Phlebolymphology

ISSN 1286-0107

Vol 31 | No. 2 | 2024 | P49-76

No. 113

Phlebolymphology

Aims and Scope

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

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

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

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

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

Correspondence

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

Publication Director
Christophe CHARPENTIER
Suresnes, France

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

Indexed in EMBASE, Index Copernicus, and Scopus.

ISSN 1286-0107

Content

Vol 31, No. 2, 2024 No. 113

Editorial

Dear Readers,

In this new issue of *Phlebolymphology*, which is dedicated to the treatment of superficial venous insufficiency with the techniques used in current daily practice, you will find the articles as below:

"Overview of the advances in thermal ablation techniques. Where do we stand?" Current guidelines have recognized thermal ablation with laser or radiofrequency as the treatment of choice for lower-limb varicose veins. **D. KONTOTHANASSIS *(Italy)*** discusses the evolution of all thermal ablation techniques currently used, along with their indications, mechanisms of action, and outcomes.

"Outcomes of different approaches for the treatment of large-diameter incompetent great saphenous veins." **C. S. KARATHANOS and A. D. GIANNOUKAS *(Greece)*** discuss the effectiveness of currently used techniques for the treatment of lower-limb varicose veins when the greater saphenous vein is dilated.

"Pathogenesis, diagnosis, and treatment of endothermal heat-induced thrombosis (EHIT)." **S. R. PANDEY *(Nepal)*** discusses the mechanisms of the diagnostic approach and the treatment options for endothermal heat-induced thrombosis, which may occur at the saphenofemoral junction as a complication of the endothermal treatment of an incompetent greater saphenous vein.

"Overview on foam sclerotherapy in the treatment of varicose veins." Foam sclerotherapy is a nontumescent, nonthermal treatment option for lower-limb varicose veins that is very popular and widely used in clinical practice. **T. URBANEK *(Poland)*** discusses the indications, technique, potential complications, and outcomes of foam sclerotherapy.

Enjoy reading this issue!

Co-Editor of the issue
Athanasios D. Giannoukas

Phlebolymphology Vol 31 | No. 2 | 2024

Overview of the advances in thermal ablation techniques. Where do we stand?

Dimitrios Kontothanassis, MD, Prof, MS

Department of Phlebology, Istituto Flebologico Italiano, Padova, Italy

General and Vascular Surgeon, CEO Istituto Flebologico Italiano, Padova, Italy

ABSTRACT

Varicose veins are a very common condition and have been the subject of a recent proliferation of treatment modalities. The last 2 decades have seen extraordinary expansion in superficial venous surgery. Traditional surgical procedures (crossectomy and stripping) are now being replaced to a greater or lesser extent by new, less invasive endovenous methods, but the advent of the endovenous treatment era has led to a confusing array of different modalities of treatment. This paper provides an overview of the advances in thermal ablation techniques. All modalities offer excellent results in the right situation, and each has its own treatment profile. Endovenous thermal ablation techniques have matured and have a reassuring and reliable outcome. Our aim is to provide an up-to-date review of all available endovenous thermal techniques (laser, radiofrequency, steam), describing the indications, the procedure, mechanism of action, and the outcomes. In experienced hands, all endovenous techniques are safe and effective, with long-term results comparable to conventional surgical procedures.

Keywords

chronic venous disease | endovenous thermal ablation | laser | radiofrequency | steam | varicose veins

Phlebolymphology. 2024;31(2):52-59.

www.phlebolymphology.org

Introduction

Endovenous thermal techniques, namely, radiofrequency (RF) ablation, endovenous laser ablation (EVLA), and steam ablation, were introduced around the 21st century and have revolutionized the way varicose veins are treated.[1] These minimally invasive techniques are associated with an earlier return to normal activity and less pain, and they enable procedures to be carried out as day cases. However, they are also known to cause a number of side effects and involve infiltration of tumescent fluid, which can cause discomfort.[2] On systematic review, the clinical practice guidelines from the Society for Vascular Surgery (SVS)/American Venous Forum (AVF) in 2011 and from the SVS/AVF/American Vein and Lymphatic Society (AVLS) in 2023 highly recommend such techniques (Grade 1b) for the treatment of saphenous incompetence in symptomatic patients over high ligation and stripping (quality of evidence B; *Table I*).[3]

GUIDELINES		Grade of recommendation	Quality of evidence
4.1.1.	For patients with symptomatic varicose veins and axial reflux in the GSV, who are candidates for intervention, we recommend treatment with endovenous ablation over high ligation and stripping (HL&S) of the GSV.	1 (strong)	B (moderate)
4.1.2.	For patients with symptomatic varicose veins and axial reflux in the SSV, who are candidates for intervention, we recommend treatment with endovenous ablation, over ligation and stripping of the SSV.	1 (strong)	C (low to very low)

Table I. Endovenous ablation versus high ligation and stripping. From the 2023 SVS/AVF/AVLS Clinical Practice Guidelines for the management of varicose veins of the lower extremities (Part II).

Abbreviations: AVF, American Venous Forum; AVLS, American Vein and Lymphatic Society; GSV, great saphenous vein; SSV, small saphenous vein; SVS, Society for Vascular Surgery.

After reference 3: Gloviczki et al. *J Vasc Surg Venous Lymphat Disord*. 2024;12(1):101670. © 2023 The Author(s). Published by Elsevier Inc. on behalf of the Society for Vascular Surgery.

GUIDELINES		Grade of recommendation	Quality of evidence
4.2.1.	For patients with symptomatic axial reflux of the GSV, we recommend either thermal or nonthermal ablation from the groin to below the knee, depending on the available expertise of the treating physician and the preference of the patient.	1 (strong)	B (moderate)
4.2.2.	For patients wth symptomatic axial reflux of the SSV, we recommend either thermal or nonthermal ablation from the knee to the upper or midcalf, depending on the available expertise of the treating physician and the preference of the patient.	1 (strong)	C (low to very low)
4.2.3.	For patients wth symptomatic axial reflux of the AAGSV or PAGSV, we suggest either thermal or nonthermal ablation, with additional phlebectomy, if needed, depending on the available expertise of the treating physician and the preference of the patient.	2 (weak)	C (low to very low)
Factors affecting choice of superficial truncal ablation and outcome			
5.2.5.	In patients with reflux in the below-knee GSV, ablation to the lowest point of reflux resulted in better early outcome. Nonthermal techniques are better for ablation of refluxing distal calf saphenous veins, to avoid thermal nerve injury.		
5.2.6.	In patients with an epifascial or superficial saphenous vein, thermal ablation may result in skin burns, hyperpigmentation, or induration, while nonthermal techniques may cause hyperpigmentation or induration. Miniphlebectomy or limited stripping is safe and effective if the saphenous vein is close to the skin (<0.5 cm).		
5.2.7.	For patients with large (>10 mm), nonaneurysmal saphenous veins, thermal ablation with EVLA or RFA should be performed rather than using nonthermal ablation techniques.		
5.2.8.	The incidence of superficial thrombophlebitis has been reported to be similar for thermal and nonthermal ablations.		
5.2.9.	In patients with uncomplicated C2 disease (no venous claudication, thigh swelling, suprapubic or abdominal wall varicosities) due to concurrent superficial incompetence and iliac or iliofemoral venous obstruction, treatment of superficial incompetence first is indicated.		

Table II. Top panel) Thermal versus nonthermal ablation of superficial truncal veins. Bottom panel) Factors affecting choice of superficial truncal ablation and outcome. From the 2023 SVS/AVF/AVLS Clinical Practice Guidelines for the management of varicose veins of the lower extremities (Part II).

Abbreviations: AAGSV, anterior accessory great saphenous vein; AVF, American Venous Forum; AVLS, American Vein and Lymphatic Society; EVLA, endovenous laser ablation; GSV, great saphenous vein; PAGSV, posterior accessory great saphenous vein; RFA, radiofrequency ablation; SSV, small saphenous vein; SVS, Society for Vascular Surgery.

After reference 3: Gloviczki et al. *J Vasc Surg Venous Lymphat Disord*. 2024;12(1):101670. © 2023 The Author(s). Published by Elsevier Inc. on behalf of the Society for Vascular Surgery.

Although RF ablation was the pioneer endovenous technique introduced in 1998, laser ablation introduced immediately afterward in 1999 spread globally and faster with very promising results. The 810-nm and 980-nm diode laser using bare fibers dominated the global scientific scene for at least 5 years up to 2005 because results were much better than with the first generation of RF generators. The second generation of RF generators (ClosureFast) achieved better results in terms of closure rates after saphenous ablation, reduction in postoperative pain, and less bruising than with the 810-nm and 980-nm diode laser. Results were equalized again after the introduction of new wavelengths for laser devices (1470 nm and 1940 nm) and development of new high-quality fibers (radial optical fibers, single or double ring, normal or slim). New promising results are being observed with the next-generation RF generator (Venclose), which is a multi-voltage energy delivery system with touchscreen control that automatically sets the nonadjustable treatment parameters for the Venclose System Catheters. The author believes that this technique, with proper studies in future trials, should seek to standardize the modality of treatment and the clinical terminology, and that it will provide more evidence on outcomes of treatments on long-term follow-up. Steam was introduced in 2011 but never spread globally; even today, it accounts for only a small part of thermal and tumescent procedures.

However, the 2023 SVS/AVF/AVLS clinical practice guidelines recommend either thermal or nonthermal ablation from the groin to below the knee, depending on the available expertise of the treating physician and the preference of the patient. For patients with large (>10 mm), nonaneurysmal saphenous veins, thermal ablation with EVLA or RFA should be performed rather than using nonthermal ablation techniques. *(Table II-5.2.7)*.[3]

How it works

All endothermal techniques can be offered as outpatient procedures that can be done under local anesthesia. Proper evaluation of a patient's condition has to be done so that in high-risk patients a further evaluation of risk factors prior to operation can be offered. For patients that present emotional problems, a combination of oral or endovenous mild sedation can be given in addition to local anesthesia. All techniques require ultrasound assistance to perform vascular access, navigate inside the vein, target and identify the correct point of entry into the vein, and landmark the point for starting a correct ablation. All techniques can be done by using a 16–18-gauge needle and inserting a guide wire or using a micropuncture kit. Usually, the sheath used for vascular access is 6F; no sheath is required for the steam procedure.

Tumescent anesthesia is mandatory for thermal techniques, and large amounts of tumescent liquid have to be delivered around the vein in order to dissect it from the surrounding tissues and cause extreme spasm of the vein wall around the catheter *(Figure 1)*.

Laser	Radiofrequency	Steam
• Outpatient	• Outpatient	• Outpatient
• Local anesthesia	• Local anesthesia	• Anesthesia
• Oral/e.v. sedation	• Oral/e.v. sedation	• Oral/e.v. sedation
• Anti-Trendelenburg	• Anti-Trendelenburg	• Anti-Trendelenburg
• Duplex US	• Duplex US	• Duplex US
• Vein diameter >3 mm	• Vein diameter >3 mm	• Vein diameter >3 mm
• Venous access	• Venous access	• Venous access
• Micropuncture	• Micropuncture	• Micropuncture
• Needle 16-18 G	• Needle 16-18 G	• Needle 16-18 G
• Guide wire	• Guide wire	• Guide wire
• Sheath 6F	• Sheath 7F	• No sheath
• Laser fiber	• RF catheter	• Steam catheter
• Landmark S.E.V.	• Landmark S.E.V.	• Landmark S.E.V
• Tumescent anesthesia	• Tumescent anesthesia	• Tumescent anesthesia
• Lidocaine 5 mg/kg	• Lidocaine 5 mg/kg	• Lidocaine 5 mg/kg
• Generator	• Generator	• Generator

Figure 1. Set up of endothermal procedures: left) laser; center) radiofrequency; and right) steam.
Abbreviations: e.v., endovenous sedation; RF, radiofrequency; US, ultrasound.
Courtesy of Prof D. Kontothanassis.

Contraindications to endothermal ablation techniques

For all endothermal techniques, it is very important to assess all the contraindications to transcatheter ablation *(Figure 2)* and to use the following criteria to make your treatment selection:

- Presence of anatomical variability of saphenous veins (duplication, aplasia, hypoplasia, extra fascial saphenous veins).
- Distance between the vein and the skin (is it >3 mm?).
- Presence of dilatation and tortuosity of the saphenous vein axis. (Do not treat veins with a diameter >25 mm unless you are very skilled in EVLA).
- Integrity of the deep venous system, assessed by excluding the presence of deep venous thrombosis (DVT) or venous narrowing after DVT.
- Patency of the great saphenous vein (GSV) and the small saphenous vein (SSV) before the operation.

Contraindications to transcatheter ablation

- **Anatomical variability**
- **Extreme tortuosity**
- **Extreme dilatation**
- **Extreme superficiality**
- **Anarchic recurrent varicose veins**
- **Vein segments with length <3 cm**
- **Difficult negotiation of the guide wire**
- **Difficult negotiation of the introducer sheath**

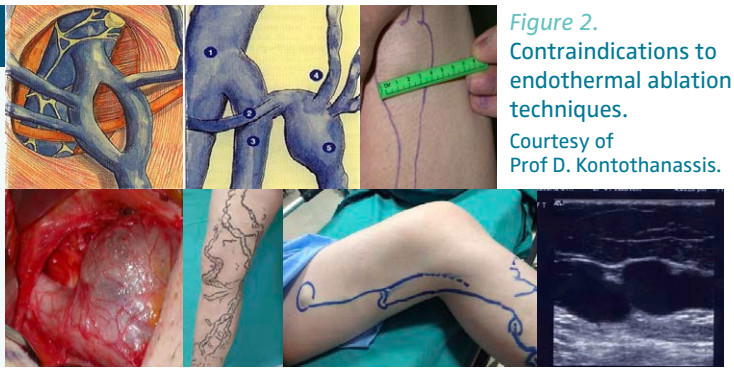


Figure 2. Contraindications to endothermal ablation techniques. Courtesy of Prof D. Kontothanassis.

Complications of endothermal techniques

The most common intraoperative complications of thermal techniques are the inability to cannulate the target vein or to advance the endovenous ablation catheter, an allergic reaction to tumescent anesthesia, a vasovagal response, hypotension, and bleeding. Postoperative complications are thrombophlebitis, endovenous heat-induced thrombosis (EHIT), pulmonary embolism, skin burn, discoloration, paresthesia, chronic pain, numbness, infection, hematoma, bruising, and persistent patency of the ablated vein. *Table III* shows complications of endovenous ablation in randomized controlled trials.[4]

Complication	L + S (N=975)	RFA (N=317)	EVLA (N=1057)
DVT/PE	0.7%	0.5%	0.4%
Infection	**2.1%**	1.0%	0.7%
Paresthesia	**6.7%**	**7.8%**	3.3%
SVT	2.9%	**5.2%**	**5.5%**
Bruising	**36.1%**	3.1%	**34.5%**
Hematoma	**13.5%**	0.2%	**2.1%**
Skin burn	N/A	0.7%	0.7%

Table III. Complications of endovenous thermal techniques in randomized controlled trials.

Abbreviations: DVT: deep venous thrombosis; EVLA, endovenous laser ablation; L+S, conventional ligation plus stripping; N, number of treated limbs; PE, pulmonary embolism; RFA, radiofrequency ablation; SVT, superficial venous thrombosis or thrombophlebitis.
Based on reference 4: Dermody M, O'Donnell TF, Balk EM. *J Vasc Surg Venous Lymphat Disord*. 2013;1:427-436.e1.

Treatment of below-knee veins

Below-knee veins are often problematic to treat with thermal techniques because of the high risk for injury of the saphenous vein (SV). During harvest of the SV, the most important relationship to take into account is the saphenous nerve (SN) in order to avoid pain and paresthesia after surgery. The most vulnerable area is the inferior third of the leg because of vein and nervous adhesion. Use of large amounts of tumescent anesthesia aims to completely

separate the vein from all the other tissues and prevent nerve damage *(Figure 3)*. When the risk of nerve damage during ablation is high, one should ask the patient to report any pain or electric stimulation and stop immediately if the answer is positive. In case of risk of nerve injury, you can reduce the amount of the delivered energy or pull back the laser fiber or the RF catheter 1 to 2 cm. Thanks to its longer wavelength, the 1940-nm diode laser is very promising for treating below-knee veins; this innovative endovenous laser requires significantly less energy. However, these promising results are for a 3-year follow-up period, whereas long-term results, greater than 10 years, are needed.

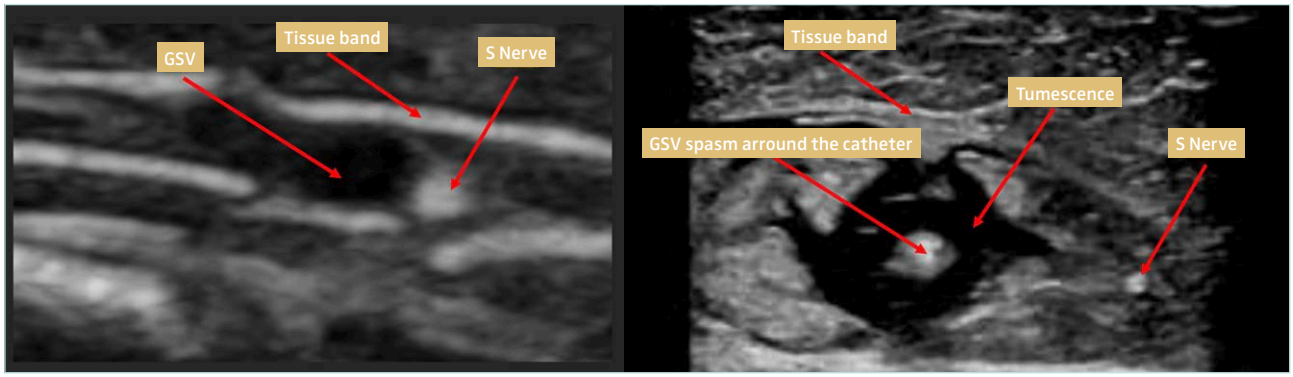


Figure 3. **High volume tumescent anesthesia to separate the saphenous nerve from the saphenous vein.**
Abbreviation: GSV, great saphenous vein.
Courtesy of Prof D. Kontothanassis.

How much energy dispense is needed to ablate the target vein?

The amount of energy depends on the individual vein, and this is the biggest difference between standardized and nonstandardized techniques. The risk associated with increasing the delivered energy rate for laser (J/cm) using different wavelengths is perforation of the vein wall. Usually, the higher the laser wavelength the less energy required for treating target veins, but it is very difficult to standardize. RF catheters for vein ablation (standardized techniques) deliver thermal energy constantly and uniformly via a dedicated microprocessor-controlled generator.

With the new devices that generate heat at 120 °C, boiling, vaporization, and carbonization of the tissues are avoided. The temperature of the electrodes (7- or 10-cm length) has increased from 120 °C (second-generation RF; Medtronic) up to 130 °C (next-generation electrode; Venclose, BD). The heating element is energized by the Venclose RF Generator, which is a multi-voltage energy delivery system with touchscreen control that automatically sets the nonadjustable treatment parameters for the Venclose System Catheters. A button on the catheter begins an automated treatment cycle 20 seconds long at a set temperature of 130 °C (Venclose RF Ablation Catheter). The treatment stops automatically when complete.

The procedure of steam ablation is very similar to EVLA, and it is a nonstandardized thermal technique. Though a step-by-step procedure is lacking in the literature, after activation, the catheter releases small "puffs" of steam, and the catheter is pulled back in a stepwise manner. A physicist calculated that approximately 2258 J is released when 1 g of steam condenses.[5]

Histological findings and results

During endovenous RF ablation, the thermal energy delivered to the venous segment to be treated causes direct injury with acute and posttreatment effects. Acute endovenous RF ablation effects of thermal injury are endothelial denudation, thickening of the vein wall, contraction of the vein wall collagen fibrils, and necrosis of the smooth muscle and vein wall components. Posttreatment effects of thermal injury are extensive growth of fibroblasts, new collagen synthesis, further thickening of the vein wall, and a further fibrotic sealing of extensively narrowed vessels *(Figure 4)*.

Microscopic examination of veins immediately after steam ablation showed disappearance of the endothelial layer. Microscopic examination of treated veins that were removed 20 days after steam ablation showed endothelial destruction, fibrotic thrombosis with inflammatory reaction of the

media, major alterations of elastic and collagen fibers in the media, and lesions in the adventitia with liponecrosis and lipogranuloma *(Figure 5)*.

Microscopic examination of veins immediately after laser ablation showed eosinophilia, congestion, thrombosis, as well as necrosis of the endothelium. With regard to the periadventitial tissues, there was evidence of fragmentation of connective fibers and adipose areolas, as well as brownish deposits of burnt material *(Figure 6)*.

Figure 4. Histological findings after radiofrequency ablation.
Abbreviation: EVRFA, endovenous radiofrequency ablation.
Images courtesy of R. Weiss and M. Goldman.
Courtesy of Prof D. Kontothanassis.

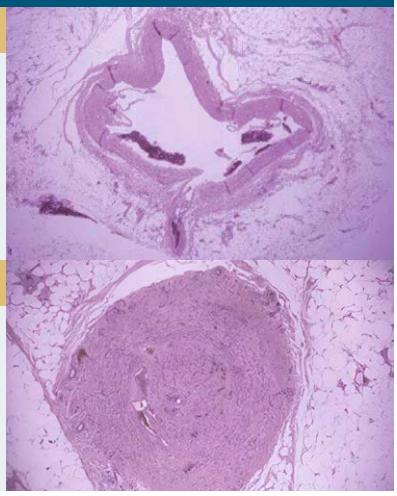
Endovenous radiofrequency ablation (EVRFA) - histological findings

ACUTE EFFECTS

- Endothelial denudation
- Thickening of vein wall
- Contraction of vein wall and cellular components
- Shrinkage and thickening of vein wall collagen fibrils
- Necrosis of smooth muscle and vein wall components

POSTTREATMENT EFFECTS

- Extensive growth of fibroblasts
- New collagen synthesis
- Further thickening of vein wall
- Further fibrotic sealing of extensively narrowed vessel



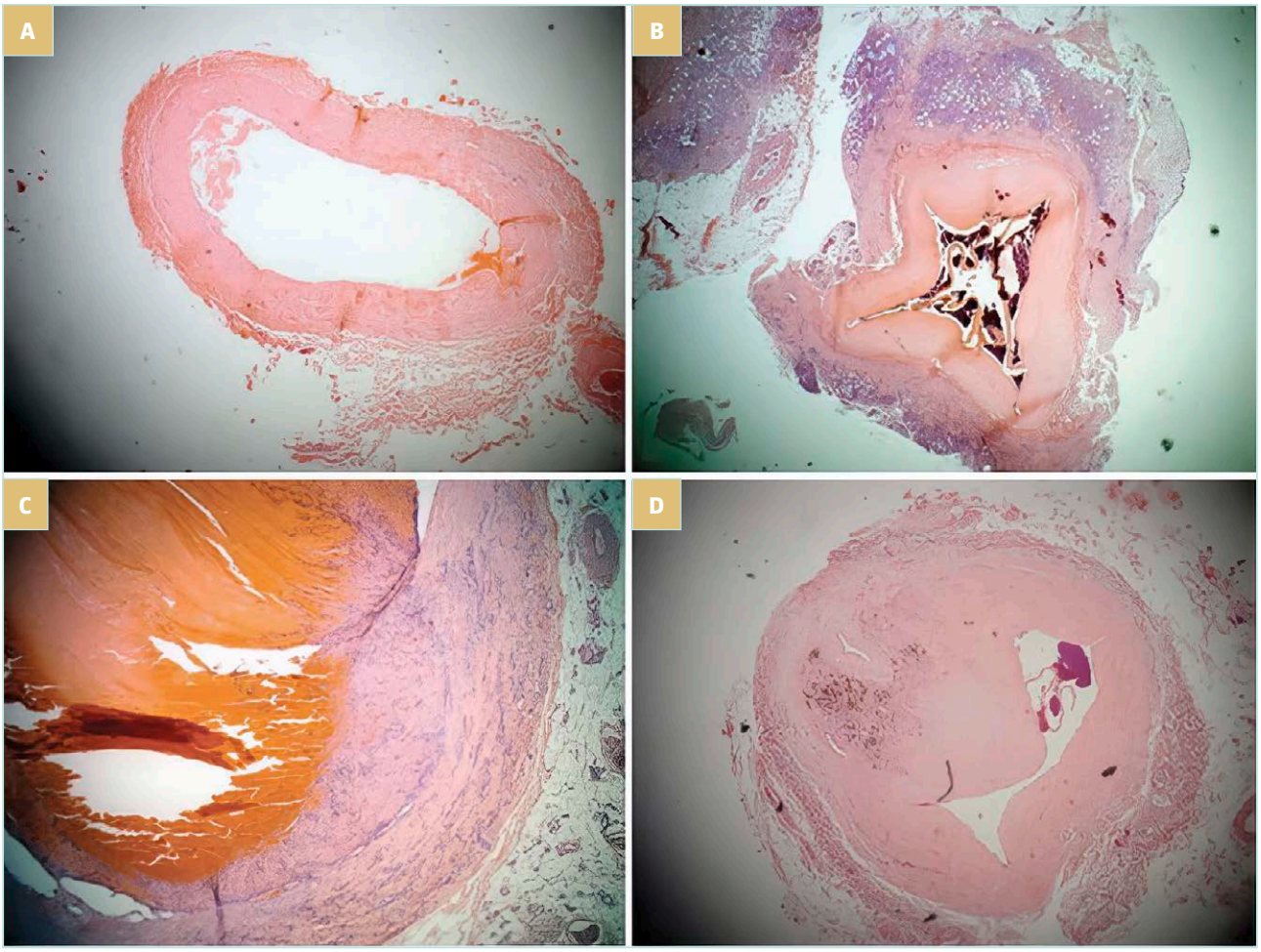


Figure 5. Microscopic examination after steam ablation: A) immediately after steam ablation; B, C) after 20 days; and D) after 3 months. **After reference 5:** van den Bos et al. *J Vasc Surg*. 2011;53(1):181-186. © 2011 Society for Vascular Surgery. Published by Mosby, Inc. All rights reserved.

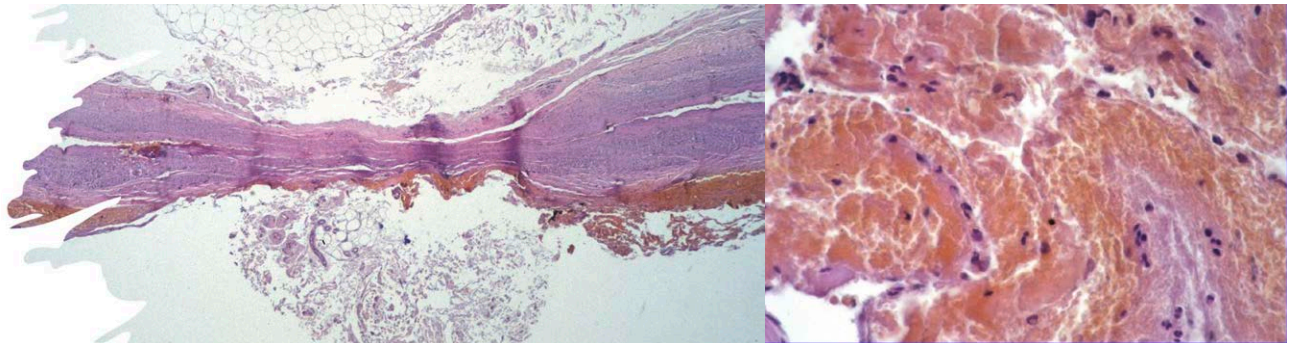


Figure 6. Microscopic examination (histological findings) after endovenous laser ablation.
Courtesy of Prof D. Kontothanassis.

Conclusion

Early treatment of symptomatic chronic venous disease (CVD) improves quality of life, signs, and symptoms; it slows down progression, but cannot prevent recurrence of varicose veins.[1,2,6]

RF ablation and laser ablation are both equal and highly recommended techniques for treatment of CVD.[4] The recanalization rate during follow-up is the same for both techniques, but the occlusion rate does not reflect clinical success. There is no difference in postoperative pain and bruising. The use of laser needs a longer learning curve than RF. The RF Venclose system is designed for more efficiency and can be considered the next-generation thermal system, but long-term follow-up evaluation is mandatory. Venclose RF can be 30% faster than other thermal techniques because of the 10-cm heating electrode, which can reduce the overall procedure time and cost of operation. Both RF ablation and EVLA should be offered in combination with foam and glue when necessary to achieve better outcomes when dealing with complex vein anatomy.[2]

International guidelines, multiple reviews, and long-term follow-up studies available in the literature clearly support thermal techniques rather than nonthermal techniques. When comparing RF and laser with foam we have to keep in mind that we are comparing standardized techniques with nonstandardized techniques, and that clinical practice guidelines support thermal techniques when dealing with larger-diameter veins (> 10 mm).[3]

Reduced time of operation and number of treatment sessions is clearly achievable with thermal techniques when treating full-length GSV, GSV plus anterior saphenous vein, bilateral GSV or SSV; there is no risk in using thermal techniques in patients with patent foramen ovale and for below-knee ablation.

CORRESPONDING AUTHOR

Dr Dimitrios Kontothanassis

Via N. Tommasseo 50
– 35131 Padova, Italy

EMAIL: *direzione@istitutoflebologico.it*

References

1. Davies AH. The seriousness of chronic venous disease: a review of real-world evidence. *Adv Ther*. 2019;36(Suppl 1):5-12.
2. Kontothanassis D. *Endovenous Ablation Techniques. Mastering Endovascular Techniques, Tips and Tricks in Endovascular Surgery.* Springer; 2024:721-730.
3. Gloviczki P, Lawrence PF, Wasan SM, et al. The 2023 Society for Vascular Surgery, American Venous Forum, and American Vein and Lymphatic Society clinical practice guidelines for the management of varicose veins of the lower extremities. Part II: Endorsed by the Society of Interventional Radiology and the Society for Vascular Medicine. *J Vasc Surg Venous Lymphat Disord*. 2024;12(1):101670.
4. Dermody M, O'Donnell TF, Balk EM. Complications of endovenous ablation in randomized controlled trials. *J Vasc Surg Venous Lymphat Disord*. 2013;1:427-436. e1.
5. van den Bos RR, Milleret R, Neumann M, Nijstenet T. Proof-of-principle study of steam ablation as novel thermal therapy for saphenous varicose veins. *J Vasc Surg*. 2011;53(1):181-186.
6. Raffetto JD, Mannello F. Pathophysiology of chronic venous disease. *Int Angiol*. 2014;33(3):212-221.

Phlebolymphology Vol 31 | No. 2 | 2024

Outcomes of different approaches for the treatment of large-diameter incompetent great saphenous veins

Christos S. Karathanos, MD, PhD

Department of Vascular Surgery, University Hospital of Larissa, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece

Athanasios D. Giannoukas, MD, PhD

Department of Vascular Surgery, University Hospital of Larissa, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece

ABSTRACT

Chronic venous disease is a common disorder reported to affect up to 60% of the general population. Treatment options include conservative treatment, conventional surgery, and endovenous techniques. Great saphenous vein (GSV) diameter remains a controversial issue when considering optimal treatment, as a limited number of studies included patients with large-diameter GSV. This review focuses on the role of GSV diameter in the outcomes of different approaches for the treatment of incompetent GSV. Endovenous thermal ablation techniques are considered the first-choice treatment, with lower recurrence and complication rates in large-diameter GSV than observed with conventional surgery and nonthermal ablation techniques. Higher laser wavelengths are more effective than lower laser wavelengths in large GSV. Nonthermal ablation techniques seem not to be appropriate treatment for GSV diameters larger than 6 mm.

Keywords

cyanoacrylate adhesive closure | endovenous laser ablation | endovenous thermal ablation | high ligation and stripping | large-diameter great saphenous vein | mechanochemical ablation | radiofrequency ablation | ultrasound-guided foam sclerotherapy

Phlebolymphology. 2024;31(2):60-65.

www.phlebolymphology.org

Introduction

Chronic venous disease (CVD) is a common disorder reported to affect up to 60% of the general population.[1] The annual incidence of patients with varicose veins (VVs) ranged from 0.2% to 2.3%, whereas one-third of patients with uncomplicated VVs will develop skin changes and venous ulcers in the next 6 years.[2]

The symptoms attributed to CVD vary to different degrees of severity, from asymptomatic forms to leg pain, burning sensation, itching, heaviness, nocturnal cramps, skin changes, and ulceration of the limbs, affecting patients' quality of life (QOL). Symptoms usually increase with age and are more commonly reported in females.[2]

In patients with VVs, management strategies depend on clinical presentation (symptoms and signs), duplex ultrasound (DUS) findings, complications such as superficial vein thrombosis or hemorrhage, QOL impairment and a patient's preference. Treatment options include conservative treatment (compression stockings and venoactive drugs), conventional surgery with ligation of the saphenofemoral junction and stripping of the incompetent saphenous vein, and endovenous techniques. Numerous studies have shown the beneficial effect of intervention on venous symptoms, not only in CVD patients presenting with skin changes and venous ulcers (CEAP [clinical-etiological-anatomical-pathophysiological] clinical class C4 to C6), but also in those with uncomplicated VVs.[3,4] Additionally, other studies have shown the cost-effectiveness of interventional treatment versus conservative treatment in these patients.[5,6] According to the current guidelines from the European Society for Vascular Surgery, patients with superficial venous incompetence presenting with symptomatic VVs (CEAP clinical class C2S), interventional treatment is recommended (level of evidence A, class I).[7]

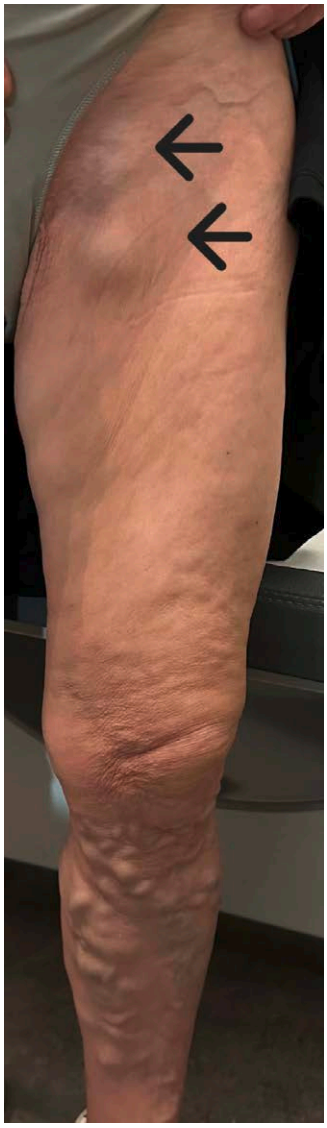


Figure 1. **Patient with chronic venous disease of the left limb. Notice the visible large-diameter great saphenous vein.**

Photo provided courtesy of the Department of Vascular Surgery, University Hospital of Larissa, Larissa, Greece.

Superficial vein incompetence is mainly attributed to the great saphenous vein (GSV) and its branches. GSV size plays an important role in clinical disease severity and also in postoperative outcomes.[8] The concept of large-diameter veins does not have a common definition as there is variation among different studies with regard to reported diameters for the large GSV trunk and in the site where GSV measurement is taken. Reported diameters for the large GSV trunk vary between 8 and 15 mm.[9,10] Some studies measure the GSV trunk 3 cm below the saphenofemoral junction (SFJ),[11,12] others at the level of the thigh,[13] whereas others do not specify the site of measurement at all.[14,15] According to the recommendations from the International Union of Phlebology (UIP) consensus document, maximum GSV diameter should be measured on DUS in the standing position, at the level of the thigh, in a tubular part of the trunk, excluding focal dilatation or aneurysms *(Figure 1 and Figure 2)*.[16]

The diameter of GSV remains a controversial issue when choosing the optimal treatment as there is a limited number of studies that included patients with large-diameter GSV and reported the effectiveness of treatment approaches.

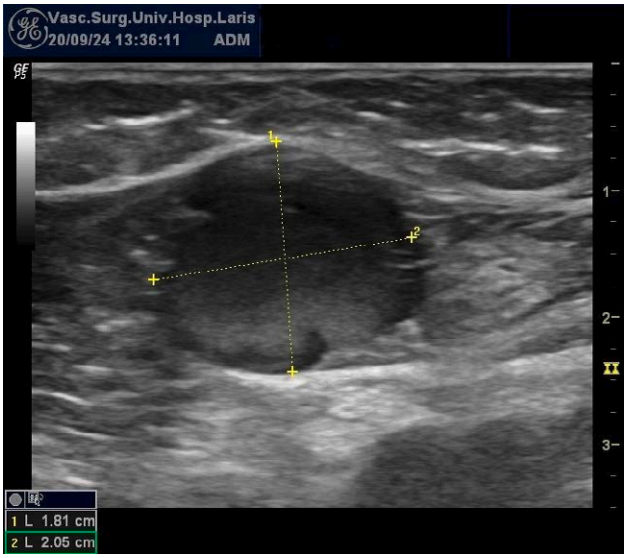


Figure 2. **Large-diameter great saphenous vein on duplex ultrasound.**

Photo provided courtesy of the Department of Vascular Surgery, University Hospital of Larissa, Larissa, Greece.

Many studies have reported that open surgery should be recommended for large-diameter GSVs as endovenous techniques are associated with higher recurrence and complication rates,[17,18] whereas others reported that large GSVs may be treated effectively with endovenous treatment.[11,13,19] This review focuses on the role of GSV diameter in the outcomes of different approaches for the treatment of incompetent GSV.

High ligation and stripping

High ligation of the SFJ and stripping (HLS) of the incompetent saphenous vein has been the standard treatment of superficial vein incompetence for many years. Over the past decade, conventional surgery has been substantially replaced by endovenous techniques, although HLS should be considered if endovenous thermal ablation (EVTA) options are not available (level of evidence A, class IIa).[7] Two randomized controlled trials (RCT) with long-term outcomes reported a recurrence rate of 4% and 11% after HLS at 5 and 11 years of follow-up, respectively.[20,21] A meta-analysis by Hamann et al, found that long-term (5 years) recurrence rates were significantly lower after HLS than after endovenous laser ablation (EVLA) (12%, 95% CI 7%-20% vs 22%, 95% CI 14%-32%; *P*=0.038).[22] Others reported that long-term results of HLS do not differ from those of EVTA with respect to recurrence.[23,24] Nevertheless, HLS is associated with more frequent postoperative complications, such as hematoma, wound infection, paresthesia, and longer hospitalization and recovery than with EVLA.[25]

Many practitioners consider HLS to be a superior treatment option for large-diameter GSV.[17,18] In a retrospective study by Kubat et al comparing 5 different approaches in patients with GSV diameter ≥10 mm, HLS-treated patients had lower recurrence rates compared with 980-nm EVLA, 1470-nm EVLA, radiofrequency ablation (RFA), and cyanoacrylate adhesive closure (CAC).[14] Nevertheless, the study concluded that recurrence rates were not statistically significantly different at 6 months and 1 year among HLS, 1470-nm EVLA, and RFA.[14] Another multicenter retrospective study including patients with GSV ≥14 mm found that HLS was associated with more adverse events, such as postoperative pain, hemorrhage, and incidence of paresthesia, although recurrence rates were similar to those with RFA.[12]

Thermal ablation techniques

Since the first EVLA procedure performed in 1999,[26] endovenous techniques have become very popular as a minimally invasive alternative procedure to traditional surgery. The two most commonly used EVTA techniques are EVLA and RFA. The recently published European Society for Vascular Surgery guidelines recommend EVTA in preference to surgery and to foam sclerotherapy for the treatment of incompetent GSV (level of evidence A, class I).[7] Endovenous steam ablation and endovenous microwave ablation are two alternative EVTA techniques, although there is limited data about these in the literature. The technique is similar for all EVTA methods. The procedure is performed under DUS guidance and requires the use of buffered solutions for tumescent anesthesia. Percutaneously, a laser fiber or RFA catheter is inserted and advanced distal to the SFJ or saphenopopliteal junction. While withdrawing the catheter or fiber, thermal energy is emitted into the vein wall causing endothelial damage and vein occlusion.

Efficacy and safety of EVTA techniques heavily depend on multiple parameters, such as anatomical characteristics, technical device parameters, and proper technique. Initially, low laser wavelengths (hemoglobin targeting) with bare-tip fibers have been replaced by higher laser wavelengths (water targeting) with different configuration fiber tips (radial ring, jacketed tip, tulip tip). In the water-targeting lasers (>1320 nm), the absorption of the energy by the venous wall is higher; thus, by delivering less energy, increased efficiency and reduced complications are achieved. Many studies comparing 980-nm with 1470-nm fibers reported that the higher wavelength was associated with comparable occlusion rates, less postoperative pain, ecchymosis, paresthesia, and induration.[27-29] Similarly, the second-generation RFA catheters are more efficient and safer than first-generation catheters, as the thermocouple is enclosed in a lubricated sheath that ensures obliteration and prevents target-vein carbonization and thrombosis.[13,30]

Previous EVTA studies reported that larger GSVs had lower occlusion rates and higher complication rates, including endothermal heat-induced thrombosis (EHIT), although the latter conclusion was mainly based on patients treated with hemoglobin-targeting laser fibers and first-generation RFA catheters.[17,18,31] A prospective comparative study, including GSV >15 mm, displayed excellent occlusion (95%) and healing ulcer rates (88%) in patients treated with the 1560-nm EVLA wavelength.[32] Another retrospective study, including GSV >10 mm, found similar recurrence rates among 1470-nm EVLA, RFA, and HLS (5.5%, 5.7%, and 3.3%, respectively) at 1-year follow-up.[14] In addition, the recurrence rates of EVLA

at the 980-nm wavelength and of CAC-treated patients were higher than in other groups (14.6% and 15.2%).[14] A prospective comparative study, comparing 1470-nm EVLA and RFA in patients with GSV >10 mm, reported comparable occlusion rates, although there were lower complication rates in the 1470-nm EVLA group, such as postoperative pain and ecchymosis.[15] Another unpublished study, presented at the UIP 2023 World Congress and American Vein & Lymphatic Society (AVLS) 2023 Annual Congress, reported that 1470-nm EVLA and RFA in patients with GSV >12 mm had comparable results in terms of occlusion rates, complications, venous clinical severity score (VCSS) and Chronic Venous Insufficiency Quality-of-Life Questionnaire (CIVIQ) scores.[33] Two more studies, investigating the efficacy of RFA in large-diameter GSV >12 mm, found high occlusion rates (96% and 100%) and low complication rates (8% and 13.6%) at 1-year follow-up.[11,13] A recent systematic review and meta-analysis by Bontinis et al reported excellent occlusion (95.9%) and technical success rates (99.9%) for the EVTA of GSV >12 mm.[34] Furthermore, the study found no association between occlusion rates, the type of device used, and the length of follow-up.[34]

Although there is controversy around EVTA techniques and large-diameter GSV, newer-generation devices, variable application of energy and tumescent anesthesia, external compression and multi-pass technique during ablation, and also closer surveillance for early detection of complications have increased the efficacy and safety of EVTA.[10,11,19,33] Current guidelines recommend that in patients with an incompetent GSV >12 mm, EVTA should be considered (level of evidence IIa, class C).[7]

Nonthermal ablation techniques

Nonthermal endovenous techniques are ultrasound-guided foam sclerotherapy (UGFS), mechanochemical ablation (MOCA), and catheter-directed injection of cyanoacrylate glue, known as CAC. There are many similarities among these treatments, such as saphenous vein cannulation, endovenous substance infusion, and no need for tumescent anesthesia.

During UGFS, a sclerosing agent, most commonly polidocanol or sodium tetradecyl sulphate in various concentrations, is injected into the target vein to cause fibrosis of the vein. Many studies with long-term follow-up have shown that recurrence rates are higher in patients treated with UGFS than with EVTA and HLS.[35,36] Nevertheless, the advantages of UGFS are that it can be easily applied for tortuous veins where there are difficulties in advancing the ablation device and it's suitable for recurrent VVs. An alternative to the classical UGFS is catheter-directed foam sclerotherapy (CDFS) with or without tumescent anesthesia in order to reduce the vein caliber. A systematic review and meta-analysis showed a higher occlusion rate of 82.4% after CDFS and 62.9% after UGFS at 3-year follow-up.[37] Regarding GSV diameter, Shadid et al, reported higher recurrence rates after UGFS in patients with mid-thigh GSV diameter >6 mm (62.6%) versus smaller ones (42%) at 2-year follow-up.[38] Another study also reported worse success rates for veins >6 mm (hazard ratio [HR] 2.22; 95% CI 1.40-3.50) compared with veins <5 mm.[39] Venermo et al also found an association between larger-diameter and GSV patency.[40] The occlusion rate after UGFS was less than 40% in mid-thigh GSVs ≥9 mm compared with 75% in GSVs <6 mm.[40] Therefore, UGFS should be preferably used for veins smaller than 6 mm in diameter.[38-40]

The MOCA technique uses a dual-injury mechanism that combines mechanical disruption of the intima with chemical endovenous ablation. Damage of the endothelium is achieved through a rotating wire or sharp hook at the tip of the catheter while chemical ablation is performed by injecting a foam sclerosant. A systematic review and meta-analysis have shown that the pooled anatomic success after MOCA was 94.1% at 1-year follow-up.[41] One RCT reporting outcomes at 3 years found a significantly lower occlusion rate after MOCA than with EVTA (80% vs 100%).[42] The study also found a strong association between recanalization and GSV diameter. The occlusion rates for a preoperative GSV diameter of 6 mm, 7 mm, and 8 mm were 100%, 87.5%, and 75%, respectively.[42]

Upon CAC, intravenous injection of cyanoacrylate rapidly solidifies via a polymerization reaction and produces an inflammatory reaction of the vein wall. Currently, 3 types of CAC devices are commercially available, and the main differences relate to the cyanoacrylate formulation and application techniques. Several studies have shown that CAC is safe and effective to ablate the incompetent GSV, with cumulative occlusion rates comparable to those for EVTA and better compared with other nonthermal ablation techniques (up to 93.6% at 5 years).[42-44] For patients with superficial venous incompetence of a saphenous trunk requiring treatment, CAC should be considered when a nonthermal nontumescent technique is preferred (level of evidence IIa, class A).[7] Chan et al, found that a mean GSV diameter ≥8 mm was a significant predicting factor for recanalization (HR, 6.92; 95% CI, 1.34–35.67; *P*=0.021).[45] A saphenous vein diameter of >8 mm has also been reported as a risk factor for hypersensitivity reaction after CAC.[46] Another study reported that in patients with GSV >10 mm, 1-year recurrence rates with CAC were higher than with 1470-nm EVLA and RFA (15.2%, 5.5%, and 5.7%, respectively).[14] A network meta-analysis on the efficacy and safety of thermal and nonthermal endovenous ablation treatments found a trend for a considerably decreased efficacy with both CAC and MOCA than with RFA and EVLA for larger GSV diameters.[47]

Conclusions

Interventional treatment remains the optimal therapy for patients with superficial venous incompetence presenting with symptomatic VVs. EVTA techniques are considered the first-choice treatment regardless of GSV diameter. Higher laser wavelengths are more effective than lower laser wavelengths in large GSV. Nonthermal ablation techniques seem to be inappropriate treatment for GSV diameters larger than 6 mm.

CORRESPONDING AUTHOR

Christos S. Karathanos, MD, MSc, PhD

Department of Vascular Surgery, University Hospital of Larissa, Mezourlo, 41 110 Larissa, Greece

EMAIL: *christoskarathanos@yahoo.gr*

CO-AUTHOR

Athanasios D. Giannoukas, MD, PhD

Department of Vascular Surgery, University Hospital of Larissa, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece

References

1. Robertson L, Evans C, Fowkes FG. Epidemiology of chronic venous disease. *Phlebology*. 2008;23(3):103- 111.
2. Lee AJ, Robertson LA, Boghossian SM, et al. Progression of varicose veins and chronic venous insufficiency in the general population in the Edinburgh Vein Study. *J Vasc Surg Venous Lymphat Disord*. 2015;3:18-26.
3. Carradice D, Wallace T, Gohil R, Chetter I. A comparison of the effectiveness of treating those with and without the complications of superficial venous insufficiency. *Ann Surg*. 2014;260:396-401.
4. Michaels JA, Brazier JE, Campbell WB, MacIntyre JB, Palfreyman SJ, Ratcliffe J. Randomized clinical trial comparing surgery with conservative treatment for uncomplicated varicose veins. *Br J Surg*. 2006;93:175-181.
5. Ratcliffe J, Brazier JE, Campbell WB, Palfreyman S, MacIntyre JB, Michaels JA. Cost-effectiveness analysis of surgery versus conservative treatment for uncomplicated varicose veins in a randomized clinical trial. *Br J Surg*. 2006;93:182-186.
6. Marsden G, Perry M, Bradbury A, et al. A cost-effectiveness analysis of surgery, endothermal ablation, ultrasound-guided foam sclerotherapy and compression stockings for symptomatic varicose veins. *Eur J Vasc Endovasc Surg*. 2015;50:794-801.
7. De Maeseneer MG, Kakkos SK, Aherne T, et al. Editor's Choice – European Society for Vascular Surgery (ESVS) 2022 clinical practice guidelines on the management of chronic venous disease of the lower limbs. *Eur J Vasc Endovasc Surg*. 2022;63:184-267.
8. Lane TR, Varatharajan L, Fiorentino F, et al. Truncal varicose vein diameter and patient reported outcome measures. *Br J Surg*. 2017;104:1648-1655.
9. Hamel-Desnos CM, De Maeseneer M, Josnin M, Gillet JL, Allaert FA; DIAGRAVES Study Group. Great saphenous vein diameters in phlebological practice in France: a report of the DIAGRAVES Study by the French Society of Phlebology. *Eur J Vasc Endovasc Surg*. 2019;58:96-103.
10. Dabbs EB, Mainsiouw LE, Holdstock JM, Price BA, Whiteley MS. A description of the 'smile sign' and multi-pass technique for endovenous laser ablation of large diameter great saphenous veins. *Phlebology*. 2018;33(8):534-539.
11. Woo HY, Kim SM, Kim D, Chung JK, Jung IM. Outcome of ClosureFAST radiofrequency ablation for large-diameter incompetent great saphenous vein. *Ann Surg Treat Res*. 2019;96:313-318.
12. Shaidakov EV, Grigoryan AG, Ilyukhin EA, Bulatov VL, Rosukhovskiy DA. Radiofrequency ablation or stripping of large-diameter incompetent great saphenous varicose veins with C2 or C3 disease. *J Vasc Surg Venous Lymphat Disord*. 2016;4:45-50.
13. Fernandez MC, Lopez IM, Hernandez Mateo MM, Marques de Marino P, Artero IC, Serrano Hernando FJS. Prospective study of safety and effectiveness in the use of radiofrequency ablation for incompetent great saphenous vein >12 mm. *J Vasc Surg Venous Lymphat Disord*. 2017;5:810-816.
14. Kubat E, Ünal CS, Geldi O, Çetin E, Keskin A. What is the optimal treatment technique for great saphenous vein diameter of ≥10 mm? Comparison of five different approaches. *Acta Chirurgica Belgica*. 2021;121(2):94-101.
15. Mese B, Bozoglan O, Eroglu E, et al. A comparison of 1470 nm endovenous laser ablation and radiofrequency ablation in the treatment of great saphenous veins 10 mm or more in size. *Ann Vasc Surg*. 2015;29(7):1368-1372.

16. Maeseneer M, Pichot O, Cavezzi A, et al. Duplex ultrasound investigation of the veins of the lower limbs after treatment of varicose veins UIP consensus document. *Eur J Vasc Endovasc Surg*. 2011;42:89-102.

17. van den Bos R, Neumann M, de Roos K, et al. Endovenous laser ablation-induced complications: review of the literature and new cases. *Dermatol Surg*. 2009;35:1206-1214.

18. Corcos L, Dini S, Peruzzi C, et al. Duplex ultrasound changes in the great saphenous vein after endosaphenous laser occlusion with 808-nm wavelength. *J Vasc Surg*. 2008;48:1262-1271.

19. Atasoy M. Efficacy and safety of endovenous laser ablation in very large and tortuous great saphenous veins. *J Vasc Interv Radiol*. 2015;26:1347-1352.

20. Dwerryhouse S, Davies B, Harradine K, et al. Stripping the long saphenous vein reduces the rate of reoperation for recurrent varicose veins: five-year results of a randomized trial. *J Vasc Surg*. 1999;29(4):589-592.

21. Winterborn RJ, Foy C, Earnshaw JJ. Causes of varicose vein recurrence: late results of a randomized controlled trial of stripping the long saphenous vein. *J Vasc Surg*. 2004;40:634-639.

22. Hamann SAS, Giang J, De Maeseneer MGR, Nijsten TEC, van denBos RR. Editor's Choice - Five year results of great saphenous vein treatment: a meta-analysis. *Eur J Vasc Endovasc Surg*. 2017;54:760-770.

23. Whing J, Nandhra S, Nesbitt C, Stansby G. Interventions for great saphenous vein incompetence. *Cochrane Database Syst Rev*. 2021;8:CD005624.

24. Kheirelseid EAH, Crowe G, Sehgal R, et al. Systematic review and meta-analysis of randomized controlled trials evaluating long term outcomes of endovenous management of lower extremity varicose veins. *J Vasc Surg Venous Lymphat Disord*. 2018;6:256-270.

25. Pan Y, Zhao J, Mei J, Shao M, Zhang J. Comparison of endovenous laser ablation and high ligation and stripping for varicose vein treatment: a meta-analysis. *Phlebology*. 2014;29:109-119.

26. Boné SC. Tratamiento Endoluminal de las varices con laser de diodo. Estudio preliminar. *Patologia Vascular*. 1999;5:32-39.

27. Doganci S, Demirkilic U. Comparison of 980 nm laser and bare tip fibre with 1470 nm laser and radial fibre in the treatment of great saphenous vein varicosities: a prospective randomized clinical trial. *Eur J Vasc Endovasc Surg*. 2010;40:254-259.

28. Hirokawa M, Ogawa T, Sugawara H, Shokoku S, Sato S. Comparison of 1470 nm laser and radial 2ring fiber with 980 nm laser and bare-tip fiber in endovenous laser ablation of saphenous varicose veins: a multicenter, prospective, randomized, non-blind study. *Ann Vasc Dis*. 2015;8:282-289.

29. Arslan U, Calik E, Tort M, et al. More successful results with less energy in endovenous laser ablation treatment: long-term comparison of bare-tip fiber 980 nm laser and radial-tip fiber 1470 nm laser application. *Ann Vasc Surg*. 2017;45:166-172.

30. Zuniga JM, Hingorani A, Ascher E, et al. Short term outcome analysis of radiofrequency ablation using ClosurePlus vs ClosureFast catheters in the treatment of incompetent great saphenous vein. *J Vasc Surg*. 2012;55:1048-1051.

31. Gloviczki P, Comerota AJ, Michael C, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg*. 2011;53(Suppl):2S-48S.

32. Starodubtsev V, Lukyanenko M, Karpenko A, Ignatenko P. Endovenous laser ablation in patients with severe primary chronic venous insufficiency. *Int Angiol*. 2017;36:368-374.

33. Karathanos C, Spanos K, Batzalexis K, et al. Endovenous thermal ablation techniques for the treatment of large diameter incompetent great saphenous veins. Paper presented at: Union International Phlebology 2023 World Congress and American Vein and Lymphatic Society; September 17-21, 2023; Miami, Florida, USA.

34. Bontinis V, Bontinis A, Koutsoumpelis A, et al. Endovenous thermal ablation in the treatment of large great saphenous veins of diameters > 12 mm: a systematic review meta-analysis and meta-regression. *Vasc Med*. 2023;28(5):449-457.

35. Brittenden J, Cooper D, Dimitrova M, et al. Five-year outcomes of a randomized trial of treatments for varicose veins. *N Engl J Med*. 2019;381:912-922.

36. van der Velden SK, Biemans AA, De Maeseneer MG, et al. Five-year results of a randomized clinical trial of conventional surgery, endovenous laser ablation and ultrasound-guided foam sclerotherapy in patients with great saphenous varicose veins. *Br J Surg*. 2015;102:1184-1194.

37. Lim SY, Tan JX, D'Cruz RT, Syn N, Chong TT, Tang TY. Catheter-directed foam sclerotherapy, an alternative to ultrasound-guided foam sclerotherapy for varicose vein treatment: a systematic review and meta-analysis. *Phlebology*. 2020;35:369-383.

38. Shadid N, Nelemans P, Lawson J, Sommer A. Predictors of recurrence of great saphenous vein reflux following treatment with ultrasound-guided foam sclerotherapy. *Phlebology*. 2015;30:194-199.

39. Myers KA, Jolley D, Clough A, Kirwan J. Outcome of ultrasound guided sclerotherapy for varicose veins: medium-term results assessed by ultrasound surveillance. *Eur J Vasc Endovasc Surg*. 2007;33:116-121.

40. Venermo M, Saarinen J, Eskelinen E, et al. Randomized clinical trial comparing surgery, endovenous laser ablation and ultrasound-guided foam sclerotherapy for the treatment of great saphenous varicose veins. *Br J Surg*. 2016;103:1438-1444.

41. Vos CG, Unlu C, Bosma J, van Vlijmen CJ, de Nie AJ, Schreve MA. A systematic review and meta-analysis of two novel techniques of non thermal endovenous ablation of the great saphenous vein. *J Vasc Surg Venous Lymphat Disord*. 2017;5:880-896.

42. Vähäaho S, Halmesmäki K, Mahmoud O, Albäck A, Noronen K, Venermo M. Three-year results of a randomized controlled trial comparing mechanochemical and thermal ablation in the treatment of insufficient great saphenous veins. *J Vasc Surg Venous Lymphat Disord*. 2021;9:652-659.

43. Morrison N, Gibson K, Vasquez M, Weiss R, Jones A. Five-year extension study of patients from a randomized clinical trial (VeClose) comparing cyanoacrylate closure versus radiofrequency ablation for the treatment of incompetent great saphenous veins. *J Vasc Surg Venous Lymphat Disord*. 2020;8:978-989.

44. Garcia-Carpintero E, Carmona M, Chalco-Orrego JP, Gonzalez-Enriquez J, Imaz Iglesia I. Systematic review and meta-analysis of endovenous cyanoacrylate adhesive ablation for incompetent saphenous veins. *J Vasc Surg Venous Lymphat Disord*. 2020;8:287-296.

45. Chan YC, Law Y, Cheung GC, Ting AC, Cheng SW. Cyanoacrylate glue used to treat great saphenous reflux: measures of outcome. *Phlebology*. 2017;32:99-106.

46. Sermsathanasawadi N, Hanaroonsomboon P, Pruekprasert K, et al. Hypersensitivity reaction after cyanoacrylate closure of incompetent saphenous veins in patients with chronic venous disease: a retrospective study. *J Vasc Surg Venous Lymphat Disord*. 2021;9:910-915.

47. Bontinis V, Bontinis A, Koutsoumpelis A, et al. A network meta-analysis on the efficacy and safety of thermal and nonthermal endovenous ablation treatments. *J Vasc Surg Venous Lymphat Disord*. 2023;11(4):854-865.

Phlebolymphology Vol 31 | No. 2 | 2024

Pathogenesis, diagnosis, and treatment of endothermal heat-induced thrombosis (EHIT)

Sandeep Raj Pandey, MS, FVES, FIDF, FIUA

Annapurna Hospital, Kathmandu, Nepal

ABSTRACT

Propagation of a thrombus from a superficial vein into a deeper vein post endovenous thermal ablation is called endothermal heat-induced thrombosis (EHIT). It is generally considered clinically insignificant if the thrombus does not propagate to the deep venous system. Diagnosis of EHIT is based mainly on 4 classification categories for both saphenofemoral junction and saphenopopliteal junction. The condition can be treated with antiplatelet or anticoagulation therapy, although monitoring may be sufficient, especially in less-severe cases. Rivaroxaban may be a promising alternative for treatment of severe EHIT because the dosage regimen is simplified without compromising efficacy or safety and is easily available as an oral anticoagulant and is more cost-effective than perenteral enoxaparin. Prospective, randomized, controlled studies are needed to better understand EHIT and to develop more definitive recommendations on prevention and treatment options for this condition. Therefore, the true clinical significance of EHIT is still being determined.

Keywords

chronic venous insufficiency | deep venous thrombosis | endothermal heat-induced thrombosis | saphenofemoral junction | saphenopopliteal junction | thermal ablation | varicose veins

Phlebolymphology. 2024;31(2):66-73.

www.phlebolymphology.org

Introduction

There is evidence that the population is significantly impacted by chronic venous insufficiency (CVI). Often asymptomatic, CVI may also present as varicose veins (in 20% to 30% of the population), edema, skin changes (up to 6%), and ulceration (active venous ulcerations in up to 0.5%).[1,2] Related issues such as cosmetic concerns, debilitating symptoms, and complications that may be limb threatening (eg, postthrombotic syndrome) or even life threatening (eg, venous thromboembolism, sepsis) may also affect quality of life.[2,3]

A common cause of CVI is superficial venous reflux disease, treatment of which has seen revolutionary change with the advent of endovenous thermal ablation technologies. Of these, the most robustly investigated—endovenous laser ablation (EVLA) and radiofrequency ablation (RFA)—have been determined to be safe, effective, and durable as conservative varicose therapies.[2,4] Furthermore, both these therapies (carried out under tumescent anesthesia application) allow transition of care to the ambulatory setting. Periprocedural outcomes are improved and the return to work is speedier than with surgical stripping.[2,5] These days, RFA and laser have replaced surgical stripping almost everywhere.

However, with use of these heat-inducing techniques (endovenous thermal ablations), reports began to emerge of an association with deep venous thrombosis (DVT). For example, in 2004, Hingorani et al, in a study based on postprocedure surveillance ultrasound findings, showed its association with DVT of the common femoral vein (CFV).[2,6] An increased risk of DVT (from 0% to 8%) was also reported in other publications from the early 2000s.[2,7] Later reports, believing these postoperative thrombi to be distinct from DVT, called them thrombus extension.[2,8] And although not considered abnormal to find on ultrasound imaging a superficial thrombus in a vein segment that's been treated, the propagation of such a thrombus could be a risk for development of symptomatic DVT and pulmonary embolism (PE). *Figure 1* shows DVT after endovenous heat-induced thrombosis (EHIT).[9]

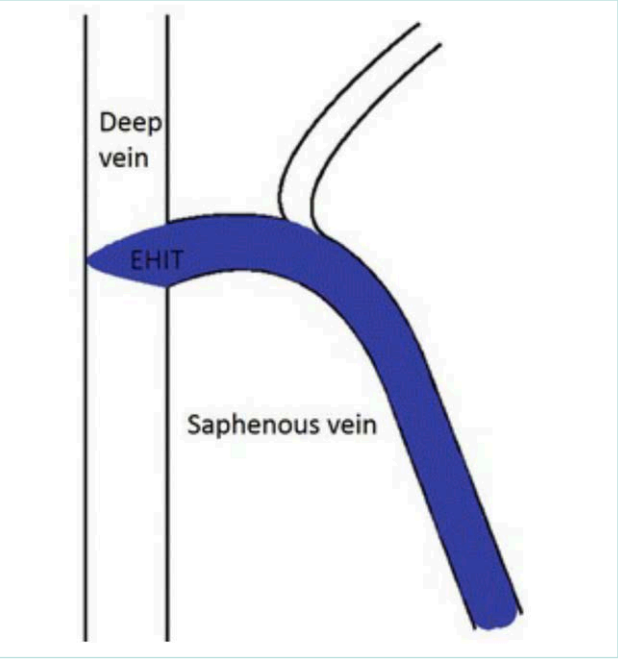


Figure 1. **Diagram of endothermal heat-induced thrombosis (EHIT) extending into a deep vein.**
After reference 9: Thoracic Key. https://thoracickey.com/complications-of-the-treatment-of-venous-insufficiency/

This term, EHIT, to refer to such thrombi was introduced in 2006 by Kabnick et al (and in 2021, Kabnick et al published an article on the classification and treatment of EHIT,[2] largely referred to here); they defined it as the propagation of thrombus into the deep vein contiguous with the ablated superficial vein, a definition now widely adopted.[2,10] We use this definition of EHIT in Nepal as well.

EHIT and classic DVT are considered diagnostically and clinically to be separate entities. The ultrasonographic appearance of EHIT is distinct, showing up as a hyperechogenic, noncompressible area that has an abnormal venous flow and augmentation involving the saphenofemoral junction (SFJ) or saphenopopliteal junction (SPJ) after ablation of the great saphenous vein (GSV) or small saphenous vein (SSV), respectively.[2,11] DVT on the other hand shows up as a hypoechogenic area. EHIT behaves like a stable thrombus, and spontaneous regression often occurs within a few weeks of observation or after a short anticoagulation treatment.[2] *Figure 2* shows thrombus echogenicity of DVT and EHIT on duplex ultrasound.

Reported rates of EHIT after endovenous ablation range from 0% to 3%.[2] It is usually on routine follow-up with duplex ultrasound that it's diagnosed, as most are asymptomatic, and that can be anywhere from 24 hours up to 2 weeks after the procedure (local ultrasound protocols vary),[2] In our practice, we usually have high-risk patients come in for ultrasound follow-up, aiming to prevent EHIT. Whereas most EHIT are asymptomatic (ie, silent), a history of recent endothermal venous ablation or a thrombus at the junction has been associated with PE (rare cases).[2]

Anatomically, EHIT (which, as the term evokes, is provoked) is considered to be a form of DVT; however, with regard to *clinical* course, EHIT is more benign than DVT that is unprovoked or that occurs in a remote vein segment.[2] Exactly how the mechanism of excessive thrombus formation differs between the heat-inducing procedures EVLA and RFA is not known.[2]

For thrombotic complications after venous ablation, reports should take into consideration all postprocedure ultrasound findings. For example, EHIT reports most often describe thrombi that protrude into the CFV or the popliteal vein, but a deep calf thrombus can also be considered EHIT when it extends into a calf vein from a treated perforator, a treated

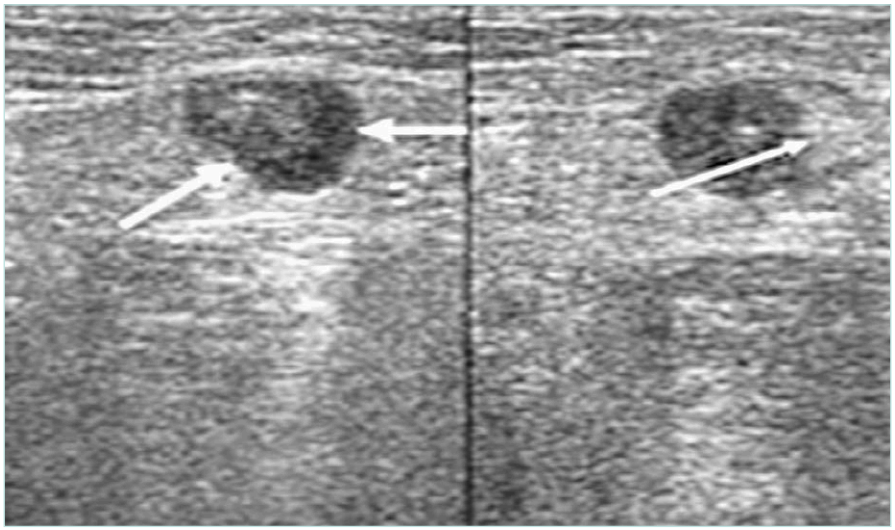


Figure 2. **Thrombus echogenicity in ultrasonography. Deep venous thrombosis (DVT) is hyperechoic (left, white arrow), and endovenous heat-induced thrombosis (EHIT) is hyperechoic (right, white arrow).**
Image courtesy of S.R. Pandey.

SSV that drains directly into a gastrocnemius vein, or a treated below-knee GSV through a perforator.[2] DVTs that would not be considered EHIT (ie, non-EHIT DVT) include a deep vein thrombus nonadjacent to the SFJ after GSV ablation, a thrombus remote from the SPJ after SSV ablation, a remote calf vein thrombus after GSV ablation, and a DVT in the contralateral limb.[2] It's possible to find both EHIT and non-EHIT DVT in the same patient.[2,12] Proper clinical history and ultrasonography findings may be helpful in differentiating them.

DVT after endovenous ablation is reported in current literature to have an overall rate of <1%, with EHIT more likely (3 to 4 times more so) than non-EHIT DVT.[2,13] Whereas EHIT can retract or resolve early, classic (ie, non-EHIT) DVTs do not do so as early. This may be because classic DVTs are likely elicited by other factors, including a high degree of immobilization, poorly fitting compression hosiery, and activation of the coagulation cascade during endovenous thermal ablation at a remote vein site.[2]

Although considered the gold standard, ultrasonography for DVT diagnosis does have a wide variation in sensitivity, particularly when duplex ultrasound is used for below-knee scans. For that reason, the incidence of calf DVT after endovenous ablation could be higher than reported, possibly accounting for some cases of PE of unknown source.[2] Anatomic location should clearly distinguish between EHIT and non-EHIT DVT, but whether pathologic differentiation can be made on the basis of ultrasound appearance of the thrombus—mainly echogenicity, hypo or hyper—is unclear.[2]

Preclinical studies in animals have shown significantly greater hypercellular response, fibroblastic reaction, and edema in histologic specimens of EHIT after RFA than for classic DVT, with thrombi from the EHIT specimens appearing more echogenic than those of DVT.[2] A greater echogenicity of EHIT on ultrasound examination has been shown as well in preliminary human studies, with EHIT's mildly echoreflective thrombus distinguishing it from a classic acute DVT's echolucency.[2,14]

The time frame for development of EHIT is not completely clear: whereas EHIT usually develops within 72 hours, it has also been identified 1 to 4 weeks after endovenous ablation on occasion via postprocedure surveillance ultrasound examination.[2] This lack of clarity with regard to timing makes it uncertain whether an EHIT that develops more than 1 week after ablation should be considered EHIT and treated as such or as a classic DVT.[2]

Indeed, evidence suggesting that thrombi occurring at the site of endovenous ablation within 30 days of the procedure is potentially related to the procedure itself (directly or indirectly) was shown in a prospective study by Lurie and Kistner.[12] In their investigation in patients undergoing RFA of the GSV, levels of both C-reactive protein and D-dimer—markers of inflammation and hemostatic activation—significantly increased at 24 to 36 hours after treatment and returned to baseline levels at 1 month, indicating that these processes are present for a prolonged period of time after venous surgical trauma.[2]

Rather than EHIT, another broader term "postablation superficial thrombus extension" has been used by some for a thrombus extension from the superficial to the deep system after endovenous ablation via any kind of chemical or thermal technique.[15] They note that such extension differs from a classic DVT in that it typically occurs within 1 week, there is no progression, and within 2 weeks it has usually resolved.

Definitions of the terms EHIT, non-EHIT DVT, and postablation superficial thrombosis are recommended by Kabnick et al[2] below to help provide clinical guidelines for the management of thromboembolic events that follow endovenous thermal ablation, events that can lead to serious consequences (eg, PE):

- *EHIT:* any thrombus detected by ultrasound within 4 weeks of endovenous thermal ablation originating from the treated vein and protruding into a deep vein.
- *Non-EHIT DVT:* a DVT occurring in a venous segment not contiguous with the thermally ablated vein.

- *Postablation superficial venous thrombosis:* presence of thrombus in a superficial vein other than the treated vein. This vein may or may not be contiguous with the ablated vein.

In order to validate or revise proposed definitions, Kabnick et al recommend that future reporting for thromboembolic events after endovenous thermal ablation include detailed information on anatomic location, clinical presentation, and time of occurrence of these events.[2] If possible, reports should include detailed sonographic features and progression of all these thrombi at follow-up ultrasound examination.[2]

It's important that other—non-EHIT—thrombotic events are also recognized and reported because non-EHIT thrombotic events occurring during thermal ablation are probably triggered by systemic factors more related to an acquired prothrombotic state than to the thermal energy itself.[2]

Pathophysiology

As mentioned above, with the advent of endothermal ablation technologies, including EVLA and RFA, for treatment of superficial venous reflux, thrombus propagation associated with these procedures emerged, and though incidence was low, it was recognized early. Over time, the concept of EHIT was differentiated from DVT as a separate entity, with EHIT's pathophysiology believed directly related to the heat-induced injury during treatment.[16] Classification systems for EHIT were developed, supporting its recognition as a distinct process[16] (4 of these that have gained prominence in the literature are outlined in the section on Diagnosis below).

The rarity of EHIT made it difficult to identify its risk factors. These include a vein diameter >10 mm, operative time >40 minutes, a Caprini score >6, multiple phlebectomies, old age, etc. Notable, there has been a progressive reduction in the incidence of EHIT, possibly related to practitioner experience or changes in technique (eg, increasing the ablation distance from the SFJ).[16]

Treatment of EHIT is chosen on the basis of the extent of thrombus propagation. A fully occlusive EHIT appears to be exceedingly rare, and as most EHIT resolve spontaneously or with a limited course of antiplatelet or anticoagulation therapy, their true clinical and pathological significance is unclear.[16]

Diagnosis

The causes behind pain and swelling after a therapeutic procedure can be difficult to differentiate; without duplex ultrasound imaging, it is also difficult to clinically distinguish EHIT from DVT.[9] With significant differences in the natural course of EHIT and DVT and in their treatment, the etiology of postoperative complications should be determined in all patients with pain and swelling.[9]

Duplex ultrasound

Postprocedure duplex ultrasound is not necessary for all patients to evaluate them for EHIT or DVT.[9] However, in those that have significant postoperative pain or swelling and those at high risk for DVT and EHIT, duplex ultrasound imaging should be used to assess the site of ablation for hematoma or superficial branch or truncal vein thrombus, with both B mode and color flow, using 2–10 MHz transducers *(Figure 3)*,[9] in both the supine and standing position.[9] The transducer wavelength should be chosen in accordance with the patient's body habitus and the depth of the superficial and deep venous system at the site under evaluation.[9] Measurements (via electronic cursor) taken in transverse, axial, and orthogonal positions can be used to determine the distance and relationship between any thrombus identified and the vein wall, as well as the presence, absence, and extent of protrusion into the deep system.[9]

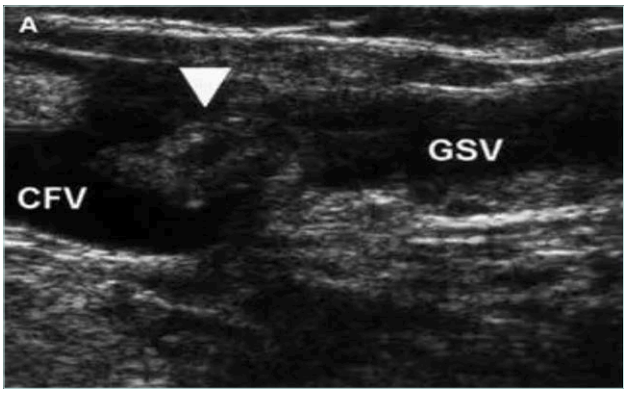


Figure 3. **Ultrasound appearance of endothermal heat-induced thrombosis (EHIT), when thrombus has extended into the deep vein from the saphenous vein.**

Abbreviations: CFV, common femoral vein; GSV, great saphenous vein.

After reference 9: Thoracic Key. https://thoracickey.com/complications-of-the-treatment-of-venous-insufficiency/

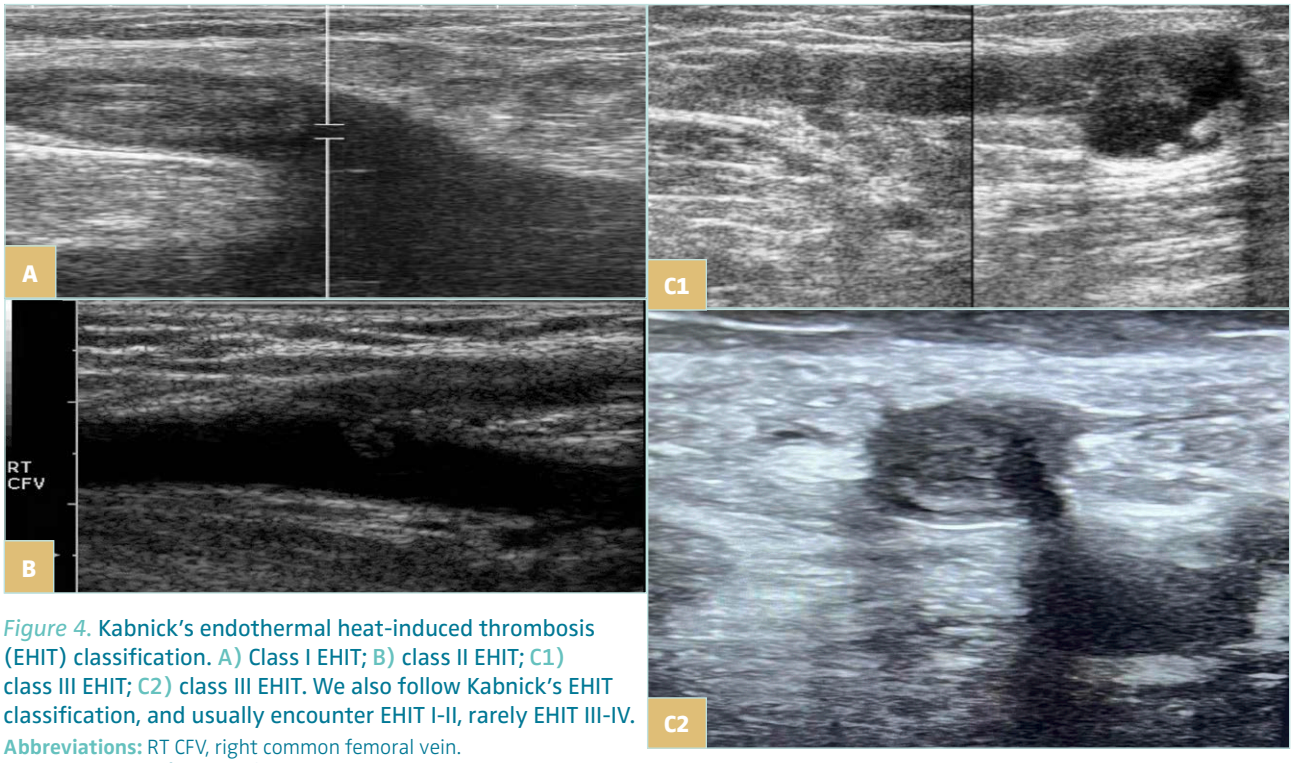


Figure 4. Kabnick's endothermal heat-induced thrombosis (EHIT) classification. A) Class I EHIT; B) class II EHIT; C1) class III EHIT; C2) class III EHIT. We also follow Kabnick's EHIT classification, and usually encounter EHIT I-II, rarely EHIT III-IV.
Abbreviations: RT CFV, right common femoral vein.
Images courtesy of S.R. Pandey.

Classification of EHIT

Different EHIT classification systems have been published. In general, EHIT classification systems take into account the extent of thrombus propagation relative to the SPJs; for example, the greater the extent of propagation into the contiguous deep vein, the higher the class assigned.[16]

Classification systems by Kabnick, Lawrence, Harlander-Locke, and the American Venous Forum, are outlined here[2]:

1. The Kabnick EHIT classification (Class I-IV) is defined as follows: Class I) Extension of thrombus up to and including the deep vein junction *(Figure 4A)*; Class II) Propagation of thrombus into the adjacent deep vein but comprising <50% of the deep vein lumen *(Figure 4B)*; Class III) Propagation of thrombus into the adjacent deep vein but comprising >50% of the deep vein lumen *(Figure 4C1,C2)*; and Class IV) Deep vein occlusive thrombus contiguous with the treated superficial vein *(Figure 1)*.

2. The Lawrence EHIT classification[17] (Level 1-6) is defined as follows: Level 1) Thrombus extension that remains peripheral to the epigastric vein; Level 2) Thrombus extension that is flush with the orifice of the epigastric vein; Level 3) Thrombus extension that is flush with the saphenofemoral junction (SFJ); Level 4) Thrombus bulging into the CFV; Level 5) Thrombus bulging into the CFV and adherent to the wall of the CFV past the SFJ; and Level 6) Thrombus extension into the CFV consistent with a DVT.

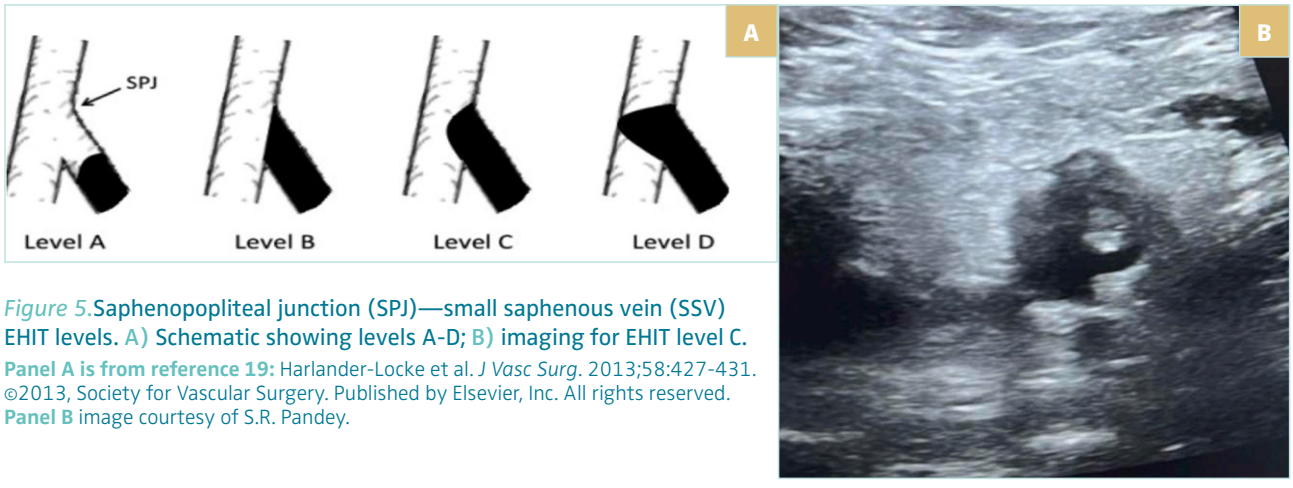


Figure 5. Saphenopopliteal junction (SPJ)—small saphenous vein (SSV) EHIT levels. A) Schematic showing levels A-D; B) imaging for EHIT level C.
Panel A is from reference 19: Harlander-Locke et al. *J Vasc Surg*. 2013;58:427-431.

Panel B image courtesy of S.R. Pandey.

3. The Harlander-Locke classification for EHIT (Level A-D), specific for SSV *(Figure 5A,B)* is defined as follows: Level A) Thrombus propagation peripheral to the SPJ; Level B) Thrombus propagation extending to the SPJ; Level C) Thrombus propagation into the popliteal vein but nonocclusive; and Level D) Occlusive DVT of the popliteal vein.

4. The American Venous Forum (AVF) classification for EHIT (Class I-IV) is defined as follows: Class I) Thrombus without propagation into the deep vein; a, Peripheral to superficial epigastric vein; b, Central to superficial epigastric vein, up to and including the deep vein junction; Class II) Thrombus propagation into the adjacent deep vein but comprising <50% of the deep vein lumen; Class III) Thrombus propagation into the adjacent deep vein but comprising >50% of the deep vein lumen; and Class IV) Occlusive deep vein thrombus contiguous with the treated superficial vein.

Treatment

As the natural history of EHIT is considered more benign than that of classic DVT, its management remains controversial. Indeed, EHIT is often asymptomatic, progression to PE is rarely reported, and there is no conclusive evidence that treating it reduces the incidence of PE. Additionally, much more conservative treatment methods are in use now than those employed for early case series when EHIT was recognized as a complication of thermal ablation (those used inferior vena cava filter placement and saphenofemoral thrombectomy with ligation).[18] Notable, most of the EHIT treatment reports were made before widespread use of direct oral anticoagulants, an evolution in treatment that should be taken into account.

Conducting a prospective randomized trial on EHIT is challenging because of its low incidence. Because of this, treatment recommendations are based primarily on retrospective institutional case series, though also influenced by surgeon preference and anecdotal experience. Of the EHIT classifications in the literature, the main ones are the above-mentioned Kabnick classification and the Lawrence classification for GSV ablations[19]; there is also a proposed modification for the SSV by the Harlander-Locke classification. The AVF EHIT classification combines these different systems.

With an eye to reduce the number of EHITs from the outset, Sadek et al[20] demonstrated that increasing the ablation distance to >2.5 cm from the deep venous junction could be helpful.

Rivaroxaban may be a promising alternative for treatment of severe EHIT because the dosage regimen is simplified without compromising efficacy or safety and is easily available as an oral anticoagulant and is more cost-effective than perenteral enoxaparin.

Treatment based on EHIT classification

With the suggestion that treatment should be based on an accepted EHIT classification system, recommendations for antiplatelet and anticoagulant therapies for EHIT have lessened.[2] Treatment based on the combined AVF-EHIT classification is described below:

Treatment of EHIT after ablation of the GSV

EHIT I: No treatment is suggested for EHIT I; surveillance only.

EHIT II: No treatment is suggested for EHIT II; weekly surveillance until thrombus resolution. In high-risk patients, consideration may be given to antiplatelet therapy versus prophylactic or therapeutic anticoagulation with weekly surveillance. Treatment would cease after thrombus retraction or resolution to the SFJ (GSV) or SPJ (SSV).

EHIT III: Treatment with therapeutic anticoagulation is suggested for EHIT III, with weekly surveillance, and cessation of treatment after thrombus retraction or resolution to the SFJ (GSV) or SPJ (SSV).

EHIT IV: Treatment for EHIT IV should be individualized, taking into account the risks and benefits to the patient. A DVT line of treatment should be followed: anticoagulation, thrombolysis, or thrombectomy.
Delayed presentation of EHIT have been treated by thrombolysis and open thrombectomy *(Figures 6 and 7)*.[21]

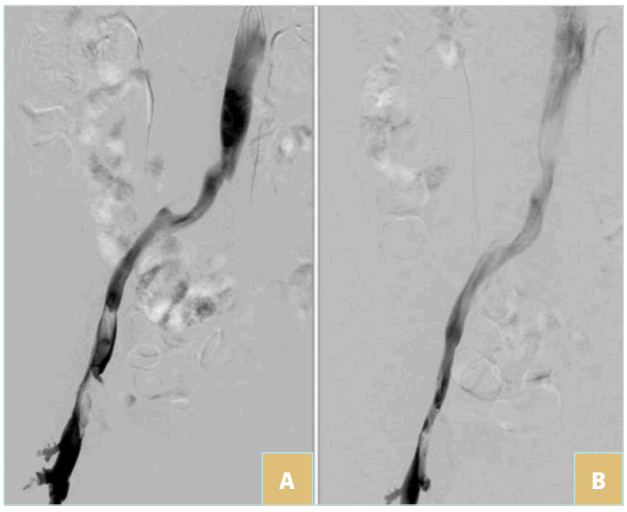


Figure 6. A) Venography showing femoral and iliac vein filling defect caused by thrombotic occlusion. B) Follow-up venography after aspiration thrombectomy and catheter-directed thrombolysis.

After reference 21: Kwak et al. *Vasc Specialist Int*. 2016;32(2):72-76.

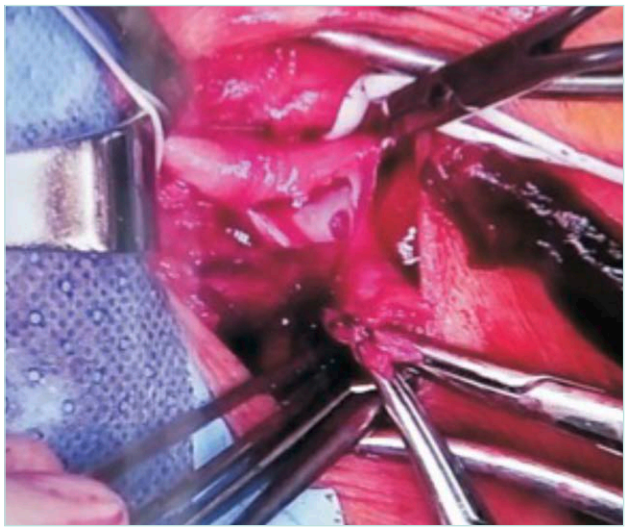


Figure 7. Open thrombectomy of the left saphenofemoral junction. Thrombus (that nearly obliterated the vein) removed via a small longitudinal venotomy. The thrombus extended from the great saphenous vein that was obliterated by the previous endovenous laser ablation.

After reference 21: Kwak et al. *Vasc Specialist Int.* 2016;32(2):72-76.

Conclusion

EHIT behaves differently than a spontaneous DVT, displaying ultrasonography chronicity at a much earlier time. Close duplex ultrasound observation of EHIT I without pharmacologic prescription is suggested. Treatment of EHIT II with low-molecular-weight heparin or non–vitamin K antagonist oral anticoagulants (NOACs) until the EHIT can be reclassified to EHIT I by duplex ultrasonography is suggested. EHIT III or IV should be treated according to the suggested guidelines for DVT.

CORRESPONDING AUTHOR

Sandeep Raj Pandey, MS, FVES, FIDF, FIUA

Annapurna Hospital, Kathmandu, Nepal

EMAIL: *sandeeprajpandey@gmail.com*

References

1. Gloviczki P, Comerota AJ, Dalsing MC, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg.* 2011;53(Suppl):2S-48S.
2. Kabnick LS, Sadek M, Bjarnason H, et al. Classification and treatment of endothermal heat-induced thrombosis: Recommendations from the American Venous Forum and the Society for Vascular Surgery. *Phlebology*. 2021;36(1):8-25.
3. Pyne JM, Sieber WJ, David K, Kaplan RM, Hyman Rapaport M, Keith Williams D. Use of the quality of well-being self-administered version (QWB-SA) in assessing health-related quality of life in depressed patients. *J Affect Disord*. 2003;76:237-247.
4. Mundy L, Merlin TL, Fitridge RA, Hiller JE. Systematic review of endovenous laser treatment for varicose veins. *Br J Surg*. 2005;92:1189-1194.
5. Leopardi D, Hoggan BL, Fitridge RA, Woodruff PW, Maddern GJ. Systematic review of treatments for varicose veins. *Ann Vasc Surg*. 2009;23:264-276.
6. Hingorani AP, Ascher E, Markevich N, et al. Deep venous thrombosis after radiofrequency ablation of greater saphenous vein: a word of caution. *J Vasc Surg*. 2004;40:500-504.
7. Chandler JG, Pichot O, Sessa C, Schuller-Petrovic S, Osse FJ, Bergan JJ. Defining the role of extended saphenofemoral junction ligation: a prospective comparative study. *J Vasc Surg*. 2000;32:941-953.
8. Puggioni A, Kalra M, Carmo M, Mozes G, Gloviczki P. Endovenous laser therapy and radiofrequency ablation of the great saphenous vein: analysis of early efficacy and complications. *J Vasc Surg*. 2005;42:488-493.
9. Complications of the treatment of venous insufficiency. *Thoracic Key*. Published January 19, 2018. Accessed August 2024. https://thoracickey.com/complications-of-the-treatment-of-venous-insufficiency/
10. Kabnick LS, Ombrellino M, Agis H, et al. Endovenous heat induced thrombosis (EHIT) at the superficial deep venous junction: a new post-treatment clinical entity, classification and potential treatment strategies. Presented at: the 18th Annual Meeting of the American Venous Forum; February 22-26, 2006; Miami, Florida, USA.
11. Sufian S, Arnez A, Lakhanpal S. Case of the disappearing heat-induced thrombus causing pulmonary embolism during ultrasound evaluation. *J Vasc Surg*. 2012;55:529-531.
12. Lurie F, Kistner RL. Pretreatment elevated D-dimer levels without systemic inflammatory response are associated with thrombotic complications of thermal ablation of the great saphenous vein. *J Vasc Surg Venous Lymphat Disord*. 2013;1:154-158.
13. Marsh P, Price BA, Holdstock J, Harrison C, Whiteley MS. Deep vein thrombosis (DVT) after venous thermoablation techniques: rates of endovenous heat-induced thrombosis (EHIT) and classical DVT after radiofrequency and endovenous laser ablation in a single centre. *Eur J Vasc* Endovasc Surg. 2010;40:521-527.
14. Haqqani OP, Vasiliu C, O'Donnell TF, Iafrati MD. Great saphenous vein patency and endovenous heat-induced thrombosis after endovenous thermal ablation with modified catheter tip positioning. *J Vasc Surg*. 2011;54(Suppl):10S-17S.
15. Passariello F. Post ablation superficial thrombus extension (PASTE) as a consequence of endovenous ablation. An up-to-date review. *Rev Vasc Med*. 2014;2:62-66.
16. Sadek M, Almeida JI, Kabnick LS. Endothermal heat-induced thrombosis. In: Almeida JI, ed. *Atlas of Endovascular Venous Surgery*. 2nd ed. Elsevier; 2019:397-407. https://doi.org/10.1016/B978-0-323-51139-1.00016-4
17. Lawrence PF, Chandra A, Wu M, et al. Classification of proximal endovenous closure levels and treatment algorithm. *J Vasc Surg*. 2010;52:388-393.
18. Marsh P, Price BA, Holdstock J, Harrison C, Whiteley MS. Deep vein thrombosis (DVT) after venous thermoablation techniques: rates of EHIT and classical DVT after radiofrequency and endovenous laser ablation in a single centre. *Eur J Vasc Endovasc Surg*. 2010;40:521-527.
19. Harlander-Locke M, Jimenez JC, Lawrence PF, et al. Management of endovenous heat-induced thrombus using a classification system and treatment algorithm following segmental thermal ablation of the small saphenous vein. *J Vasc Surg*. 2013;58:427-431.
20. Sadek M, Kabnick LS, Rockman CB, et al. Increasing ablation distance peripheral to the saphenofemoral junction may result in a diminished rate of endothermal heat-induced thrombosis. *J Vasc Surg Venous Lymphat Disord*. 2013;1:257-262.
21. Kwak JH, Min SI, Kim SY, et al. Delayed presentation of endovenous heat-induced thrombosis treated by thrombolysis and subsequent open thrombectomy. *Vasc Specialist Int*. 2016;32(2):72-76.

Phlebolymphology Vol 31 | No. 2 | 2024

Overview on foam sclerotherapy in the treatment of varicose veins

Tomasz Urbanek, MD

Department of General Surgery, Vascular Surgery, Angiology and Phlebology; Medical University of Silesia, Katowice, Poland; European Center of Phlebology, Katowice, Poland

ABSTRACT

Foam sclerotherapy has become an important part of the treatment for patients with chronic venous diseases (CVD), including both medical and esthetical indications. The wide implementation of foam sclerotherapy in C1 to C6 patients, together with growing clinical experience and number of performed studies, positions foam sclerotherapy as a valuable treatment method in the current CVD management guidelines as well as several consensus documents. The technological progress and improvement in good-quality foam preparation, as well as an improvement in its administration adjusted to the treated pathology, allow the achievement of satisfactory results in a variety of patients and clinical conditions. This article presents an overview of the current position of foam sclerotherapy treatment in the CVD management guidelines, together with an update on physician-compounded, as well as standardized, foam preparation and administration options. The options for treatment of truncal vein incompetence followed by varicose vein/tributary and C1 foam sclerotherapy are also discussed in light of current clinical experience, technical solution availability, and study results. Foam sclerotherapy remains an important compound for phlebological treatment, as it's often the method of choice or a complementary part of CVD patient management.

Keywords

chronic venous disease | foam sclerotherapy | saphenous vein | treatment | varicose veins

Phlebolymphology. 2024;31(1):74-83.

www.phlebolymphology.org

Introduction

Sclerotherapy remains a basic treatment technique in many centers treating patients with varicose veins and other chronic venous disease (CVD)-related pathologies that cause esthetic as well as often severe medical problems. Introducing foam as a method of drug administration expanded the indications and increased the efficacy of sclerotherapy in the treatment of CVD.[1] In daily practice, foam is used as a treatment for a wide range of venous pathologies, from C1 to C6 class, including patients with varicose vein recurrence and patients with venous leg ulcer (VLU), and also for cosmetic indications in patients with CVD. Wide acceptance of the fact that foam formulations of the sclerosing agent is at least twice as effective as liquid, with 4 or 5 times less sclerosing agent needed, opened up new treatment possibilities.[1,2] However, several limitations and precautions concerning foam administration should be considered during the planning and performance of the procedure.[2]

Foam sclerotherapy: foam production and optimization of foam quality

In most countries, the use of foam in sclerotherapies remains based on physician-compounded foam (PCF) production. It is widely accepted and also suggested in the sclerotherapy guidelines: the use of small, good-quality bubbles in a homogeneous and viscous foam is advised.[1,2]

Sclerosant foam is usually generated by mixing a liquid detergent with a gas—in most cases, air. As an alternative, carbon dioxide (CO_2) or a combination of CO_2 and oxygen (O_2) can be used.[1,2] According to the Tessari method for foam creation, 2 syringes connected by a 3-way stopcock can be used with a liquid/air ratio of 1 to 4 *(Figure 1A)*.[3] Another commonly used method (the double-syringe system [DSS]) uses 2 syringes and a 2-way connector *(Figure 1B)*.[4] Irrespective of the method of foam creation, the generated foam can be classified as macrofoam (>500 µm), minifoam (250-500 µm), and the most desired, microfoam (<250 µm), depending on the bubble diameter achieved.[2]

Several factors have been suggested as possible influencers of foam quality, and even different foam doses prepared by the same physician can significantly differ in terms of quality.[1,2,5-7] To avoid foam degradation, the time between foam creation and its clinical use should be the shortest possible, and during foam preparation, a variety of potentially related factors affecting foam stability and bubble size should be considered. This is also related to the materials used for foam production.[1,2] A higher sclerosing-agent concentration allows creation of a more stable foam. Foam stability can be significantly reduced by the silicone content of the inner surface of the syringes used for foam creation.[1,2] In this aspect, the syringes containing a reduced amount of silicone should be preferred. The use of alternative gases, proposed by some authors, to decrease the potential adverse events rate related to the foam can also be important.[2,8,9] With respect to gas content, foam containing CO_2 only is significantly less stable, leaving a shorter time for its application than standard air-based foam. One of the proposed solutions to increase CO_2 foam stability is to use nitrogen-free or low-nitrogen foam based on the CO_2/O_2 gas mixture usage.[2] As the liquid plus gas fraction remains an important factor related to foam stability, for PCF, the most commonly implemented liquid/air ratio is that of the Tessari foam (1:4), although some other combinations are also available.[2] It should be emphasized that usage of foam created with macrobubbles (>500 µm) can potentially and more likely lead to cerebral artery air embolization in patients predisposed to paradoxical embolism.[2]

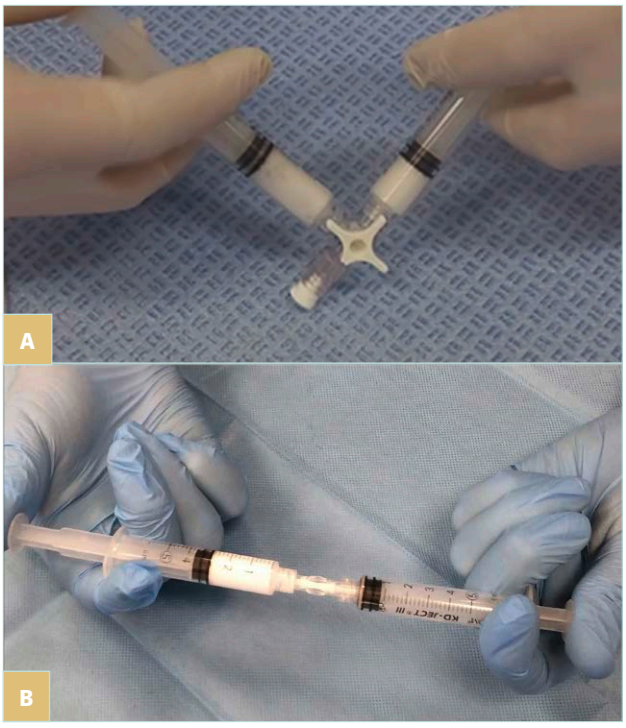


Figure 1. A) Foam preparation: 3-way stopcock and Tessari method. B) Foam preparation: double-syringe system (DSS) method.

To obtain good-quality foam via an operator-dependent technique, eg, PCF, there are a few points to consider. When using PCF, the liquid sclerosing agent is pumped back and forth between 2 connected syringes through a connector. A factor that can potentially influence foam quality and stability is the pressure within the foam creation system. To obtain good-quality foam, high pressure should be applied to both syringes compressing their content during foam creation. This can be done by appropriate finger pressure application on the syringe plungers during the pumping of the syringe content back and forth. Another modification proposed by some authors is the use of filters that can be inserted into the foam production system to increase the possibility of microbubble generation.[1,2]

Another factor that should not be forgotten during planning of the foam sclerotherapy procedure is the size of the needle used, as very small needles can lead to foam degradation. It is commonly accepted that for foam-based procedures, needles that are 25 G or larger (preferred) should be used in order to avoid needle-related foam destruction and degradation.[1] The best-quality foam can be maintained when large needles or catheters are used.

As mentioned above, due to multiple factors, PCF is not only operator dependent, but also susceptible to differences in quality depending on the materials, syringes, drug concentration, or air/liquid formula used.[1] Such observations open up the field to research on options for standardized foam creation that would be repeatable and operator independent. Some solutions are already available on the market and can be mentioned here. One of these is the EasyFoam kit (Kreussler), which, however, does not exclude operator influence. The kit consists of a 10-mL, low-silicone, disposable syringe filled with the required amount of sterile air with a fixed bidirectional check valve and connector; a 5-mL low-silicone disposable syringe (for injection purposes); and needles. Foam that is stable, homogeneous, viscous, and with fine bubbles can be obtained under standardized conditions; however, even if easy to handle, the system requires manual operation (foam creation) by the physician after filling the smaller syringe with the proper amount of the sclerosing agent.[10] Among other products commercially available on some markets, Varithena (Boston Scientific) can be mentioned. Varithena (polidocanol injectable foam) contains 1% polidocanol and low nitrogen (<0.8%), O_2/CO_2 gas mixture (65:35), with a gas/liquid ratio of 7:1 *(Figure 2)*. The Varithena system enables microfoam production with a median bubble diameter of <100 µm and no bubbles that are >500 µm; the high gas/liquid ratio in the stable foam enhanced blood displacement from the treated vessels.[11] The efficacy of Varithena has been confirmed in several trials.[12-14] There are also a few Varithena limitations, including the fixed sclerosant concentration and sclerosant type, lack of worldwide availability, as well as a significant cost. Looking for other options, the machine-supported mixing of the sclerosing agent with gas by a dedicated semiautomatic device has also been proposed. This concept aims to obtain the same number and speed of the syringe plunger movements in the DSS, which has to be introduced and fixed in the machine before gas/liquid mixing (eg, the TurboFoam device; Kreussler).[15] The most recent and very promising proposal to obtain standardized and good-quality foam is the Varixio device (Automated Microfoam Preparation System, VB Devices) *(Figure 3)*, which allows the preparation of microfoam with air or physiological gases (O_2/CO_2; low nitrogen 2%-10% N_2) and various (also very low) concentrations of the sclerosing agent. In this standardized, automated procedure, the sclerosing agent is added to special sterile capsules containing air or gases and that are designed to produce good-quality microfoam with a bubble diameter less than 250 µm (from 84±14 to 119±6; average 100 µm), with a mean foam half-life of 5.2 minutes and gas/liquid ratio between 1:5 and 1:7. The capsules are connected to the preprogrammed magnetic

Figure 2. Varithena (polidocanol injectable foam): 1% polidocanol and low nitrogen, O_2/CO_2 gas mixture.
Image courtesy of F. Lurie.

Figure 3. Foam preparation by Varixio.

stirrer machine, and foam of standard but also, if needed, with very low concentration of the sclerosing agents can be obtained (which with high quality was earlier not available for very low concentrations via the standard Tessari method protocol, eg, for 0.2% polidocanol).[16] Scientific evidence with regard to this new method is currently growing.[17]

To summarize, the commonly seen differences in foam quality (among various physicians and centers), as well as the official sclerotherapy-drug registration issues and the fact that in some countries only some concentrations of the drugs are registered as a foam formula, encourage and stimulate further research on foam standardization. Undoubtedly, this research should be continued.

Saphenous vein foam sclerotherapy, large vein sclerotherapy

The use of sclerotherapy for treatment of saphenous vein incompetence should be based on ultrasound-guided foam sclerotherapy (UGFS) performed via direct vein puncture or catheter introduction followed by foam injection. Using direct vein puncture by needle or short catheters (always ultrasound guided), the length and size of the treated vein segment should also be taken into consideration, as mixing foam with the blood in long vein segments treated from a single vein access point can lead to procedure failure or incomplete vein closure due to sclerosing agent deactivation by blood proteins.[1,2,18,19] To avoid such an issue, instead of the single vein puncture (eg, in the upper thigh in the treatment of the incompetent great saphenous vein [GSV]), multiple vein punctures with separate foam administration can be used, especially when treating longer vein segments (eg, from upper calf to the saphenofemoral junction, *Figure 4)*. The same approach can be applied to the long incompetent small saphenous vein (SSV) segments or any other long superficial vein treated. Alternatively (especially for long incompetent GSV and SSV), catheter-directed foam sclerotherapy (CDFS) can be applied with the use of long catheters and ultrasound guidance. The option of using ultrasound-guided CDFS in saphenous vein treatment is currently also included in the recent European Society for Vascular Surgery (ESVS) guidelines (recommendation class IIB, level B).[20] An analysis of evidence from 3689 patients (systematic review and meta-analysis) by Lim and coworkers suggests a higher rate of occlusion with CDFS than with UGFS in 3-year follow-up (82.4% vs 62.9%).[21] According to the 2022 ESVS guidelines, in patients with GSV incompetence, first-line therapy (if anatomically feasible) remains endovenous thermal ablation in preference to surgical high ligation or UGFS (class I, level A of recommendations).[20] With regard to UGFS as a method for GSV treatment, the authors of the ESVS guidelines suggest UGFS (if this method is chosen) for patients with GSV trunk diameter less than 6 mm.[20] The same guidelines

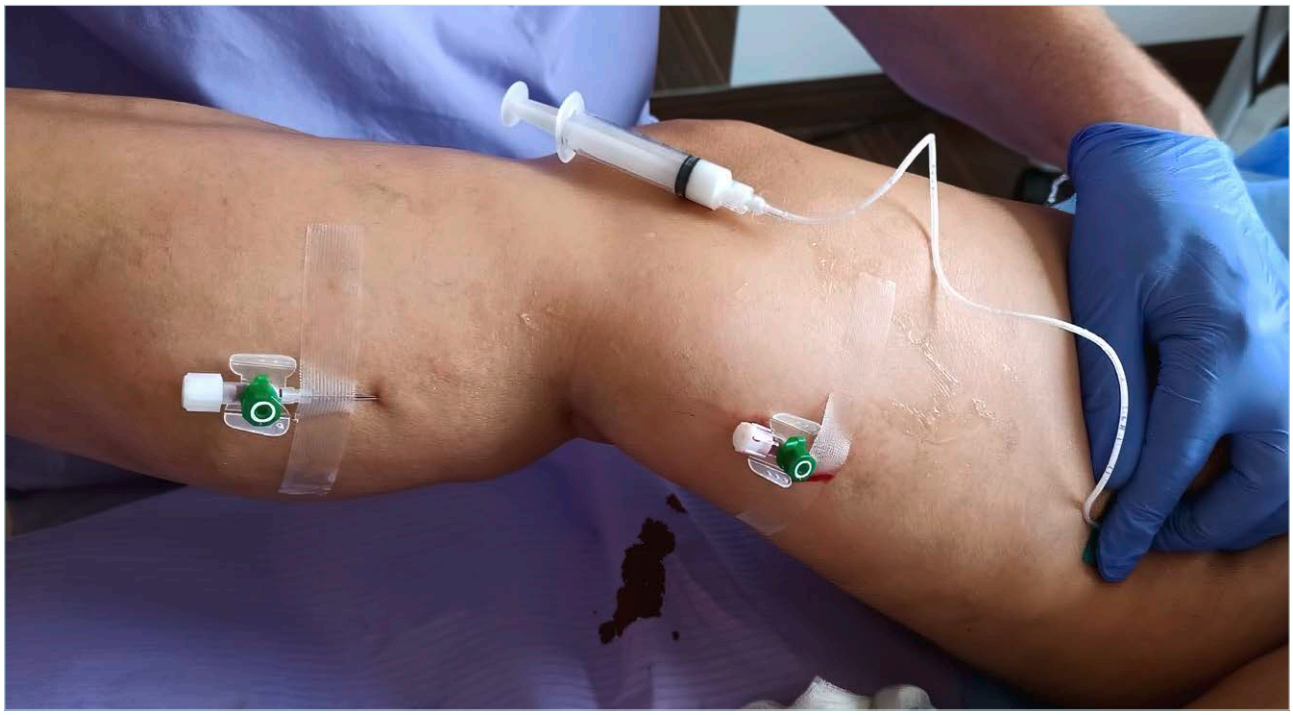


Figure 4. Great saphenous vein (GSV) sclerotherapy with multiple injections (ultrasound-guided foam sclerotherapy). GSV incompetence from the upper calf to the saphenofemoral junction.

also prefer the use of thermal methods in treatment of SSV incompetence in preference to surgery or UGFS.[20] The reason for not using foam sclerotherapy as first-line therapy for large incompetent lower-limb truncal veins is based on long-term results of GSV foam sclerotherapy. Keep in mind, however, that the lower rates of GSV occlusion in UGFS versus other (especially thermal) methods can be related to several factors, also including the way the procedure is performed (eg, one single foam injection into the thigh part of the GSV instead of repeated foam injections along the long incompetent GSV segments) and the use of foam in treatment of large and very large GSV. Rasmussen et al, in 3-year follow-up results of GSV treatment (laser ablation, radiofrequency ablation, surgery, and UGFS), documented treatment failure in 6.8% to 7% of cases after thermal ablation and 26.4% of cases after UGFS.[22] After 5 years of follow-up in this study, the GSV complete occlusion rate was only 33.3%, which corresponds with previously reported 5-year results published by van der Velden et al (23% GSV occlusion rate after 5-year follow-up).[23,24]

Apart from the guidelines and the often-unsatisfactory anatomical success in long-term results, the use of UGFS in truncal vein treatment continues in many centers, at least for some indications, owing to cost-efficacy, patient satisfaction, and tolerance, as well as satisfactory postprocedure quality of life.[20] Such indications include varicose vein recurrence, small vein diameter, and angulated course. The saphenous vein incompetence treatment in locations not amenable to thermal methods should also be mentioned (eg, distal calf saphenous vein segments).[1,2,20] In the qualification for truncal vein UGFS, size of the treated vein should also be taken into consideration. Shadid et al, comparing results of GSV treatment in veins that were smaller or larger than 6 mm (when measured at mid-thigh), confirmed a higher 2-year reflux recurrence rate in veins over 6 mm in diameter (62.6% vs 42% for the veins less than 6 mm).[25] Venermo et al, in the randomized controlled trial (RCT) comparing endovenous laser ablation (EVLA), high ligation with stripping, and UGFS in a cohort of 214 patients, documented a 1-year occlusion rate of 51% in the UGFS group (vs 97% for the thermal method and for surgery). The results of UGFS differed significantly between the subgroups of patients with veins under 6 mm in diameter (75% occlusion rate) and those with veins over 9 mm (40% occlusion rate).[26]

With regard to published SSV treatment results, those with UGFS remain inferior to those with thermal methods. Boersma et al, in a systematic review and meta-analysis of 49 studies including 5 RCT, documented a pooled success rate of 98.5% after EVLA (mean follow-up of 12.5 months), 94.1% for radiofrequency ablation (RFA; mean follow-up of 14.3 months), and 63.6% for UGFS (mean follow-up of 10.4 months).[27] In the recent FOVELASS study (RCT Comparing EVLA Versus Polidocanol Foam in the Treatment of SSV Insufficiency), focusing on the SSV, 161 patients were randomized to EVLA or UGFS groups. According to 36-month follow-up results, the rate for lack of reflux was significantly better after EVLA (86%) than after UGFS (56%) (odds ratio [OR] 5.36; 95% CI, 2.31-12.44).[28]

Other possibilities for UGFS in truncal vein incompetence treatment have also been proposed. Some authors suggest that use of long catheters in UGFS for saphenous vein incompetence treatment can be supported by application of a perivenous tumescent solution.[29,30] This approach allows for vein compression and successful removal of a significant amount of blood from the treated vein segment, as well as a decrease in the volume of foam used. In an RCT performed by Devereux and coworkers, comparing saphenous vein ultrasound-guided CDFS with the same treatment but supported by perivenous tumescent local anesthesia, the full 1-year occlusion rate in the tumescent anesthesia group was 73.9%, with partial occlusion in another 8.7% of the patients. However, compared with the standard treatment group, results with perivenous solution application were

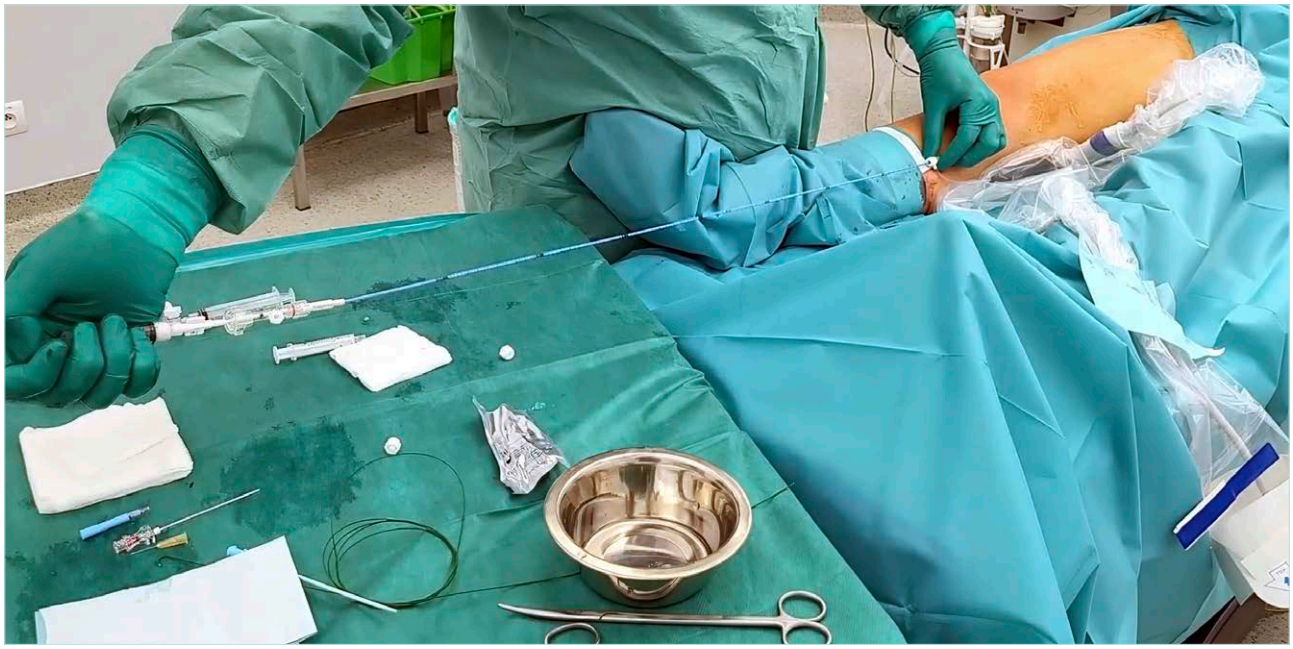


Figure 5. Foam administration by Flebogrif catheter (mechanochemical great saphenous vein ablation).

not better than those in the ultrasound-guided-CDFS-only approach.[31] Publication of results from this study triggered some discussion, as in the Devereux study, tumescent solution that did not include adrenaline was given and a significant number of the patients were lost to follow-up (20% in the nontumescent and 8% in the tumescent group).[32] In the study by Ali and coworkers, 3-year results in the group of 249 patients with GSV incompetence treated via ultrasound-guided CDFS combined with tumescent anesthesia were analyzed. Permanent obliteration of the saphenous vein after 36 months of follow-up was achieved in 81.5% GSV, and 89.6% of treated patients were free of above-knee GSV reflux.[29] Similar results were presented by Cavezzi et al in a prospective observational study with 12- and 36-month GSV occlusion rates of 94.3% and 89.4% after ultrasound-guided CDFS with tumescent solution application and vein irrigation before foam administration. The median diameter of the treated GSV trunk in this study was 7.1 mm.[30] Further studies are needed to confirm the benefits of tumescent solution–based vein compression on the more effective permanent saphenous vein occlusion rate when treated by UGFS. On the other hand, the significant foam volume reduction achieved with tumescent solution application can already be an interesting option for patients with large varicose veins, including varicose vein recurrence, for example, in the form of large groin neovascularization.

There are several observations and trials suggesting the use of UGFS together with thermal ablation. Besides the commonly used concept of truncal vein thermal ablation and saphenous vein tributary foam sclerotherapy treatment, some special treatment options have also been proposed. In the laser-assisted foam sclerotherapy (LAFOS) technique, proposed by Frullini and Fortuna, the specially designed laser Ho:YAG (Holmium:Yttrium-Aluminium-Garnet) 2100-nm ablation is used to shrink the vein immediately before foam administration, which allows the use of a smaller amount of foam and no tumescent anesthesia.[33] Sclerofoam-assisted laser therapy (SFALT) is another technique proposed by Italian authors.[34] For this technique, a 1470-nm laser with radial fiber is used. Initially, a short occlusion of the saphenous vein 1 cm below the superficial epigastric vein is created by laser ablation. After creation of this shrunk plug in the proximal saphenous vein segment, 1% polidocanol or 1% sodium tetradecyl sulfate (STS) foam is administered, causing the vein to shrink, which is followed by laser ablation with a significant reduction in the usual energy fluence. The authors of this method did not use tumescent anesthesia (except its use in the proximal 1-cm saphenous vein laser ablation); however, mild intravenous sedation was used in the treated patient cohort.[34] Among the other proposed foam-based treatment options, use of long sheaths for endovenous laser fiber introduction as well as for local foam application (eg, into groin neovascularization) followed by standard truncal laser ablation in the GSV segment below can be mentioned. Some technical solutions with special designed laser fibers and an additional injection canal (designed originally by the fiber inventors for vein saline flushing) are now also available.[35]

Foam application can also be part of the mechanochemical ablation. This concept is used for the Flebogrif catheter (Balton) designed for truncal vein mechanochemical ablation *(Figure 5)*. The specially designed tip of the catheter, with hooks irritating the vein wall (and cutting the internal layer of the vein wall) after catheter-tip opening, provokes vein spasm, which is followed by direct foam application during catheter pullback in the treated veins. In a study based on 200 treated patients with GSV incompetence, its Polish authors documented a 92% 24-month follow-up success rate.[36] The efficacy of this device is currently being tested in new clinical trials—further studies, including long-term follow-up studies need to be performed to define the group of the patients with GSV incompetence that would benefit most from this procedure. In another mechanochemical ablation system available on the market (Clarivein, Merit Medical), a liquid sclerosing-agent solution is administered with another rotational mechanism, leading to vein-wall spasm. Another commercially available concept focusing on the potential increase in UGFS efficacy is the aspiration infusion kit (Sclerosafe, VVT Medical Ltd) dedicated to foam application with simultaneous blood aspiration from the vein lumen via a specially designed catheter and double-syringe kit. Despite the interesting concept, until now, only evidence from a small patient series with limited follow-up has been available.[37]

Tributaries, varicose veins, and small-vein foam sclerotherapy

Foam sclerotherapy is an interesting and efficient alternative to surgical phlebectomy/miniphlebectomy procedures in the incompetent tributaries, as well as to varicose vein treatment, including both saphenous- and nonsaphenous-related ones. The choice of the sclerosing-agent concentration used for tributaries/varicose vein sclerotherapy depends on the size of the treated veins *(Table I)*.

Visible varicose veins and visible tributaries can be treated with vein access under visual control (with blood aspiration to confirm needle presence in vein lumen). In some of these cases, especially for large veins, many reflux sources and complex pathology, or for veins that are not well visible, UGFS can be a valuable option. To facilitate mid- and small-size vein punctures, other vein visualization technologies can be used, including transillumination or near infrared imaging (NIR) *(Figures 6 and 7)*. Recent advancement in ultrasound technology (especially high-frequency ultrasound) also allows the diagnosis and treatment of very small reticular or feeding veins under ultrasound guidance *(Figure 8)*.

	Indications	Concentration %
	Polidocanol	Sodium tetradecyl sulfate (STS)
Telangiectasias	up to 0.5% (Grade 1B)	up to 0.25% (Grade 2C)
Reticular varicose veins	up to 0.5% (Grade 2C)	up to 0.5% (Grade 2C)
Tributary varicose veins	up to 2% (Grade 1B)	up to 1% (Grade 1C)
Saphenous veins		
< 4 mm	up to 1% (Grade 1B)	up to 1% (Grade 1C)
≥ 4 mm and ≤ 8 mm	1%-3% (Grade 1A)	1%-3% (Grade 1B)
> 8 mm	3% (Grade 1A)	3% (Grade 1B)
Incompetent perforating veins	1%–3% (Grade 2B)	1%–3% (Grade 2B)
Recurrent varicose veins	1%–3% (Grade 2B)	1%–3% (Grade 2B)
Venous malformation	1%–3% (Grade 2B)	1%–3% (Grade 2B)

Table I. Suggested polidocanol and sodium tetradecyl sulfate concentrations in foam sclerotherapy according to the European Guidelines for Sclerotherapy with grade of recommendations.
Based on reference 1: Rabe et al. *Phlebology*. 2014;29:338-354.

To achieve the best possible results, proper preoperative reflux mapping and elimination of the reflux sources in primary as well as recurrent varicose veins should always be incorporated.[1,2,20] In patients with tributary incompetence related to saphenous trunk incompetence, the tributary treatment (by sclerotherapy or miniphlebectomy) can be performed as part of the concomitant or staged treatment.[20] In the latter approach, tributary foam sclerotherapy is performed during a separate procedure after a previous saphenous vein ablation or surgery. Following general rules concerning sclerotherapy of the tributary, varicose veins, or small veins, treatment from proximal to distal leakage points and from larger to smaller varicose veins is suggested.[1]

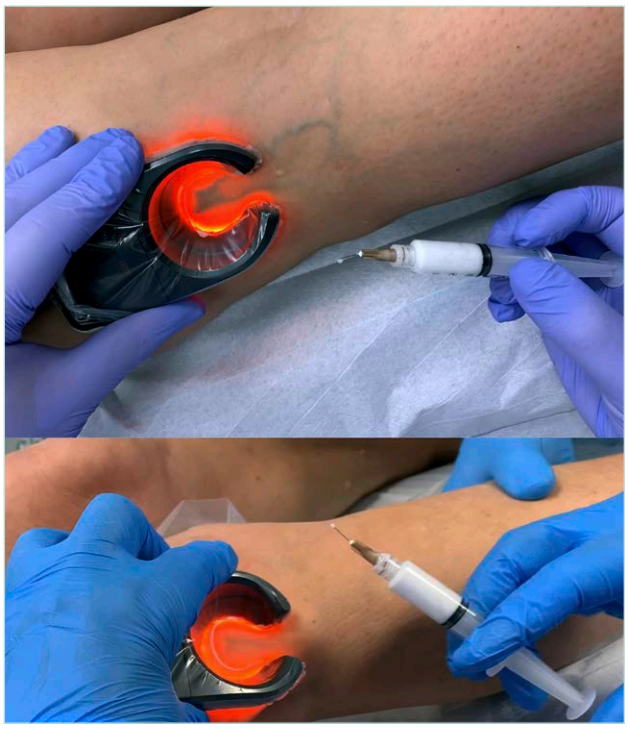


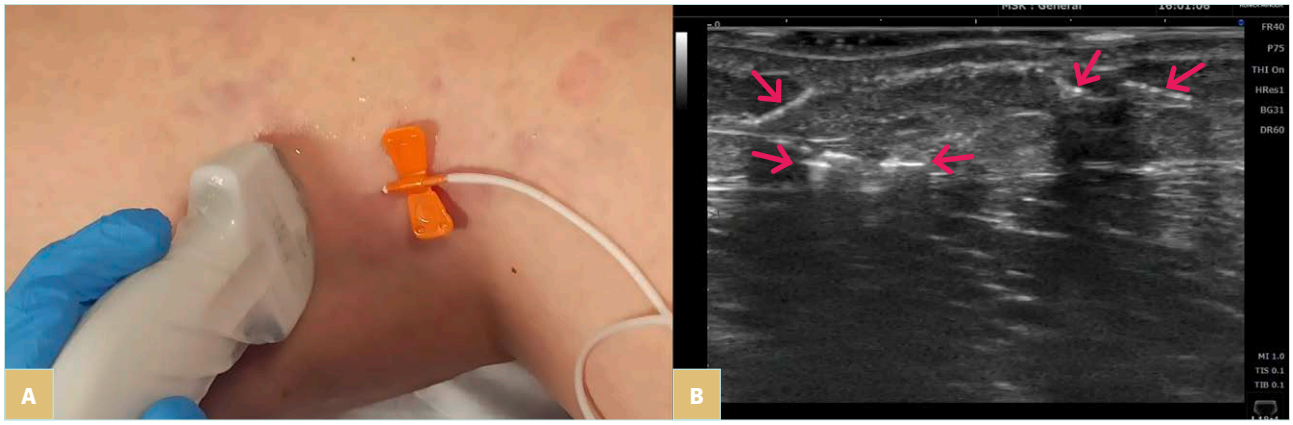
Figure 6. Transillumination-assisted foam sclerotherapy.

For performance of the procedure, smooth-moving syringes with slow intravenous foam injection, as well as multiple injections, are proposed.[1,2] In many cases including patients with more extensive pathology, repeated sessions may be necessary. According to current ESVS guidelines, "For patients with CVD requiring treatment of varicose tributaries, ambulatory phlebectomy, UGFS or a combination of both are recommended."[20] Choosing the proper techniques depends largely on a physician's experience and preference in terms of a patient's expectations and should be individually discussed. In patients looking for a good cosmetic outcome, with large and very superficially located tributaries, as well as in patients with unaccepted hyperpigmentation after previous sclerotherapy, ambulatory phlebectomy can be chosen as a treatment option and should be individually discussed with the patient.[1,2,20] In patients with advanced trophic skin changes, performance of phlebectomies may be affected by the number of local complications, which makes UGFS a valid alternative option.[20] According to the EVRA study (A Randomized Trial of Early Endovenous Ablation in Venous Ulceration)[38] and daily practice, successful reflux ablation increases the rate of healed venous leg ulcers (VLU). One of the most important parts of successful venous hypertension elimination is not only the truncal or tributary as well as varicose vein treatment but also elimination of the reflux in the subulcer VLU plexus, which is identified in many VLU patients.[1,39]

The discussion concerning the amount of foam that can be used during one sclerotherapy session is still open. According to the European guidelines for sclerotherapy, experts suggest that during routine procedures the amount of foam injected should not exceed 10 mL, and in cases where a larger amount is considered, an individual risk-benefit evaluation should always be undertaken.[1] Among the factors that need to be evaluated, vein location and its direct connection to the deep vein system should be mentioned (eg, proximal part of the truncal vein). The Australasian College of Phlebology Standards guidelines suggest use of 10 mL of foam for truncal vein incompetence and (in a separate session) up to 15-20 mL for tributaries

Figure 7. A,B) Near infrared (NIR) imaging in vessel identification during sclerotherapy procedure: foam sclerotherapy under NIR guidance. C) NIR imaging visualization–based procedure with C1 feeding vein identification and low-concentration foam sclerotherapy. D) Foam sclerotherapy of feeding veins in C1 patient.

Figure 8. A,B) High-frequency ultrasound-guided C1 foam sclerotherapy (foam visible in the feeding vessels).



(provided foam is not noted on ultrasound to extend into the deep system).[40] According to the recent ESVS guidelines, a foam volume limit of up to 16 mL is suggested, which (with low level of evidence) complies with European regulations.[41] Further studies are needed to establish the maximum and safe amount of foam for various kinds of sclerotherapy.

The beneficial effects of sclerotherapy in treating tributaries and nonsaphenous varicose veins have been widely described in the literature.[42-45] Currently, foam is also used in small-vein (C1) treatment; however, the formula used for proper application as well as drug concentration remain subjects of continuous discussion. According to the European Guidelines for sclerotherapy in CVD, in C1 pathology, both liquid and foam treatment can be applied.[1] Like in other CVD patients, also in this case, potential local complications related to administration of the sclerosing agent, including hyperpigmentation and matting, need to be taken into consideration. Apart from patient-related factors (eg, previous hyperpigmentation or matting, skin type, estrogen, or other medical therapy exposure, as well as concomitant condition presence), administration of an agent that is too strong, high pressure during injection, as well as treatment of large areas with a single injection may have a potential role in the occurrence of this complication. As previously suggested, foam is usually much more potent than liquid.[20] This leads to the suggestion that in C1 pathology treatment, a very low foam concentration for sclerotherapy should be used (according to the European Guidelines for sclerotherapy, up to 0.5% polidocanol and up to 0.25% STS in telangiectasia treatment, and up to 0.5% polidocanol and STS for reticular veins was proposed).[1] Besides occurrence of the various possible local pathologies in C1 patients (from simple telangiectasia to complex reticular veins or difficult-to-identify feeding veins), the issues related to low-concentration, good-quality foam creation should also be mentioned. Using standard PCF with a very low sclerosing-agent concentration (eg, 0.25% polidocanol, 0.2% or lower STS), low-quality foam can usually be obtained, which is also potentially degraded by the use of very small needles. Another factor to potentially take into consideration is that in some countries, the lowest sclerosing-agent concentration is not registered as suitable for foam applications, which makes foam sclerotherapy in C1 patients an off-label approach. Despite these facts, the use of a low-concentration foam

remains an interesting alternative for liquid sclerotherapy in C1 pathology, which is especially effective in complex reticular vein treatment. The problem of low-concentration foam stability can potentially be overcome with the new automated foam creation modalities.[46] In the discussion of a potential skin hyperpigmentation risk in patients undergoing C1 foam sclerotherapy, the systematic review performed by Bossart and coworkers should be mentioned.[47] According to this systematic review, there is a comparable incidence of hyperpigmentation for 0.25% polidocanol in liquid and foam. Two available direct comparison studies show no differences[48] or liquid superiority[49]; however, the second of these studies was based on a very limited number of patients (20 cases).[48,49] The authors of the systematic review emphasized that the rate of hyperpigmentation grows in accordance to the concentration of polidocanol in C1 pathology treatment for both liquid and foam (from 2%-25% for 0.25% polidocanol to 13%-73% for 1% polidocanol—liquid and foam).[47]

Conclusions

The use of foam has become standard of care in many CVD-related pathologies. Knowledge of treatment limitations, potential contraindications, as well as complications of foam sclerotherapy treatment should be an integral part of phlebological education as well as sclerotherapy planning.[1,2] The absolute contraindications to foam sclerotherapy (hypersensitivity to sclerosing agent, acute venous thromboembolism, severe neurological or cardiac adverse events including known symptomatic patent foramen ovale [PFO], acute systemic illness, infection or uncontrolled chronic disease, or severe peripheral arterial disease) should be accepted, but knowledge about several relative contraindications is also mandatory.[1,2] Length restrictions for the current article do not allow for discussion of all possible foam sclerotherapy complications, but knowledge of possible sclerotherapy complications, also concerning complications that are more commonly seen in patients treated with foam versus liquid (eg, visual disturbances, headache, and migraine), is required and should be continuously updated on the basis of previously published documents and new publications *(see References 1 and 2)*.

CORRESPONDING AUTHOR

Prof Tomasz Urbanek, MD

Department of General Surgery, Vascular Surgery, Angiology and Phlebology, Medical University of Silesia, Katowice, Poland
European Centre of Phlebology, Katowice, Poland

EMAIL: *urbanek.tom@interia.pl*

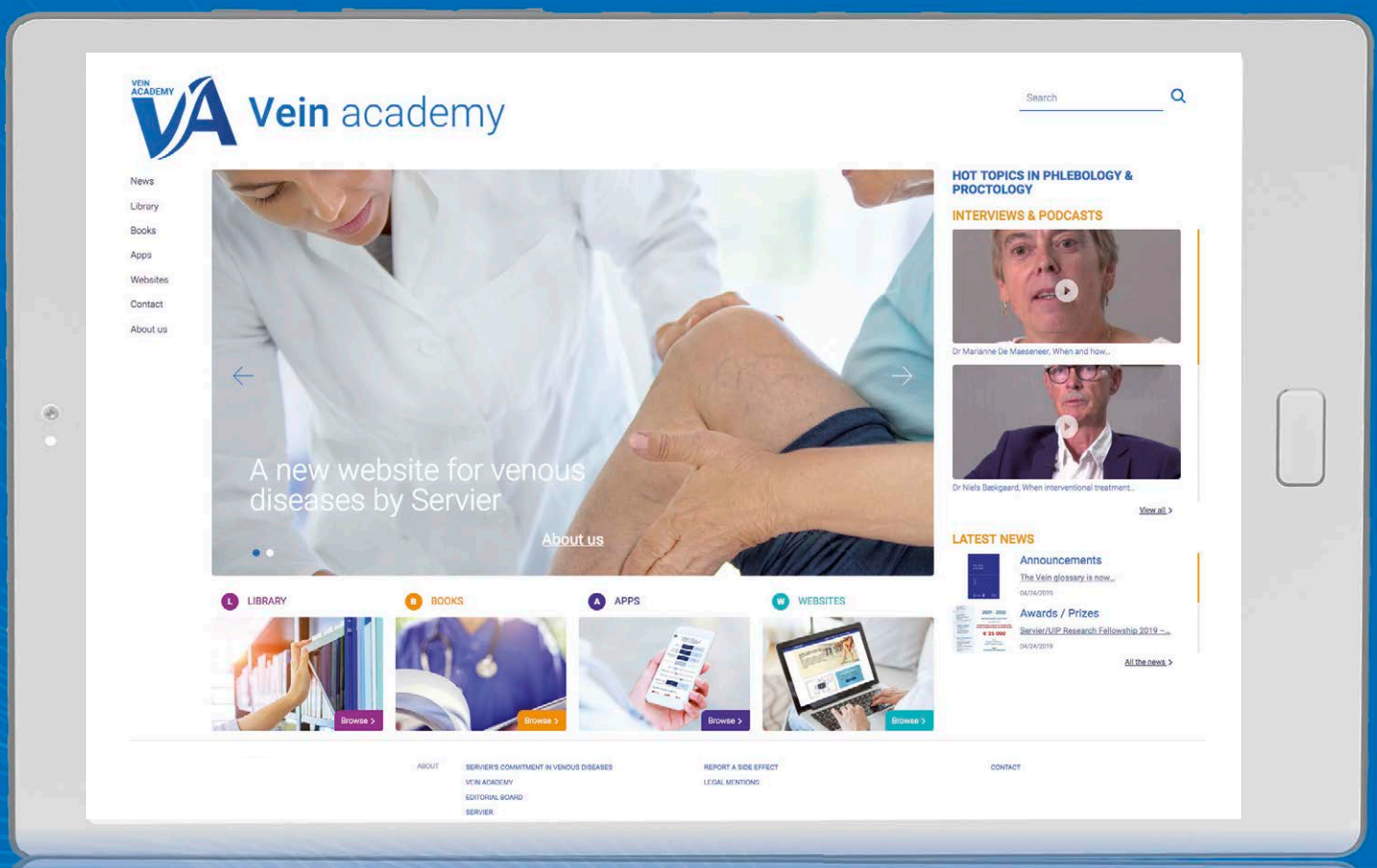
References

1. Rabe E, Breu FX, Cavezzi A, et al. European guidelines for sclerotherapy in chronic venous disorders. *Phlebology*. 2014;29:338-354.
2. Wong M, Parsi K, Myers K, et al. Sclerotherapy of lower limb veins: indications, contraindications and treatment strategies to prevent complications – a consensus document of the International Union of Phlebology-2023. *Phlebology*. 2023;38:205-258.
3. Tessari L, Cavezzi A, Frullini A. Preliminary experience with a new sclerosing foam in the treatment of varicose veins. *Dermatol Surg*. 2001;27:58-60.
4. Rao J, Goldman MP. Stability of foam in sclerotherapy: differences between sodium tetradecyl sulfate and polidocanol and the type of connector used in the double-syringe system technique. *Dermatol Surg*. 2005;31:19-22.
5. Meghdadi A, Jones SA, Patel VA, Lewis AL, Millar TM, Carugo D. Foam-in-vein: a review of rheological properties and characterization methods for optimization of sclerosing foams. *J Biomed Mater Res B Appl Biomater*. 2021;109:69-91.
6. Roberts TG, Cox SJ, Lewis AL, Jones SA. Characterisation and optimisation of foams for varicose vein sclerotherapy. *Biorheology*. 2020;57:77-85.
7. Cavezzi A, Tessari L. Foam sclerotherapy techniques: different gases and methods of preparation, catheter versus direct injection. *Phlebology*. 2009;24:247-251.
8. Morrison N, Neuhardt DL, Rogers CR, et al. Comparisons of side effects using air and carbon dioxide foam for endovenous chemical ablation. *J Vasc Surg. 2008*; 47:830-836.
9. Morrison N, Neuhardt DL, Rogers C, et al. Incidence of side effects using carbon dioxide-oxygen foam for chemical ablation of superficial veins of the lower extremity. *Eur J Vasc Endovasc Surg*. 2010;40:407-413.
10. Rabe E, Otto J, Schliephake D, Pannier F. Efficacy and safety of great saphenous vein sclerotherapy using standardised polidocanol foam (ESAF): a randomised controlled multicentre clinical trial. *Eur J Vasc Endovasc Surg*. 2008;35:238-245.
11. Varithena website. Home page. https://www.varithena.com/en-us/home.html
12. Gibson K, Kabnick L; Varithena® 013 Investigator Group. A multicenter, randomized, placebo-controlled study to evaluate the efficacy and safety of Varithena® (polidocanol endovenous microfoam 1%) for symptomatic, visible varicose veins with saphenofemoral junction incompetence. *Phlebology*. 2017;32:185-193.

13. Todd KL 3rd, Wright DI; VANISH-2 Investigator Group. Durability of treatment effect with polidocanol endovenous microfoam on varicose vein symptoms and appearance (VANISH-2). *J Vasc Surg Venous Lymphat Disord*. 2015;3:258-264.
14. Star P, Connor DE, Parsi K. Novel developments in foam sclerotherapy: focus on Varithena (polidocanol endovenous microfoam) in the management of varicose veins. *Phlebology*. 2018;33:150-162.
15. Blaise S, Bosson JL, Diamand JM. Ultrasound-guided sclerotherapy of the great saphenous vein with 1% vs. 3% polidocanol foam: a multicentre double-blind randomised trial with 3-year follow-up. *Eur J Vasc Endovasc Surg*. 2010;39:779-786.
16. Varixio website. Home page. www.varixio.com/professionals
17. Alongi G, Bissacco D, Cervi E. Three-year follow-up analysis of automated microfoam preparation system for great saphenous vein incompetence and varicose veins sclerotherapy treatment. *Phlebology*. 2024;39(7):471-476.
18. Watkins MR. Deactivatio of sodium tetradecyl sulphate injection by blood proteins. *Eur J Vasc Endovasc Surg*. 2011;41:521-525.
19. Bottaro E, Paterson JAJ, Quercia L, et al. In vitro and ex vivo evaluation of the biological performance of sclerosing foams. *Sci Rep*. 2019;9:9880.
20. De Maeseneer MG, Kakkos SK, Aherne T, et al. Editor's Choice—European Society for Vascular Surgery (ESVS) 2022 Clinical practice guidelines on the management of chronic venous disease of the lower limbs. *Eur J Vasc Endovasc Surg*. 2022;63:184-267.
21. Lim SY, Tan JXD, D'Cruz RT, Syn N, Chong TT, Tang TY. Catheter-directed foam sclerotherapy, an alternative to ultrasound-guided foam sclerotherapy for varicose vein treatment: a systematic review and meta-analysis. *Phlebology*. 2020;35:369-383.
22. Rasmussen L, Lawaetz M, Serup J, et al. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy, and surgical stripping for great saphenous varicose veins with 3-year follow-up. *J Vasc Surg Venous Lymphat Disord*. 2013;1:349-356.
23. Brittenden J, Cooper D, Dimitrova M, et al. Five-year outcomes of a randomized trial of treatments for varicose veins. *N Engl J Med*. 2019;381:912-922.
24. van der Velden SK, Biemans AA, De Maeseneer MG, et al. Five-year results of a randomized clinical trial of conventional surgery, endovenous laser ablation and ultrasound-guided foam sclerotherapy in patients with great saphenous varicose veins. *Br J Surg*. 2015;102:1184-1194.
25. Shadid N, Nelemans P, Lawson J, Sommer A. Predictors of recurrence of great saphenous vein reflux following treatment with ultrasound-guided foam sclerotherapy. *Phlebology*. 2015;30:194-199.
26. Venermo M, Saarinen J, Eskelinen E, et al. Randomized clinical trial comparing surgery, endovenous laser ablation and ultrasound-guided foam sclerotherapy for the treatment of great saphenous varicose veins. *Br J Surg*. 2016;103:1438-1444.
27. Boersma D, Kornmann V, van Eekeren R, et al. Treatment modalities for small saphenous vein insufficiency: systematic review and meta-analysis. *J Endovasc Ther*. 2016;23:199-211.
28. Hamel-Desnos C, Nyamekye I, Chauzat B, Gracia S, Josnin M, Abbadie F. FOVELASS: a randomised trial of endovenous laser ablation versus polidocanol foam for small saphenous vein incompetence. *Eur J Vasc Endovasc Surg*. 2023;65:415-423.
29. Ali H, Elbadawy A, Saleh M, Mahmoud O. Mid-term results of catheter directed foam sclerotherapy combined with tumescent local anaesthesia for treatment of great saphenous vein incompetence. *Eur J Vasc Endovasc Surg*. 2017;54:363-368.
30. Cavezzi A, Mosti G, Campana F, Tessari L, Bastiani L, Urso SU. Catheter foam sclerotherapy of the great saphenous vein, with perisaphenous tumescence infiltration and saphenous irrigation. *Eur J Vasc Endovasc Surg*. 2017;54:629-635.
31. Devereux N, Recke AL, Westermann L, Recke A, Kahle B. Catheter-directed foam sclerotherapy of great saphenous veins in combination with pre-treatment reduction of the diameter employing the principals of perivenous tumescent local anesthesia. *Eur J Vasc Endovasc Surg*. 2014;47:187-195.
32. Cavezzi A, Mosti G, Di Paolo S, Tessari L, Campana F, Urso SU. Re: 'Catheter-directed foam sclerotherapy of great saphenous veins in combination with pre-treatment reduction of the diameter employing the principals of perivenous tumescent local anesthesia.' *Eur J Vasc Endovasc Surg*. 2014;48:597.
33. Frullini A, Fortuna B. Laser assisted foam sclerotherapy (LAFOS): a new approach to the treatment of incompetent saphenous veins. *Phlebologie*. 2013;66(1):51-54.
34. Zini F, Tessari L, Torre R. Sclerofoam assisted laser therapy for saphenous refluxes: an innovative tumescence-free technique. *Veins Lymphatics*. 2015;4:5141. https://doi.org/10.4081/vl.2015.5141
35. vascularnews. Biolitec reveals new ELVeS Radial 2ring Pro laser fibre for severely tortuous veins. Published February 3, 2020. www.vascularnews.com/biolitec-reveals-new-elves-radial-2ring-pro-laser-fibre-for-severely-tortuous-veins/
36. Iżżecki M, Terlecki P, Przywara S, Iżżecka J, Dave S, Zubilewicz T. The novel minimally invasive mechano-chemical technique of the saphenous vein ablation. Our center experience: results of 24 months follow-up. *Acta Angiologica*. 2019;25:127-132.
37. Kolvenbach R, Olami H, Brandeis Z. Retrospective evaluation of safety and efficacy for sclerosafe device – case report summary. www.i-t-d.de/download/Case_Report_Summary_for_ScleroSafe.pdf
38. Gohel MS, Heatley F, Liu X, et al; EVRA Trial Investigators. A randomized trial of early endovenous ablation in venous ulceration. *N Engl J Med*. 2018;378:2105-2114.
39. Bush R. New technique to heal venous ulcers: terminal interruption of the reflux source (TIRS). *Perspect Vasc Surg Endovasc Ther*. 2010;22:194-199.
40. Australasian College of Phlebology. Ultrasound guided sclerotherapy: diagnose venous disease and treat superficial venous incompetence with injected sclerosants under ultrasound guidance. www.phlebology.com.au/newsletter_docs/ACPUGSStandard2016.pdf
41. European Medicine Compendium. Summary of Product Characteristics for Fibrovein 3% solution for injection. https://www.medicines.org.uk/emc/product/1199/smpc#gref
42. Zhang J, Jing Z, Schliephake DE, Otto J, Malouf GM, Gu YQ. Efficacy and safety of Aethoxysklerol® (polidocanol) 0.5%, 1% and 3% in comparison with placebo solution for the treatment of varicose veins of the lower extremities in Chinese patients (ESA-China Study). *Phlebology*. 2012;27:184-190.
43. Michaels JA, Campbell WB, Brazier JE, et al. Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial). *Health Technol Assess*. 2006;10:196.
44. de Roos KP, Nieman FH, Neumann HA. Ambulatory phlebectomy versus compression sclerotherapy: results of a randomized controlled trial. *Dermatol Surg*. 2003;29:221-226.
45. Vasquez M, Gasparis AP. A multicenter, randomized, placebo controlled trial of endovenous thermal ablation with or without polidocanol endovenous microfoam treatment in patients with great saphenous vein incompetence and visible varicosities. *Phlebology*. 2017;32:272-281.
46. Roche E, Pons R, Roche O, Puig A. A new automated system for the preparation of sclerosant foam: a study of the physical characteristics produced and the device settings required. *Phlebology*. 2020;35(9):724-733.
47. Bossart S, Daneluzzi C, Cazzaniga S, et al. Skin hyperpigmentations after sclerotherapy with polidocanol: a systematic review. *J Eur Acad Dermatol Venerol*. 2023;37(2):274-283.
48. Kern P, Ramelet AA, Wutschert R, Bounameaux H, Hayoz D. Single-blind, randomized study comparing chromated glycerin, polidocanol solution, and polidocanol foam for treatment of telangiectatic leg veins. *Dermatol Surg*. 2004;30:367-372.
49. Benigni JP, Sadoun S, Thirion V, Sica M, Demagny A, Chahim M. Télangiectasies et varices réticulaires. Traitement par la mousse d'Aetoxysclérol à. 0,25%. Présentation d'une étude pilote. *Phlébologie*. 1999;52:283-290.

Discover the website on venous diseases by SERVIER

Vein academy



- One point of access to evidence-based medical education in Phlebology and Proctology.
- Recent scientific news, interviews, and podcasts on hot topics by international experts.
- Library with videos, books, slide sets on anatomy, epidemiology, and pathophysiology, treatments, and surgical techniques.
- Links to a selection of articles, practical applications, and relevant websites on venous diseases.

… go to

vein-academy.servier.com

SERVIER
moved by you

Correspondent

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

www.servier.com