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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 wellknown 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.

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Mark S. WHITELEY (UK)

Editorial

Dear Readers,

In this new issue, **Andrew Nicolaides (Cyprus)** provides a clear understanding of the actions of micronized purified flavonoid fraction (MPFF) at various pathophysiological stages of chronic venous disease, the mechanisms that underlie its efficacy, and the evidence for clinical applications for symptom relief, reversal of skin changes, healing of leg ulcers, and improving quality of life, with perspectives from the 2018 international guidelines. He emphasizes that MPFF is strongly recommended for the treatment of pain, heaviness, feeling of swelling, functional discomfort, cramps, leg redness, skin changes, edema, and quality of life, as well as for the healing of leg ulcers in patients with chronic venous disease.

In part 2 of his "State of art in lymphedema management" series, **Byung-Boong Lee (USA)** further discusses the contemporary concepts regarding the management of chronic lymphedema, focusing on the surgical treatment approaches.

Peter Neglen (Cyprus) and **Bo Eklöf (Sweden)** present the basic principles and the key learning experiences of the European Venous Forum (EVF) HOW and EVF HOW plus courses, which are hands-on training courses on the practical management of patients with venous disease.

Endothermal treatments are now considered the new gold-standard treatment for eliminating venous reflux in patients with chronic venous insufficiency. In a quest to minimize the invasiveness of these procedures, nonthermal techniques that do not require tumescent anesthesia have been developed in the last decade. These new nonthermal and tumescent-less techniques are well tolerated, resulting in equivalent outcomes compared with endothermal ablations. In this review, **Raghu Kolluri (USA)** discusses the data and the procedural steps on the VenoSeal technique.

Mark Whiteley (UK) summarizes the 15.4-year results from their study on using VNUS Closure radiofrequency ablation on incompetent truncal veins. These results were published in 2017 and the paper highlights the differences between the original VNUS closure techniques and modern endovenous thermal ablation.

Enjoy reading this issue! Editorial Manager Dr. H. Pelin Yaltirik



The place of MPFF in the management of chronic venous disease

Andrew NICOLAIDES

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Keywords:

chronic venous disease; guidelines; MPFF; quality of life

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Abstract

The aim of this review is to provide a clear understanding of the actions of the micronized purified flavonoid fraction (MPFF) at various pathophysiological stages of chronic venous disease (CVD), the mechanisms that underlie its efficacy, and the evidence for clinical applications for symptom relief, reversal of skin changes, healing of leg ulcers, and improving quality of life (QOL), with perspectives from the 2018 international guidelines. MPFF relieves symptoms, edema, skin changes, and improves QOL. MPFF can be used alone in the early stages or as an adjunct to surgery, sclerotherapy, endovenous thermal ablation, or compression. It can be used at all stages of the clinical, etiological, anatomical, and pathophysiological (CEAP) classification (C_{0s} and $C_1 - C_s$). MPFF is an alternative therapy when surgery is not feasible, not indicated, or when patients are unable to use compression. In the 2018 international guidelines, which determine the magnitude of the effect of individual venoactive drugs on individual symptoms, MPFF is strongly recommended for the treatment of pain, heaviness, feeling of swelling, functional discomfort, cramps, leg redness, skin changes, edema, and quality of life, as well as for the healing of leg ulcers in patients with CVD.

Introduction

Chronic venous disease (CVD) is a common, but complex, disorder. It presents with a variable combination of symptoms and signs, a complex pathophysiology, and it is associated with complicated venous hemodynamics, making it difficult to understand without being familiar with the theory of hemodynamics in collapsible tubes. In addition, it is a progressive condition.

The symptoms¹ and signs² related to CVD are shown in *Table I.* Symptoms describe what the patient feels and signs are elicited by the doctor and are typically used to define the clinical classes according to the clinical, etiological, anatomical, and pathophysiological (CEAP) classification. One of the diagnostic problems is that symptoms are not specific for CVD and there is a poor correlation between symptoms and signs. However, what the patient seeks is relief of symptoms, often

SYMPTOMS

- Heaviness
- Pain
- Sensation of swelling
- Restless legs
- Paresthesia
- Nighttime cramps
- Tiredness
- Throbbing
- Itching

SIGNS AND CEAP CLINICAL CLASS

- C₀: No visible or palpable signs of disease
- C₁: Telangiectasias, reticular veins
- C₂: Varicose veins
- C₃: Edema
 - C₄: Skin changes
 - Pigmentation, eczema
 - Lipodermatosclerosis, atrophie blanche
- C₅: Healed venous ulcer
- C₆: Active venous ulcer

Table I. Symptoms, signs, and CEAP clinical class

more than improved appearance. What the doctor aims for is not only to relieve symptoms and improve appearance, but also to stop disease progression.

Micronized purified flavonoid fraction (MPFF) is highly effective in relieving symptoms in patients with CVD. It contains purified flavonoids (90% diosmin with 10% hesperidin and other concomitant flavonoids) that have been extracted from *Rutaceae aurantiae* (a variety of small-size oranges) and micronized to help improve intestinal absorption.³ It has multiple beneficial actions and it is effective at all stages of CVD.

The aim of this review is to provide a clear understanding of the actions of MPFF at various pathophysiological stages of CVD and the mechanisms that underlie its efficacy, as well as the evidence for clinical applications for symptom relief, reversal of skin changes, healing of leg ulcers, and improvement in quality of life (QOL), with perspectives from the 2018 international guidelines.⁴

Prevalence of CVD

Epidemiological studies have demonstrated that the prevalence of CVD varies between 25% and 85% depending on severity considered and age group,⁴ with

telangiectasia and reticular veins being the most common (80% in men and 85% in women). In the adult population, varicose veins are present in 25% to 33% of females and 10% to 40% of males. The prevalence of edema and skin changes due to CVD, such as hyperpigmentation and eczema, varies from 3% to 11% of the population. Venous ulcers occur in about 0.3% of the adult population in western countries. Of the patients with CVD, 6% present with venous ulcers with high recurrence rates. It is reported that venous ulcers recur within 1 year in 26% to 69% of the patients.⁵

Mechanisms underlying the pathophysiology of CVD

Primary CVD

As indicated above, primary varicose veins are very common in the adult population and are frequently responsible for skin changes and 40% of venous leg ulcers, despite the presence of normal deep veins.⁴ In recent years, the role of the leukocyte-endothelium interaction as a key factor in the initiation of primary CVD has become better understood. This process starts with leukocyte adhesion, degranulation, and migration under the endothelium, producing chronic inflammation with eventual remodeling of the venous walls and valves.^{6,7} The resulting damage produces valve damage, reflux, and venous hypertension.⁸

While standing, venous pressure in the veins of the foot and ankle is approximately 90 mm Hg depending on the height of the individual, which is the hydrostatic pressure from the level of the heart to the foot. In a normal person with competent venous valves and a healthy calf muscle pump, the pressure decreases to 25 mm Hg while walking. In the presence of damaged valves, the venous pressure while walking is determined by the rate of reflux (mL/sec), ie, volume of blood refluxing during the period of 1 to 1.5 seconds when the foot is off the ground and before the onset of the next step and muscular contraction. A high rate of reflux is associated with rapid filling of the veins before the next muscle contraction ensues, resulting in a rapid elevation in pressure and a high mean venous pressure (steady state) during each step cycle. A low rate of reflux is associated with a slow filling of the veins before the next muscle contraction ensues, resulting in a slow elevation in pressure and a low mean venous pressure during each step cycle. The rate of reflux, ambulatory venous pressure, and duration of standing or sitting periods determine the mean venous pressure throughout the day and the prevalence of skin changes and ulceration.⁸

Secondary CVD

The postthrombotic syndrome is responsible for edema, skin changes, and 60% of venous ulcers; in addition, it is responsible for the development of secondary varicose veins that act as collateral vessels. Persistent obstruction due to failed recanalization and recurrence of deep venous thrombosis or reflux due to damage of the deep venous valves also results in venous hypertension. The combination of both reflux and obstruction of the deep veins is responsible for the most severe symptoms and signs. In cases of severe outflow obstruction, venous pressure while walking may increase to levels above 90 mm Hg.

Changes in the microcirculation

Venous hypertension is transmitted to the microcirculation, which increases the hydrostatic pressure in capillaries, resulting in transcapillary filtration that exceeds lymphatic drainage and thus contributes to interstitial edema formation. Venous hypertension slows blood flow in capillaries, prompting leukocyte adhesion to the capillary endothelium and initiating an inflammatory reaction.⁹ In patients with venous hypertension, capillaries become markedly dilated, elongated, and tortuous, especially at skin sites with hyperpigmentation and lipodermatosclerosis. These changes are associated with a high overall microvascular blood flow in the dermis¹⁰ and a decreased flow in nutritional capillaries with decreased oxygen delivery.¹¹

Laser Doppler studies show that, in addition to increased blood flow (red blood cell flux) in the dermis, there is a loss of the rhythmic vasomotor activity seen in normal skin and abolition of the venoarteriolar reflex. The venoarteriolar reflex is an axon reflex elicited by any postural change that increases venous pressure by 40 mm Hg or more. The ensuing arteriolar vasoconstriction and reduction in skin blood flow is a protective mechanism in the sitting or standing position.¹²

Over the last 10 years, an improved capillaroscopic technique, the orthogonal polarization spectral imaging technique used in the Cytoscan (Lekam Medical Ltd, UK), has allowed alterations in skin capillaries to be studied in patients assigned C_1 to C_6 of the CEAP classification. The Cytoscan has a small handheld probe that can be noninvasively applied to the skin to evaluate microcirculatory parameters, such as functional capillary density (capillaries/mm²), diameter of dermal papilla (µm) to quantify edema, the largest diameter of the capillary bulk (µm) to assess its degree of change, capillary limb diameter (µm) to describe

diameter changes, and capillary morphology (% of abnormal capillaries per field). It has been demonstrated that all of these parameters are progressively altered in C_1 to C_6 patients and that values in patients with CVD were significantly different from those in healthy subjects (P<0.05).¹³ In a more recent study, significant changes have been shown between C_{0a} and C_{0s} patients despite the presence of normal conventional duplex scans.¹⁴

Alteration of lymphatic vessels

Spontaneous contractility of lymphatic vessels contributes to lymph transport. Internal extensions of lymphatic endothelial cells act as valves and guarantee a one-way lymph flow.¹⁵ In a steady state, extravasation of fluids and proteins from blood vessels is balanced by lymphatic drainage and return into the bloodstream. If microvascular filtration in blood capillaries and venules, as occurs in advanced CVD, exceeds the capacity for lymphatic drainage for sufficiently long periods, edema develops in afflicted areas due to the accumulation of tissue fluid.

Pathophysiology of symptoms

Pain, which is a vague and unpleasant feeling, is the result of an increase in venous pressure that is transmitted to the microcirculation, resulting in activation of sensory multimodal nociceptors of myelinated A δ and unmyelinated C fibers^{16,17} via local inflammatory mediators. Throbbing occurs more often in patients with varicose veins and this observation is indicative of a hemodynamic mechanism. Tightness is common in patients with iliocaval obstruction, which is thought to be related to fluid accumulation and increased pressure in the anatomical compartments. Venous claudication is the result of severe venous outflow obstruction when the arterial inflow exceeds the venous outflow. In these patients, the recovery time is long; often more than 15 minutes.¹ Heaviness and feeling of swelling are often related to edema, but can be present in the absence of edema. It is thought that these symptoms are produced by microedema in the microcirculation, as they are relieved by venoactive drugs without any actual reduction in leg volume.¹ Itching is often associated with skin changes, but it can be an isolated symptom. Inflammation, cytokine, and matrix metalloproteinase activation have all been implicated in the pathophysiology.¹ The exact cause of cramps, restless legs, tingling, and burning is not clear.

Actions of MPFF

MPFF has anti-inflammatory, antioxidant, and powerful free-radical scavenging properties.³ MPFF decreases the

expression of adhesion molecules by neutrophils and monocytes in patients with CVD.

Oxidative stress increases endothelin-1 and tumor necrosis factor- α (TNF- α) release, indicating endothelial damage. In a controlled clinical study, treatment with MPFF for 12 weeks reduced the release of endothelin-1 and TNF- α , confirming the anti-inflammatory and protective effects on the venous walls in women with varicose veins.¹⁸ In an experimental study, MPFF reduced the increase in microvascular permeability induced by bradykinin or ischemia and protected aortic endothelial cells and human skin fibroblasts from lipid peroxidation.¹⁹

MPFF reduces leukocyte rolling, adhesion, and migration through the endothelium. In addition, it reduces the expression of CD62L by monocytes and neutrophils and the activation of intercellular adhesion molecule 1 and vascular cell adhesion molecule 1 on human leukocytes from patients with venous leg ulcers.^{19,20}

MPFF improves venous tone by modulating noradrenergic signaling and reducing norepinephrine metabolism.²¹ Treatment with MPFF 500 mg twice daily reduced venous distensibility and venous capacitance in women with various grades of CVD.²² In another controlled trial, the same dose improved venous tone in female volunteers with abnormal venous elasticity associated with a family history of varicose veins.²³

MPFF increases the contractility of mesenteric lymphatics with improved drainage in the experimental animal.²⁴ It decreases intralymphatic pressure and increases the number of functional lymphatic capillaries, which results in improved lymphatic drainage in patients suffering from skin changes.²⁵

Given the above effects, it is not surprising that MPFF reduces capillary hyperpermeability. It reduces capillary leakage in the ischemia-reperfusion injury in the experimental animal²⁶ and reduces edema in patients with CVD (see clinical studies below). In addition, the restoration of normal venous tone can make incompetent valves become competent and abolish early reflux as shown in the studies by Tsukanov.^{27,28} In the first study, he investigated 41 C_{0s} women with duplex scanning in the morning (before 10 AM) and in the afternoon (after 6 PM)²⁷; 15 did not have any reflux at any time. The remaining 26 patients had reflux in the great saphenous vein (GSV) only in the evening (situational reflux); 2 patients had axial reflux and

24 segmental reflux. The evening diameter of the GSV was larger in those with reflux (P<0.05). The difference in the GSV diameter between the evening and morning was also greater in the patients with evening reflux than in those without reflux. After 2 months of MPFF treatment, 22 patients no longer had reflux in the evening, the GSV diameter decreased, along with the difference in diameter between the morning and evening (P<0.0001). There was a parallel significant decrease in the intensity of symptoms as demonstrated by the visual analog scale score and a significant improvement in QOL (CIVIQ) (P<0.00001).

In a subsequent study by Tsukanov,²⁸ involving 294 patients, the prevalence of situational reflux in the GSV was investigated. It was detected in 21 (38.2%) of 55 patients classified as $C_{0s'}$ 25 (49.0%) of 51 classified as $C_{1s'}$ and in 32 (17.0%) of 188 classified as C_2 . After treatment with MPFF 1000 mg for 90 days, reflux disappeared in 76.1% of the 46 women with transient reflux in classes C_{0s} and $C_{1s'}$ and there was a significant decrease in the GSV diameters. The intensity of symptoms decreased from 5.2 to 1.7 (*P*<0.001) according to the 10-cm visual analog scale. The global index score (CIVIQ-20) decreased from 47.2±7.9 to 28.8±9.1 (*P*<0.001), confirming the improvement in the patients' quality of life.

As stated in the 2018 international guidelines, these studies show that MPFF has at least the potential to prevent the development and progression of CVDs and its different manifestations.

Clinical efficacy of MPFF on symptoms, signs, QOL, and rate of ulcer healing

Efficacy on symptoms

The Cochrane review of 2005²⁹ and other recent metaanalyses by Allaert,³⁰ Boyle et al,³¹ and Kakkos et al³² demonstrated that looking at the effect of individual drugs on individual symptoms is feasible and can provide a meaningful measurement of the magnitude of the effect as well as the number of patients needed to treat to have benefit in one patient. As a result of the above, the faculty revising the guidelines on CVD in 2018⁴ decided to scrutinize both old and new meta-analyses that provide data so as to allow the level of available evidence for the magnitude of the effect each venoactive drug has on each symptom to be determined. The rules of evidence are presented in *Table II.* What emerged as a result of this exercise, as summarized in *Table III*, was that convergent

RULES OF EVIDENCE

Levels of evidence range from Level A to Level C and strength of recommendation is either 1 or 2

Level A evidence derives from two or more scientifically sound randomized controlled trials (RCTs) or systematic reviews and meta-analyses in which the results are clear-cut and are directly applicable to the target population. Level A evidence implies that further research is very unlikely to change our confidence in the estimate of effect.

Level B evidence is provided by one well conducted RCT or more than one RCT with less consistent results, limited power or other methodological problems, which are directly applicable to the target population as well as by RCTs extrapolated to the target population from a different group of patients. Level B evidence implies that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Level C evidence results from poorly designed trials, observational studies, or small case series. Level C evidence implies that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

A strong recommendation (1) is made if benefits outweigh the risks.

A weak recommendation (2) is made if the benefits and risks are closely balanced or if there is uncertainty about the magnitude of the benefits and risks

Table II. Rules of evidence as published in the 2018 international guidelines. From reference 4: Nicolaides A et al. Int Angiol. 2018;37(3):181-254.

data confirmed the important role of venoactive drugs in the management of CVD, either alone in the early stages or in combination with interventional procedures in the more advanced stages. The recent systematic review and metaanalysis of randomized, double-blind, placebo-controlled trials for the efficacy of MPFF to improve individual venous symptoms by Kakkos and Nicolaides identified ten publications of randomized placebo-controlled studies involving 1692 patients.³³ There was generally a minimal risk of bias in most of these trials. CEAP clinical class ranged between C_0 to C_6 with some studies allowing inclusion of patients with a postthrombotic syndrome.

Pain

Pain was reduced with the use of MPFF compared with placebo when assessed as a continuous variable in three studies, each one significant, and involving 839 patients (standardized mean difference (SMD), -0.25; 95% CI, -0.38 to -0.11.^{34-36,39-40} It was also reduced when assessed as a categorical variable in three studies, involving 271 patients, two of which were significant.^{34,35,37} The risk ratio was 0.53 (95% CI, 0.38 to 0.73) and the NNT was 4.2 (95% CI, 2.8 to 7.9). The level of evidence was high (Grade A).

Heaviness

Heaviness was reduced compared with placebo when assessed as a continuous variable in two studies, both

significant and involving 254 patients (SMD, -0.80; 95% CI, -1.05 to -0.54).^{34,35} It was also reduced when assessed as a categorical variable in three studies involving 283 patients, two of which were significant. The risk ratio was 0.35 (95% CI, 0.24 to 0.51) and the NNT was 2.9 (95% CI, 2.2 to 4.2).^{33,35,38} The level of evidence was high (Grade A).

Feeling of swelling

The feeling of swelling was reduced compared with placebo when assessed as a continuous variable in two studies involving 254 patients, each one significant (SMD, -0.99; 95% Cl, -1.25 to -0.73).^{34,35} The feeling of swelling was also reduced when assessed as a categorical variable in three studies involving 267 patients, two of which were significant.^{34,35,37} The risk ratio was 0.39 (95% Cl, 0.27 to 0.56) and the NNT was 3.1 (95% Cl, 2.3 to 4.8). The level of evidence was high (Grade A).

Cramps

Cramp severity was reduced compared with placebo when assessed as a continuous variable in one study involving 150 patients (SMD, -0.46; 95% Cl, -0.78 to -0.14).³⁴ A significant effect was also observed for cramp reduction compared with placebo when assessed as a categorical variable in two studies involving 119 patients, one of which was significant.^{35,37} The risk ratio was 0.51 (95% Cl, 0.29

Symptom/sign	MPFF	Ruscus	Oxerutins	HCSE	Calcium dobesilate
Pain (NNT) SMD	A (4.2) -0.25	A (5) -0.80	B - 1.07	A (5.1)	B (1.4)
Heaviness (NNT) SMD	A (2.9) -0.80	A (2.4) -1.23	B (17) -1.00		A (1)
Feeling of swelling (NNT) SMD	A (3.1) -0.99	A (4) -2.27			
Functional discomfort (NNT) SMD	A (3.0) -0.87				B (4)
Leg fatigue (NNT) SMD	NS*	B -1.16			
Cramps (NNT) SMD	B (4.8) -0.46	B/C	B -1.7		
Paresthesiae (NNT) SMD	B/C (3.5) -0.11	A (1.8) -0.86			В (2)
Burning (NNT) SMD	B/C -0.46	NS*			
Pruritus/itching (NNT)		B/C		A (6.1)	
Tightness (NNT)	NS*				
Restless legs (NNT)	NS*				
Leg redness (NNT) SMD	B (3.6) -0.32				
Skin changes (NNT)	A (1.6)				
Ankle circumference (NNT) SMD	В -0.59	A -0.74	NS*	A (4)	
Foot or leg volume SMD	NS*	A -0.61	NS*	A -0.34	A -11.4
Quality of life SMD	A -0.21				NS*

*NS: not significant

Table III. Level of evidence that merits grade A or B for the effect of the main venoactive drugs on individual symptoms, signs, and QOL with magnitude effect as published in the 2018 international guidelines. The number needed to treat (NNT) to benefit one patient and standardized mean difference (SMD) are also shown. Only randomized placebo controlled trials and meta-analyses were considered.

From reference 4: Nicolaides A et al. Int Angiol. 2018;37(3):181-254.

to 0.92) and the NNT was 4.8 (95% Cl, 2.7 to 22.9). The level of evidence was moderate (Grade B).

Paresthesia

Paresthesia (tingling) was not reduced with the use of MPFF compared with placebo when assessed as a continuous variable of end of treatment values in one study involving 150 patients (SMD, -0.11; 95% CI, -0.44 to 0.21).³⁴ However, a significant effect was observed compared with placebo when assessed as a categorical variable in another study

involving 61 patients.³⁵ The risk ratio was 0.45 (95% Cl, 0.22 to 0.94) and the NNT was 3.5 (95% Cl, 1.9 to 20). The level of evidence was moderate to low (Grade B/C).

Burning sensation

Burning sensation was reduced compared with placebo when assessed as a continuous variable in one study involving 150 patients (SMD, -0.46; 95% Cl, -0.78 to -0.14).³⁴ A significant effect was not observed when assessed as a categorical variable in two other studies involving 96 patients.^{35,38} The risk ratio was 0.67 (95% Cl, 0.38 to 1.17). The level of evidence was moderate to low (Grade B/C).

Discomfort

Functional discomfort was significantly reduced compared with placebo when assessed as a continuous variable in two studies involving 254 patients, both being significant (SMD, -0.87; 95% Cl, -1.13 to -0.61).^{34,35} It was also significantly reduced in two studies involving 134 patients, both being significant.^{35,38} The risk ratio was 0.41 (95% Cl, 0.25 to 0.67) and the NNT was 3.0 (95% Cl, 2.1 to 5.8). The level of evidence was high (Grade A).

Other symptoms

Tightness,³⁹ fatigue,⁴⁰ and restless leg symptoms³⁹ were nonsignificantly reduced with the use of MPFF compared with placebo.

Efficacy on signs

Leg redness

Leg redness was reduced compared with placebo when assessed as a continuous variable in two studies (one significant) involving 254 patients (SMD, -0.32; 95% Cl, -0.56 to -0.07),^{34,35} and it was reduced in one study involving 66 patients when assessed as a categorical variable.³⁵ The risk ratio was 0.50 (95% Cl, 0.27 to 0.94) and the NNT was 3.6 (95% Cl, 2.0 to 20.6). The level of evidence was moderate (Grade B).

Skin changes

Skin changes were improved compared with placebo when assessed as a categorical variable in two studies involving 61 patients, both being significant.^{34,35} The risk ratio was 0.18 (95% CI, 0.07 to 0.46) and the NNT was 1.6 (95% CI, 1.2 to 2.2). The level of evidence was high (Grade A).

Ankle circumference

Ankle circumference was reduced with the use of MPFF compared with placebo when assessed as a continuous variable in two studies involving 282 patients, one of them being significant (SMD, was -0.59; 95% Cl, -1.15 to -0.02).^{35,39} The level of evidence was moderate to low (Grade B).

Efficacy on quality of life

Quality of life improved with the use of MPFF compared with placebo when assessed as a continuous variable in two studies, both significant and involving 601 patients. (SMD, -0.21; 95% CI, -0.37 to -0.04).^{36,40} The level of evidence was high (Grade A).

Efficacy on rate of leg ulcer healing

A meta-analysis of five randomized controlled trials involving 723 patients with venous ulcers⁴¹ demonstrated that, at 6 months, ulcers healed faster when MPFF was combined with compression than with compression alone. Compression in addition to MPFF was compared with compression plus placebo in two of the studies (n=309) or with compression alone in three studies (n=414). At 6 months, the chance of ulcer healing was 32% higher in patients treated with the combined therapy than in those managed by compression alone (relative risk ratio [RRR], 32%; 95% CI, 3% to 70%), translating to a NNT of 7.3 (95% Cl, 4.6 to 17.1). This difference was present from month 2 (RRR, 44%; 95% CI, 7% to 94%) and was associated with a shorter time to healing (16 weeks vs 21 weeks; P=0.0034). The level of evidence was high (Grade A). Table IV presents the level of evidence for the effects of the main medications on leg ulcer healing.

Safety

MPFF, at the recommended dose (either 500 mg twice daily or 1000 mg once daily), is extremely safe and has no substantial side effects. In several human studies, the adverse effects reported (mainly GI disorders) did not differ from adverse effects reported with placebo. The incidence of adverse effects did not vary with age, concomitant diseases (hypertension, atherosclerosis, diabetes mellitus, neurological or psychiatric disease), or daily treatment for 1 year. There was no interaction with other drugs.^{42,43}

Based on the 2018 findings (magnitude of effects on individual symptoms or signs vs side effects), the strength of recommendations for MPFF is 1 (strong) for the treatment of pain, heaviness, feeling of swelling, functional discomfort, cramps, leg redness, skin changes, edema, and quality of life, and it is 2 (weak) for paresthesia and burning (Table V).

	MPFF	Pentoxifyline	Sulodexide	Hydroxyethylrutosides
Healing of leg ulcers	Grade A	Grade A	Grade A	Grade B

Table IV. Level of evidence for the effects of the main medications on the healing of leg ulcers for MPFF. Adapted from reference 4: Nicolaides A et al. Int Angiol. 2018;37(3):181-254.

	MPFF	Ruscus	Oxerutins	HCSE	Calcium dobesilate
Pain	Strong	Strong	Strong	Strong	
Heaviness	Strong	Strong	Strong	-	
Feeling of swelling	Strong	Strong	-	-	
Functional discomfort	Strong	-	-	-	
Cramps	Strong	Weak	Strong	-	Weak
Leg redness	Strong	-	-	-	the possibility
Skin changes	Strong	-	-	-	agranulocytosis
Edema	Strong	Strong	Weak	Strong	
Quality of life	Strong	-	-	-	
Paresthesia	Weak	Strong	-	-	
Burning	Weak	-	-	-	
Leg fatigue	-	Strong	-	-	

Table V. Strength of recommendations based on magnitude of effects on individual symptoms or signs vs side effects for the main venoactive drugs as published in the 2018 international guidelines. Adapted from reference 4: Nicolaides A et al. Int Angiol. 2018;37(3):181-254.

Conclusions

Chronic venous disease is a complex condition characterized by chronic inflammation and remodeling of the venous wall, resulting in valve damage, reflux, and venous hypertension. Chronic inflammation eventually affects the microcirculation, producing skin changes and ulceration.

MPFF has a unique combination of actions: antiinflammatory, antioxidant, and powerful free-radical scavenging properties. It decreases the expression of adhesion molecules on neutrophils and monocytes in patients with CVD, providing particularly protective effects in the venous walls and valves. In addition, it improves venous tone and increases lymphatic drainage. The studies show that MPFF at least has the potential to prevent the development and progression of CVD and its different manifestations. Given the above actions, it is not surprising to see the remarkable clinical results. MPFF relieves symptoms, reduces edema, and skin changes, as well as helps in leg ulcer healing. In addition, MPFF improves quality of life, a property not shown by any other venoactive drug.

MPFF can be used alone in the early stages or as an adjunct to surgery, sclerotherapy, endovenous thermal

ablation, or compression. It can be used at all stages of CEAP (C_{0s} and C_1 - C_{δ}). MPFF is an alternative therapy when surgery is not feasible, not indicated, or when patients are unable to use compression. The low NNT suggests cost-effectiveness, while requiring confirmation from further prospective randomized controlled trials.

In the 2018 international guidelines, which determine the magnitude of the effect of individual venoactive drugs on individual symptoms, MPFF is strongly recommended for the treatment of pain, heaviness, feeling of swelling, functional discomfort, cramps, leg redness, skin changes, edema, and quality of life, as well as for the healing of leg ulcers in patients with CVD.



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State of art in lymphedema management: part 2

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Keywords:

lymphedema; lymphovenous bypass; lymphatic reconstructions; manual lymphatic drainage

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Abstract

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

Surgical treatment: reconstructive surgery

General overview

Currently, no treatments are available to provide a "cure" for lymphedema and all available treatments are so far limited to palliate the condition. However, in recent years, there has been a rapid evolution in surgical treatments using reconstructive methods with newly developed microsurgical techniques.¹⁻⁴ Reconstructive surgery aims to restore lymphatic drainage with physiological methods by creating new lymphatic channels and to achieve an effective reduction in swelling, with the ultimate goal being to reduce the chance of infection as its ultimate goal.⁵⁻⁸ A new concept of surgical reconstruction of lymph vessels and lymph nodes has evolved rapidly over the last 50 years and various modalities of microsurgical

No.	Guidelines	Grade of recommendation (1, we recommend; 2, we suggest)	Grade of evidence (A, high quality; B, moderate quality; C, low or very low quality)
6.4.1	All interventions for chronic lymphedema should be preceded by at least 6 months of nonoperative compression treatment	1	С
6.4.1	We suggest excisional operations or liposuction only to patients with late-stage, nonpitting lymphedema, who fail conservative measures	1	С
6.4.3	We suggest microsurgical lymphatic reconstructions in centers of excellence for selected patients with secondary lymphedema, if performed early in the course of the disease	2	С

Table I. Guidelines of the American Venous Forum on surgical treatment of chronic Lymphedema.

From reference 40: Guidelines 6.4.0. on medical and physical therapy. In: Gloviczki P, ed. Handbook of Venous Disorders: Guidelines of the American Venous Forum. 3rd Edition. London, UK: Hodder Arnold; 2009:663.

lymphatic reconstructions were introduced based on anastomotic reconstruction of lymph vessels to veins⁹⁻¹² and lymph nodes to veins,¹³⁻¹⁶ in addition to lymphatic grafting to bypass the lymphatic obstructions.¹⁷⁻²⁰

A lymphovenous bypass that drains into the venous circulation can be performed by anastomosing functioning lymphatic vessels located within a diseased area to the regional veins.²¹ A lymphatic-lymphatic bypass can also be done using an interposition graft to connect to healthy lymphatic channels beyond the affected region using a transplanted lymphatic vessel or vein.²² Among these three different types of lymphatic reconstructions, developed based on microsurgical and supermicrosurgical techniques, lymphovenous bypass and anastomosis have remained the most popular approach for decades.²³⁻²⁶ For many reasons, the interest in this logical approach that offers a chance of a "cure" have waxed and waned over the years. In particular, the technically demanding microsurgical techniques have hampered the widespread acceptance of this approach as a first-line treatment, meaning that this noble approach remained available only at specialized centers to provide an active lymphatic surgical reconstruction.

Recently, the new concept of "supermicrosurgery" rekindled the enthusiasm for lymphatic reconstructions with microsurgical and supermicrosurgical techniques.²³⁻²⁶ The popularity of lymphovenous or lymphaticovenular bypass and anastomosis has improved in recent years.^{14,27-29} In addition, the newly developed technique of vascularized lymph node transfer and transplantation (VLNT) as a free flap was a welcomed new approach with a more promising

future,³⁰⁻³³ especially for the candidates who failed to meet the indication for conventional anastomotic reconstruction. Together with lymphaticovenular anastomosis, VLNT is the most commonly practiced procedure today.

So far, reconstructive surgery with various microsurgical lymphovenous anastomoses can deliver the best outcome when performed in clinical stage I and II (early stage) before the progression to the advanced fatty fibrous stages.^{34,35} Reconstructive surgery with autologous free lymph node transplant surgery also provides a promising future for patients with primary lymphedema in clinical stage II and III with defective lymph nodes, particularly lymphadenodysplasia.³⁶⁻³⁹

Nevertheless, the majority of the data that is available for thorough review belong to grade 2B or 2C when assessed using the system developed by Guyatt et al, and, at best, only a small number belong to grade 1C or 2A because of the unique condition of observational studies, as discussed in Part 1 (1. Introduction:1-1. Background) (Table 1⁴⁰).

Principles of patient selection

Reconstructive surgery is often considered as an additional procedure to improve the efficacy of the management when manual lymphatic drainage (MLD)-based DLT fails to prevent a steady progress of the condition with no response to a maximum of MLD-based DLT for a minimum 6 months.^{41,42} However, its indication should be extended further to the patients with multiple recurrent episodes of cellulitis and/or lymphangitis, chylous-reflux combined with extremity lymphedema, and poor tolerance to DLT-based

treatment physically, mentally, and socioeconomically. In addition, reconstruction can be performed as a preventive measure when the excision of major lymph nodes for malignancy should carry a high likelihood of developing subsequent lymphedema.^{1,2}

Early stage lymphedema is an ideal period for reconstructive surgery and unnecessarily delaying surgical intervention for more than 1 year will definitely allow further damage of the lymphatic vessel, especially its contractibility, and increase the risk of surgical failure. Therefore, the timing of lymphatic reconstruction is crucial and this waiting period should be shortened whenever possible to avoid permanent damage of the lymphatic vessels, thus making lymphatic reconstruction futile.^{1,2} In general, advanced stages of chronic lymphedema will show a poor response, with the poorest candidate for reconstruction being primary lymphedema caused by hypoplasia or aplasia of the lymph vessels with lymphatic fibrosis.

The current policy to delay lymphatic reconstruction until the failure of maximal DLT-based therapy for a substantial period has been confirmed to cause further damage to the lymphatic system, which will increase the risk of procedure failure. In fact, the majority of patients who receive lymphatic reconstruction already have significant damage due to long-term lymphatic obstruction and hypertension. Therefore, postoperative DLT is essential to maintain good long-term outcomes following successful reconstructive surgery on these partly damaged lymph vessels.^{3,4} The single most important factor to maintain a successful outcome is "patient compliance" with a life-long commitment to DLT, especially when the surgery is done after a substantial delay while waiting for DLT-based therapy to fail.^{8,34}

In addition, a timely intervention for systemic and local infections, such as cellulitis and erysipelas, are equally as important in preventing further injury to already damaged lymph vessels before surgery.⁴² While the benefits of reconstructive surgery are maximal when performed at an "early" stage of lymphedema with a chance of full restoration of paralyzed lymph vessel function, the procedure is still beneficial when performed at a "late" stage, because increasing lymph flow subsequently improves immune response, which decreases the overall risk of infection.⁴³

Secondary lymphedema is generally more suitable for lymphatic reconstructions since surgically correctable conditions present along the major lymphatics with documented proximal (pelvic, axillary) lymphatic obstruction, while distal lymphatics remain patent.⁴⁴⁻⁴⁷ However, primary lymphedema presents with extremely variable forms (eg, aplasia, hypoplasia, and hyperplasia) and with variable extents of dysplastic conditions (eg, lymphangiodysplasia, lymphadenodysplasia, and lymph-angio-adenodysplasia) as a truncular lymphatic malformation. Therefore, proper conditions for reconstruction are rare and the outcomes of surgery are generally not as effective as among those with secondary lymphedema.⁴⁸⁻⁵⁰ Nevertheless, excellent results have been reported, even in primary lymphedema, with suitable lymph vessels for the reconstruction with a prevailing condition of lymphadenodysplasia rather than lymphangiodysplasia.^{48,50}

Lymphovenous anastomosis

Lymphaticovenular anastomosis aims to drain lymph directly into the venous system through an anastomosis between lymphatic vessels and the vein to relieve distal lymphatic obstruction caused by acquired or primary iliac lymphatic obstruction.⁵¹⁻⁵⁴ However, occasionally, lymphaticovenular anastomosis can be successfully used for congenital lymphangiectasia.^{54,55} Lymphaticovenular anastomosis is ideal for patients after excision of proximal lymph nodes for cancer treatment.⁵¹⁻⁵⁴ Most microvascular surgeons perform lymphovenous or lymphaticovenular bypass with direct end-to-end or end-toside anastomoses to create new channels between subdermal lymphatic vessels and adjacent venules (<0.8 mm) using highpower magnification and 8–11/0 microsutures (*Figures 1 and 2*).^{9,10,21}



Figure 1. Lymphovenous anastomosis.

Panel A. Microsurgical technique of direct anastomosis in endto-end and end-to-side fashion for lymphatic vessels-to-vein anastomosis at the groin. Panel B. End-to-end and end-to-side techniques for lymph node-to-vein anastomosis, another form of lymphovenous anastomosis.



Figure 2. Lymphovenous anastomosis.

Images showing two different techniques for anastomosis, which are direct end-to-end lymphovenous anastomosis (top) and lymphatic-venous-lymphatic anastomoses with a vein graft interposition between the lymphatics using an invagination technique to insert multiple lymphatics to the vein segment (bottom).

So far, lymphaticovenular anastomosis is a well-accepted procedure, especially in the early stages of lymphedema (stages I and II),^{1,2} yielding better results with an average patency rate of 50% at 3 to 8 months after surgery.^{10,11} However, its clinical effectiveness is difficult to assess since almost all studies in published series are uncontrolled and combined with adjuvant compression therapy (*Figure 3*). Nevertheless, secondary lymphedema shows better results than primary lymphedema in general. A meta-analysis of outcomes after lymphaticovenular anastomosis have shown that 89% of patients had a subjective improvement, 88% of patients had a quantitative improvement, and 56% of patients were able to discontinue compression therapy based on pooled results from 22 studies.⁵⁶

Lympho-lymphatic bypass surgery

Lymphatic grafting was also introduced to relieve localized obstruction or interruption of lymph nodes and/or lymph vessels of either secondary or primary origin.⁵⁷ This procedure is ideal for mild-to-moderate upper extremity lymphedema with minimal fibrosis and a moderate number of functioning lymphatics.⁵⁸

Secondary lymphedema due to a locally interrupted lymphatic system is the main indication for lymphatic grafting.^{18,59} Arm edema after axillary node dissection or leg edema after interventions in the inguinal or pelvic region can be treated by transposing lymphatic vessels from the healthy to the affected side. Lymphatic grafting has a unique role in bypassing lymphatic obstruction. Two to three lymph vessels are harvested from the unaffected lower limb out of the perisaphenous superficial lymphatic bundles, and either a free graft is used for the axillary lymphatic obstruction due to postmastectomy lymphedema (*Figure 4A*) or a suprapubic cross-femoral transposition





Panel A. Preoperative drawing of an anastomotic site for reconstructive lymphatic surgery with multiple lymphovenous anastomoses at the popliteal level (Krylov's method). Panel B. Presentation of the operative field to prepare for direct anastomoses between functioning lymph vessels and a defunctionalized vein. Panel C. Preoperative lymphedema status. Panel D. Postoperative status with clinical improvement in lymphedema following successful lymphaticovenular anastomosis. Panel E. Also shows preoperative lymphoscintigraphic findings showing diffuse dermal backflow to confirm advanced lymphatic dysfunction. Panel F. Shows postoperative lymphoscintigraphic findings to confirm remarkable improvement following successfully restored lymphatic function by lymphaticovenular anastomosis.



Figure 4. Lympho-lymphatic bypass surgery.

Panel A. Transplantation and transposition technique of two lymph channels and vessels, which were harvested from the lower extremity and transplanted on the upper extremity to bypass the axillary lymphatic obstruction and treat the postmastectomy lymphedema. Panel B. Cross-femoral lymph vessel transposition for unilateral lower extremity lymphedema.

graft is used for iliac or iliofemoral lymphatic obstruction to relieve unilateral lower limb lymphedema (*Figure 4B*).¹⁷

End-to-end or end-to-side anastomoses can be performed with 10-0 absorbable suture material using a "tensionfree" technique to establish lymph flow to the healthy side via the grafts (*Figures 5*). Despite tedious operations,⁵⁷ the long-term results have shown an excellent improvement in limb volume reduction in 80% of patients (mean followup of 3 years).¹⁸ Transposed suprapubic lymph vessels have also been well documented for their patency with lymphoscintigraphy.¹⁹



Figure 5. Lympho-lymphatic anastomoses.

Panel A. Lymphatico-lymphatic end-to-end anastomosis using a tension-free technique without turning the vessel. Panel B. Lympholymphatic end-to-side anastomosis using the same technique.



Figure 6. Lymph node-to-venous anastomosis.

The procedure from the preparation of the vein for lymph node-venous bypass to the subsequent anastomosis of transected lymph nodes directly to the vein segment to establish a microsurgical technique.

Lymph node-to-venous anastomosis

Lymph node-to-vein bypass is performed as end-toend or end-to-side anastomoses between transected inguinal lymph nodes and saphenous or femoral veins (Figures 1A and 6).¹⁵ However, except for results from a few uncontrolled studies, the scarring over the cut surface of the lymph nodes often failed to provide a long-term improvement.^{13,15} Therefore, this new approach failed to receive a widespread application in most types of secondary lymphedema except filariasis. Filariasis often causes an enlargement of lymphatic vessels, even within the lymph nodes, and high lymph flow. In patients with filariasis, lymph node-to-vein bypass gave good results in 90% of patients with parasitic lymphatic infections.²² Also, good results were obtained in patients with congenital lymphangiectasia after lymph node-venous shunts when constructed in the inguinal area.^{16,22}

Vascularized lymph node transfer and transplantation

The VLNT procedure transplants healthy lymph nodes harvested from one region (eg, supraclavicular region) to the affected area by microsurgically connecting the lymph nodes to recipient vessels in the intended location. The procedure was originally done as an avascular graft,⁶⁰ but it is now done by transferring the lymph nodes together with surrounding fat as part of a vascularized tissue flap. It is considered that the transferred nodes promote lymphangiogenesis and act as a lymphatic pump.⁶¹ VLNT is a way to make a bridge across the lymphatic obstruction for postmastectomy lymphedema, eg, by transferring lymph nodes harvested as a free flap from the groin by the anastomoses of the feeding artery and the draining vein to the appropriate vessels in the axillary fossa using standard microsurgical techniques.^{32,63} Donor sites to harvest lymph nodes for a free transfer include the superficial groin, supraclavicular, submental, thoracic, and omental groups.

VLNT can be performed either alone or as a combined procedure with lymphaticovenular anastomosis.⁵⁸ However, VLNT is generally recommended for advanced conditions, ie, in grades II to IV lymphedema,⁶³ although the greatest improvement was reported in the early stages of lymphedema. VLNT is therefore indicated as a choice when: (i) the local condition precludes lymphaticovenular anastomosis due to fibrosis; (ii) a total occlusion of the lymphatic vessels is evidenced on lymphoscintigraphy; and (ii) at stage II,⁶⁴ with or without repeated episodes of cellulitis (Figure 7). Although the volume of the limb either decreased or returned to normal at 5 years or more after lymph node transplantation,^{32,62} only 31% were able to demonstrate activity of the transplanted nodes on isotopic lymphoscintigraphy. There are also some concerns about the potentially serious complication and risk of the donor site developing de novo lymphedema.^{58,62}



Figure 7. Clinical case of vascularized lymph node transplantation.

Panel A. Schematic drawing of lymph nodes harvested from the right posterior axillary group with intact arteries and veins for a free graft. Panel B. Actual operative field for the lymph node harvest with intact arteries and veins for a free graft. Panel C. End-to-end anastomoses of donor and recipient arteries and veins. Panel D. Preoperative status of lymphedema. Panel E. Postoperative status with remarkable clinical improvement in the following successful free lymph node graft. Panel F. Preoperative lymphoscintigraphic findings with no visible lymph nodes in the left axilla. Panel G. Postoperative lymphoscintigraphic findings with new lymph nodes appearing in the left axilla to confirm the successful vascularized lymph node transplantation.

VLNT can improve both lymphatic drainage and regional immunological function and resistance to infection. VLNT becomes the source of vascular endothelial growth factor C (VEGF-C) and other cytokines that induce and regulate lymphangiogenesis.^{65,66} Increasing evidence shows that VLNT reverses the disease process to obviate the need for a lifelong commitment to DLT, etc.⁶² VLNT is now one of the two most popular microsurgical procedures to deliver improved lymphatic function successfully together with lymphaticovenular anastomosis as a reconstructive surgical modality. However, VLNT has been focusing on reducing the fluid volume of the lymphedema and failed to encounter existing fat hypertrophy and tissue fibrosis; the tissue damage that has already developed cannot be reversed completely.

Although surgical treatment of lymphedema is generally reserved only for when the condition becomes refractory to DLT, the paradigm has shifted toward earlier intervention with physiological surgery, such as VLNT and lymphaticovenular anastomosis.⁵⁸ VLNT is expected to become the most suitable treatment modality with better prospects for primary lymphedema caused by the unique condition of lymphadenodysplasia.²

Surgical treatment: reductive and ablative surgery

Reductive surgical approaches are one of two surgical options, together with physiological approaches, that are performed alone or together. Reductive approaches aim to decrease the morbidity caused by excess volume of the affected limb by removing the fibrofatty tissue with direct excision methods or liposuction.^{2,67,70}

Excisional and debulking surgery

Excisional and debulking surgery is generally offered as a supplemental measure of last resort for clinical stages III and IV (end stage) to improve the efficacy of available DLT.^{67,70} Once the lymphedema advances to late and end stage, steady progress of the condition results in massive limb changes by fibrotic induration despite aggressive DLT.^{68,71}

Often, a highly disfigured swollen limb would not allow proper wrapping with a bandage to deliver effective compression to the local tissue. Subsequently, the condition would continue to progress to become irreversible with an increasing risk of local and systemic sepsis in the majority. Since the early 1900s, various debulking operations were introduced to remove disfiguring, scarred, lymphedematous tissue from affected limbs.⁷²⁻⁷⁵ However, the indiscriminate use of these procedures generally resulted in poor outcomes,⁷⁵⁻⁷⁷ and, for many decades, they were virtually abandoned by the majority of surgeons due to the associated morbidity and questionable long-term efficacy.^{74,78} However, interest was rekindled recently after modifications were made to the original techniques, with improved outcomes (eg, the modified Auchincloss and Homan procedure).^{69,70}

Excisional surgery has been resurrected for the treatment of lymphedema with limited application in patients with endstage chronic lymphedema as a supplemental treatment to failing DLT,^{2,68} the excision of fibrosclerotic soft tissue overgrowth improves the efficacy of subsequent DLT and compression bandaging.^{68,69} Excisional surgery can also be performed in advanced stages with no additional risk of injury to the remaining lymphatic vessels when associated with recurrent local and systemic sepsis that is refractory to maximum DLT.^{68,69} Hence, the indications should include progression of the disease to end stages despite maximum available treatment, increased frequency and/or severity of local and/or systemic sepsis, and failure to implement proper care at clinical stages III and IV (end stage) (Figure 8).^{1,2} The outcome of surgery is dependent on appropriate postoperative DLT.^{3,4} The patient's compliance to keep postoperative maintenance DLT is a major critical issue for its long-term success. The initial excellence of the surgical achievements cannot be maintained without

proper postoperative DLT. Surgery alone is highly likely to fail in the long term.⁶⁸

Excisional surgery is a viable option to play a new supplemental role in the non- to poor-responding DLT group. As adjunctive therapy, it would improve the efficacy of DLT on the treatment of intractable end-stage lymphedema. Surgery and DLT have mutually complementary effects. Nevertheless, there is no consensus yet on the optimal timing of the intervention or the choice of procedure.

Suction-assisted lipectomy for the management of lymphedema

Liposuction is an additional debulking technique that is less radical than excisional surgery. The aim is to obliterate the epifascial compartment using a "circumferential" suction-assisted lipectomy instead of resecting the entire fibrosclerotic soft tissue overgrowth.^{74,79} Therefore, it avoids the complications and morbidity associated with the traditional open surgical method by using an excisional technique.^{74,79-81}

Liposuction is a method to remove fat, not fluid, meaning that it should not be performed before DLT is used to transform pitting edema, which is caused by accumulated lymph, into nonpitting edema. Percutaneous liposuction removes excessive adipose tissue along with cannulas attached to vacuum suction during the adipofibrous (mid) stage (clinical stage II and III). Therefore, the patient who gets the most benefit from this procedure is the one who



Figure 8. Clinical case of a bilateral excisional and debulking surgery of the lower extremities.

Panel A. Clinical appearance of bilateral lower extremities with advanced lymphedema in clinical stage III before institution of excisional surgery to make the local condition amenable to effective decongestive lymphatic therapy for better rehabilitation. Panel B. Actual operative field for a debulking procedure to excise most of the soft tissue layer down to the muscle, including the muscle fascia, using a modified Auchincloss approach to save the skin. Panel C. Shows the outcome of successful excisional surgery on both lower extremities.

developed a unique condition of excess fat accumulation as a manifestation of the secondary lymphedema of the upper limb following breast cancer treatment.^{74,79} In addition, the control of the hydrostatic component of lymphedema should be done with conventional DLT before and after the liposuction.

Liposuction was reported to be effective with significant long-term volume reduction in secondary lymphedema.⁸² However, many remain concerned with the risk of collateral damage to the viable lymph vessel system, since this procedure will have to be done for effective removal of adipose tissue in the early stages, while the remaining lymphatic system has substantial lymphatic function.^{1,2} The efficacy of liposuction has not been proven for primary lymphedema, a clinical manifestation of truncular lymphatic malformation, which has a completely different pathogenesis, ie, a congenital origin. The clinical course of primary lymphedema is not the same as that of secondary lymphedema, as it mostly affects the lower extremities; there is no proven evidence for selective overgrowth of the adipose tissue among this group, unlike that of the group with secondary lymphedema.^{38,39,45,47}

Furthermore, primary lymphedema is a clinical manifestation of truncular lymphatic malformation with a significant risk for combined extratruncular lymphatic malformation. When a coexisting extratruncular lymphatic malformation is stimulated by liposuction, its mesenchymal cell characteristics would precipitate its rapid growth, making the condition worse.⁸³⁻⁸⁵

In primary lymphedema, the timing and safety risks of liposuction on the potential to exacerbate the condition by damaging residual functioning lymphatic channels remains to be established.^{45,47,86,87} This technique, however, can improve quality of life^{88,89} and reduce the incidence of erysipelas that is related to lymphedema among patients receiving breast cancer therapy, although it requires more vigorous compression therapy following the procedure and lifelong compression garments to prevent recurrence and maintain the reduced limb volume.⁸⁷⁹⁰

Conclusion

A new concept of surgical reconstruction of lymph vessels and lymph nodes has been rapidly evolving throughout the last 50 years and various modalities of microsurgical lymphatic reconstructions were introduced based on anastomotic reconstruction of lymph vessels to veins and lymph nodes to veins in addition to lymphatic grafting to bypass the lymphatic obstructions. Among these three different types of lymphatic reconstructions, developed based on microsurgical techniques, lymphovenous bypass/ anastomosis has remained the most popular approach for decades. So far, reconstructive surgery with various microsurgical lymphovenous anastomoses can deliver the best outcome when performed in patients at clinical stages I and II (early stages) before the progression to the advanced fatty fibrous stages.

Reconstructive surgery with autologous free lymph node transplant surgery also provides a promising future for primary lymphedema in clinical stages II and III with defective lymph nodes, which is known as lymphadeno-dysplasia in particular. Reductive surgical approaches are one of two surgical options together with physiologic approaches, performed alone or together. Reductive approaches aim to decrease the morbidity caused by excess volume of the affected limb either by removing the fibrofatty tissue with direct excision methods or liposuction. Excisional surgery is a viable option to play a new supplemental role in the non- to poor-responding DLT group; as adjunctive therapy, it would improve the efficacy of DLT on the treatment of intractable lymphedema in the end stages. Surgery and DLT have mutually complementary effects. However, there is no consensus yet on either the optimal timing of the interventions or the choice of procedure.

Liposuction is an additional debulking technique that is a less radical approach than excisional surgery. The aim of liposuction is to obliterate the epifascial compartment by "circumferential" suction-assisted lipectomy, instead of resecting the entire fibrosclerotic soft tissue overgrowth. Therefore, it can avoid the complications and morbidity associated with the traditional open surgical method with excisional technique.



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Small, structured workshops: an improved learning experience?

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curriculum; European Training Requirement; EVF HOW; phlebology; training

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Abstract

The need to define a curriculum, instructional plan, and training for future phlebologists has been obvious for years. In 2017, the European Union of Medical Specialists approved the European Training Requirement (ETR) in phlebology, which outlined an instruction plan. Training practices included hands-on training using phantom limbs, demonstrations on live subjects, videos on procedures, case discussions, and attending "live" procedures. We believe that the European Venous Forum Hands-On Workshop (EVF HOW) shows a model of instruction that can meet the goals set by the ETR. The basic principles of the EVF HOW are to include a low number of learners (100) to facilitate interactions with instructors (faculty: learner ratio is high [1:3]); to make the hands-on sessions truly hands-on for the learners; to promote informal and uninhibited communication between delegates, faculty members, and industry representatives; to provide sufficient time for discussions, with the greatest interaction occurring at the workshop stations; to encourage learners to bring clinical cases for presentation and discussion; and to include no exhibition or parallel activity. Success has not been measured by the number of participants, but by the impact on knowledge and practice. In 2014-2017, web-based tests with multiple-choice questions were performed before and after the workshops, showing a substantial 29% to 50% median improvement in the results. Although the strictly scientific presentations are important, training needs to be complemented by small group, hands-on courses, such as EVF HOW, for the practical management of patients with venous disease.

Introduction

The interest in acute and chronic venous disorders have markedly increased, especially in the last decade, with the introduction of duplex ultrasound scanning, the development of minimally invasive techniques to treat venous diseases and disorders, the increased awareness about the impact of venous disease on patients' quality of life, and favorable reimbursement schedules. Various specialties provide treatment of a multitude of disorders, but few have a comprehensive approach to disease in the deep and superficial system. For years, there has been an obvious need to define a curriculum, instructional plan, and training for future phlebologist. In 2010, the International Union of Phlebology published a Phlebology Training Curriculum,¹ and, in 2012, the American Venous Forum suggested a Venous Curriculum.² However, none of these were implemented in the community. In Europe, major progress in this aspect was achieved in October 2017 when the European Union of Medical Specialists approved the European Training Requirement (ETR) in phlebology, which was presented by the European Board of Phlebology.³ This was the final step in a long process. This process that started 2015 with the Multidisciplinary Joint Committee in phlebology led to the creation of the European Board of Phlebology in October 2016 under the leadership Jean-Jerome Guex (France). The board set up an ETR Task Force with 19 members representing 12 countries. The final document contained a specialty curriculum and training program for phlebology, including training requirements for trainees, instructors, and training centers. To receive the Competency Degree in Phlebology and the Competency Degree in Phlebological Procedures, a phlebologist needs to show defined goals of knowledge, skills, and competence in various assessments. The ultimate aim is to ensure the best quality of care of patients with venous disorders. To receive a European Diploma of Phlebology, the candidate fulfilling the stated criteria will have to pass a two-part test: a written multiple-choice test and an oral examination in both phlebology and phlebology procedures.

With increased interest and awareness of the importance of venous disease and implementation of a curriculum, the demand for education and practical instruction on the management and use of modern techniques with clear learning objectives have increased. The ETR also outlined an instruction plan. Training practices included practice with a hands-on phantom, demonstrations on live subjects, videos on procedures followed by analysis of techniques, management of case presentations, and attendance of "live" procedures. Requirements of centers and instructors to provide the necessary teaching and training are also outlined in the ETR. We are convinced that implementing this plan cannot be achieved without industry support in the form of unconditional educational grants.

Perhaps it is time to reevaluate the educational impact and usefulness of instruction for various types of events. Although there are several symposia, congresses, etc, organized on vascular medicine, most are centered around presentations, discussions, and occasionally demonstrations on techniques rather than actual hands-on training. Most devote little time to venous disease, although lately this has increased. Although workshops were offered, the number of participants were low, the faculty few, and rarely did every learner put their hands on the devices and perform the procedure. No assessment of impact on the learners was generally performed. There is an increasing need and demand for more practical instruction on the management and use of modern techniques in a comprehensive manner. We believe that the European Venous Forum Hands-On Workshop (EVF HOW) shows a model of instruction, where these goals can be met. The first workshop was organized in 2010 in Larnaca, Cyprus and the last in 2018 in Limassol, Cyprus.

Workshop objectives

This workshop fits well with the objectives of both the European Venous Forum (EVF) to develop and expand practical venous education and the suggested teaching practices of the ETR as indicated above. The general objectives are to educate, train, and update learners in the current clinical management of patients with venous disease by a close and informal interaction with venous experts during lectures, videos, live demonstrations, case discussions, and hands-on activities in small groups. At the end of this course, the learner should be able to:

- Identify venous disease in patients;
- Apply appropriate venous investigations;
- Construct a management plan;
- Understand different interventional procedures;
- Successfully incorporate treatment of patients with venous disease into their practice; and
- Realize when to refer a patient for higher-level care.

Venous therapists have various background and specialties. Although not all venous therapists perform all procedures, it is considered important that venous therapists are familiar with various interventions and their applications. It is important to perform phlebology procedures skillfully, but it is also just as important to know when to refer a patient for higher-level treatment when necessary. The workshop should, therefore, be comprehensive and represent most types of interventions available. The founding academic organizing committee was familiar with the objective structured clinical examination (OSCE) used to test medical students. The learners are examined in a standardized way in a circuit of short stations on clinical skills, such as reading an ECG, placing a urinary catheter, recognizing a murmur, etc. Candidates rotate through the stations, completing all the stations on their circuit according to a controlled time schedule. A grade is given based on how the learner fulfills a set of objectives at each station. This concept was adapted to construct a circuit of 24 workshop stations. Instead of being tested, the learners have structured hands-on training. Each station gives a short description of the content and 3 to 5 objectives to be reached. The delegates attend each station for 30 min in small groups (4 to 5 learners), giving each learner time to try out varying devices, practice applying bandages on each other, perform ultrasound scanning on patients, perform saphenous ablation on phantom models, etc (Figures 1 to 5). At least one faculty member provides the medical instruction at each station, working in collaboration with an industry expert who offers information about the product.



Figure 1. One of four stations with learners practicing duplex ultrasound scanning.



Figure 2. Training on ultrasound-guided ablation using a phantom limb model.



Figure 3. Learners practicing bandaging techniques on each other under the supervision of an instructor.



Figure 4. Learners performing venous intravascular ultrasound on a vessel model with artificial stenosis.



Figure 5. Live demonstration of duplex ultrasound scanning on a patient.

Basic principles of the EVF HOW program

The workshops take place over 3 days to accomplish 4 hours of hands-on instruction daily, which is the central activity of the workshop. In addition, the faculty members present up-to-date information on the modern practical management of venous disease illustrated by case management discussions and video/live demonstrations. In principle, each day is dedicated to one aspect, ie, primary venous disease, acute thrombotic disease, and chronic postthrombotic disease. The learners are encouraged to bring their own cases and the best presentation is awarded with a cash prize. At the meeting in 2017, about 30 case presentations were discussed. No more than 100 learners are accepted for the workshop to ensure that all participants receive a very concentrated experience. With a faculty of approximately 35 instructors, an unusually high instructor-learner ratio (1:3) is ensured, which allows for intense interactions between learners and faculty members in an unprecedented way, especially at the workshop stations. In addition, this communication is enhanced by the time that is set aside for lengthy discussions between lectures and the fact that there is no exhibition or parallel activity. These principles are listed in Table I.4

The all-day program is very concentrated and demanding for both learners and instructors. There is little time for extracurricular activities and the presence of the delegates is obligatory at all learning activities. Despite the "harsh" schedule, the learners have responded well. We have been particularly impressed by the hard work and constant input by the faculty. This workshop is not a meeting you fly

- The number of learners is limited to 100 to facilitate interaction between instructors and delegates and thus the faculty/learner ratio is high (1:3).
- The hands-on sessions are truly hands-on for the learners, not small lectures or only a demonstration of procedures.
- All learning sessions are informal in a relaxed setting to allow uninhibited communication between delegates, faculty members, and industry representatives.
- Plenty of time is set aside for discussion with the greatest interaction occurring at the workshop stations.
- The learners are encouraged to bring their own cases for presentation and discussion.
- There is no exhibition or parallel activity.

Table I. The basic principles of the EVF HOW.

into, have a presentation, and then leave. The workshop requires a full 3-day commitment, in addition to traveling time, from each faculty member. The venous experts also share their contact information with the learners, providing support after the meeting if wished. Despite this commitment, most instructors have thoroughly enjoyed the workshop, especially the stimulation obtained by the frequent interaction with the learners. The majority of the instructors have returned when asked.

Workshop assessment

Success has not been measured by the number of participants, as the attendance is limited, but by its impact on knowledge and practice. In 2014–2017, web-based tests containing 25 multiple-choice questions that needed to be answered within 30 minutes were performed before and after the workshops, each time with the same questions. The validity of the questions was assessed by letting the faculty take the test too. Questions that were doubtful were excluded from the test results. *Table II* lists the results from each year. The results have shown a substantial 29% to 50% median improvement in the scores. The result depends on the level of knowledge before the workshop. When the knowledge level is high, the percentage improvement

	2014	2015	2016	2017
Assessed (n)	72	85	67	54
No improvement (n; %)	4 (6%)	3 (4%)	12 (18%)	7 (13%)
Pretest result median (range)	10 (0-20)	14 (3-23)	14 (1-22)	12 (2-22)
Posttest result median (range)	16 (2-24)	19 (4-24)	18 (9-23)	18 (7-24)
Improvement median (range)	5 (1-13)	4 (1-16)	4 (1-16)	5 (1-15)
Improvement (%)	50%	29%	29%	42%

Table II. Results from the EVF HOW multiple-choice test before and after the workshop (2014-2017).

between the pre- and posttest is of a lower magnitude and the number of those not improving at all increased. This is further illustrated in *Figure 6* in a scatter diagram, which shows individual test results in 54 learners from the workshop in 2017.

In the general assessment of the workshop, >90% of learners indicated that the workshop would influence and change their clinical practice in the future. These results have been similar in all seven workshops, clearly indicating that the workshop has had the intended impact.



Figure 6. Scatter diagram of MCQ-test results before and after the workshop in 2017. The number of points of each 54 learners are given before (blue diamond) and after (orange square). Although improvements of individual learners vary, the overall improvement is illustrated by the tighter band of orange squares at the top of the test results as compared with the wide scatter of results prior to taking the workshop.

Internet-based learning tool

In 2013, the EVF HOW-associated website was introduced as an additional learning tool. This platform is a web-based password-protected portfolio. Each learner participating in the workshop receives access to the

presentations, important references and guidelines, case reports for discussion, videos of procedures, supplementary information about the workshop stations, and other study material. Access is available for 1 year after the workshop, which gives the learners a possibility to reinforce and enhance their learning experience. The response from the learners has been extremely positive. Most learners (80%) used the website before the start of the workshop and as many as 85% accessed it during the workshop, with 94% returning for up to 30 visits. In the assessment, all participants fully or partially agreed that the website was a valuable supporting tool, especially by giving access to the presentations online, having references and guidelines in pdf format available, and the ability to return to posted video material. The applications, multiple-choice questions, and course assessments are now incorporated into this website and performed online. The EVF HOW is also present on Facebook and Twitter.

EVF HOW Plus courses

During the early EVF HOW workshops, learners frequently asked for the possibility to receive more in-depth instruction about details of various procedures in clinical practice. Therefore, the advanced EVF HOW Plus courses were created to offer an opportunity to improve various skill sets for venous therapists. These were started in 2015. In order to be accepted in the EVF HOW Plus courses, the learners should have attended an EVF HOW workshop. The main objective of these in-depth mini-courses is to ensure that the learner has sufficient skills to initiate the use of a procedure by providing detailed knowledge, simulator training, and preceptorship in a clinical setting. Most courses are 2 days with only 4 to 10 participants, depending on the type of subject, which often provides an opportunity for the learners to participate at the interventional/surgical table. These courses are set up by collaborations between the

EVF and enthusiastic colleagues, who want to share their experience and devote time to instruction. For example, in Modena, Italy, Drs. Lugli and Maleti each arranged successful courses in venous stenting and deep venous valve repair, respectively. Each of these Plus courses had 4 learners, who were given the possibility of assisting in the procedures.

The success of EVF HOW and EVF Plus could not have been sustained through the years without the support of dedicated faculty members and a strong commitment of industry partners. Although the necessity to cooperate with the industry may raise concern, in the end, the integrity and the scientific delivery of the workshop must be maintained by the organizing committee, who has the final say. Occasionally, the industry must look beyond an immediate "return on investment" after sponsoring individual events and shoulder its responsibility for teaching and increasing awareness about venous disease. In the longer term, this program will be beneficial for all stakeholders.

Participation of the industry in EVF HOW has been a winwin situation for all involved. The learners have been provided with training material, phantoms, and models to practice on and close interaction with faculty members. The industry representatives are not only guaranteed to meet every learner, but also allowed to attend the scientific program, which has been greatly appreciated by industry representatives who are given the possibility of remaining up-to-date and participating in discussions and case presentations.

Conclusions

Structured instruction and practical hands-on workshops with assessment, such as EVF HOW and EVF HOW Plus, are in line with the training practices outlined in the ETR in phlebology. The EVF can now not only provide an annual scientific meeting, but also hands-on training in a basic format (EVF HOW) and an advanced format (EVF HOW Plus). It would be of great value if a third step were developed by creating a network of venous centers to allow individual venous therapists to join them for a longer or shorter period for further advanced training. Although strictly scientific meetings are important, training needs to be complemented by small group, hands-on courses on the practical management of patients with venous disease. The industry, instructors, and the learners all agree on this. For detailed information regarding future EVF HOW and EVF HOW Plus events, go to www.evfvip.com.



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VenaSeal[™] closure system for varicose veins

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Keywords:

cyanoacrylate closure; incompetent saphenous vein; nonthermal nontumescent technique; VenaSeal™; venous re1ux

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Abstract

Endothermal treatments are now considered the new gold-standard treatment for eliminating venous reflux in patients with chronic venous insufficiency. In a quest to minimize the invasiveness, nonthermal techniques that do not require tumescent anesthesia have been developed in the last decade. These new nonthermal, tumescent-less techniques are well tolerated and result in equivalent outcomes compared with endothermal ablations. VenaSeal™, one such technique, utilizes a proprietary cyanoacrylate glue to occlude the saphenous vein. Studies using VenaSeal[™] have demonstrated high anatomic success rates with closure rates >90% reported at 3 years. Sustained improvements in patient-reported clinical outcomes have been reported up to 36 months. No major adverse events or thrombotic complications have been reported with this procedure. Phlebitis and skin reactions are the most common minor adverse events. Adoption of a particular nonthermal procedure depends on several factors, such as the learning curve, initial set-up costs, overall cost-effectiveness, and reimbursement. VenaSeal[™] does not have any other initial set-up costs, and the procedure is simple, consistent, and easy to learn. To date, no data regarding cost-effectiveness are available. The purpose of this document is to summarize the VenaSeal™ data and discuss the procedural steps.

Introduction

Chronic venous disease is a fairly common condition, with the prevalence estimated at 175 million in the US.¹ However, the prevalence of advanced, symptomatic venous disease (chronic venous insufficiency) is relatively lower; it is estimated to be 5% of the population.² Advanced stages of chronic venous insufficiency can result in significant disability and affect quality of life.³ The last 20 years have seen a major transformation in the management of chronic venous insufficiency, with guidelines recommending endovenous therapies as the preferred methods of treatment over surgical vein stripping.^{4,5}

The newer nonthermal nontumescent techniques do not require the use of tumescent anesthesia and include cyanoacrylate glue, VenaSeal™, mechanochemical ablation, Clarivein, and the proprietary endovenous microfoam, Varithena. All of these techniques are approved for use in saphenous veins. The advantages

of nonthermal nontumescent techniques, apart from fewer needle sticks and the discomfort associated with tumescent anesthesia, include the lack of heat-induced thrombosis and skin injuries. Treatment from the saphenofemoral junction to the most distal refluxing portion of the saphenous veins, without concern for nerve injury is also an advantage of the nonthermal nontumescent technologies.

Cyanoacrylate glue has long been used in the management of intracranial arteriovenous malformations, pelvic variceal, and gastric variceal treatments.⁶ VenaSeal[™], a proprietary cyanoacrylate glue, is an n-butyl cyanoacrylate with unique properties, including quick polymerization upon contact with blood and high viscosity. These properties help prevent embolization. VenaSeal[™] cyanoacrylate glue is also designed to be pliable and to allow flexion and torsion once solidified.

A preclinical swine model demonstrated that induction of an inflammatory reaction in the vein wall led to fibrotic occlusion of the vein over the implant, which is a distinctly different finding compared with the endothelial injury caused by thermal ablation or sclerotherapy.⁷ VenaSeal[™] received the CE mark in 2011 and it was approved by the US Food and Drug Administration (FDA) in February 2015. *Table I* shows the current worldwide availability of VenaSeal[™].

Region	Country
North America	USA, Canada
South America and Central America	Colombia, Chile, Ecuador, Panama, Peru, Puerto Rico
Europe	All countries including Russia
Asia	Asia, UAE, Saudi Arabia, Kuwait, Qatar, Hong Kong, Korea, Malaysia, Philippines, Singapore, Thailand Vietnam
Africa	South Africa, Egypt
Australia	Australia, New Zealand

Table I. VenaSeal™ worldwide availability.

Clinical Studies

In an initial preclinical feasibility study, Almeida et al studied the VenaSeal™ procedure in 38 patients.⁸ No postprocedural compression therapy was used and no

adjunctive therapies were allowed for 6 months after the incident procedure. The maximum diameter of the saphenofemoral junction in this study was 8±2.2 cm. At 3 years, a 94.7% occlusion rate was noted. The mean Venous Clinical Severity Score (VCSS) improved from baseline (6.1±2.7) to 3 years (2.2±0.4) (P<0.0001). While no major complications were noted, mild and self-limited phlebitis was reported in 15.8% of patients, which was responsive to nonsteroidal anti-inflammatory treatment. Postprocedural duplex ultrasounds also demonstrated thread-like thrombus and glue extensions into the common femoral vein in 8 patients (21.1%), which resolved after a few weeks of anticoagulation therapy. In this study, the catheter tip was positioned 1.5 to 2 cm away from the saphenofemoral junction and the first two aliquots of cyanoacrylate glue injected simultaneously. The technique was modified for all subsequent trials by positioning the catheter tip 5 cm away from the saphenofemoral junction and by injecting the first two aliquots of the cyanoacrylate glue 1 cm apart, rather than simultaneously.⁹ This modification was made in the VenaSeal[™] instructions-for-use document as well.¹⁰

The next VenaSeal[™] study was eSCOPE, a European prospective multicenter registry involving 70 subjects. VenaSeal[™] treatment resulted in a 92.9% closure rate at the 12-month end point.¹¹ The study design was similar to the feasibility study; no postprocedure compression socks were used for this study. The average volume of glue used in this study was 1.58 mL. Adverse events included a mild, self-limited phlebitis in 11.4% of the patients. No thrombotic events were reported.

The VeClose study, a pivotal trial in the US, is a prospective, multicenter, randomized (1:1) clinical trial comparing VenaSeal[™] cyanoacrylate glue (n=108) with radiofrequency ablation (n=112). This study was designed to demonstrate statistical noninferiority of cyanoacrylate glue to radiofrequency ablation. Both arms received compression therapy to avoid any confounding factors. No adjunctive therapies were allowed up to 3 months after the incident procedure. Data collection included closure rates, patient-reported quality-of-life scores, including the clinical, etiological, anatomical, and pathophysiological (CEAP) classification, VCSS, EuroQual-5D (EQ-5D), and Aberdeen Varicose Vein Questionnaire (AVVQ). The primary end point of the study, complete closure of the great saphenous vein at the end of 3 months, was achieved in 99% of patients in the VenaSeal[™] group and 96% in the radiofrequency ablation group (adjudicated by Core lab). At 36 months, these closure rates were 94.4% and 91.9%, respectively.¹²

Surprisingly, the intraoperative pain scores were not statistically different between the two groups, despite the use of tumescent anesthesia in the radiofrequency ablation group. Ecchymosis rates in the treated segment were significantly lower in the cyanoacrylate glue group compared with the radiofrequency ablation group. The VCSS and AVVQ scores improved significantly at 3 months and were sustained over the study time (up to 36 months) in both groups without any significant betweengroup differences. Multiple imputation models (optimistic and pessimistic models) showed that cyanoacrylate glue was noninferior to radiofrequency ablation. No deep vein thrombosis (DVT) or pulmonary embolus (PE) occurred. Phlebitis occurred in 20% of the patients in the VenaSeal™ group and 14% of the patients in the radiofrequency ablation group (P=0.36). In both groups, most of these episodes were mild, transient, and treated successfully with anti-inflammatory therapy. At 36 months, late-onset phlebitis was reported in one patient and an access site scar was reported in the VenaSeal[™] group, while no adverse events were reported in the radiofrequency ablation group.

The VeClose group also published results from the 20-patient "roll-in" cohort. These patients were enrolled in the roll-in phase of the trial. In order to train the investigators in the procedural details, the study mandated VenaSeal™ treatment for two patients at each of the 10 participating sites, prior to randomization. Occlusion rates in this cohort were 100% at the 12-month follow-up and the clinical results (VCSS, AVVQ, and EQ-5D) were similar to the randomized clinical trial cohorts.¹³

Postmarket investigator-sponsored studies

All of the previously discussed studies were industry initiated and sponsored. The WAVES study (Lake Washington Vascular VenaSeal Post-Market Evaluation) is an investigator initiated, single-center study that assessed the use of VenaSeal™ in great saphenous veins (n=48), small saphenous veins (n=8), and accessory saphenous veins (n=14).¹⁴ The study also specifically included larger saphenous veins with diameters up to 20 mm. No compression therapy was used postprocedure. The primary end point was closure of the saphenous vein at 3 months. Intraoperative pain scores, and the VCSS, AVVQ, and EQ-5D scores were similar to the VeClose study. The overall vein closure rate was 99% at 3 months, and the VCSS, AVVQ, and EQ-5D scores all improved at 3 months compared with baseline. Mild phlebitis, which was either self-limiting or resolved with anti-inflammatory treatment, occurred in 10 patients (7%). Allergic reactions were reported in one patient requiring

antihistamine and oral corticosteroid use. No deep vein thrombosis or pulmonary embolism occurred.

Another study from Hong Kong reported a lower anatomic success of 78.5% at the 12-month follow-up.¹⁵ However, all patients showed improvements in the VCSS and AVVQ scores. However, 60% of the enrolled patients were lost to follow-up at 12 months, which is one of the criticisms of this study. No major adverse events were reported.

The first Korean report on the use of VenaSeal[™] in great and small saphenous veins was recently published. Cyanoacrylate glue was used to treat 47 great and 16 small saphenous veins. At 3 months, a closure rate of 100% was reported. The VCSS score improved during the followup period. Adverse events included phlebitis-like "abnormal skin reactions" in 8 patients (23.5%) with a full recovery at 2 weeks.¹⁶

A Canadian study compared outcomes of VenaSeal[™] (n=148) with radiofrequency ablation (n=328) in a single-center, nonrandomized setting. The VenaSeal[™] group included great saphenous veins (n=112), small saphenous veins (n=24), and accessory saphenous veins (n=2). "Treatment success" (not defined in the publication) was 100% in the VenaSeal[™] group and 99% in the radiofrequency ablation group. Superficial phlebitis was noted in 5% of the patients in the VenaSeal[™] group and 16% of the patients in the radiofrequency ablation group.¹⁷

Off-label use of VenaSeal[™] in incompetent perforator veins was studied in a small feasibility study in The Netherlands. A total of 33 perforator veins from 27 limbs in 23 patients were treated with a modified off-label technique, with a 76% (25/33) occlusion rate at the 3-month follow-up. No major complications occurred. A larger study is needed for further assessment.¹⁸

Indications and contraindications

Indications for using cyanoacrylate glue treatment are no different from the indications for other ablative therapies. However, it is important to discuss procedural outcomes and set appropriate expectations with the patient. In asymptomatic patients with documented reflux, the goal is to improve cosmesis. In symptomatic patients, the goal is to improve symptoms, speed up ulcer healing, and reduce recurrence rates. As per the FDA approved instructions for use document,¹⁰ absolute contraindications include previous hypersensitivity reactions to cyanoacrylate glue or cyanoacrylates, acute superficial thrombophlebitis, thrombophlebitis migrans, and the presence of acute sepsis.

Procedure

Procedure kit

The VenaSeal closure system (*Figure 1*) procedure pack is a self-contained sterile, single-patient kit comprised of the cyanoacrylate glue and the cyanoacrylate glue delivery system components, including a glue disperser gun, 5 mL of the cyanoacrylate glue in a small bottle, 5-F delivery catheter, 7-F introducer/dilator, 2 dispenser tips (blunt tip needles), two 3-mL syringes, and a 0.035" J-wire guidewire. Other required tools that are not included in the procedure pack include a micropuncture set for Seldinger access, sterile ultrasound gel packs, ultrasound probe covers, and 10 mL syringes for flushing.



Figure 1. The Venaseal glue dispenser with the cyanoacrylate glue primed catheter, housed in a 7-F dilator. Courtesy of Medtronic 2018.

Preprocedure set up

Standard patient-procedure preparation for endovascular procedures is followed for VenaSeal[™] procedure. The patient is placed in a prone or supine position for small saphenous vein or great saphenous vein treatment, respectively. The area to be treated is disinfected and a sterile drape is applied. At the author's institution, the setup uses two tables-"dry" and "wet." The cyanoacrylate glue container, dispenser gun, dispenser tips, and the 5-F delivery sheath are placed on the "dry" table (*Figure 2*). Careful precautions are taken to avoid any contact with saline or blood to prevent polymerization of the cyanoacrylate glue.



Figure 2. The dry" table with the cyanoacrylate glue, dispenser, 3-mL syringes, and the 5-F catheter.



Figure 3. The wet" table with the 0.035" wire and other components of the kit.

The rest of the components, including the micropuncture set, saline container, lidocaine container, gauze pads, towel, gel packs, saline syringes, 7-F introducer sheath, and a 0.035" J-wire guidewire, are placed on the "wet" table (*Figure 3*). Once the set-up is complete, the 3-mL syringe is filled with cyanoacrylate glue and attached to the disperser gun. The 5-F delivery catheter is then connected to the syringe and is primed with cyanoacrylate glue (by squeezing the dispenser gun plunger) up to a mark that is 3 cm from the tip of the catheter.

Technical steps

- 1. Identify the most caudad point of reflux in the target vein with ultrasound and administer topical anesthetic.
- 2. Access the vein using an ultrasound-guided Seldinger technique, and a micropuncture needle with a 0.018" wire.
- 3. Place a 7-F introducer sheath over the 0.018" wire and pass a dilator into the introducer sheath.
- Exchange the 0.018" wire for a 0.035" J-wire guidewire (Figure 4), pass a 7-F dilator over the guidewire (Figure 5), and use a saline-filled syringe to flush the



Figure 4. The 0.035" wire in the introducer sheath.



Figure 5. The 7-F dilator is passed over the 0.035" wire.



Figure 6. Dilator is flushed with saline and the syringe is locked to the dilator until the 5-F catheter is ready to be inserted.



Figure 7. The 5-F catheter primed with cyanoacrylate glue is exchanged for the 0.035" wire.



Figure 8. A cyanoacrylate glue aliquot is delivered by squeezing the handle of the dispenser gun for 3 seconds.

dilator to prevent backwash of any blood into the dilator (*Figure 6*).

5. Prime a 5-F introducer catheter with cyanoacrylate glue (described above) and advance the catheter to the saphenofemoral junction (*Figure 7*). Under ultrasound guidance, position the catheter tip 5.0 cm caudal to the saphenofemoral junction.

- 6. Use an ultrasound probe to apply pressure 2 to 3 cm cephalad to the tip of the catheter.
- 7. Make two injections with approximately 0.10 mL cyanoacrylate glue (achieved by squeezing the dispenser gun handle for 3 seconds) (*Figure 8*); these injections should be given 1 cm apart at this location.
- 8. Maintain pressure with the ultrasound probe for 3 minutes.
- 9. Pull the catheter back 3 cm and inject another 0.10 mL of cyanoacrylate glue.
- 10. Maintain manual compression 30 seconds.
- 11. Continue the procedure every 3 cm with cyanoacrylate glue injection and the 30-second ultrasound probe / manual compression sequences until the entire length of the target vein segment is treated.
- 12. Remove the sheath and catheter and apply compression at the access site until hemostasis is achieved.
- 13. Apply an adhesive bandage at the access site.
- 14. Confirm venous occlusion using duplex ultrasound.

Adjunctive procedures for tributary vein treatments are either performed in the same setting or staged based on several clinical factors. Compression therapy is not needed



Figure 9. A duplex image acquired 6 months after the VenaSeal™ procedure. Note the hyperechoic great saphenous vein (white arrow).

after the procedure unless concomitant phlebectomy or sclerotherapy are performed. Follow-up requirements for the clinical exam and venous duplex vary based on the provider's personal preference, patient complaints, and patient risk factors for venous thrombosis. As noted in the animal histologic exams, follow-up ultrasound exams demonstrate no evidence of thrombotic occlusion of the veins. There seems to be a collapse of the vein over the VenaSealTM implant. Ultrasound images of the treated vein demonstrate a hyperechoic vein with a nonsignificant reduction in diameter, even at the 1-year follow-up (*Figure 9*), unlike the veins treated with thermal ablations or sclerotherapy.

Discussion

VenaSeal™, a cyanoacrylate glue treatment of incompetent truncal veins, has been demonstrated to be a safe and effective treatment. Other than mild phlebitis episodes and rare reports of allergy that are self-limiting. No serious complications, particularly related to venous thrombosis are reported with this technique, making it an attractive option in patients with other comorbidities. Since there is no dosage limit for the cyanoacrylate glue, unlike other nonthermal nontumescent treatments, such as the sclerotherapy, multiple veins can be treated in the same setting. Except for the randomized control trial,¹⁹ all other trials required no postprocedural compression therapy. VenaSeal™ is also an attractive option in patients with a disproportionately large thigh circumference (compared with the calf), which results in sliding of the postprocedure compression garments that are required for other nonthermal nontumescent treatments, such as foam sclerotherapy, mechanochemical ablation, and proprietary endovenous microfoam treatment. Young and active patients, who do not wish to wear postprocedural compression garments, prefer VenaSeal[™] treatment of multiple veins in a single session. Similarly, patients who fear needle sticks also prefer this treatment.

While saphenous occlusion rates are high in all except one study,¹⁶ long-term data in larger cohorts is lacking at this time. The improvement in patient-reported outcomes and quality measures, such as VCSS, AVVQ, and EuroQual scores is encouraging. Advancing the stiff VenaSeal[™] catheter is challenging in chronic postthrombotic veins, tortuous tributaries, and neovascularized veins, similar to thermal techniques. Foam sclerotherapy and phlebectomy remain the preferred treatments in this setting. Subdermal, superficial saphenous veins are also not ideal for VenaSeal[™] treatment due to the fibrotic changes in the treated veins, which is again similar to thermal ablation.

Venous ulcers are the most common leg ulcers,²⁰ as 278 000 venous leg ulcers are reportedly managed by the UK National Health Services each year, at an annual cost of €1024 million.²¹ The landmark EVRA trial (Early Venous Reflux Ablation) demonstrated faster healing of venous leg ulcers and more ulcer-free time, with early endovenous ablation of superficial venous reflux rather than deferring these treatments.²² Epstein et al have also demonstrated that venous interventions are more effective and less expensive in the long run compared with compression therapy alone.²¹ There are no VenaSeal[™] outcome data in advanced venous disease and venous ulcerations at this time and further studies are needed in this population.

Finally, another n-butyl-cyanoacrylate based polymer with limited modifications, Biolas VariClose®, received the CE mark in 2013 and several studies have been reported from Turkey. Due to the limited modification, the glue is less viscous and polymerizes much quicker than VenaSeal™, which has the potential disadvantage of distal embolization and adhesion of the catheter tip to the vein wall during the procedure. While VenaSeal™ is a segmental procedure with aliquots delivered every few centimeters, VariClose® requires continuous delivery of the low viscous cyanoacrylate glue. The VariClose® studies have also reported a high degree of anatomic success (>95%) at 12 months. The reported phlebitis rates are lower compared with VenaSeal.^{23,24} However, the definition of phlebitis and the rigor for monitoring these adverse effects vary significantly between the clinical studies reported on these 2 products. VariClose[®] is not available in the USA and there have been no head-to-head comparison studies of these products thus far.

Conclusions

In summary, VenaSeal[™] is a simple procedure, with consistent procedural steps. No major adverse events have been noted. Minor complications include phlebitis episodes and rare reports of allergies to the cyanoacrylate glue. In the hands of experienced endovenous physicians without prior VenaSeal[™] experience, the procedure resulted in good anatomic and clinical success rates, along with a relatively short learning curve.¹³ Future VenaSeal[™] research should focus on treatment outcomes in late stage venous disease, venous ulcer healing and cost effectiveness.



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VNUS Closure radiofrequency ablation to eliminate truncal venous relux in patients with varicose veins: 15-year results

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Abstract

In 2017, we published our 15.4-year results on using VNUS Closure radiofrequency ablation on incompetent truncal veins. The original operations were performed between 1999 and 2001 using the method available at the time, ie, general anesthesia with Esmarch compression bandaging; no tumescence was used. Of 101 truncal veins analyzed, 89 (88%) were ablated successfully and 12 (12%) were ablated partially (partial failure) with reopening of the proximal stump and venous reflux into a proximal varicose vein. There were no complete failures. Despite using first-generation endovenous thermal ablation catheters, very basic intraoperative ultrasound, no tumescence, and without the linear endovenous energy density having been described, these ablation rates are at least as good, if not significantly better than, the ablation rates subsequently reported by those using endovenous thermal ablation. The reasons for these poor ablation rates may be the use of tumescence, poor understanding of the thermal spread from other devices, or rigidity in treatment protocols between different patients with different sized veins. At 15.4 years, 56% (determined subjectively) and 30% (determined objectively) of patients were free from varicose veins. Recurrences were most often due to disease progression, new reflux in veins that were competent at the original operation. There were no cases suggesting that hemodynamic factors were the cause of recurrence in untreated tributary perforators in the groin. We suggest that such "hemodynamic" causes of recurrence are more likely to be biological causes due to neovascularization.

Introduction

Endovenous thermal ablation (EVTA) has become the first-line recommended treatment for symptomatic varicose veins caused by incompetent truncal veins in the American, UK, and European guidelines.¹⁻³ These EVTA techniques are predominantly catheter-based radiofrequency ablation or endovenous laser ablation systems, although there are other catheter-based systems that use heat to ablate truncal veins, such as steam vein sclerotherapy⁴ and microwave.⁵

I performed the first percutaneous catheter-based EVTA procedure in the UK on March 12, 1999⁶ using the original VNUS Closure catheter (*Figure 1*). Initially, following the introduction of this technique, there was a lot of skepticism as to what the medium- and long-term success rates might be. Over the years, we have continued to present our results and now we have published our 15-year results from using this original device.⁷ Despite the considerable changes that have subsequently occurred in the design of EVTA devices and the methods of treatment, these results not only look very good when compared with stripping in the medium to long term,⁸ but also serve to teach us certain lessons about venous disease and help us understand some of the mechanisms for recurrences after open surgery.



Figure 1. Original VNUS Closure catheter – 5 FG (later 6FG) and 8 FG.

Arrows indicate the position of the thermocouple on the electrode.

Summary of the published paper

In our practice, we identified 189 patients who had undergone VNUS Closure of at least one symptomatic incompetent venous trunk between 1999 and 2001.⁷ It must be remembered that, at this time, the radiofrequency ablation technique using the original VNUS Closure device was still very new. Of the 189 patients who we attempted to contact, 5 had died, 54 responded to the invitation, and 4 had reattended by chance for other reasons; in total, we had a study group containing 58 patients (31.5%). All patients were reviewed between June and September 2016, giving a mean follow-up of 15.4 years from the date of the operation. The patient demographics were unremarkable, with the expected preponderance of females (female: male = 43: 15), the mean age at the time of the index procedure was 52.6 years (range, 31 to 69 years), and with the majority of patients presenting with legs classified as C_2 according to the clinical, etiological, anatomical, and pathophysiological (CEAP) score.

Two veins were excluded from the analysis as they had been treated originally with VNUS Closure and then the patients concerned reported that they had further treatment on these veins, but were unable to give any details. Therefore, our analysis included 101 treated incompetent venous trunks. Of these, 73 presented with primary incompetence and 18 with recurrent incompetence having had previous treatment on the target vein, usually attempted stripping, but sometimes sclerotherapy. The most commonly treated vein was the great saphenous vein, comprising 87 of the 101 veins (86%), the other veins being 2 small saphenous veins (2%), 7 anterior accessory saphenous veins (7%), and 5 Giacomini veins (5%). At follow-up, all patients were initially assessed clinically and an objective assessment of recurrence was noted. Patients were asked if they subjectively thought they had had a recurrence. This assessment was followed by venous duplex ultrasonography by a trained clinical vascular scientist.

The technical success or failure of target vein closure was reported using a scale with 4 grades of success or failure (grade 1, complete success; grade 2, partial success; grade 3, partial failure; and grade 4, complete failure) (*Figure 2*).^o A full venous duplex scan was performed on all of the other veins in the leg to check for any new reflux in previously competent veins. Finally, patients were asked about their satisfaction with the treatment and about whether they would recommend it to friends and family.

The results showed that ablation in 89 of the 101 treated veins (88%) resulted in successful treatment of the target vein, with either complete ablation and atrophy (grade 1, 73%) or had minor inconsequential openings with no clinical relevance (grade 2, 16%). None of the veins showed complete reopening (grade 4, 0%), but 12 veins showed partial failure (grade 3, 12%). All of these partial failures showed the same pattern of reopening of the proximal great saphenous vein at the saphenofemoral junction with pathological reflux into the anterior accessory saphenous veins. Patient satisfaction was correspondingly



Figure 2. The grading system used to report the success or failure of ablation of the target vein.

Panel A. Grade 1: Successful ablation of the whole target vein. Panel B. Grade 2: Partial success with minor and inconsequential areas where the vein reopened. Panel C. Grade 3: Partial failure where part of the treated vein reopened, allowing venous reflux into a clinical varicose vein. Panel D. Grade 4: Complete failure where the whole target vein reopened.

Abbreviations: CFV, common femoral vein; GSV, great saphenous vein; POP, popliteal vein; SPJ, saphenopopliteal junction; SSV, small saphenous vein; X, venous reflux.

From reference 9: Taylor D, Whiteley A, Holdstock J, Price B, Whiteley MS. Long term results of thermoablation of the great saphenous vein – outcomes ten years after treatment. In: Whiteley M, Dabbs, eds. Advances in Phlebology and Venous Surgery Volume 1. Guildford: Whiteley Publishing; 2017:50-59. © 2017, Whiteley Publishing Ltd, Guildford, UK.

high with 58 (100%) saying they were pleased that they had undergone VNUS Closure and 57 (98%) saying that they would recommend the procedure.

However, despite these excellent long-term results with the first-generation EVTA device, patients with varicose veins and venous reflux still have the risk of disease progression. Therefore, it is not surprising that, in a long-term study such as this, it was found that only 56% of patients subjectively thought they were free of varicose veins 15 years after the procedure, whereas the external assessment by the clinical vascular scientist reported that only 30% were objectively free of varicose veins at this stage. Furthermore, venous duplex ultrasonography of the other veins in the legs, apart from the target vein, showed significant reflux in 47 of 91 legs (51.6%) in veins that had been competent at the time of the original procedure. The majority of this new reflux was found in incompetent perforating veins. Although this level of de novo reflux is in line with the expected disease progression in a population of patients known to be at risk of venous disease,¹⁰ the pattern of recurrence is worth discussing and is addressed below.

Differences between the original VNUS Closure technique and modern EVTA

Reports of long-term results are always open to the criticism that "we don't do it like that anymore." Certainly, the technique and the equipment used between 1999 and 2001 are markedly different from that used today. I will go through the major differences and point out where any major discrepancies may occur between what we should expect now and what we have reported in this paper.

Ultrasound

One of the most overlooked differences between our endovenous treatments in 1999 to 2001 and those we perform now is not related to the EVTA device itself, but rather to the ultrasound used to guide the procedure. In the early days of EVTA, we did not have dedicated venous theaters and so the cases reported in this paper were performed in general theaters. There was no routine usage of intraoperative duplex ultrasound for venous cases and so hospitals were not equipped for constant and routine provision of appropriate ultrasound equipment for intraoperative use. Therefore, when we started performing EVTA, although there were relatively good systems available for outpatients for diagnostic purposes, the intraoperative guidance was performed using a very early portable ultrasound with comparatively poor resolution. The equipment used for most of our early cases was the original Sonosite portable ultrasound machine, with a screen measuring approximately 5 cm x 5 cm. The beam width (Z-axis) was very wide, meaning that all cannulation procedures had to be performed using a transverse image. A longitudinal image could often show both the needle and the vein appearing to be in the same place, while in fact they were side-by-side. However, despite this very basic intraoperative duplex ultrasound, the long-term outcomes of ablation turned out to be excellent⁷ and so a better ultrasound system could only have improved these and not made them worse.

Anesthesia

In the reported series,⁷ we used the original technique as recommended at the time by the manufacturers, VNUS Inc, which was general anesthesia with an Esmarch rubber bandage compression to ensure exsanguination of the target vein and good apposition of the vein wall to the device. Tumescence had not been developed and popularized at this stage, meaning that it was not used. Once again, it is clear that this technique worked well in view of the excellent long-term results. Indeed, there are now many series published reporting the results of EVTA using tumescence, showing significant early failure rates.¹¹ The fact that we were able to attain complete ablation in virtually all treated veins, with the only failures being small proximal reopenings, indicates that the thermal destruction of the vein wall is permanent if performed correctly. Hence, such failures cannot be due to thermal ablation itself, but must be due to other factors, such as tumescence, the use of different devices, inconsistencies or poor understanding of the power/thermal energy transfer, or differences in how the procedure is performed, such as patient position or pullback rate. As we have already seen that compression with an Esmarch bandage (rather than tumescence) can result in excellent treatment, it would certainly indicate that such compression is more likely to cause complete exsanguination than tumescence in some hands. Other factors will be discussed below.

The original VNUS Closure device

The original VNUS Closure device that was used in this study was a bipolar radiofrequency ablation device (Figure 1). The catheter was passed up the inside of the vein in the "closed" position, in which the peripheral electrodes were covered by a retractable sheath. When in position, the sheath was withdrawn and the electrodes were free to spring outward. However, when in a vein, and particularly when that vein was being compressed, these electrodes formed a "ring electrode" behind the leading ball electrode, which allowed electrical current to be passed from the leading ball electrode to the ring electrodes and back again at radiofrequency rates, inducing heating within the vein wall.¹² As I published in 2004, when performed correctly, this resulted in transmural death of the cells in the vein wall, which I hypothesized both in 2004 and 2006 to be the reason that veins treated in this manner fibrosed and atrophied, rather than thrombosed and reopened.^{12,13}

However, it is not enough to simply pass thermal energy into the vein wall. The thermal energy must be at a power sufficient enough to cause thermal destruction of the vein wall, but applied slowly enough to avoid carbonization of the inner part of the wall, which can cause the device to stick.¹⁴⁻¹⁶ The power level determines the temperature at the point of heat generation and the time of heat application is controlled by the pullback speed. The combination of power and pullback speed needs to be balanced to allow the thermal energy to defuse through the whole vein wall¹⁴⁻¹⁶ with enough energy to cause death, or to induce apoptosis, in all of the cells in the vein wall out to the adventitia.¹⁷¹⁸

It is interesting to note that the original device also included a heparin saline infusion through the central lumen of the device to reduce the risk of "thrombosis" on the end of the device. However, subsequent work has suggested that most of the debris that can accumulate in thermal ablation is probably carbonization of the vein wall rather than venous thrombosis.^{14,15,17}

The concept of cell death in the vein wall was not widely understood outside of our unit in 1999–2001; instead, it was generally thought at that time that the closure of the vein was due to protein contraction. It was known that collagen contracted at temperatures over 70°C and so the original VNUS Closure device had a thermocouple on one of the peripheral electrodes in order to feedback the temperature of the inner wall of the vein during treatment. The plan was initially to raise the temperature to 85°C, which was later increased to 90°C, to try to increase the speed of treatment.¹⁸

Of course, now that we understand the need for the thermal energy to penetrate the whole thickness of the vein wall for successful ablation, it is clear that the thermocouple is not required on the inner aspect of the vein, but rather on the adventitia. Unfortunately, this is not possible. As such, that original feature turned out to be useless. If an operator used the temperature of the inside of the vein to indicate that sufficient power had been passed into a segment of vein and used intimal temperature to monitor the pullback speed, the result would be a very fast pullback and inadequate treatment of the vein. The vein either would fail to close primarily or would appear to close, due to thrombosis, which would have a high risk of subsequent reopening. When first performing VNUS Closure and using the reported temperature to inform pullback speed, we saw such early failure in closure and fortunately recognized the cause on the table. These veins were immediately retreated at a slower rate, and through this experience, we came to understand the need for time to allow thermal spread

through the vein wall in order to cause transmural cell death. $^{\rm 10}$

Positioning of the device at the beginning of treatment

In 1999-2001, the current trend for recommending that EVTA start a minimum of 2 cm distal to the saphenofemoral junction had not been started; therefore, we had followed the original surgical principles of attempting "flush ligation," which we attained in 40% of cases.¹² In 1999, we identified 1 patient in whom a thrombus was emerging from the closed great saphenous vein and passing through the saphenofemoral junction, protruding into the common femoral vein. Having never seen this before, we removed this surgically and reported it in 2004_{12}^{12} 6 months before Hingorani drew attention to what he thought was an increased risk of deep vein thrombosis with VNUS Closure¹⁹ and Kabnick went on to name this as endovenous heatinduced thrombosis (EHIT) and produce a grading system for EHIT.²⁰ It is interesting that there is a current trend to go back to attempting flush ligation with EVTA techniques now that devices and ultrasonography have improved so much.

Power and thermal energy transfer to the wall

In 2005, Proebstle introduced the concept of linear endovenous energy density (LEED) to numerate how much power was being used per centimeter of vein during ablation.²¹ Recently, I have published further work to show that LEED is inadequate as a measure unless a power or pullback rate is quoted at the same time.²² However, in 1999-2001, these concepts of energy transfer into the vein wall had not been enumerated or given a name. As indicated above and as we published in 2004_{12}^{12} we had already understood the need for both a certain amount of power to be supplied to cause the thermal energy and a certain time being required to allow that energy to spread through the vein wall without excessive carbonization of the inner layers, causing the catheter to stick and potentially preventing further treatment.¹² Indeed, for this study, we totally ignored the heat being indicated by the thermocouple, and, as we were not able to vary the power on the original VNUS Closure machine, we merely ensured that the catheter pullback rate was 1 cm every 20 seconds.⁷

It is very interesting to see how these results, showing the practical outcome of our understanding of EVTA that we used in our patients in 1999–2001⁷ and published in 2004 and 2006,^{12,13} compare with the large number of EVTA studies published subsequently using radiofrequency ablation and endovenous laser ablation, where the ablation rates

reported are significantly inferior to this long-term study. As suggested previously, these relatively poor results could be due to changing from direct physical compression of the vein onto the device with an Esmarch bandage to a less secure "compression" with tumescence, with or without the Trendelenburg position. However, it is more likely that these inferior results are due to a combination of factors, including the lack of understanding of how thermal energy is developed and transferred by different devices (as different devices have different methods of producing and distributing their energy), lack of understanding of how different vein and vein wall sizes require different amounts of energy to be given over different time periods, and how both of these factors could inform the optimal technique to be used for any particular device in each individual patient.

Therefore, the results reported in this paper could be used as a "minimum" ablation rate to be expected in the long term for any new EVTA device and technique and could be used as a comparison value. Any series with ablation rates lower than those reported in this study need to be questioned, as these results might indicate a problem with the EVTA device or the technique of how that device is being used.

Causes of recurrence

Analysis of the major causes of recurrence in this paper shows that proximal failure of EVTA leading to reflux in the anterior accessory saphenous veins occurred in 12 veins (12% of the treated truncal veins). The major cause of recurrence was de novo reflux or disease progression in veins that had been competent at the original procedure. As outlined above, the rate of this occurring was shown to be in line with the expected rate of disease progression in a similar population from published literature. In addition, 8 legs (17% of the legs showing recurrence) showed recurrence due to previously undiagnosed pelvic vein incompetence, as this was generally not looked for at the time of the original treatment.

Neovascularization was only seen in 3 patients; these patients had all been treated for recurrent varicose veins and they had previously undergone open surgery, which were almost definitely the cause of this neovascular tissue. This result would be in line with our previous publication showing that neovascularization does not happen after radiofrequency ablation.²³ A further 8 legs (17% of the legs showing recurrence) showed evidence of primary avalvular varicose anomalies,²⁴ a condition that had not

been described at the time of the original diagnosis and intervention.

What is very interesting is that, in this long-term series of thermal ablation, there is no evidence of any hemodynamic recurrence into groin tributaries that were not closed by radiofrequency ablation. The absence of such recurrence following thermal ablation suggests that such causes of recurrence, which have been widely reported following open surgery at the saphenofemoral junction, are not actually due to hemodynamic factors, but are more likely due to biological factors of regrowth and neovascularization. it has shown that there are potential difficulties in using tumescence with or without the Trendelenburg position and in getting the optimal amount of energy into the vein wall with different devices and techniques over the optimal time period to cause the transmural death. In addition, we have shown that, after EVTA, the most common cause of recurrence is disease progression, and the lack of recurrence due to groin tributaries suggests that hemodynamic factors do not cause recurrence in unclosed tributaries after treatment of the great saphenous vein in the groin.

Conclusion

The report of ablation rates of truncal veins following EVTA with the original bipolar VNUS Closure device confirms the principal of thermal ablation of a truncal vein. It shows that it is possible to completely ablate a truncal vein with thermal energy in the long term. However, considering many subsequent studies have failed to reproduce such good ablation rates even in the short- and medium-term,



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Instructions for authors

AIM AND SCOPE

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Articles

Articles should discuss a topic of current interest, outline recent knowledge on the subject, provide personal views and analyze the different opinions regarding the topic, and cite the latest data from the literature. The article should contain:

- A title page that includes a concise and informative title, the full names of all the authors (first name, middle initial, and last name), the highest academic degrees of all authors (in country of origin language) and affiliations (names of department[s] and institution[s] at the time the work was done), a short running title (no more than 50 characters and spaces), 5 to 10 keywords, the corresponding author's complete mailing address, telephone number, and e-mail address.
- An abstract (200 to 230 words).
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Journal article that has been accepted and published online ahead of print: Gulcu A, Ozutemiz C, Ugurlu B, Kose T. Duplex ultrasonography findings are not related to menstrual cycle phases in women with early symptoms of lower extremity chronic venous disease. J Clin Ultrasound. 2015 July 16. Epub ahead of print.

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

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

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

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

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