs more frequently in larger blood vessels; coagulum retention is usually associated with tenderness and may predispose the patient to posttreatment pigmentation.

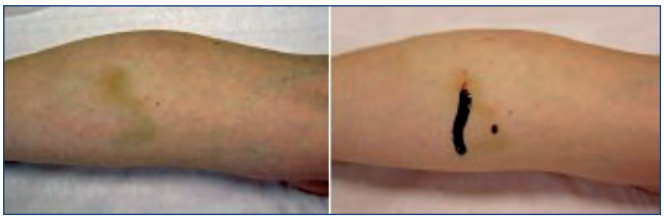

Figure 14. Drainage of postsclerotherapy intravascular thrombi helps to prevent hyperpigmentation.

Prevention

Good technique should focus on minimizing the mixture of sclerosant with the intravascular blood, selecting an adequate sclerosant concentration, injecting small volumes from a single point of entry, and applying adequate compression.[6] Microthrombi can be minimized with external compression following sclerotherapy *(Figure 10)*.[8] It is mandatory to avoid an underlying source of untreated venous insufficiency *(Figure 3)*.[81]

Transitory general effects

Transitory general effects are short-lasting disturbances, where recovery occurs within minutes. Chest tightness and dry cough are the most reported effects, but nausea and a metallic taste can also occur. Patients describe two different forms of chest tightness: a simple chest pressure or painful chest tightness. The pathophysiology is not clear. In chest tightness, it is hypothesized that a coronary vasospasm is provoked by air bubbles[36] or ET-1 release[35]; it does not seem to be related to a myocardial infarction and no increase in troponin levels has been observed.[63] The type of gas used to prepare foam is a controversial topic. According to Morrison,[53] transitory general side effects (tightness, dry cough, and dizziness) are more frequent when injecting a large volume of foam (>15 mL), and the frequency is reduced by substituting CO_2 for air. Peterson et al showed no differences in efficacy or side-effects between air and CO_2 foam sclerotherapy for reticular veins.[54] If high volumes of foam are injected, the use of low nitrogen sclerosing foam reduces the early onset of reversible side effects.[53] However, no benefits on transitory general effects in patients treated with either a CO_2-O_2–based foam or an air-based foam in low volumes have been observed.[54]

To improve the general safety of foam sclerotherapy the European guidelines recommend: (i) injecting a highly viscous foam into varicose veins (C_2) (level 1C); (ii) avoiding patient or leg movement for a few minutes after the injection and avoiding a Valsalva maneuver by the patient (level 1C) *(Figure 7-8)*; and (iii) selecting the best type of gas (air or physiological gas) used to prepare the foam,

keeping in mind that this is still a controversial topic *(Figure 6)*.[7,8]

Stress-related symptoms

Vasovagal reflex

Vasovagal reflex is nonspecific and benign, but the patient is at risk for falling. It is the most common cause of a simple loss of consciousness.[87] The vasovagal reflex is a common adverse sequelae of any surgical or invasive procedure. It has been estimated to occur in 1% of patients during sclerotherapy[9] and must be managed according to the protocol or syncope management.[87] A characteristic of a vasovagal response is dysfunction of the autonomic nervous system, with parasympathetic activation that results in initial bradycardia and loss of sympathetic stimulation, which, in turn, causes initial hypotension. An environmental trigger, such as a needle stick, is a common cause.[87]

Vasovagal reactions typically present with a prodrome of nausea, pallor, and diaphoresis, although a sudden loss of consciousness is also possible. Other common symptoms include lightheadedness, feeling hot, and tinnitus. The patient may also have shortness of breath and palpitations. Lack of blood flow to the brain can result in confusion or even syncope that usually provokes the most concern from the physician and staff.[87] As the reaction progresses, a seizure may occur, as well as cardiac arrhythmia with a rapid decrease in cardiac output and even cardiac arrest.[9] Vasovagal reactions are most often preceded by a painful injection, but may even occur from the patient seeing the needle or smelling the topical isopropyl alcohol or sclerosing solution.

Prevention

The main concern with a vasovagal reaction is that the patient will fall and sustain injuries. Therefore, both the nurse and physician should watch the patient closely for signs of restlessness, paleness, and excessive perspiration. All patients should be warned to sit down if they become dizzy. It is also helpful for the patient to hold onto an arm rail or other support when needle placement is performed on a standing patient, although treatment while the patient is standing is not recommended. All such reactions are easily reversible when the patient assumes the supine or Trendelenburg position. Preventive measures consist of recommending that the patient eat a light meal before the appointment, maintaining good ventilation in the treatment room, and maintaining constant communication with the patient during the procedure.

Underlying medical disease

Other serious stress-induced problems include exacerbation of certain underlying medical diseases. Wheezing may occur in patients with a history of asthma or angina may develop in patients with cardiovascular disease. Polidocanol is a negative inotropic agent and slows cardiac contractility in a dose-dependent manner.

Urticaria

Urticaria and periorbital edema may be related to histamine release from irritated perivascular mast cells. Urticarial reactions have been rarely observed when using graduated compression stockings. Urticaria may be a sign of a systemic allergy. Therefore, the use of the sclerosing agent in future treatment sessions should be carefully evaluated.

Transitory local side effects

Transient local side effects are common to all sclerosants; they tend to be mild, transient, and somewhat expected. Such complications are usually self-limiting, and they can be treated with topical agents.[6] The possible side effects include: (i) injection site reactions (injection pain, minor bruising, urticaria, pruritus, wheals, local swelling, indurations, and erythema) that are self-limited; (ii) skin irritation (itching and an irritant contact dermatitis may follow the use of compression stockings) and excessive xeroderma (dry skin) that can be prevented and/or treated with emollient creams or oils; (iii) tape compression blisters, commonly seen behind the knees, can be prevented by using a tubular support bandage to hold the compression pads instead of tape *(Figure 15)*; (iv) tape compression

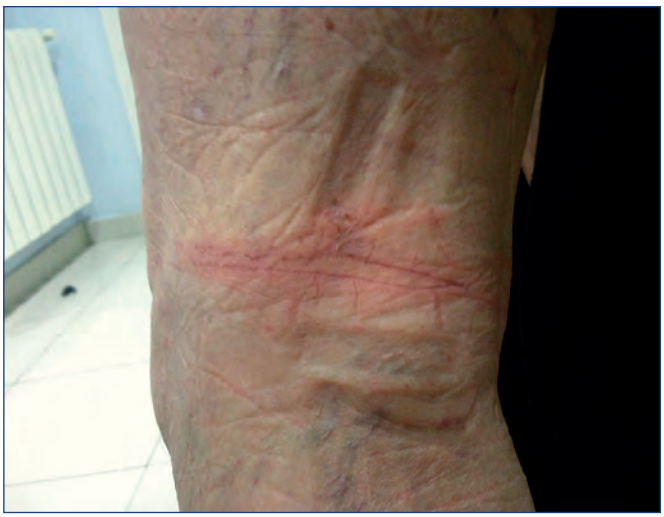

Figure 15. Skin irritation secondary to tape application behind the knees.

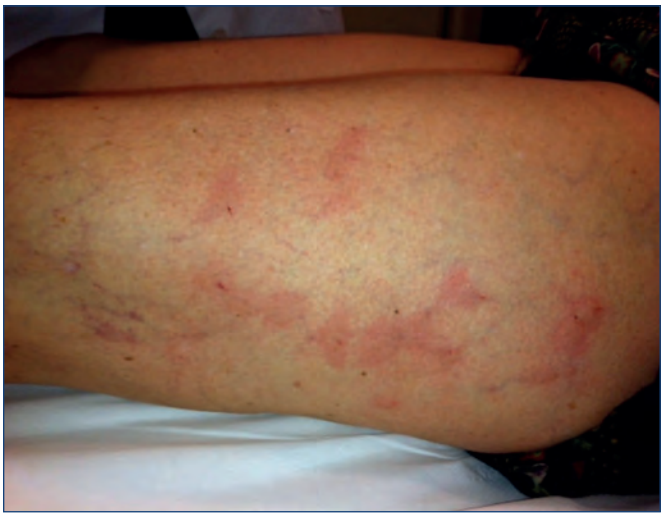

Figure 16. Transitory localized urticaria after injection.

folliculitis secondary to the occlusion of any hairy area can be prevented by not using tape in hairy areas for a long time; (iv) localized urticarial, often in the form of a wheal associated with itching, is usually relieved within 30 minutes *(Figure 16)*; it can be prevented by applying topical steroids and by limiting the injection quantity per injection site.[9]

Conclusion

Sclerotherapy is an effective and safe treatment when used by trained and careful hands. Bad results are usually the consequence of an inappropriate use or indication. The best treatment is prevention. Good technique, satisfactory imaging, general precautions, and compliance with posttreatment instructions may help avoid some of the adverse events. Sclerotherapy must be practiced according to the rules of good practice, governed by the respect of the guidelines and international recommendations.

Foam sclerotherapy is a versatile, effective, and generally safe technique used to obliterate incompetent veins. As with every medical treatment, side effects and complications may occur. Fortunately, most of them are benign, but physicians must be aware of the potential serious events and they should be trained to prevent these events. As with general sclerotherapy, bad results from foam sclerotherapy are usually the consequence of an inadequate use or indication. Complications can happen even to the most experienced practitioner. Adequate knowledge of venous anatomy, ultrasonography, and venous hemodynamics and skills with sclerotherapy techniques are paramount. Furthermore, accurate diagnosis, mapping of the reflux pathway, a detailed management strategy that includes an appropriate follow-up; postsclerotherapy treatment should be used to minimize possible complications. Our improved knowledge of complications allows us to implement a careful approach for decreasing their incidence. Treatment techniques should be optimized to reduce the total volume of the sclerosant foam used in each individual treatment session.

According to Hamel-Desnos' presentation at the 2016 Controversies & Updates In Vascular Surgery meeting, 10 rules must be followed to avoid complications after sclerotherapy:

1. The operator needs to have a good training that is specific to the practice of visual and ultrasound-guided sclerotherapy, a good knowledge of venous disease, and a good practice with venous ultrasound. A regular activity in this practice is paramount.
2. The foam should be made by mixing 1 volume of sclerosing agent with 4 or 5 volumes of gas, with the help of a two-way connector (or a three-way stopcock), it must be of good quality, with no visible bubbles, it must be injected quickly after its preparation to avoid injecting a degraded form, ie, within the shortest possible time between its preparation and its use (<90 seconds).
3. The initial assessment of the pathology must be established in a precise manner to select the best possible tactic, which is adapted to each clinical case. If the incorrect tactic is chosen, then good dexterity is not sufficient. Thus, the choice of the first injection site is decisive, established after a thorough clinical analysis and an ultrasound assessment, and respects the safety of the chosen site.
4. The injections should be administered from the zones of reflux, which are the highest up, toward the distally located veins, and from the largest to the smallest varicose veins. Staged injections allow for the action of the foam, given that the sclerosants is extremely vulnerable once in contact with blood.
5. The choice of the concentration of the sclerosing product is determined according to the diameter of the venous segment to be treated, which is measured while the patient is standing up.
6. The volume injected is determined by the occurrence of a spasm in the target vein and by the homogeneous and compact filling of this vein by the sclerosing foam. The volumes injected are dosed and graduated to avoid overdosing, as opposed to administering a bolus

dose at a single point of injection. Treatment techniques should be optimized to reduce the total volume of sclerosant foam used in each individual treatment session.

7. For optimal precision, use a direct needle puncture.

8. Ultrasound guidance should always be used when it is technically possible. It not only provides permanent ultrasound monitoring throughout the procedure, but it is also useful pretreatment (during the assessment and location phases to determine the safety and pertinence of puncture sites) and posttreatment (monitoring of the foam distribution and the occurrence of a spasm in the treated vein).

9. Indications must be correctly targeted, large saphenous veins (>6 mm) can be treated, but this may lead to more recanalizations.

10. The follow-up assessment on the efficiency after foam sclerotherapy should be performed at least 6 weeks after the injection.

Corresponding author
Lourdes REINA GUTIÉRREZ, MD, Specialist in Angiology and Vascular Surgery, Head of Department of Vascular Surgery, Hospital Central de la Cruz Roja, Madrid, Spain

Email: reina.lourdes@gmail.com

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Transcutaneous ultrasound investigation in chronic deep venous disease: venous obstruction - semantics and ultrasound analysis

Philippe LEMASLE

15 rue Pottier
78150 Le Chesnay

Keywords:

collateral pathway; nutcracker syndrome; ultrasound algorithm; ultrasound criteria; venous obliteration; venous obstruction

Abstract

Venous obliteration is an anatomical definition that corresponds to a reduction in the circulating channel of a vein, regardless of the cause. Complete obliteration is known as occlusion. Venous obliteration is characterized by direct ultrasound criteria at the stenotic site, and it involves obtaining the ratio of the prestenotic to the stenotic diameter as well as the ratio of the prestenotic to the stenotic velocity. Venous obstruction is a hemodynamic notion that corresponds to a reduction in the venous flow, which results in a lack of drainage of the obliterated vein's territory and venous hyperpressure in the distal afferences. The obstruction may have a functional or an anatomical origin, secondary in the latter case to the obliteration. It is characterized by indirect ultrasound criteria in the distal veins. The three main criteria, which are recorded in the common femoral vein ipsilateral to the proximal stenosis, are the single-phase flow profile, velocity, and flow indices. Substitution is also a hemodynamic notion, inseparable from that of obstruction. It imposes hemodynamic changes to a preexisting venous network, characterized essentially by an increase in venous diameter and circulatory velocities. These terms, defined based on venous insufficiency of the lower limbs, remain relevant in the other territories. In particular, they enable a consistent approach to the management of the nutcracker syndrome in the context of pelvic varicosities.

Introduction

How useful can words be if we don't use them accurately?
Natasha Illumin Berg

Chronic venous insufficiency results from two pathological mechanisms: reflux and venous obstruction. Venous reflux is well defined, whereas venous obstruction is not so well defined, and this semantic imprecision could generate inaccuracies in the interpretation of study results and ultimately in the therapeutic management.

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Venous obliteration and obstruction - semantics

In work that proposes ultrasound criteria to characterize venous obstruction, obstruction or obliteration or other is often used to define a reduction in vein diameter. However, we believe that venous obliteration and venous obstruction are not synonymous; however, venous obliteration and venous stenosis are synonymous. This distinction is not new and François Becker had already defined it in 2008.[1]

Venous obliteration is an anatomical definition that corresponds to a reduction in the circulating channel of a vein, regardless of the cause. Complete venous obliteration (absence of a circulating channel) is known as venous occlusion. Venous obliteration can have several origins: (i) thrombotic, ie, acute venous thrombosis or postthrombotic anatomical sequelae; (ii) extrinsic compression, ie, May-Thurner syndrome, nutcracker syndrome, and tumor compression *(Figure 1)*; (iii) tumor invasion; and (iv) congenital, ie, hypoplasia or venous agenesis.

With these definitions, which are also relevant for the arterial sector, it should be noted that: (i) direct ultrasound criteria, which is measured at the site of stenosis, only measures the degree of venous obliteration; (ii) only indirect ultrasound criteria, measured at distal veins, afferences of the obliterated proximal vein, reflect the degree of obstruction. Considering this information, it means that intravascular ultrasound, which is used to quantify the reduction in the diameter of the proximal venous axis and evaluate the feasibility of a recanalization procedure, does not allow for the evaluation of venous obstruction.

It is evident that there is a relationship between the degree of obliteration of the proximal vein and the obstruction recorded in the distal veins. The difference between an obliteration that will be obstructive and one that will not is the development of an effective collateral pathway *(Figure 2)*. This point was illustrated in the study by Kurstjen et al.[2] The author hypothesized that postthrombotic syndrome complaints do not always reflect the severity of postthrombotic lesions during an imaging examination and that this discrepancy could be explained by the development

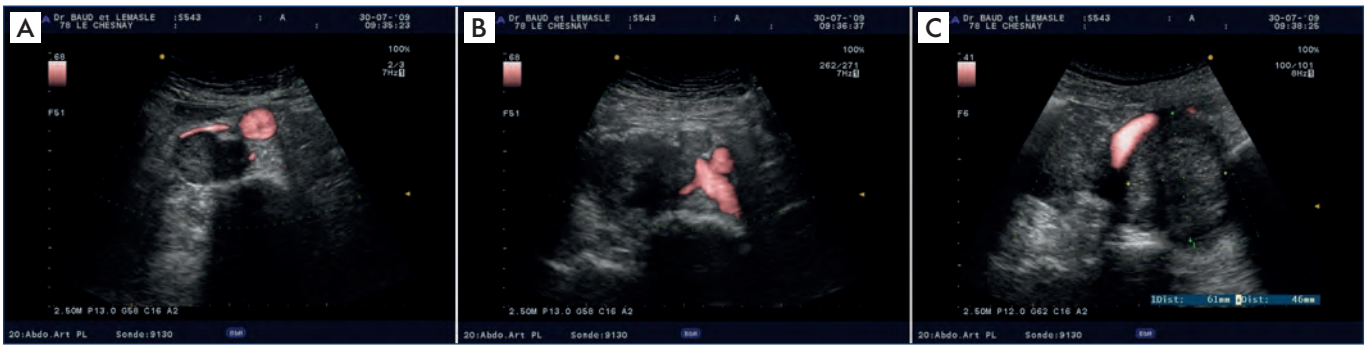

Figure 1. Iliocaval obliteration by extrinsic compression due to voluminous adenopathies.

Known adenocarcinoma of the prostate gland in a 68-year-old male. For several weeks, he has had an intermittent, painless edema in the right lower limb. Panel A. Compression of the inferior vena cava. Panel B. Compression of the right common iliac vein ending, but no compression of the left common iliac vein. Panel C. Compression of the right external iliac vein, laminated by two adenopathies.

Venous obstruction is a hemodynamic notion that corresponds to a reduction and impairment of venous blood flow that can be either anatomical (eg, secondary to an obliteration, regardless of the cause) or functional (eg, secondary to right-sided heart failure or congestive heart failure), the latter meaning venous obstruction without obliteration, so the two terms cannot be superimposed. Due to the reduced blood flow, venous obstruction is characterized by a lack of drainage of the obliterated vein's territory and venous hyperpressure in the distal afferences.

of collateral circulation. To test this hypothesis, he measured intravenous pressure at rest in the decubitus position in 14 patients with unilateral iliofemoral postthrombotic venous obliteration in the two common femoral veins. Secondarily, he measured the pressure of the common femoral vein of the healthy limb after abrupt occlusion of the external iliac vein with a balloon. As expected, the results *(Table I)* show that the common femoral venous pressure is increased in postthrombotic ipsilateral proximal vein obliteration, but not as much as after an abrupt balloon occlusion. This

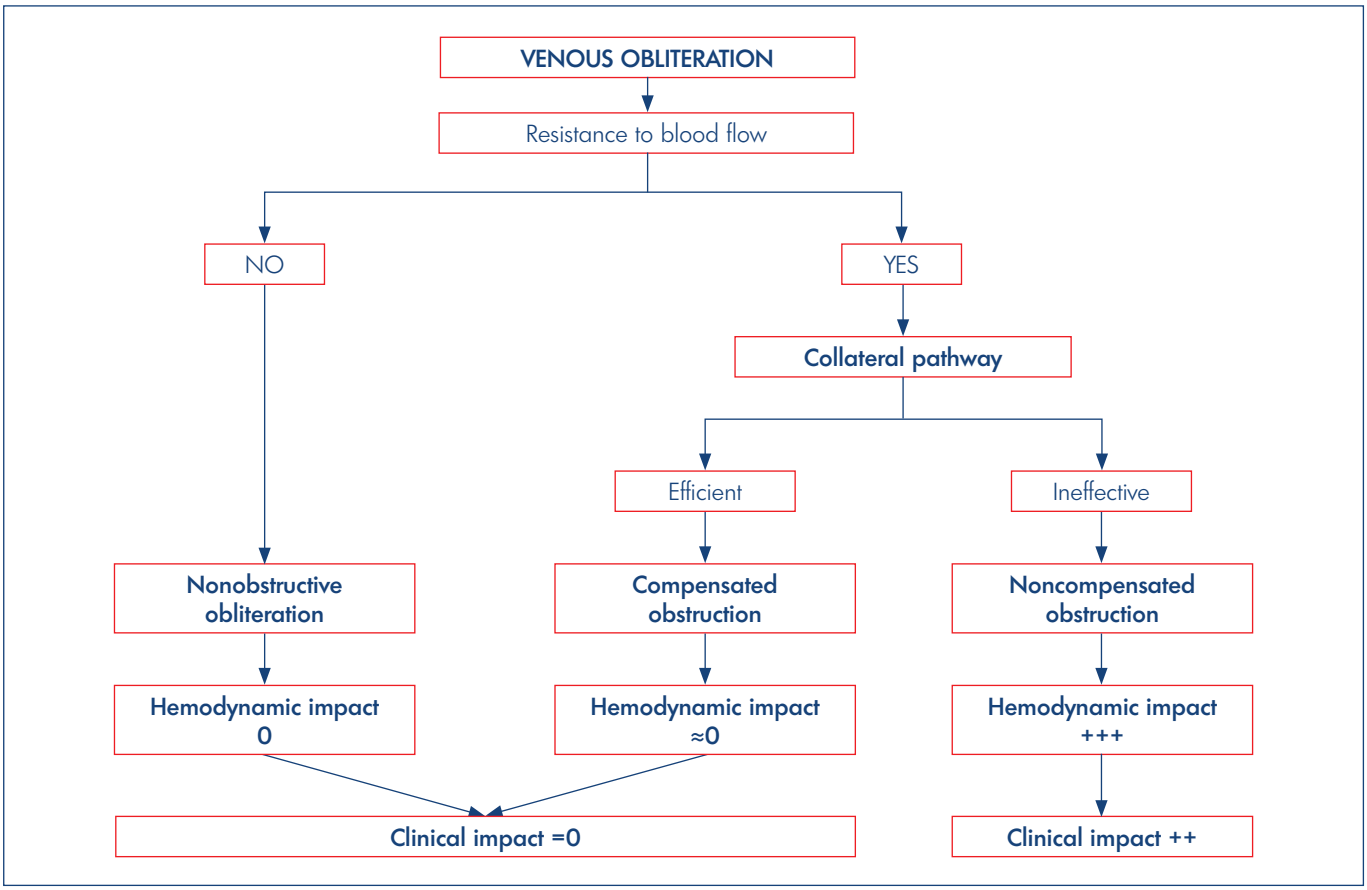

Figure 2. Pathophysiology of venous obstruction.

	Mean venous pressure in the common femoral vein (mm Hg)	*P*
Affected lower limb	17.0	
Healthy lower limb	12.8	0.001
Healthy lower limb after balloon occlusion	23.5	0.009

Table I. Results of Kurstjens' study.

Based on data from reference 2: Kurstjens RL et al. Phlebology. *2015;30(suppl 1):27-34.*

difference can only be explained by the development of collateral circulation, which is more or less effective, but present during a chronic occlusion and absent in the case of a brutal occlusion.

Venous obliteration and obstruction: ultrasound criteria

It is interesting to review the ultrasound criteria proposed for the diagnosis of proximal venous obstructions against these two definitions. In 2016, Metzger et al[3] proposed an ultrasound algorithm for, according to his terms, the detection of iliac venous obstructions. In this prospective study, 51 patients with iliac venous obliteration with chronic venous insufficiency (clinical, etiological, anatomical, physiological [CEAP] class 3 to 6) received a duplex computed tomography scan, intravascular ultrasound, and a phlebography. Five ultrasound parameters were collected: (i) the monophasic profile of venous flow in the femoral vein of the affected limb; (ii) a femoral venous flow rate index (ie, ratio of venous flow rates at the common femoral veins and the ipsilateral control; (iii) femoral venous velocity index (ie, ratio of venous velocity peaks in common femoral veins and the ipsilateral control); (iv) a ratio of the velocities at and just before the iliac venous stenosis; and (v) a ratio of the diameters at and just before the iliac venous stenosis.

In this article, the term "obstruction" is used interchangeably to refer to the reduction in the diameter of the iliac vein (the diameter ratio is referred to as the obstruction ratio) and hemodynamic consequences in the distal veins. However, only the velocity index, the flow-rate index, and the monophasic-flow profile of the common femoral vein reflect the hemodynamic impact on the distal veins and thus

the venous obstruction. Velocity and diameter ratios only measure the reduction in venous diameter (or obliteration), which is in agreement with Labropoulos et al,[4] who, in 2007, proposed that a ratio of stenotic to prestenotic velocity >2.5 was the best ultrasound criteria for detecting venous stenosis >50% (evaluated by a pressure gradient >3 mm Hg). These remarks do not call into question the relevance of the ultrasound algorithm proposed by Metzger et al[3] for the detection of proximal venous lesions.

In this proximal venous obliteration context, the indirect ultrasound criteria, considered the most relevant, are always recorded at the common femoral vein. The indirect criteria include breathing demodulation, a decrease in the response to the Valsalva maneuver, a decrease in circulatory speeds, and a decrease in flow rates.

In 2007, Lin et al,[5] in a retrospective study, analyzed 2936 ultrasound examinations. He identified 124 single-phase fluxes in the femoral vein, 64% of which corresponded to an iliac venous obliteration diagnosed by angioCT. No cause was determined for 45 monophasic fluxes, and the causes of iliac obliteration were postthrombotic syndrome (47/79), extrinsic compression (26/79), or hypoplasia of the common iliac veins (6/79). The authors found that this flow pattern was systematically investigated at the external iliac vein and common femoral veins and, in the case of a positive result, another imaging examination was done to determine the cause.

In 2016, Kayılıoğlu et al[6] specified the analysis of femoral venous flux profile in a retrospective study that included 86 patients. All patients had iliocaval obliteration, which was confirmed by intravascular ultrasound or angioCT. Three flux profiles in the femoral vein were described: (i) normal breathing modulation, with respiratory arrest *(Figure 3A)*; (ii) decreased breathing modulation, without respiratory arrest; and (iii) monophasic, permanent, single-phase flux that is not modulated by breathing *(Figure 2B)*. In addition, three types of responses to the Valsalva maneuver were identified: (i) complete stop in the flow; (ii) flow reversal; and (iii) flow that is not stopped.

In the statistical analysis, the last two profiles were combined and named continuous flows. Monophasic and continuous fluxes were associated in 38% of cases. In this study, two criteria appear to be particularly relevant: the single-phase femoral venous flow and the combination of single-phase spontaneous flow and continuous flow (as defined above) during the Valsalva maneuver *(Table II)*. An analysis of the results showed that the sensitivity of the mentioned ultrasound criteria to detect proximal venous obliteration increases with the degree of venous stenosis. Sensitivity is always inferior to specificity, which reflects the fact that venous obliteration may not be obstructive in the case of an active and sufficient substitution. The simple reduction in respiratory modulation of venous flow has a very low diagnostic value.

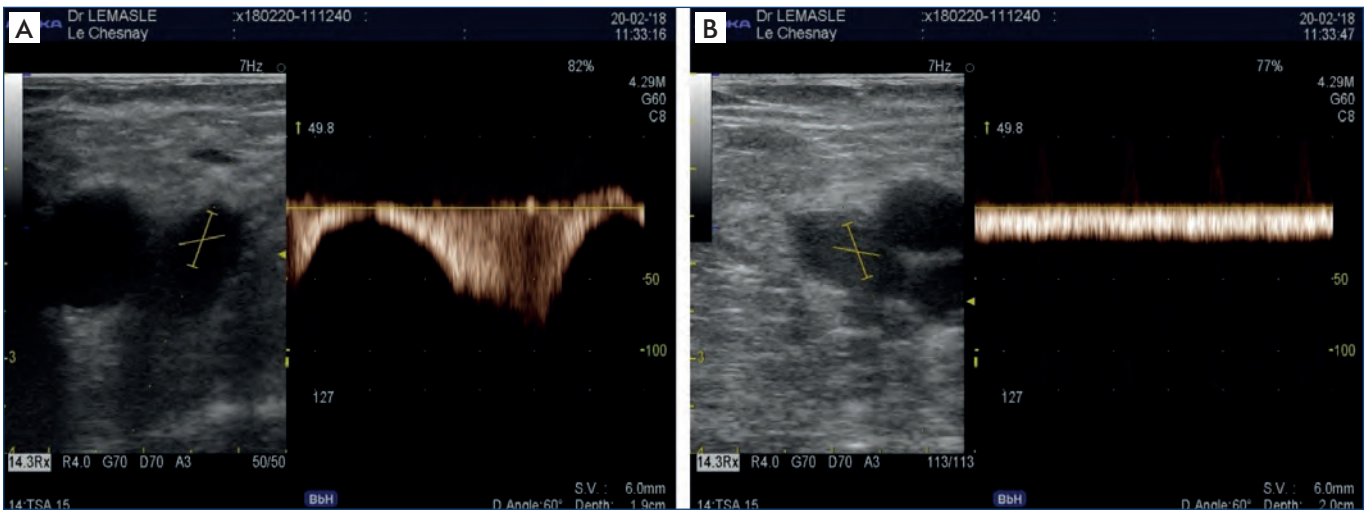

Figure 3. Profile of venous flow in the common femoral vein.

Panel A. Healthy control limb, normal profile with a strong respiratory modulation and circulatory arrest upon inspiration. Panel B. Affected limb with proximal venous obliteration, permanent flow that is not modulated by breathing, and reduced circulatory velocities.

	Sensibility (%)			Specificity (%)			Positive predictive value (%)			Negative predictive value (%)		
Degree of stenosis	Any	>50	100	Any	>50	100	Any	>50	100	Any	>50	100
Monophasic flow	54	65.7	90.1	94.7	92.7	80	93.0	87.7	50.8	58.1	77.3	97.3
Combination of a monophasic and continuous-flow at Valsalva maneuver	38.1	44.4	64.0	100	98.1	93.1	100	95.8	76.1	55.8	67.5	88.3

Table II. The sensitivity, specificity, positive predictive value, and negative predictive value of common femoral vein flow and response to the Valsalva maneuver for the diagnosis of obstruction.

Based on data from reference 6: Kayıloğlu et al. J Vasc Surg Venous Lymphat Disord. *2016;4(1):2-8.*

In these two previous studies, the analysis of femoral venous fluxes is qualitative. Metzge et al[3] proposed a quantitative approach. In his study, the best threshold values to detect proximal venous stenosis greater than 50% were 0.9 for the velocity index and 0.7 for the flow index; however, the real issue may be occurring somewhere else. By using indirect hemodynamic criteria, it should be possible to provide a better definition of the group of patients who are at risk of developing severe chronic venous insufficiency and not only to predict the degree of proximal venous stenosis.

Venous obstruction and substitution

The risk of venous obstruction is directly related to the degree of venous stenosis, but with an equal reduction in diameter, the hemodynamic consequences will vary according to the quality and efficiency of the collateral pathway. First, the quality of substitution depends on local anatomical networks. At best, the territory is drained by several venous axes and the obliteration of one axis will be compensated naturally and efficiently by the other drainage axes. At worst, the obliteration concerns a single, poorly connected collector axis or a venous junction, particularly a femoral junction, and compensation will always be insufficient. In addition, this preexisting collateral network will have to adapt to the new hemodynamic constraints.

The modification of venous pressure gradients is always accompanied by an inversion of the flow in the surrogate vein. This inversion can be very segmental; for example, the great saphenous vein, supplying a femoral obliteration, circulates physiologically, but the passage of the deep venous flow toward the superficial pathway imposes an inverted flow in a connection between the two networks. It can be extended; for example, inversion of the flow of the internal iliac vein causing a secondary obliteration of the common ipsilateral iliac vein *(Figure 4)*. The hyperflow in the replacement network will result in an increase in venous

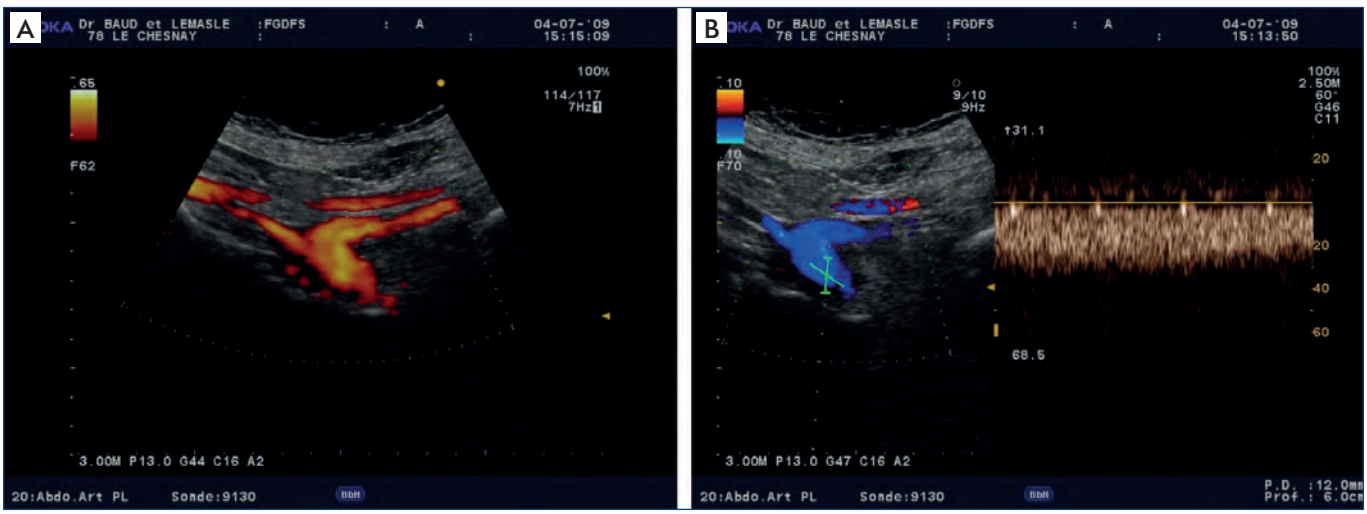

Figure 4. Chronic postthrombotic obliteration of the left common iliac vein.

Panel A. Drainage of the external iliac vein by the enlarged internal iliac vein – distal common iliac vein with decreased caliber. Panel B. Permanent, demodulated, inverted flow in the substitute internal iliac vein.

diameter and circulatory velocities, with a permanent flow, and little or no modulation by breathing *(Figures 5 and 7A)*.

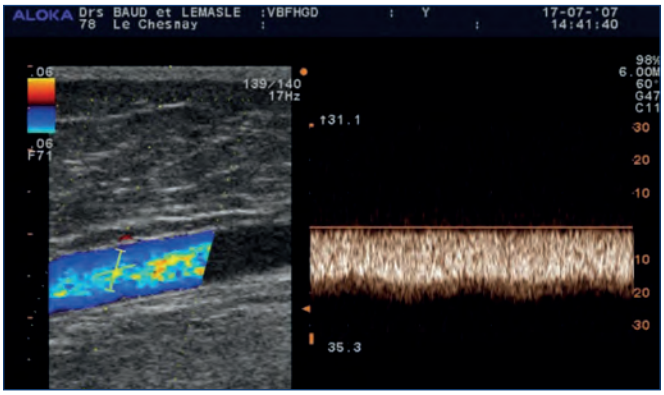

Figure 5. Replacement flux in the greater thigh saphenous vein after obliteration of the femoral vein.

The reflux is a spontaneous, permanent flux of 20 cm/second that is not modulated by breathing.

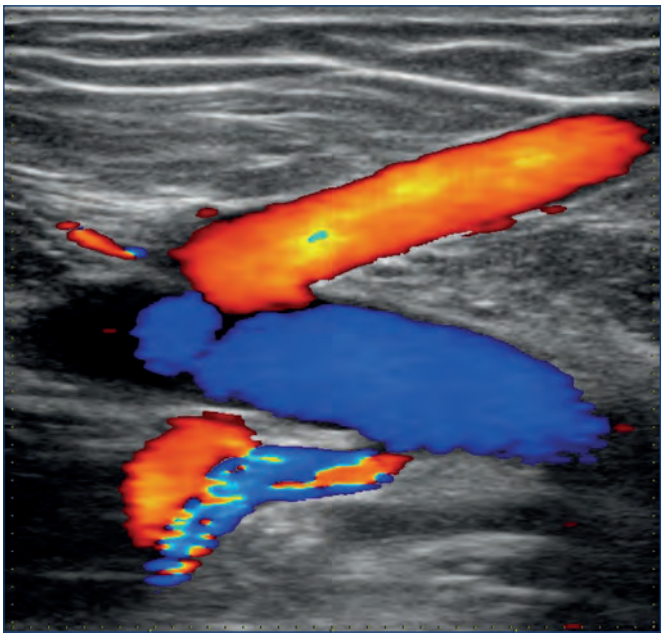

Figure 6. Replacement of an iliac venous obliteration by the saphenofemoral junction and a circumflex vein, afference of the common femoral vein, ie, inverted fluxes.

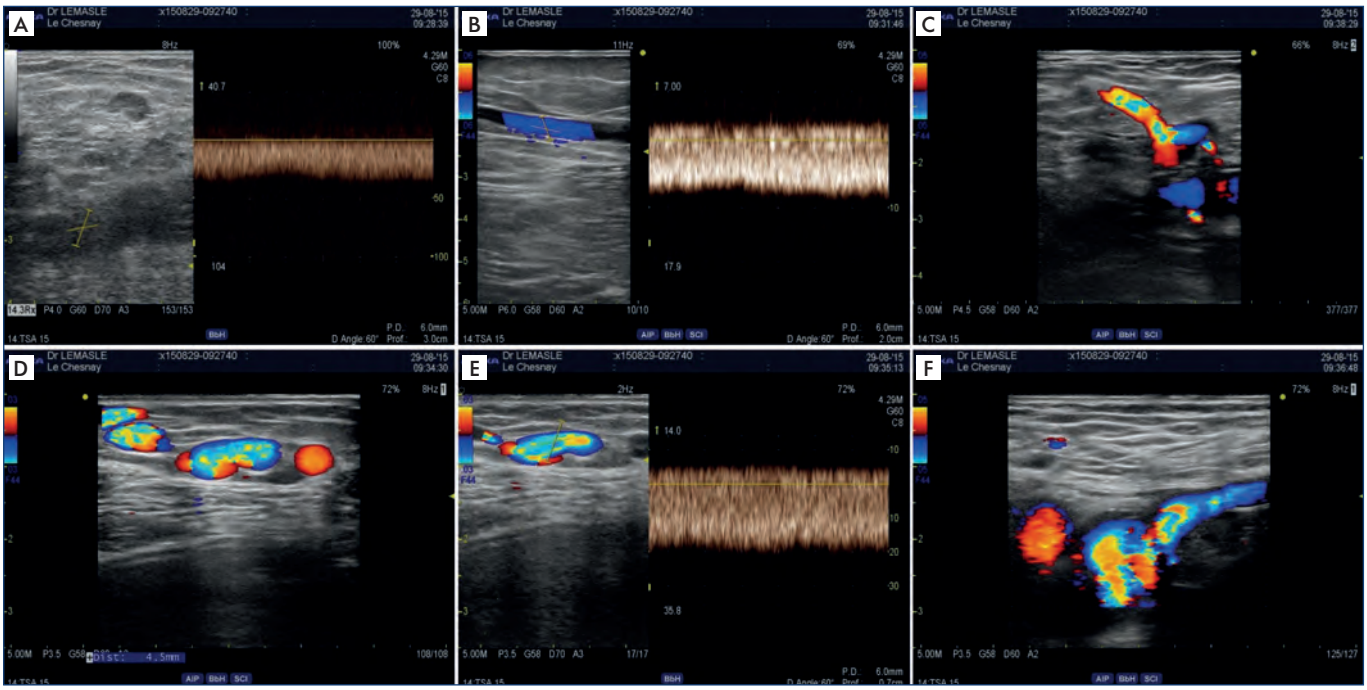

Figure 7. Postthrombotic left iliac venous obstruction and substitution syndrome.

Left popliteal-femoral-iliac thrombosis in a 22-year-old girl, on oral contraception, after a 14-hour flight. An assessment performed 3 years later showed persistence of a left iliac venous obstruction (Panel A) and persistence of significant substitution (Panels B–F). Panel A. At the ipsilateral femoral vein, there is a permanent, demodulated flow, with slow velocities. Panel B. Alternative flux at the left greater thigh saphenous vein with a permanent and demodulated flux. Panel C. Flow reversal in the left superficial epigastric vein. Panel D. Dilated suprapubic network, with spontaneous left to right flux. Panel E. Spontaneous, permanent, demodulated, fast-speed alternative flux in the suprapubic network. Panel E. Drainage of the suprapubic network in the contralateral saphenofemoral junction via the superficial epigastric vein.

Therefore, substitution, like obstruction, is a hemodynamic notion. Substitution and obstruction are linked, as a chronic venous obstruction is always accompanied by the introduction of a more or less effective substitute circulation, and, conversely, the persistence of substitute circulation attests to a residual obstruction. This idea is illustrated in a recent study by Kolluri et al,[7] where, in a small population of 15 patients, inversion of the superficial epigastric vein flow was always correlated with iliocaval occlusion. Of these 15 patients, 5 benefited from a recanalization procedure, 2 were lost to follow-up, and, in 3, the flux at the superficial epigastric vein was normalized 4 to 5 weeks after the procedure.

In our practice, the afferents of the saphenofemoral junction (superficial epigastric vein, iliac circumflex vein, and lateral pudendal vein) are also substitutes when obliteration affects the femoral and common femoral veins. Therefore, the extension of a thrombosis to the saphenofemoral junction is a pejorative criterion *(Figures 6 and 7)*.

Venous obstruction and dynamic examination

The main limitation of a duplex scan in evaluating proximal venous obstruction is the impossibility to obtain a dynamic examination, which requires further investigation, such as plethysmography and/or invasive measurements of venous pressure. In 2016, Kurstjens et al[8] studied a population of 22 patients with unilateral femoro-iliac postthrombotic obliteration. Bilateral, invasive, and simultaneous pressure measurements in the femoral vein and dorsal vein of the foot were performed during a standardized treadmill test. The increase in venous pressure in the femoral vein after walking is significant on the affected side: 28 mm Hg compared with 2.1 mm Hg in the healthy control limb. However, the most discriminating factor between affected and unaffected limbs was the evolution of the pressure curve during recovery. These variations in pressure may explain venous claudication, but these measurements are not obtained with a duplex scan.

In addition, a duplex scan cannot detect lesions that do not reduce the circulating channel very much, such as parietal synechia or an intimal flap, but which can transform a laminar flow into a turbulent flow, thus generating an obstructive flow disturbance. Only dynamic examinations can reveal these lesions.

Ultrasound algorithm for the diagnosis of the nutcracker syndrome

These terms, defined based on venous insufficiency of the lower limbs, remain relevant in the other territories. In 2005, Milka Greiner proposed a classification of pelvic varicose vein disease based on pathophysiological criteria.[9-11] She defined three types (I–III) that require specific therapeutic management. Type I is secondary to parietal or valve abnormalities and is a reflux pathology; treatment is based on endovenous procedures and embolization. Type II is secondary to compression of the drainage vein and the pathology is linked to the development of drainage pathways. In this case, the isolated treatment of the refluxing vein, without lifting the compression, is potentially deleterious and can aggravate distal venous hyperpressure. Type III has a local extrinsic cause that is responsible for pelvic venous anomalies.

For the type II class, the most common case is the nutcracker syndrome. In this case, a pelvic varicose vein is fed by the reflux of the left ovarian vein, which has become the replacement pathway for the left renal vein, which is compressed at the aortomesenteric entrapment, in its anterior form (the most frequent). However, anatomical compression of the left renal vein at this clamp is very common. Therefore, the whole problem is to evaluate the hemodynamic impact in the distal veins of this anatomical compression, in other words, whether this obliteration is obstructive or not.

In our practice, we use the algorithm illustrated in *Figure 8*, where each positive step imposes the next step. The first step is to look for an extrinsic anatomical compression of the left terminal renal vein *(Figure 9)*. It is based on the measurement of the angle and distance of the aortomesenteric entrapment. According to Arima et al,[12] an aortomesenteric angle <16° and an aortomesenteric distance ≤5 mm favor compression of the left renal vein. Anatomical compression of the left renal vein is frequently found in the decubitus position. Always check that the compression persists in a seated position. If not, this compression is positional and a priori nonpathogenic.

The second step is to look for direct ultrasound criteria for venous obliteration. It combines qualitative ultrasound criteria (ie, aliasing and turbulence in color Doppler) and quantitative criteria (ie, ratio of the anteroposterior diameters and velocity peaks), which are measured at and

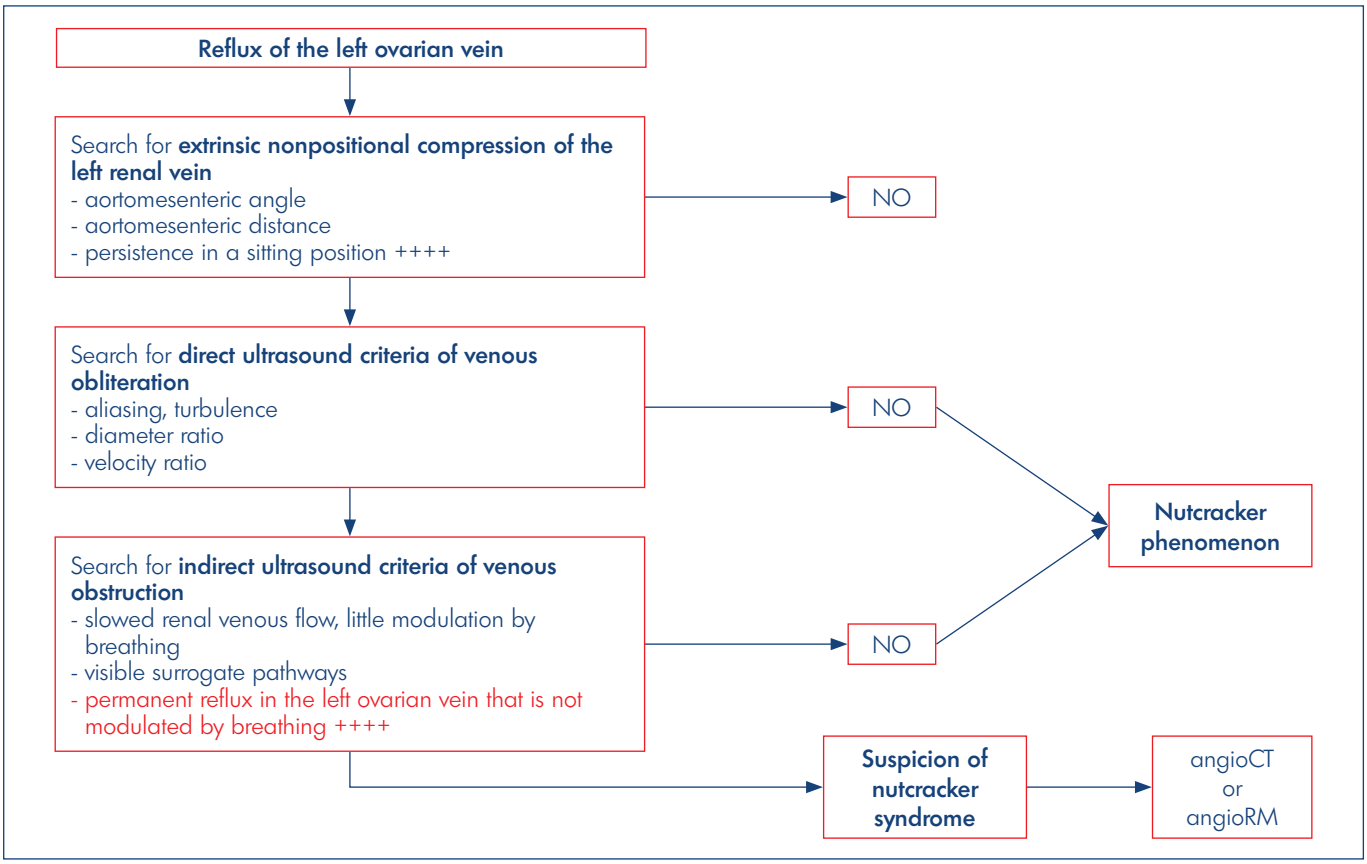

Figure 8. Decisional ultrasound algorithm in the management of nutcracker syndrome, in the context of pelvic varicose veins.

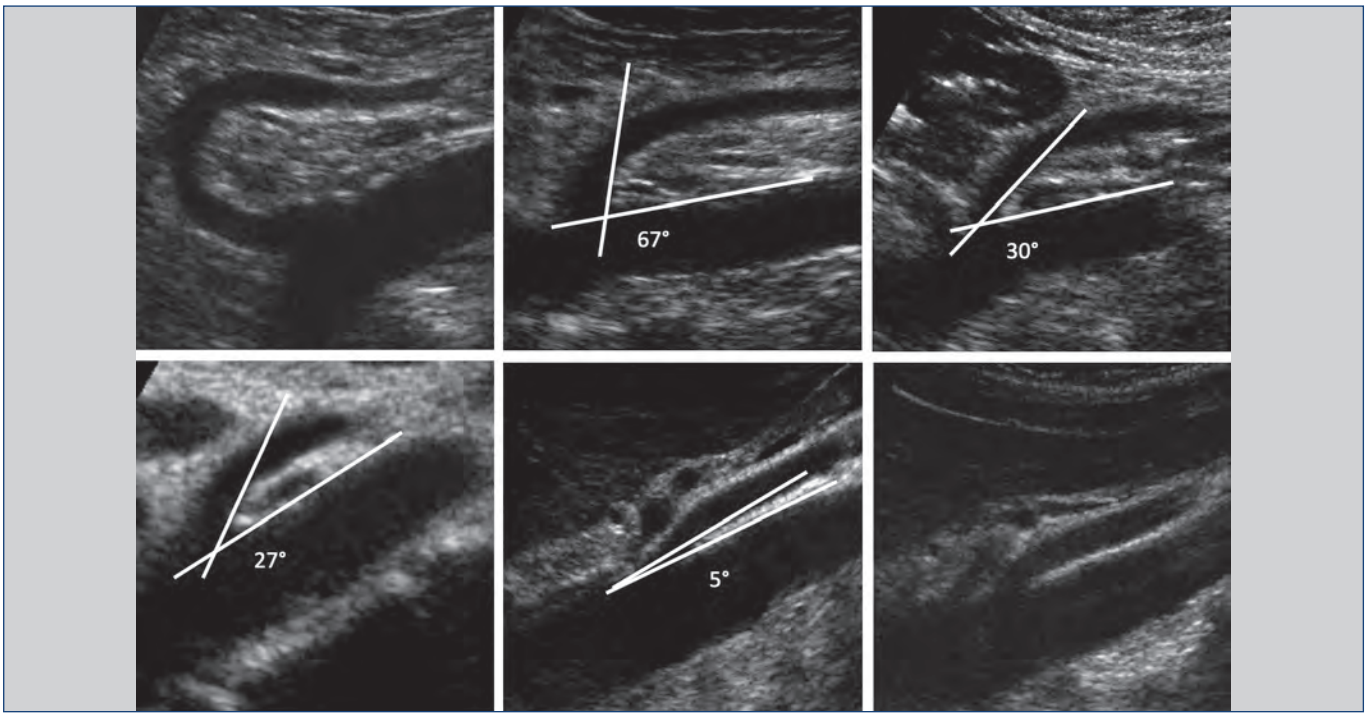

Figure 9. First step of the algorithm to determine whether the venous obliteration is obstructive.

Search for extrinsic nonpositional compression of the left renal vein, determine the aortomesenteric angle and distance, and identify persistence in a sitting position.

just before the left renal vein stenosis *(Figure 10)*. According to Kim et al,[13] the sensitivity and specificity for the diagnosis of the nutcracker syndrome is 69% and 89%, respectively, for anatomical criteria and 90% and 94% for the velocity criteria, when the ratios are greater than 5. When the two ratios are combined, sensitivity and specificity are 90% and 100%. This study was based on a population of 16 patients with nutcracker syndrome who were compared with a control population.

The third step should look for indirect ultrasound criteria of venous obstruction. The venous flow of renal drainage is slowed, with little modulation by breathing. It has a circulatory profile similar to that of the surrogate ovarian vein. There is no obstruction without the introduction of a more or less effective substitute circulation. They become abnormally visible because they are dilated, with rapid circulatory velocities. In our practice and in the context of pelvic varicose vein disease, the most relevant indirect ultrasound criterion of obstruction is qualitative and corresponds to a reflux of the left ovarian vein, which is permanent and not modulated by breathing *(Figure 11)*.

The notion of obstruction is essential in the context of pelvic varicose veins. Nonobstructive compression of the left terminal renal vein associated with reflux of the

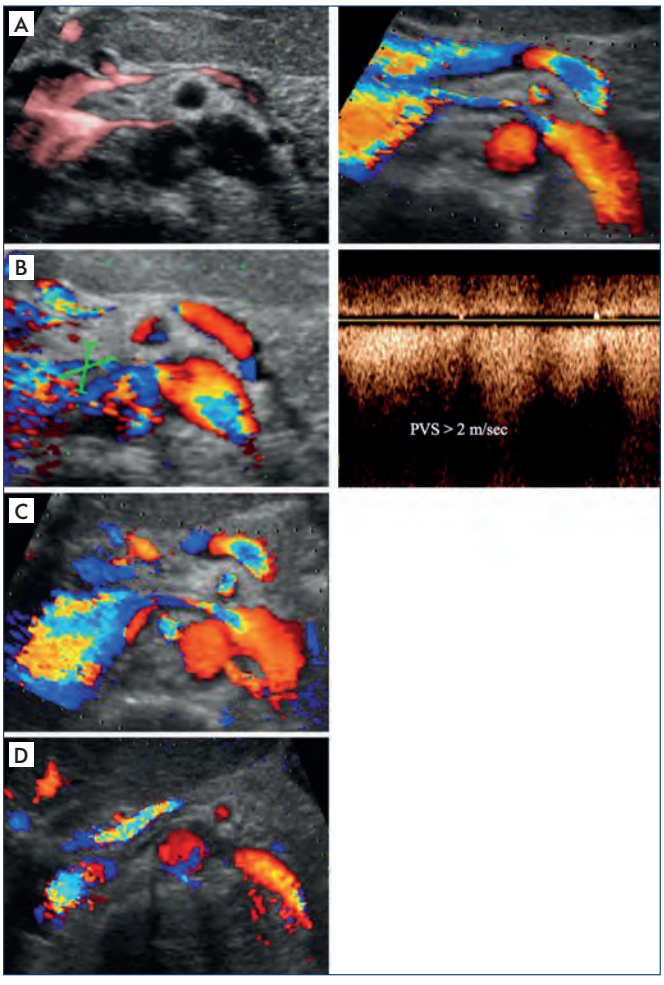

Figure 10. Second step of the algorithm to determine whether the venous obliteration is obstructive.

Search for direct ultrasound criteria of venous obliteration Panel A. Determine the ratio of the diameter of the left renal vein at and just before the aortomesenteric entrapment. Panel B. High velocities just after the left renal vein stenosis. Panel C. Aliasing at the left renal vein stenosis. Panel D. No flux at the left renal stenosis (pulse-repetition frequency and filters).

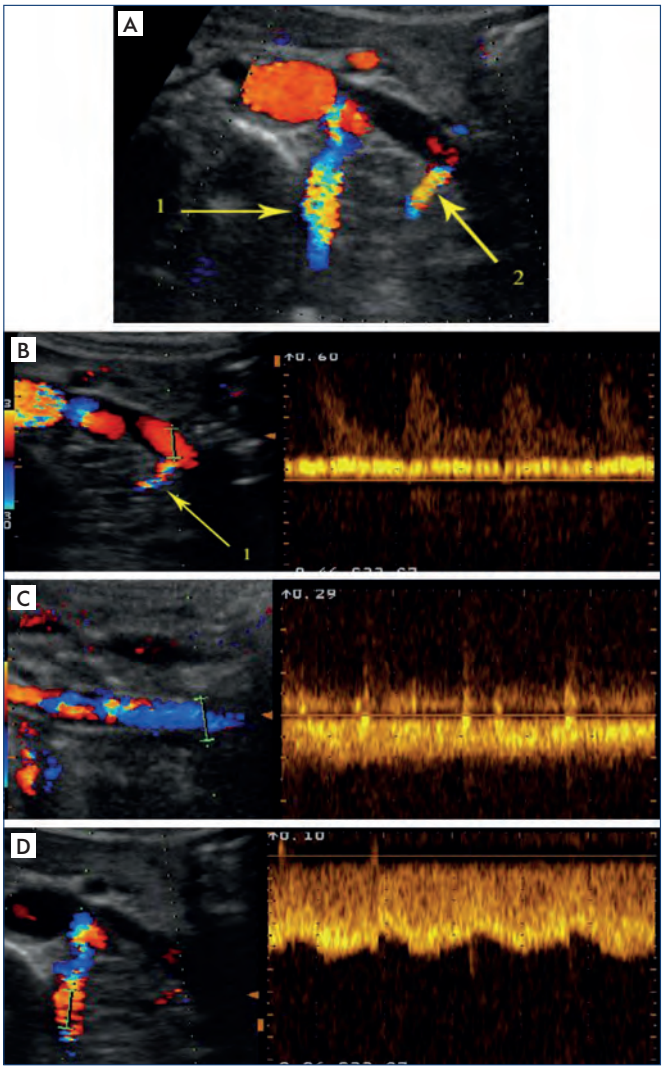

Figure 11. Third step of the algorithm to determine whether the venous obliteration is obstructive.

Search for indirect ultrasound criteria of venous obstruction Panel A. Abnormal visualization of supplying collateral pathways (1=lumbar vein; 2=ending of left ovarian vein) Panels B–D. Ultrasound criteria in favor of an alternative pathway, ie, a spontaneous, permanent, fast-speed flow that is not modulated by breathing. Panel B. Flux in the ending of the left renal vein. Panel C. Reflux in the left ovarian vein at the psoas muscle. Panel D. Flow in lumbar vein at the reno-azygo-lumbar arch.

ipsilateral ovarian vein corresponds to type I of the Greiner classification and treatment is based on embolization. Conversely, if the compression is obstructive, it is a type II class and the risk-benefit ratio of the compression treatment must be evaluated to avoid increasing renal venous pressure by removing an effective surrogate pathway. When the ultrasound examination is in favor of obstructive compression of the terminal renal vein, it is necessary to complete the assessment with an angioCT or a contrast-enhanced MR angiography.

Conclusion

It is legitimate to wonder about the real interest of this apparent semantic complexity; however, this language effort seems useful for at least two reasons. If the term "obstruction" refers at the same time to a proximal lesion (diameter reduction) and its hemodynamic consequences (impaired flow), there is an ambiguity in the language, which may induce a therapeutic ambiguity. However, the only challenge is to combat the hemodynamic impact and clinical complications, not to correct a well-compensated obliteration. Finally, it is important to obtain a definition in a common, consensual, and international language.

"All subversion begins with the vocabulary."
Confucius

Corresponding author
Philippe LEMASLE,
15 rue Pottier, 78150 Le Chesnay,
France

Email: plemasle@free.fr

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State of art in lymphedema management: part 1

Byong-Boong LEE

Professor of Surgery & Director, Center for Lymphedema and Vascular Malformation, George Washington University School of Medicine, USA

Abstract

Chronic lymphedema can be managed effectively using a sequenced and targeted treatment program based on decongestive lymphatic therapy (DLT) with compression therapy and surgery (mostly as an adjunct to DLT). In the maintenance phase, DLT is carried out using the proper combination of compression garments, meticulous personal hygiene and skin care, self-massage based on the principle of manual lymphatic drainage (if applicable), and exercises and activities to promote lymph transport. Pneumatic compression devices/therapy can be applied at home, if desired. When conservative treatment based on DLT fails or delivers suboptimal outcomes, the patient may need additional surgical interventions, either reconstructive or ablative, where applicable. These two surgical therapies are more effective in terms of outcomes when combined postoperatively with manual lymphatic drainage–based DLT. A long-term commitment to postoperative DLT, especially compression therapy, is a critical factor in determining the success of either reconstructive or palliative surgery. Recently, several causal genetic mutations have been identified among primary lymphedema syndromes, which provide possible opportunities for future molecular interventions. This new prospect of gene-oriented management is more promising as a molecular therapy for both primary and acquired lymphedema.

Keywords:

ablative surgery; compliance; compression therapy; decongestive lymphatic therapy; gene-oriented management; lymphatic malformation; primary lymphedema; reconstructive surgery; secondary lymphedema

Introduction

Over the last 20 years, the understanding of lymphatic disorders has substantially improved, providing new insights into the lymphatic system's structure and function for both primary and acquired forms of lymphedema.[1-4] This evolution in the evaluation and management of lymphatic disorders was achieved due to advanced diagnostic imaging technology and the subsequent implication of newly developed approaches regarding physical modalities, surgical interventions, and pharmacology.[5-8]

We can now more clearly understand the differences in etiopathogenesis between primary lymphedema (mostly congenital lymphatic malformations) and secondary lymphedema (acquired conditions).[9,10] This paper will present the best and most commonly used therapies available that have been thoroughly evaluated.[1,2] These therapies can ultimately be recommended as the most

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No.	Guidelines	Grade of recommendation (1, recommended; 2, suggested)	Grade of evidence (A, high quality; B, moderate quality; C, low or very low quality)
6.3.1	To reduce lymphedema, we recommend multimodal complex decongestive therapy that includes manual lymphatic drainage: multilayer short-stretch bandaging; remedial exercise; skin care; and instruction in long-term management	1	B
6.3.3	To reduce lymphedema, we recommend treatment daily, a minimum of 5 days per week, and continue until normal anatomy or a volumetric plateau is established	1	B
6.3.4	To reduce lymphedema, we suggest compression pumps in some patients	2	C
6.3.5	For maintenance of lymphedema, we recommend an appropriately fitting compression garment	1	A
6.3.6	For maintenance of lymphedema in patients with advanced (stages II or III) disease, we recommend using short-stretch bandages during the night. Alternatively, compression devices may substitute for short-stretch bandages	1	B
6.3.7	For remedial exercises, we recommend wearing compression garments or bandages	1	C
6.3.8	For cellulitis or lymphangitis, we recommend antibiotics with superior coverage of Gram-positive cocci, particularly streptococci. Examples include cephalexin, penicillin, clindamycin, and cefadroxil	1	A
6.3.9	For prophylaxis of cellulitis in patients with more than three episodes of infection we recommend antibiotics with superior coverage of Gram-positive cocci, particularly streptococci, at full strength for 1 week per month. Examples include cephalexin, penicillin, clindamycin, and cefadroxil	1	C

Table I. Guidelines 6.3.0 of the American Venous Forum on lymphedema: medical and physical therapy.

From reference 13: Gamble GL, Cheville A, Strick D. Lymphedema: medical and physical therapy. In: Gloviczki P, ed. Handbook of Venous Disorders: Guidelines of the American Venous Forum. 3rd Edition. *London, UK: Hodder Arnold; 2009:655. © 2009, Edward Arnold (Publishers) Ltd.*

updated guidelines for clinicians who are treating patients with this unique condition worldwide. This paper discusses the contemporary concepts regarding the management of chronic lymphedema, which encompass a broad range of currently available treatment options both old and new. However, the majority of the data available for review are classified as grade 2B or 2C when using the system by Guyatt et al and only a small amount of data are classified as grade 1C or 2A at best from observational studies *(Table I)*.[11-13] With consideration of this unique situation, we accept manual lymphatic drainage–based decongestive lymphatic therapy as the main treatment[14-17] and surgical management as an additional option for the management of lymphedema.[18-21]

General considerations

Chronic lymphedema starts as a simple condition of limb swelling following the mechanical failure of the lymphatic system's mechanism for collecting and transporting lymph. However, such early-stage, but "reversible," edema may become a chronic degenerative and inflammatory process. The impact of lymphatic fluid accumulation, which is initially limited to the lymphatic system and the lymph nodes, will spread to the entire surrounding soft tissue and skin, resulting in irreversible damage.[8,22,23] Chronic lymphedema is a "steadily progressive condition that affects the entire surrounding soft tissue" that results in a disabling and distressing condition, where the major risks include bacterial and fungal infections and subsequent sepsis, chronic

inflammation with dermatolipofibrosis, immunodeficiency and wasting phenomenon, and malignancies (eg, Kaposi sarcoma; lymphangiosarcoma) *(Figure 1)*.[2,7,24] Therefore, it is mandatory to treat lymphedema at the earliest detectable point in the evolution of the disease. A precise and timely diagnosis to verify its clinical stage is not only critical for proper treatment, but also for the prospective identification of early-stage disease in defined at-risk populations.[25-27]

Manual lymphatic drainage–based decongestive lymphatic therapy remains a main treatment for the contemporary management of lymphedema.[28-31] Further improvements in function and quality of life can be achieved with lifestyle modifications, including specific exercise regimens.[32] In addition, incorporating intermittent pneumatic compression may significantly reduce edema and symptoms *(Figure 2)*.[33,34] Currently, pharmacological interventions have

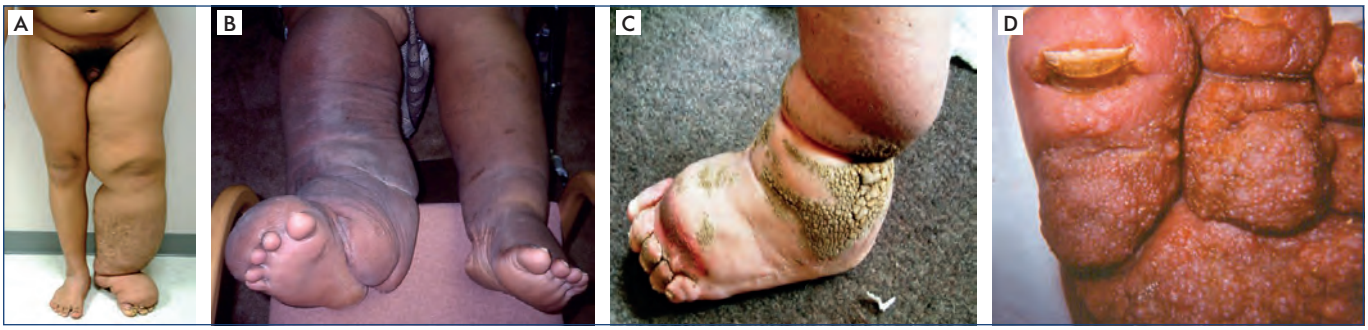

Figure 1. Chronic lymphedema at an advanced stage.

Panels A and B. Advanced condition of chronic lymphedema that cannot be controlled with decongestive lymphatic therapy, and, with recurrent infection/sepsis, the disease is steadily progressing toward a disabling and distressing condition. Panels C and D. Unique condition of dermatolipofibrosis with chronic inflammation, which increases the risk of infection and subsequent sepsis, as well as immunodeficiency and malignancy.

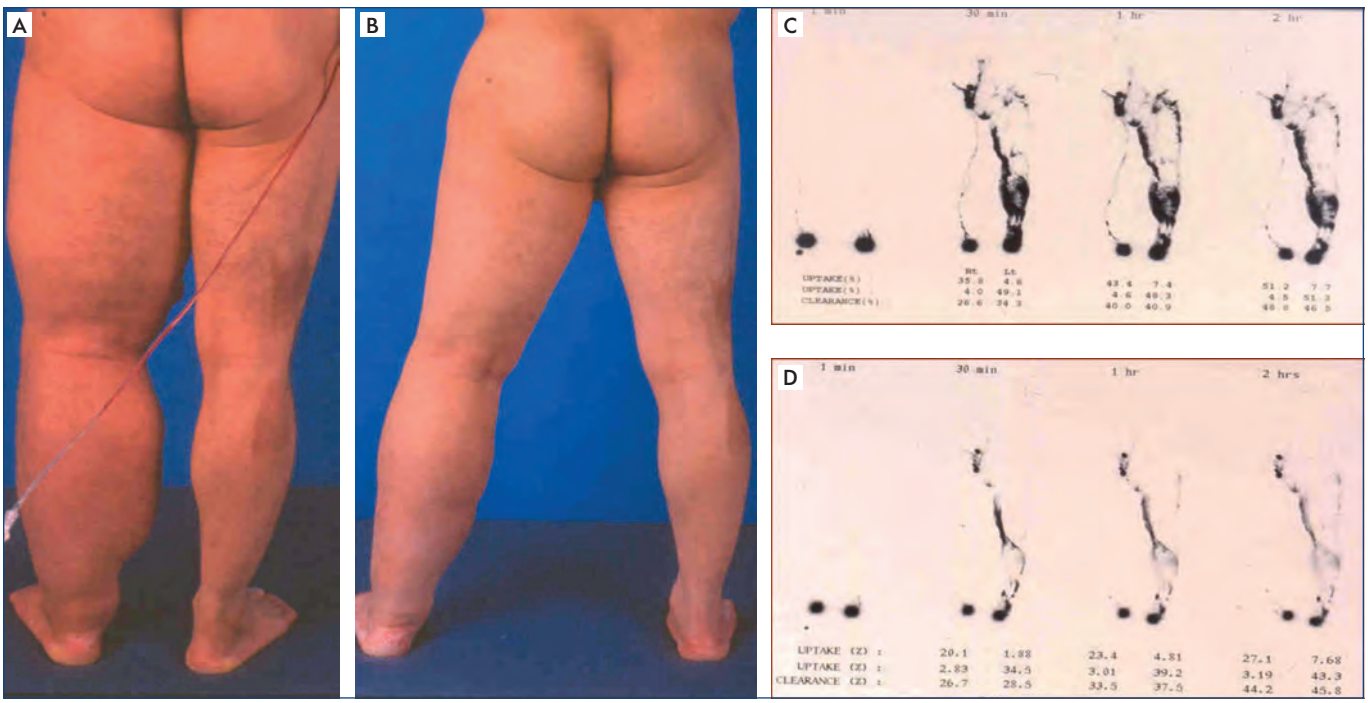

Figure 2. Clinical case of decongestive lymphatic therapy management.

Panel A. Progressive lymphedema condition with recurrent episodes of sepsis before decongestive lymphatic therapy is instituted. Panel B. Excellent clinical improvement/response to decongestive lymphatic therapy with successful disease control with the initial intensive care. Panel C. Lymphoscintigraphic findings of lymphatic dysfunction, including the dermal backflow that shows severe lymphatic obstruction. Panel D. Lymphoscintigraphic findings show an improved lymphedema status following successful decongestive lymphatic therapy with decreased dermal backflow that is compatible with clinical improvement (1-year follow-up assessment).

little applicability in the management of lymphedema[35-37]; however, antibiotic therapy is necessary for the effective control of infections,[38-40] and both growth factor–based and cellular therapies (ie, molecular modifications) continue to show great promise for the future.[41-43] During the last 10 years, the use of surgery for lymphedema has increased, mostly by using newly developed/incorporated techniques for both reconstructive *(Figure 3)*[44,45] and excisional *(Figure 4)*[46,47] surgery.

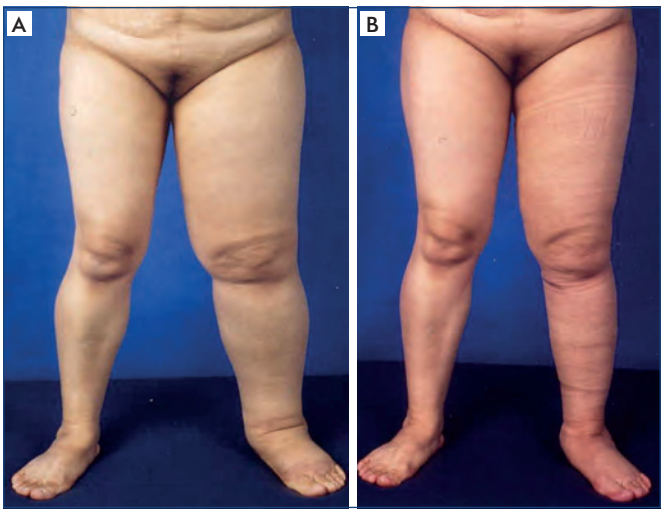

Figure 3. Clinical case of reconstructive surgery.

Panel A. Clinical status of progressive lymphedema despite maximum decongestive lymphatic therapy–based physical therapy for more than 1-year. Panel B. Excellent clinical response to additional care with reconstructive surgery with multiple lymphovenous anastomoses performed at the popliteal level (2 weeks postoperation).

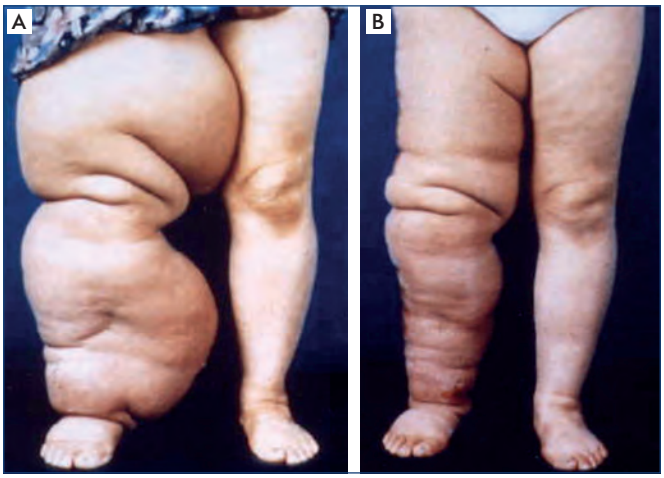

Figure 4. Clinical case of excisional/debulking surgery.

Panel A. Advanced lymphedema that is uncontrollable with conventional care based on decongestive lymphatic therapy, resulting in recurrent sepsis. Panel B. Excellent outcome of debulking surgery to change the local condition, making it amenable to compression therapy, with efficacy throughout the postoperative period.

The main treatment goals are to improve the physical condition of the affected limb or area and the patient's quality of life,[48,49] which, despite a psychologically unacceptable physical deformity, will ultimately improve the patient's social life, functional and psychological state, and the ability to perform normal physical activities, so they can return to a normal or near-normal life.

Clinical implication of genetic mutations

Primary lymphedema occurs due to abnormal development of the lymphatic system, which frequently has a specific genetic origin that is inherited. Primary lymphedema is only a major clinical sign when patients have either Fms-like tyrosine kinase 4 (FLT4)–related lymphedema (ie, Nonne-Milroy-Meige syndrome [Milroy disease]) or forkhead box protein C2 (FOXC2)–related lymphedema (ie, lymphedema-distichiasis syndrome).[51-54] In the majority of complex syndromes, lymphedema is a minor clinical manifestation, while other abnormalities dominate.[55-57]

Not all gene mutations will result in a phenotype that has a major impact on lymphatic function.[58] Some individuals of the same family do not develop the disease due to incomplete penetrance, but they remain (healthy) carriers of the genetic mutation. When the mutation results in defective development (to varying degrees), the individual is no longer a healthy carrier, particularly from the management point of view, as (unknown) modifier genes that act according to a model of genetic susceptibility are closely associated with the activity.[53] Indeed, healthy looking limbs, although infrequent, have various locoregional lymph transport abnormalities suggesting a defective development even in the absence of edema. Such a subclinical condition of lymphedema may lead to clinically significant lymphatic transport insufficiency later in life under certain conditions. Additionally, primary lymphedema contributes to many forms of secondary lymphedema due to underlying genetic susceptibility. This unique group of patients with subclinical presentation warrants special consideration in the scope of managing and preventing lymphedema.[1,2,9,10]

Physical management

General overview

Lymphedema can be managed with physical therapy (ie, nonsurgical methods); it combines multiple elements of physical maneuvering known as decongestive physiotherapy.[35] Physical therapy has three goals: (i) improve lymphatic function; (ii) soften fibrosclerotic tissues; and (iii) reduce microbial growth on the skin

to prevent opportunistic infections. This approach can achieve effective limb volume reduction through a stepwise approach from the initial acute phase of intervention to the subsequent maintenance phase, preserving the integrity of the cutaneous and subcutaneous structures.[59-61]

A multilayer compression bandage can stimulate lymphatic contractility and subsequent lymph flow through physical activity.[62] In addition, external tissue compression can increase interstitial hydrostatic pressure to subsequently reduce lymph formation. When the maximum reduction in edema volume is reached after performing multiple cycles of compression and manual lymphatic drainage, maintaining the therapeutic benefits depends on self-care strategies and the proper use of compression garments.[60] The combination of regular exercise and external compression exerted by compression garments can improve lymphedema.[63]

Another technique that may augment lymph clearance is intermittent pneumatic compression, which provides a distal-to-proximal graduated and sequential compression that results in an adjunctive benefit to the decongestive physiotherapy.[64,65] Low-level laser therapy has also been reported to produce both subjective and objective improvements in lymphedema[66,67] with both anti-inflammatory and lymphangiogenic effects.[68] Lastly, the application of vibration, heat, and external magnetic fields have also been reported to be beneficial, but few data support these reports.[69]

Decongestive lymphatic therapy

Decongestive lymphatic therapy is a nonsurgical treatment option to reduce swelling and maintain this reduction over the long term. This method uses compression, massage, and exercise to stimulate lymphatic drainage, which will reduce the swelling, soften the fibrotic tissues, and ultimately improve limb function and mobility. As skin is a barrier to infections, improving its function will reduce the rate and severity of cellulitis *(Figure 2)*.[70-73] Decongestive lymphatic therapy is a well-established treatment option for the management of lymphedema. It is an empirical strategy to control edema and it remains the treatment of choice regardless of the disease etiology (primary or secondary) or clinical stage and despite the fact that it is not a cure.

Compression therapy with bandages, garments, and intermittent pneumatic compression and manual lymphatic drainage are two major components of decongestive lymphatic therapy.[71,72] Indeed, compression bandage–based therapy is the single most important component of decongestive lymphatic therapy with or without sequential intermittent pneumatic compression–based mechanical compression.[74-77] However, basic hygienic care of the skin, movement exercises, and education for risk reduction, including the prevention of infections, are also essential components of the treatment regimen.

Decongestive lymphatic therapy has an initial phase of intensive decongestion therapy followed by a long-term maintenance phase. The primary goals of intensive treatment are to obtain a significant reduction in limb volume and changes in the tissue, and it includes a 2- to 4-week course of daily skin care, manual lymphatic drainage massage, multilayer compression bandaging, and exercise *(Table II)*. Once intensive treatment is complete, maintenance treatment should be instituted immediately with proper fitting of compression hosiery, because, along with the intensive therapy, the maintenance phase is the cornerstone of contemporary lymphedema treatment.[78,79]

Decongestive lymphatic therapy can be a life-long therapy as the risk of complications and morbidity is minimal and, in the majority of patients, it helps maintain an improved

Therapeutic option	Initial treatment phase	Maintenance phase
Manual lymph drainage	X	
Bandaging	X	(As part of self-management)
Garments/hosiery		X
Pneumatic compression	X	X
Physiotherapy	X	
Decongestive lymphatic therapy	X	
Exercise	X	X
Weight control	X	X
Skin care	X	X
Awareness	X	X
Self-management		X
Reconstructive surgery	X	
Reductive surgery	X	

Table II. Useful lymphedema interventions.

Based on data from reference 118: Damstra RJ. Upper limb lymphedema. In Lee BB, Rockson SG, eds. Lymphedema: A Concise Compendium of Theory and Practice. 2nd Ed. *Springer International Publishing AG 2011, 2018; 540.*

disease status. However, it is more effective when started in the earlier stages of lymphedema, because, in the later stages of lymphedema, the efficacy is limited and it often fails to prevent progression and complications. Successful decongestive lymphatic therapy requires good treatment compliance and that the patients be motivated to understand their condition, know the options available, and understand the absolute need for using compression daily to maintain the long-term benefits of treatment.[80] Therefore, patient involvement in management is essential, especially for home maintenance therapy and should be guided properly for an active involvement in self-management. The long-term success depends on the comprehensive medical care of many accompanying conditions/diseases that can aggravate the lymphedema. Proper management of various comorbid conditions is essential because they can influence the therapeutic outcomes. The most common conditions include hypertension, coronary heart disease, congestive heart failure, obesity, diabetes mellitus, chronic venous insufficiency, malignancies, chronic arthritis, peripheral artery occlusive disease, and peripheral polyneuropathy. Calcium-channel blockers should be avoided since they impair lymphatic pumping.[81]

There are a few contraindications to each component of decongestive lymphatic therapy, including acute erysipelas, acute thrombophlebitis, phlebothrombosis, decompensated heart failure, and stage IV peripheral artery occlusive disease. High pressure bandaging is risky for any patient with advanced peripheral arterial disease of the limb or advanced cardiac failure.

Manual lymphatic drainage

Manual lymphatic drainage is a technique that physiologically stimulates poorly functioning, if not paralyzed, lymphatic vessels and pathways to facilitate the drainage of interstitial fluid into the initial lymphatic system to reduce lymphatic congestion effectively. In addition, this technique, by improving lymphodynamics during treatment, may reduce fibrosclerosis of the involved soft tissues.[82,83]

Manual lymphatic drainage uses a massage technique to reroute the accumulated lymph in the swollen region through collateral lymphatic pathways to an area where the lymph can drain normally. The initial step of the process is to decongest the central/proximal areas to make room before massaging the edematous regions. The manual lymphatic drainage massage is an important component of decongestive lymphatic therapy, especially for midline lymphedema treatment where there are few alternatives[70]; however, it should not be used alone as a sole independent regimen, but rather as one part of the decongestive lymphatic therapy. Indeed, manual lymphatic drainage has not yet been confirmed scientifically with objective data, although it has remained an indispensable component of decongestive lymphatic therapy for decades.[84,85] Therefore, depending on local resources, manual lymphatic drainage may be included in the treatment plan despite the lack of evidence for long-term benefits.

Compression therapy

The cornerstone of physical therapy for lymphedema regardless of its etiology is compression therapy, which increases tissue pressure and subsequently decreases the transmural pressure gradient to reduce the lymphatic load by reducing microcirculatory filtration.[86] Compression therapy is generally initiated with a multicomponent bandage with high stiffness; short-stretch bandaging combined with exercises is ideal during the initial management phase and should be guided by specifically trained therapists. Following the initial decongestion phase, the maintenance phase must be well organized and use the best combination of compression garments, self-management, skin care, and exercises because this phase requires a life-long commitment.[87]

The optimal degree and duration of compression remains debatable. Recent data support an optimal pressure range around 30 mm Hg for the upper extremities and 50 to 60 mm Hg for the lower extremities; however, higher pressures may be counterproductive.[88] Lower compression pressure are more user friendly, which would improve compliance *(Table III)*. Self-management must be adjusted with the proper combination of compression bandages or Velcro devices, movement exercises, and/or self-massage to fit with individual needs best. Less bulky bandages and Velcro devices seem to allow better movement and subsequently better outcomes than the widely used heavy set multilayer and multicomponent bandages.[89,90] A recent study reported that self-adjustable Velcro devices might reduce edema more effectively than inelastic lymph bandages.[90]

Compression hosiery/stockings are made for the maintenance phase to maintain the effect achieved through the initial intensive treatment phase. Fitted garments with higher compression classes (30 to 40 mm Hg) are ideal, but they become a limiting factor, especially in patients with advanced age, obesity, and/or arthritis.

		Pressure	Maximum application time
Children	6 months–2 years		12-16 h
	2–6 years	20–30 mm Hg	16–20 h
	6–12 years	20–30 mm Hg	16–20 h
Adults	Stage I	20–30 mm Hg	12–16 h
	Stage II	30–46 mm Hg	18–22 h
	Stage III	46 mm Hg and stronger	18–22 h
	Lymphedema combination forms	Individual	Individual
Geriatric	60–70 years	30–46 mm Hg	18–22 h
	Over 70 years	20–30 mm Hg	12–16 h

Table III. Compression bandaging depends on the age of the patient and the stage of the lymphedema.

Based on data from reference 119: Földi E, Földi M, Rockson SG. Complete decongestive physiotherapy In Lee BB, Rockson SG, eds. Lymphedema: A Concise Compendium of Theory and Practice. 2nd Ed. *Springer International Publishing AG 2011, 2018;406.*

Intermittent pneumatic compression therapy

For many decades, pneumatic compression with multichamber devices has been effectively incorporated into multidisciplinary therapeutic programs as an adjunctive therapy to effectively remove excess fluid from the extremities.[33,34,64] However, this device remains controversial due to concerns that the pressures generated by the device may damage the skin lymphatics, tempering earlier enthusiasm for the benefits of this technique.[91,92] Recent studies have shown that intermittent pneumatic compression relieves symptoms, reduces episodes of cellulitis in patients with lower extremity lymphedema,[93] and increases tissue elasticity.[94]

Sequential intermittent pneumatic compression can be recommended as an adjunct treatment,[35] particularly for patients whose isotonic exercise capacity is highly compromised or absent, which means that the lymphedema can only be treated with passive physical therapy (eg, elderly, bedridden patients, patients with serious disabilities, etc).[96,97] However, sequential intermittent pneumatic compression should be used as an adjunct treatment for mixed lymphovenous edema and it should not be used in preference to exercise and compression garments. Furthermore, clinical evidence shows that the formation of new tissue channels as functional pathways by intermittent pneumatic compression promotes the clearance of edema fluid in patients with lymphedema in the limbs.[95]

Medical and pharmacological management

a range of pharmacological treatments has been available for decades to try to improve lymphatic function, such as α-benzopyrones, which include coumarin derivatives, and γ-benzopyrones (ie, flavonoids), which includes flavones, flavonols (eg, diosmin), and flavanes (eg, hesperidin). The proposed mechanism of action is that benzopyrones reduce vascular permeability,[98] which reduces the lymphatic load. Additionally, benzopyrones may increase tissue macrophage activity,[99] thereby encouraging proteolysis with favorable effects on fluid clearance and tissue composition.[100] Such drugs are all designed to help patients with lymphedema by reducing protein and extracellular fluid accumulation,[101] stimulating lymph contractility and flow,[102] and reducing protein concentration and fibrotic induration in tissues by stimulating tissue macrophage activity to increase proteolysis.[99,100] However, there has been little, if any, data to support the use of these drugs, with the exception of the flavonoid/benzopyrone groups that have demonstrated significant and objective improvements.[98,103,104]

Recent data show that the hepatotoxic effects of coumarin (5, 6, benzo-α-pyrone), which prohibit its use for the treatment of lymphedema, are a consequence of a genetic and metabolic problem relating to the breakdown of coumarin.[105] A new test that screens for genetic polymorphisms can identify people who have a functional, nonpolymorphic cytochrome P450 2A6 (CYP2A6) enzyme, a liver enzyme responsible for the metabolism of coumarin to noncytotoxic metabolites.[106] A better understanding of genetics and genomics will help determine which patients will respond well and overcome the adverse outcomes; this new pharmacogenomic test[106] helps limit the use of benzopyrones (particularly coumarin) to those patients with a functional, nonpolymorphic CYP2A6 enzyme to reduce the risk of hepatic toxicity.

Indeed, a combined approach[107] with conventional physical therapy[108] and benzopyrones as an additional medical treatment gets new attention,[109] despite the fact that the systemic use of benzopyrone is an unsettled

issue due to its hepatic toxicity. Nevertheless, until now, pharmacology has provided few therapeutic options for the management of lymphedema, except the use of antibiotics to treat and prevent recurrent episodes of soft-tissue infections, which is critical for the complete eradication of pathogens in patients with lymphedema who have a poor ability to clear pathogens and an impaired immune system trafficking mechanism due to abnormal biology of the lymphedematous tissues.[105]

Pharmacological management of infection in lymphedema

Infections and inflammation of skin and soft tissues are more common among patients with lymphedema due to lymph stasis, which allows microorganisms that are retained in the tissue fluid to grow. In these patients, not only do commensal bacteria (eg, *Staphylococcus epidermidis* and coagulase-negative strains, *S aureus*, and *Corynebacterium*) proliferate and become pathogenic, but also other pathogenic microbes originating from the perineal region (eg, *Enterococcus*, *Enterobacter*, *Acinetobacter*, *Proteus*, *Escherichia coli*, and *Pseudomonas*) cause various conditions of infection: lymphangitis, erysipelas, and necrotizing fasciitis *(Figure 5)*.[110,111]

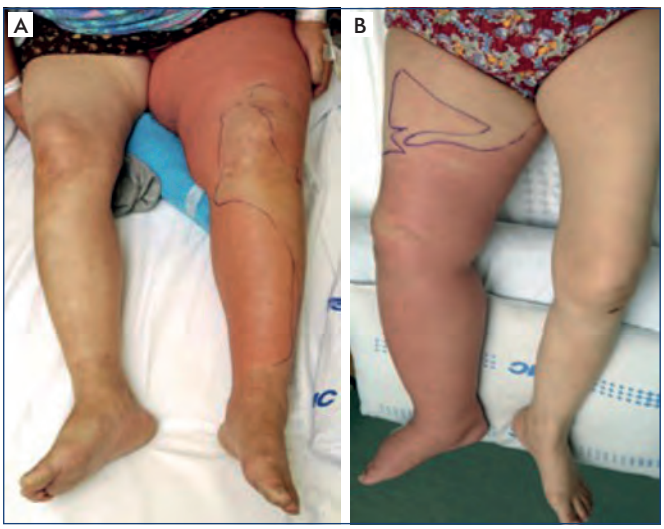

Figure 5. Clinical case of infection resulting in cellulitis.

Panels A and B. Display of two different patients with severe cellulitis affecting almost the entire lower extremity up to the upper thigh subsequently causing systemic sepsis (5B) to require in-hospital intensive care with the antibiotics.

The decreased ability of the immune system to neutralize and eradicate the microorganisms penetrating the integuments means that these organisms change into a persisting form with a decreased metabolism.[112,113] Therefore, acute episodes of a unique inflammatory condition, known as dermatolymphangioadenitis (DLA), should be treated with a wide-spectrum antibiotic therapy for 3 to 7 days, and low-dose (benzathine) penicillin should be further administered on a long-term basis to prevent the revival of dormant microbes and decrease the frequency of DLA as a chronic form *(Figure 1)*.[38-40]

Pharmacological prospects for emerging therapies

There has been a growing interest in the role of inflammation in the pathogenesis of lymphedema[114] because, in experimental models, the targeted inhibition of these inflammatory pathways significantly improved the structure and function of the lymphatic system.[15,116]

Inhibition of transforming growth factor β (TGFβ) expression improved lymphatic function by diminishing inflammation, the migration of T helper 2 type (T_H2) cells, and the expression of profibrotic T_H2-type cytokines.[41] Hence, proper inhibition of lymphangiogenesis by T_H2-type cytokines is considered a potent means of improving lymphangiogenesis by manipulating the antilymphangiogenic pathways.[42] Also, excessive generation of immature lymphatic vessels, which are essential for the pathogenesis and maintenance in lymphedema, is dependent upon an interaction between CD4 and macrophages, and lymphedema can be improved by inhibiting the activation of T helper 1 type and T helper 17 type cells.[43] These two lines of investigation show a promising future for pharmacological approaches to improve the treatment and prevention of lymphedema.

Corresponding author
Byong-Boong LEE
Division of Vascular Surgery,
Department of Surgery,
George Washington University Medical Center, 22nd and I Street, NW, 6th Floor,
Washington, DC 20037, USA

Email: bblee38@comcast.net

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