Endovenous treatments for varicose veins

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Endoveneuze behandelingen van varices

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List of frequently used abbreviations

AVVQ, Aberdeen varicose vein questionnaire
CVD, chronic venous disease
CVI, chronic venous insufficiency
DVT, deep vein thrombosis
EVLA, endovenous laser ablation
EVSA, endovenous steam ablation
EVTA, endovenous thermal ablation
GSV, great saphenous vein
HRQOL, health related quality of life
IPV, incompetent perforating vein
LMWH, low molecular weight heparin
RCT, randomized controlled trial
RFA, radiofreqency ablation
SFJ, saphenofemoral junction
SPJ, saphenopopliteal junction
SSV, small saphenous vein
UGFS, ultrasound guided foam sclerotherapy
US, ultrasound
VCSS, venous clinical severity score

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CHAPTER 1

Introduction

Introduction

Endovenous treatment is currently one of the most frequently used methods for treating varicose veins in the Netherlands. Varicose veins are tortuous and enlarged veins due to weakening in the vein's wall or valves. They are manifestations of chronic venous disease (CVD), which may lead to serious complications.

Epidemiology

Chronic venous disease (CVD) of the legs is a common medical condition. The prevalence of varicose veins is estimated to range from 2-40%.[1-4] Variations in these estimates can be explained in part by differences in study population, methods of measurement, such as self reporting or clinical examination of varicose veins and disease definition. Four surveys of the general population in which subjects were examined clinically for the presence of varicose veins, reported a prevalence of varicose veins in 10-40% in men and 26-32% in women.[1,3,5-6] However, severity of varicose veins was not specified in all the studies. The prevalence of saphenous varicose veins in two of these studies ranged from 20-40%. The incidence of venous leg ulcers, the end-stage of chronic venous insufficiency (CVI), is much lower than the incidence of varicose veins. It is very difficult, if not impossible, to predict which patient with varicose veins will develop a leg ulcer. However, it has been estimated that about half of venous leg ulcers are the result of superficial varicose veins.[7] The treatment of leg ulcers is very expensive, therefore the treatment of varicose veins, which may reduce the incidence of leg ulcers with 50%, is likely to be cost-effective.

Knowing this, it is striking that the guidelines of the Nederlands Huisartsen Genootschap (general practitioners) on varicose veins still consider varicose veins as a cosmetic rather than a medical problem and that the general practitioners are advised to treat patients with varicose veins conservatively.[8] These guidelines are in contrast with the guidelines of dermatologists and vascular surgeons, which recommend treatment of insufficient saphenous veins and tributaries.[9]

Most important risk factors for development of varicose veins are older age, history of leg injury, and deep vein thrombosis (DVT). The incidence of varicose veins increases with age in a linear manner. The overall prevalence of saphenous varicose veins in the Edinburgh Vein Study, which is a general population study, increased from 12% in those aged 18-24 years to 56% in those aged 55-64 years.[1] These findings are concordant with the Framingham Study results in which the prevalence of varicose veins in women younger than 30 years was less than 10% while in women aged 70 years and older it increased to 77%.[4] The Bochum vein

study aimed to find the prevalence of varicose veins in secondary school children. Interestingly, they found that reticular veins were already found in 10.2%. The girls had more reticular veins and telangiectasias, whereas the boys had more trunk varices, tributary varices and incompetent perforators. In children aged between 10 and 12 years, isolated reflux points were found at the saphenofemoral junction, but no varicose vein was yet visible at the trunk level or that of the lateral branches. In the adolescents aged between 14 and 16 years the number of reflux points of the saphenous vein had greatly increased and isolated incompetence was found of the trunk or tributaries, as well as insufficient perforating veins.[10-11] Multiple studies have shown that varicose veins are more common in women than in men. Selection bias may be a problem, as women consider varicose veins more often a cosmetic problem than men, present more frequently at a varicose vein clinic and are therefore more likely to participate in studies. This difference in sex prevalence was absent or less frequently found in most general population studies. For example, the Bonn Vein Study was a general population based study and found that every 6th man and every 5th woman has CVI.[12] The history of a serious leg injury is a risk factor for CVI and increases this risk 2.4-fold.[13]

Pathophysiology

CVD can be divided into primary chronic venous disorders, and secondary, mostly due to postthrombotic syndrome and congenital malformations. They all share similar clinical symptoms, but their etiology differs. Varicose veins are more distensible than control veins, suggesting a primary systemic basis for the anomaly.[14] The pre-varicose vein wall is less resistant to the pressure that is generated in the upright position. The pressure in the dorsal foot vein is approximately 80-100 mm Hg in the upright position, in supine position only 5-10 mm Hg and normal ambulatory venous pressure should ideally be < 25 mm Hg.

There are three important causes for developing varicose veins:
1) A primary anomaly of the matrix of the vein wall causes changes of its elasticity.
2) A primary anomaly of the cups of the valves leads to white cell trapping, inflammation and destruction of the cups.
3) Primary varicose veins as well as postthrombotic varicose veins cause secondary changes to the valves. Primary varicose veins cause incompetence of the valves in the superficial veins by dilation of the vein. In postthrombotic syndrome the valves of the deep veins may be damaged by the thrombotic process and this initially results in deep venous valvular incompetence. This causes secondary dilation of perforating veins and superficial varicose veins, which again induces valvular incompetence in the superficial veins.

The valves that are present in the veins are unable to perform optimally in the upright position. The insufficiency of valve functioning in the saphenofemoral or saphenopopliteal junction causes descending varicose veins. Insufficient tributaries and perforating veins, on the other hand, can cause saphenous insufficiency without incompetence of the junction. Pittaluga studied the effect of phlebectomies on saphenous vein hemodynamics. After phlebectomy, saphenous reflux duration was significantly decreased, and phlebectomy led to a significant reduction in saphenous vein diameter.[15-16] These studies support the hypothesis of an ascending development of varicose veins.

In contrast to primary varicose veins, secondary varicose veins are caused by venous hypertension, which is in most cases the result of damage to the valves and recanalization (reflux type) or residual obstruction (obstructive type) after deep vein thrombosis. Deep vein reflux is mainly due to previous thrombosis that leads to destruction of valves but can also be idiopathic, due to primary deep valvular insufficiency. In the latter case reflux is the result of floppy valve cups, valvular agenesis or aplasia.[17-19] Dysfunction of the venous macrocirculation that is not fully compensated by the calf muscle pump action leads to changes in the venous microcirculation.

In patients with CVI due to primary or secondary varicose veins there is always high capillary pressure in the skin microcirculation .[20] The resulting skin changes, from hyperpigmentation to leg ulcer, are all caused by the disturbances of the microcirculation. These changes are caused by at least two important phenomena:

a) The capillary leakage of water results in edema, and the capillary leakage of proteins results in inflammation. Together they result in fibrosis, which is clinically visible as lipodermatosclerosis.
b) Dilated capillaries cause decrease of the blood flow velocity with rouleaux formation and sludging, which lead to micro thrombosis. These changes are clinically visible as white atrophy and finally leg ulcer.

Lipodermatosclerosis as well as atrophie blanche (white atrophy) are serious skin changes that lead to a vulnerable skin in which leg ulcers may develop.[19,21-22]

Clinical characteristics

Classic symptoms associated with CVD are discomfort, heaviness, aching, muscle cramps and itching. Clinical characteristics of CVD are varicose veins, edema, hyperpigmentation, eczema, induration, lipodermatosclerosis, white atrophy, nail changes, pachyderma, subcutaneous calcification and venous ulcers. (Figure 1). Clinical characteristics of CVD appear when the compensating mechanism of insufficient venous return fails. The progression of

Figure 1. Clinical characteristics of chronic venous insufficiency. A. Telangiectases. B. Varicose veins. C. Varicose veins and hyperpigmentation. Note that the varicose vein reduces the hyperpigmentation of the skin by its own pressure. D. Lipodermatosclerosis. E. Leg ulcer. F. Leg ulcer.

CVD is characterized by signs and symptoms that increase almost linearly in time. Classically, progression of CVD is divided into three stages: from the adaptation stage to a compensation stage to a decompensation stage, finally leading to symptoms and signs, and later to complications. Venous ulcers are considered to be the end stage complication of CVD and have a lifetime prevalence of 1-2%.[23]

Chronic venous disease may have substantial impact on patient's Health Related Quality of Life (HRQOL), which is comparable to other chronic diseases and is associated with considerable health care costs.[2] Several studies confirmed that treatment of venous disease improved HRQOL.[24-25] Generic HRQOL instruments can be used in patients with CVD, but disease-specific tests provide more information about the impact of CVD and varicose veins on patients' everyday lives. The two most commonly used disease specific HRQOL tools for varicose veins and more advanced stages of CVD are respectively the Aberdeen Varicose Vein Questionnaire (AVVQ)[26] and the Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ).[27-28]

Diagnosis

The gold standard of diagnosing varicose veins is ultrasound examination.[29] Clinical and ultrasound examination are ideally performed in upright position for optimal visualization of anatomy and hemodynamics. Diameter of the veins as well as reflux time can be measured accurately. In two recently published consensus documents of the UIP (Union Internationale de Phlébologie) a detailed methodology for complete duplex ultrasound assessment of the anatomy of the veins of the lower limbs in CVD has been described.[29-30] Using standardized investigation methods should improve the quality of duplex investigation. In some exceptional cases (e.g., venous malformations, unusual presentation of recurrent varicose veins) the anatomy can be very challenging to visualize and additional phlebography or CT-venography can be valuable. Ambulatory venous pressure measurements or plethysmography can be added as diagnostic and prognostic tools.[31-33] These two investigating methods can be used for assessing and understanding complex hemodynamic problems, causing venous hypertension or when clinical signs are not corresponding with duplex ultrasound findings.

Classification

The CEAP-classification[32,34] is used for the description of Clinical signs of CVD, Etiology (congenital, primary or secondary), Anatomy (superficial, deep and perforating veins) and Pathophysiologic (reflux, obstruction or both). The CEAP-classification[32,34] serves as a systematic guide in the daily clinical investigation of patients (Table 1). It is an orderly documentation system and forms a synthesis of the phlebological status. It also helps in choosing the appropriate treatment sequence. This classification made diagnosing CVD more precise and served as a basis for more scientific analysis of management alternatives. The first CEAP consensus document was developed at the Sixth Annual Meeting of the American Venous Forum in 1994.

Another scoring system is the Venous Clinical Severity Score (VCSS), which results in a more quantitative evaluation of the disease. As it evaluates features of venous disease that may change with treatment it facilitates evaluation during follow-up and is therefore often used in clinical trials.

Treatment

There are three main reasons to treat varicose veins. First of all, treatment should prevent occurrence of complications, such as bleeding, edema, eczema, lipodermatosclerosis, and leg ulcers. Especially the treatment of leg ulcers is intensive and very expensive, and leg ulcers

Table I. Revision of CEAP-classification of chronic venous disease: summary.[32]

Clinical classification	
C_0	No visible or palpable signs of venous disease
C_1	Telangiectasies or reticular veins
C_2	Varicose veins
C_3	Edema
C_{4a}	Pigmentation or eczema
C_{4b}	Lipodermatosclerosis or atrophie blanche
C_5	Healed venous ulcer
C_6	Active venous ulcer
S	Symptomatic, including ache, pain, tightness, skin irritation, heaviness, and muscle cramps, and other complaints attributable to venous dysfunction
A	Asymptomatic
Etiologic classification	
Ec	Congenital
Ep	Primary
Es	Secondary (postthrombotic)
En	No venous cause identified
Anatomic classification	
As	Superficial veins
Ap	Perforator veins
Ad	Deep veins
An	No venous location identified
Pathophysiologic classification	
Basic CEAP	
Pr	Reflux
Po	Obstruction
Pr,o	Reflux and obstruction
Pn	No venous pathophysiology identifiable
Advanced CEAP	
Same as basic CEAP, with addition that any of 18 named venous segments can be used as locators for venous pathology	

have a major impact on patients' HRQOL. Therefore, treatment of superficial varicose veins is recommended by many experts in the field to prevent complications. Secondly, treatment also relieves complaints caused by varicose veins, such as heaviness, tired legs, and cramps. Thirdly, cosmetics play an important role and many patients find their way to a phlebologic clinic only because their varicose veins are cosmetically disturbing, and this may affect patients' HRQOL.

The treatment of varicose veins can roughly be divided into four groups: compression therapy, surgical treatment, sclerotherapy and endovenous thermal ablation.

Compression

Compression therapy plays a role since ancient time and can be used as a unique conservative treatment, or additional to other types of treatment.[35-36] Compression therapy still plays an important role in modern phlebology.

Surgical treatment

The second type of treatment is surgery and mainly consists of ambulatory phlebectomies, high ligation and stripping. The ancient Greek already recognized the implications of varicose veins and were able to treat them with ambulatory phlebectomies. The first illustration of a varicose vein, discovered at the foot of the Acropolis (Athens) dates from the fourth century BC. It is a tablet that shows a massive leg with a tortuous dilated vein on its medial side, which has all the characteristics of a varicose vein (Figure 2).

In more recent times, the surgical treatment of saphenous varicose veins is one of the very few treatments that barely changed since its invention more than a hundred years ago. In 1884 the German surgeon Madelung invented a radical operation to extirpate the great saphenous vein (GSV) and its perforators through one long skin incision from groin to ankle. In 1905 the American surgeon William Keller introduced the stripping technique using a wire and multiple small incisions.[37] Since then, the long skin incision has been abandoned.

Figure 2. Illustration of a varicose vein, discovered at the foot of the Acropolis (Athens), fourth century BC.

William Babcock, also an American surgeon, invented the tools that formed the basis for the current vein stripper.[38] The last major revision was the introduction of the high ligation at the saphenofemoral junction (SFJ) that was added to the standard procedure in 1916 by John Homans.[39] Similar to this, the small saphenous vein (SSV) was ligated at the saphenopopliteal junction (SPJ). Several variations of the initial method have been made, such as the use of different types of strippers, invaginated stripping and cryostripping, without changing the basic principles of treatment. For decades, the treatment of saphenous varicose veins consisted of ligation at the SFJ or SPJ and short stripping (from the groin to the knee for the GSV and from the popliteal fossa to mid-calf for the SSV). For treating SSV incompetence many surgeons, in particular in the Netherlands, often limited the operation to ligation of the SPJ without stripping the SSV, because of the risk for injuring the sural nerve during the stripping manoeuvre.[40] However, results of the latter technique are inferior to that of ligation and stripping the SSV to mid-calf. A recently published study showed that additional stripping of the SSV significantly reduced the rate of recurrent SPJ incompetence after one year, without increasing the rate of complications compared to SPJ ligation alone.[41]

An important disadvantage of surgery for varicose veins is the well known high recurrence rate (up to 30-60% at long-term).[42-43] The main causes for recurrence of varicose veins after surgery are insufficient understanding of venous hemodynamics, inadequate preoperative assessment, incorrect or incomplete surgery, progression of underlying venous disease and neovascularization at and around the ligated junction.[44] Improving the quality of preoperative assessment routinely performing duplex ultrasound seems to be very important to reduce recurrence. According to a randomized controlled trial, systematical use of duplex ultrasound significantly lowered the incidence of duplex detected recurrence at the SFJ or SPJ and reduced the number of reinterventions within 2 years after surgery.[45]

The last years new attention has been drawn to the surgical treatment of tributaries. Ambulatory conservative haemodynamic management of varicose veins (CHIVA), mainly performed in Italy and France, proved to give better results than stripping when considering recurrence rate.[46-47] The basic concept is that treatment of varicose veins should recover the venous hemodynamic situation. The newest idea, which is more or less related to the principles of CHIVA, is that tributaries have great impact on the problem of varicose veins. Looking at the outcome of treating only varicose tributaries helps to differentiate between ascending and descending varicose veins. The idea is that treating superficial varicose veins can be divided into two different strategies based on two pathofysiologic concepts. First, treating insufficient tributaries of the insufficient saphenous vein may lead to abolition of the saphenous reflux, so the saphenous vein need not be treated any further (this underlines the concept of ascending varicose veins). Treatment of the saphenous vein alone or in combination with tributaries is based on the descending theory. The effect on the reflux of the saphenous vein

by treating insufficient tributaries will be further investigated by our study group. Promising results after performing phlebectomies without treating GSV trunk incompetence have already been reported by Pittaluga.[16]

Sclerotherapy

The third main treatment type is sclerotherapy. Sclerotherapy was known in medicine even before stripping; i.e. since the 19th century. Chassaignac was the first to inject varicose veins with ferrochloride (1855). Since 1911 teleangiectasias and reticular veins have been injected with sodium carbonate and sodium salicylate. Later also quinine, sodium chloride and urethane were used as sclerosants. Fegan added compression to sclerotherapy in 1965 and since then sclerotherapy has always been combined with compression therapy to obtain better results.[48-49] Nowadays liquid and foam sclerotherapy are commonly used with detergent sclerosant solutions such as polidocanol and sodium tetradecyl sulfate. Ultrasound guided foam sclerotherapy (UGFS) will be discussed in detail in chapters 2 and 3. Briefly, in UGFS liquid detergent sclerosant solution is mixed with air or a physiological gas to create foam. The sclerosant reacts with the endothelial cells of the vascular wall and in this way induces contraction, thrombus ('sclerus') formation and eventually fibrosis of the vein.[50-51] Foam is four times more effective than liquid sclerotherapy because of increased contact time with the venous wall, increased surface area of the venous wall, and venous spasm.[52]

Endovenous thermal ablation

The fourth main treatment option is the group of endovenous thermal ablation (EVTA). The demand of cosmetically superior, less invasive and more successful treatment modalities has led to the introduction of minimally invasive techniques. These techniques were introduced only one decade ago and radically changed the treatment of varicose veins. The thermal endovenous techniques are endovenous laser ablation (EVLA), radiofrequency ablation (RFA) and endovenous steam ablation (EVSA) and will be discussed in detail in chapters 2,3,5,6,10,11. The advantage of EVTA is that it is minimally invasive and can easily be performed under local tumescent anesthesia without need for spinal or general anesthesia and that the recurrence rate of the thermal techniques is lower than of surgery.[53] The first EVTA procedures were performed with RFA with the VNUS Closure Plus system.[54] Immediately thereafter EVLA was developed and this became soon the most frequently used EVTA method around the world. The wavelength for EVLA differed from 800 to 1500 nm. The last years two new RFA systems have been introduced, VNUS Closure Fast (segmental RFA) and RFITT (radiofrequency induced thermotherapy). The newest invention of thermal ablation is using steam of 120°C. Ongoing studies will have to show whether this technique is as effective as EVLA and whether it is better appreciated by patients in terms of pain and discomfort. Thinking of the future, the

best invention would probably be an endovenous treatment that is effective, painless and does not need application of tumescent anesthesia.

Aims of the thesis

The first motivation for a systematic literature research was to contribute to evidence-based medicine and identify gaps in the knowledge concerning the treatment of saphenous varicose veins (chapter 2,3). After the systematic review, we pooled all the available data and performed a comparative meta-analysis, looking at the outcome after surgery, EVLA, RFA and UGFS. Then, we wanted to understand more about endovenous laser treatment specifically. This led to a review of complications of EVLA and to a technical review on EVLA. Because of the lack of standardization in EVLA treatment and the parameters used, it was useful to explore the use of different parameters and their consequences. We focused on the temperature profile induced by EVLA, because temperature influences both effectiveness and side-effects of EVLA. Several theories on the exact mechanism of EVLA have been proposed in the literature, but here again a lack of evidence exists.

The second aim was to try to unravel the exact mechanism of action of EVLA by in-vitro experiments as well as mathematical modeling (chapters 7,8,9,). By first trying to look for standardization of EVLA techniques and then trying to unravel the mechanism of action we wanted to contribute to finding the optimal EVLA method with the best risk-benefit ratio.

The third and last aim of this thesis was to describe two new techniques. The first new technique was the radiofrequency stylet, which was used to treat perforator veins. The second was EVSA, as an alternative EVTA technique for treating the incompetent GSV or SSV. The EVSA procedure itself, animal experiments, the results of the first patients treated in the Netherlands, and dose-finding experiments are presented (chapter 11,12). Our study on steam ablation is a good example of clinical and translational investigation.

In summary, first we tried to comprehend the current literature on varicose vein treatments to find evidence for what could be the most successful therapy, and to assess its complications. Then we tried to understand more about the exact action mechanism of EVLA. Finally, we introduced endovenous steam ablation and assessed its possible advantages in terms of patient satisfaction. Ideally, the results of this thesis should contribute to finding the optimal treatment for varicose veins in terms of highest success rate, highest patient satisfaction and the most favorable cost-benefit ratio.

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Minimally invasive techniques in the treatment of saphenous varicose veins

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Abstract

Lower extremity venous insufficiency is common and increases with age. In addition to classical symptoms, it may result in skin changes and venous ulcers. Chronic venous insufficiency has a great impact on patients' health-related quality of life and is associated with considerable health care costs. Surgical ligation of the junction with or without stripping has been the standard of care in the treatment of insufficient great and small saphenous veins. However, the recurrence rates are relatively high and surgery may be associated with serious adverse events and considerable down time; it is also cosmetically suboptimal. To improve efficacy, patients' health-related quality of life and treatment satisfaction and to reduce serious side effects, costs, and postoperative pain, several minimally invasive techniques have been introduced in the last decade. Dermatologists have played an important role in the development of these new therapies of truncal varicose veins. Of the new therapies, ultrasound-guided foam sclerotherapy, endovenous laser therapy, and radiofrequency ablation are the most common and challenge surgery as the "gold standard" of care for patients with varicose veins. The objective of this review is to inform clinicians about these 3 therapeutic options for truncal varicose veins and to describe and compare the procedures, indications, efficacy, and safety profile.

Introduction

Lower extremity venous insufficiency is a common medical condition. Half of the adult population has stigmata of minor venous disease[1] and about 25% of the population has lower extremity varicose veins.[2] More than 25% of people with varicose veins have insufficiency of the truncal veins of the legs. Since varicose veins increase with age in a linear manner, the prevalence of venous insufficiency will increase considerably. Classic symptoms of venous insufficiency are aching, discomfort, edema, and muscle cramps. Associated complications are eczema, lipodermatosclerosis, white atrophy, superficial thrombophlebitis, and venous ulcers. Venous ulcers have a prevalence of 1% to 2% in people older than 65 years of age.[3] Chronic venous insufficiency has a great impact on patients' health-related quality of life (HRQOL), which is comparable to other common diseases, and is associated with considerable health care costs.[4]

The treatment of varicose veins reduces the symptoms and complications of chronic venous insufficiency and improves HRQOL of patients. Surgery has been the standard of care in the treatment of truncal varicose veins. The great saphenous vein (GSV) is historically treated by high ligation at the saphenofemoral junction (SFJ) followed by a short stripping to the knee (Fig 1). Most commonly, the small saphenous vein (SSV) is ligated at the saphenopopliteal junction (SPJ) only. Recurrence rates after surgery are about 25% and 50% at 5 years for the GSV and SSV, respectively. A study with a mean follow-up of 34 years showed recurrence in 60% of 125 limbs after SFJ ligation and GSV stripping.[5] Failure after surgery may be due to neovascularization, double saphenous vein system, technical and tactical failure (up to 30%),[6] and/or incomplete procedure.[7,8] Other disadvantages of surgical therapy are the use of general or epidural anesthesia, presence of at least two fairly long scars, postoperative down-time, and risk of adverse events such as femoral artery and/or vein damage, wound
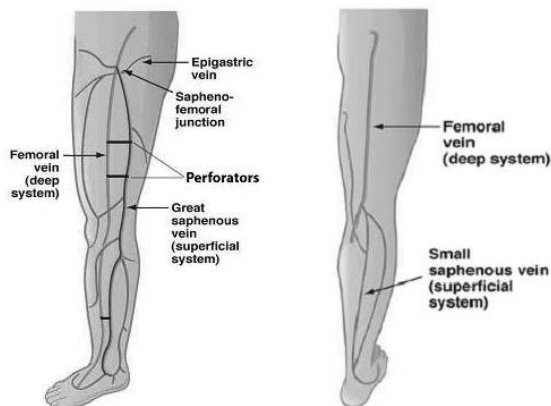
**Figure 1.** Basic anatomy of the venous system of the lower extremities.

infection, neurologic injury (about 7% in short to 40% in long stripping of GSV)[9] and lymphatic complications. To improve efficacy, patients' HRQOL, and treatment satisfaction and to reduce serious side effects, costs, and postoperative pain, new minimally invasive techniques, such as ultrasound-guided foam sclerotherapy (UGFS), endovenous laser therapy (EVLT), and radiofrequency ablation (RFA), have been introduced in the last decade.[10] Dermatologic surgeons have been on the frontier of the development of these minimally invasive techniques and were among the first to report the use of UGFS, EVLT, and RFA for truncal varicose veins. The objective of this review is to inform clinicians about the most commonly used minimally invasive therapies used for truncal varicosities, to describe the procedures, and to review their efficacy and safety.

Ultrasound-guided foam sclerotherapy (UGFS)

Procedure

In UGFS, liquid sclerosing solution, which is used in classic sclerotherapy, is mixed with air to create a foam. This foam of fine bubbles is injected intravenously with ultrasound (US) guidance. In classic sclerotherapy, the air block technique (in which an air bubble is injected before injecting the sclerosant) has been used to enhance the duration of contact with the venous wall and to reduce the "wash out" of the agent injected in the veins.[11] In UGFS, a foam (eg, 1 cc of aethoxysclerol/polidocanol or sodium tetradecyl sulfate 1% to 3% in Europe and the United States, respectively, mixed with 3 to 4 cc air) is created by connecting two syringes (Luer Lock) using a two- or three-way stopcock. One of the syringes is filled with the agent and the other with air (Fig 2A).[12-14]

Because most of the foam moves in the direction of venous flow, it is usually administered to the (most) distal part of the truncal varicose vein while the patient is in horizontal position. However, in the Second European Consensus Meeting report, it was recommended that the injection be administered at the proximal thigh, 10 cm below the junction, to achieve most optimal occlusion of the proximal part of the vein.[14] To guide access, the vein is visualized longitudinally by US (Fig 2B). The foam can be injected directly or through a cannula or butterfly needle (Fig 2C,D).[15] The volume of foam depends on the length and diameter of the vessels. The volume may vary and is restricted by the increased risk of clinically relevant air emboli. There is no high-level evidence detailing the maximum volume of foam to be used per session. Recommendations vary widely but the volume should not exceed 10 mL per session, based on the Second European Consensus opinion. For truncal varicosities, a 3% polidocanol foam appears to be more effective than 1% polidocanol foam but may cause more adverse events, such as hyperpigmentation and phlebitis.[16] After injection, patients
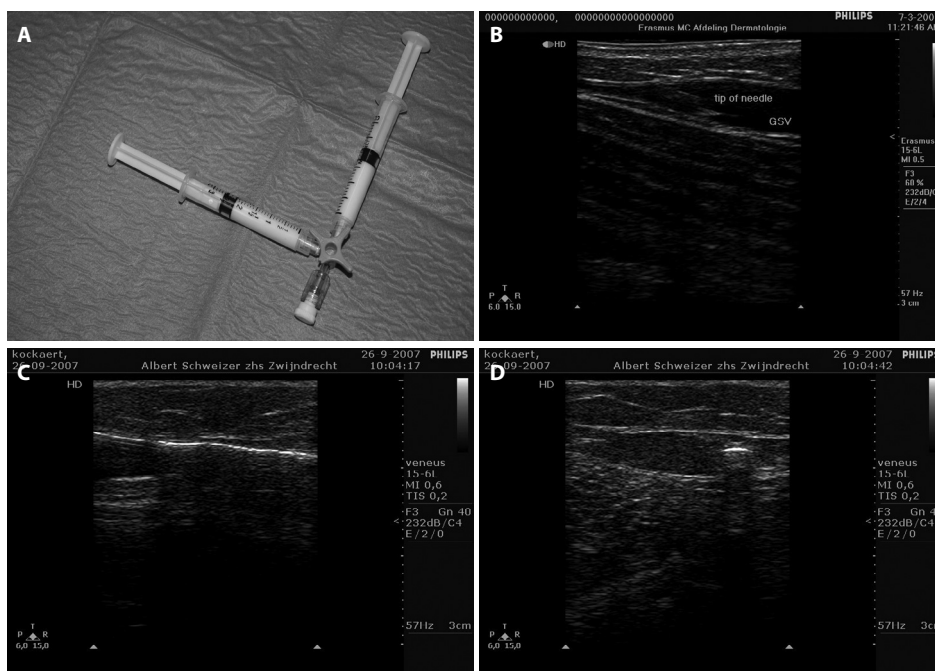
Figure 2. Creation of foam (A); gaining access to varicose vein (B); injection of foam in longitudinal (C); and cross-sectional view (D).

remain horizontally or in reverse Trendelenburg position to enhance contact for 5 minutes or more. After therapy, cotton wool or foam pads can be applied over the tract of the veins and compression therapy (bandages, antithromboembolism stockings, and/or medical elastic compression stockings class II) are recommended for a period of 1 to 6 weeks.

Indications

This technique is indicated in primary (linear and tortuous) GSV and SSV, previously treated varicosities and recurrences after surgery (ie, neovascularization). Varicosities with small and large diameters can be treated with UGFS but saphenous veins with diameters of 10 mm or more may require multiple treatments and large volumes of foam (up to 3 sessions and 15 cc of foam).[17] UGFS can be used in patients with severe chronic venous insufficiency (CVI) and may enhance ulcer healing.[18] This technique is also used to treat perforator veins and congenital venous malformations (Table I).[19-21]

Efficacy

Compared with classic liquid sclerotherapy, foam sclerotherapy is about 4 times more effective because of increased contact time with the venous wall, increased surface area of the

Table I. Indications for the different minimally invasive treatments of varicose veins

Indications	UGFS	EVLT	RFA
GSV	+	+	+
SSV	+	+	+
Accessory veins	+	+/-	+/-
Perforator veins	+	+/-	-[*]
Diameter <0.5 cm	+	-	+/-
Diameter 0.5-1.0 cm	+	+	+
Diameter >1.0 cm	+/-	+	+[†]
Tortuous vein	+	-	-
Neovascularization[‡]	+	-	-
Partial intraluminal obstruction[§]	+	-	-

EVLT, Endovenous laser therapy; *GSV*, great saphenous vein; *RFA*, radiofrequency ablation; *SSV*, small saphenous vein; *UGFS*, ultrasound-guided foam sclerotherapy.
[*]Mini RFA can be used.
[†]Maximum vein diameter equals 12 mm in conventional RFA, not in fast version.
[‡]May occur after surgical stripping.
[§]After thrombophlebitis, UGFS, EVLT, or RFA.

venous wall, and venous spasm.[22] After one UGFS session, about two thirds of the truncal varicosities were occluded and more than 90% of treatments were successful after two or three sessions.[16,18,23] Several large case series[16,24] and one multicenter study[25] have been published, but few comparative studies have been published (Table II). UGFS in 1411 limbs showed occlusion in 88% of GSVs and 82% of SSVs after a mean follow-up of 11 months.[16] Smaller series showed 69% complete sclerosis in 99 limbs after 24 months of follow-up,[17] 44% occlusion in 211 limbs after 5 years of follow-up,[26] and 88% occlusion in 143 limbs after 6 weeks of follow-up.[23] Two older trials have demonstrated that liquid classic sclerotherapy is not as effective as surgical stripping.[27-28] A small prospective randomized trial suggested that SFJ ligation and one session of UGFS was less effective in the short term, but significantly less costly and time-consuming than SFJ ligation, stripping, and multiple avulsions.[29] Several prospective randomized clinical trials are ongoing that compare UGFS with surgery.[30]

Safety

Extravenous injection of foam may cause local cutaneous side effects such as hyperpigmentation and, rarely, skin necrosis. Compared with classic liquid sclerotherapy, foam sclerotherapy is more likely to induce postinflammatory hyperpigmentation but less likely to induce skin necrosis because it has a much higher sclerosing power at a 3- to 4-fold dilution. A few weeks following therapy, patients may experience a string-like induration of the injected vein due to venous obliteration. Most adverse events are comparable with those after liquid sclerotherapy and include rare events such as migraine-like neurologic symptoms and scotomas,

Table II. Outcomes of selected studies[*]

Author(s), year	No. of treated limbs	Closure rate (%)	Mean follow-up
Ultrasound guided foam sclerotherapy			
Barrett et al, 2004[17]	100	97	23 mo
Belcaro et al, 2003[26]	211	49	10 y
Smith, 2006[15]	1411	82, 88[†]	11 mo
Endovenous laser therapy			
Agus et al, 2006[31]	1076	97	3 y
Almeida et al, 2006[32]	587	92	160 days
Gibson et al, 2007[33]	210	96	4 mo
Min et al, 2003[34]	499	93	2 y
Proebstle et al, 2004[35]	106	90	3 mo
Proebstle et al, 2005[36]	282	98	3 mo
Ravi, 2006[37]	1091	91 or 97[‡]	1 y[§]
Sharif et al, 2006[9]	145	76	1 y
Timperman et al, 2005[38]	100	100	9 mo
Radiofrequency ablation			
Almeida et al, 2006[32]	128	95	198 days
Merchant et al, 2002[39]	318	85	2 y
Merchant et al, 2005[40]	1078	89	4 y
Weiss and Weiss, 2002[41]	140	90	2 y

[*]Selection criteria: at least 100 limbs, minimal follow-up 3 months, ultrasound-based outcome.
[†]For SSV and GSV, respectively.
[‡]Two hundred limbs with 1-year follow-up.
[§]Mean follow-up not reported, but 87 of 836 limbs were followed for 4 years.

especially in people with an open foramen ovale. Although the sclerosing foam enters the systemic circulation and can be detected in the right ventricle of the heart seconds after administration, very few deep vein thromboses (DVTs) and emboli have been reported.[42] The likelihood of these serious side effects may depend on the volume of injected foam.[12] Some authors recommend the use of low-molecular-weight heparins (LMWHs) for 5 days to prevent DVTs, especially in patients with a higher risk for thromboembolic complications (Table III).[14-15]

Table III. Likelihood of specific adverse events associated with each of the three minimally invasive techniques

	UGFS	EVLT	RFA
Allergic reaction*	+	-	-
Skin necrosis/burns	+/-	+	+/-
Ecchymosis	+/-	+	-
Pain ('pulling cord') due to venous contraction	-	+	+/-
Thrombophlebitis	+	+	+
Deep venous thrombosis and emboli	+	+/-	+/-
Nerve damage (peripheral)	+/-	+/-	+
Pigmentation	+	+/-	+/-
Matting	+	-	-
Scotoma (transient)	+	-	-
Central neurological symptoms (transient)	+	-	-

EVLT, Endovenous laser therapy; RFA, radiofrequency ablation; UGFS, ultrasound-guided foam sclerotherapy.
*Allergic reaction to local anesthesia can occur with all treatments.

Endovenous laser therapy (EVLT)

Procedure

EVLT can be performed with the patient under local tumescent anesthesia in an outpatient setting. Venous access is obtained by a puncture with a 16F or 18F needle under US guidance or with direct exposure through a phlebectomy incision (Fig 3A). Most commonly, the insufficient GSV is entered at knee level because of ease of access (ie, large diameter and linear course) and the smaller risk of nerve injury. If possible, identified causes of venous insufficiency, such as insufficient perforator veins (eg, Boyd's, Dodd's, or May's perforators) should be treated concurrently. After entrance to the varicose vein is established, a guidewire is passed through the hollow needle into the vein until beyond the junction. If the varicose vein is too tortuous, has a small diameter (due to spasm) and large side branches, or contains thrombotic or sclerotic fragments (after phlebitis or prior treatment, respectively), advancing the wire can be difficult and caution is indicated because of the enhanced risk of perforation and embolic events. After the guidewire is in place, the needle is removed, and a small cutaneous incision of 3 mm is made, an introducer sheath will pass over the guidewire and is positioned a few centimeters below the junction (Fig 3C). Subsequently, the laser fiber (diameter ranges between 200 to 600 µm) can be introduced after removing the guidewire. The most pivotal step in the EVLT procedure is positioning the echo-dense tip of the sheath 1 to 2 cm distally from the junction under longitudinal US visualization (Fig 3B). The wavelengths used in EVLT target deoxygenated hemoglobin and/or water and range between 810 and
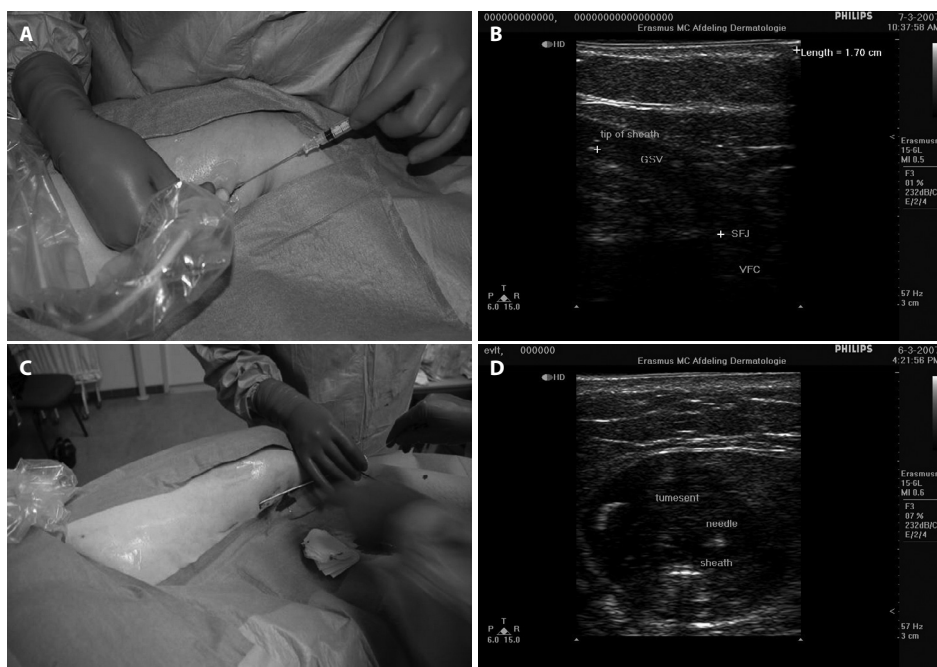
Figure 3. Gaining access to varicose vein under ultrasound examination (A); positioning of tip about 2 cm from the junction (B); passing of laser fiber through the sheath (C); application of tumescent anesthesia (D).

1500 nm. About 250 to 500 mL (depending on the length of vein treated) of tumescent anesthesia (5 mL epinephrine [5 mL bicarbonate] and 35 mL lidocaine 1% diluted in 500 mL saline solution or Ringer's lactate) is administered into the perivenous space under US guidance using a syringe or mechanical infusion pump (Fig 3D). Tumescent anesthesia is warranted because it reduces pain, cools perivenous tissue, and decreases the venous diameter. After activation, the laser is pulled back continuously (about 3-5 mm/s, depending on the power and wavelength; with the 1320-nm laser, a pull-back speed of 1 mm/s is commonly used)[43] or in a pulsed fashion with the objective to administer about 50 to 70 J/cm.

Indications

EVLT can be used in the treatment of insufficient GSVs and SSVs. Because of the rigidity and size of the disposables, linear primary truncal varicosities with a diameter of 5 mm or more are ideal for EVLT. If thinner fibers are used, EVLT can be used for more tortuous veins such as the accessory veins and perforator veins (see Table I).[44-45] In the treatment of recurrent varicose veins, caution is indicated because introducing the laser may be difficult and there might be more risk of inducing embolic events.

Efficacy

In 2001, the first case series suggesting that EVLT might be successful in the treatment of large varicosities was published.[46-47] Thereafter, multiple case series (number of treated limbs ranging from 6 to 1250) have been presented, and systematic reviews have been published.[48-50] Although the success rate of EVLT decreases over time, it remains at least 90% in the majority of the studies (see Table II).[49] In a prospective study, 93% of 499 GSVs were occluded 2 years after therapy. An Italian workgroup reported a success rate of 97% in 1000 patients with a follow-up of 3 years, and another large study with more than 1250 limbs treated showed a success rate of approximately 95%.[31,34,37] In a combined 4-year follow-up study looking at endovascular laser plus ambulatory phlebectomy for the treatment of superficial venous incompetence using an 815-nm diode, recurrence rates of 4.3% at 4 years, 3.6% at 2 years, and 5.9% at 1 year was noted, with the majority noted at 1 year.[51] Three small, short-term studies compared EVLT and surgical stripping and suggested that they were equally effective, but patient-reported outcomes were in favor of EVLT.[52-54] A small retrospective study suggested that RFA and EVLT were equally effective.[55] A recent meta-analysis showed that EVLT was significantly more effective compared with stripping, UGFS, and RFA.[56]

Safety

The high temperatures of laser energy induce multiple microperforations of the venous wall that often result in pain ("pulling cord") and ecchymosis. These common adverse events disappear spontaneously within 2 weeks and/or can be controlled by elastic stockings and painkillers. Although minimally invasive techniques may reduce side effects associated with surgery (eg, wound infection and scarring), it may be associated with specific adverse events such as DVT and skin burns (if tumescent anesthesia is not properly used). EVLT induces a symmetric and nonfloating sclerosis. From this treatment-induced sclerosis, a thrombus may progress into the deep venous system creating a DVT, usually asymptomatic. However, the likelihood of DVT is less than 1%.[31,34,37] In addition to careful instructions to the patients, some authors advise performing US examination 1 week after EVLT to exclude DVT and others use LMWH for 5 to 7 days after the procedure to prevent the development of DVT.[55] Skin burns are also rare and may occur if the energy level is too high, if superficial veins are treated, and/or the cooling effect of tumescent anesthesia is insufficient. Caution is warranted for the extrafascial part of the truncal varicose veins and the cutaneous exit site of the laser fiber. Superficial thrombosis, dysesthesia, hematoma, cellulitis, and arteriovenous fistulae have been reported after EVLT (see Table III[31,34,37,51-56])

Radiofrequency ablation (RFA)

Procedure

Access to the varicose vein is obtained with a 16-gauge needle under US guidance typically below knee level or distal to the point of reflux. The Closure catheter (VNUS Medical Technologies, Inc, Sunnyvale, Calif) (Fig4A) is positioned 1 to 2 cm distally from the junction under longitudinal US visualization. The pods of the catheter are expanded in the common femoral vein and, with US guidance, withdrawn into the orifice of the junction. A cuff or bandage can be used to compress the blood out of the vein. The small electrodes at the end of the "umbrella" catheter are in direct contact with the venous wall and omit high radiofrequency energy (regulated by power, impedance, and time) that is generated by a radiofrequency generator (VNUS Medical Technologies, Inc). The RF heats local tissue up to 85°C to 90°C at the site of direct contact, with the heat conducted to deeper tissue planes, causing collagen shrinkage, denudation of endothelium, and obliteration of the venous lumen.[57] A thermo-couple monitors the temperature during treatment. Similar to EVLT, perivenous tumescent anesthesia is applied to optimize contact surface and to decrease the pain sensation and risk of dysesthesia.[41] Also, manual compression is recommended during the treatment to enhance contact of the catheter with the vein wall. The catheter is slowly pulled back at about 3 cm/min (total pullback time is about 20 minutes on average for the GSV between SFJ and knee level) but can be faster at higher temperatures.[58] Compressive bandage or long compressive stocking class II is indicated for 1-2 weeks.
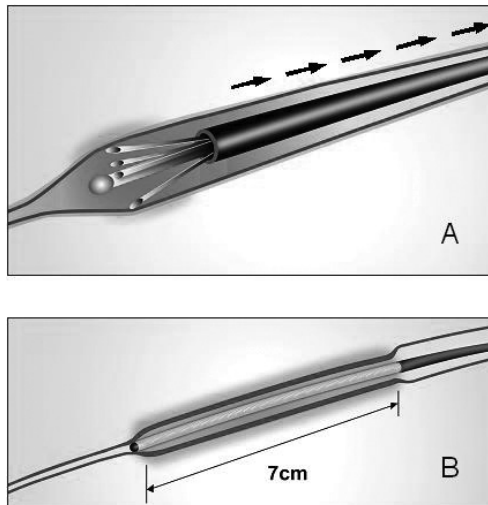
Figure 4. Catheter used in classic radiofrequency ablation technique (VNUS Closure) (A); Catheter used in new VNUS ClosureFast (B).

Recently, a new catheter (VNUS Closure fast) has been introduced, which has a 7 cm thera-peutic distal tip that heats up to 120°C (Fig 4B).[59] This technique is much faster than the previous VNUS and the first case series of 252 treated GSVs showed an occlusion rate of 99.6%.[60]

Indications

The indications for RFA are comparable to EVLT, except that with RFA it is more difficult to treat veins with diameters greater than 12 mm. Nevertheless, with ample use of tumescent anesthesia, such veins can be successfully treated. A 5F (1.7 mm) and a 8F (2.7 mm) catheter can be used for veins between 2 and 8 mm and as large as 12 mm, respectively (see Table I). The manufacturer has introduced a new catheter of uniform size that can be used independent of vein diameter. Because of the rigidity and size of the catheter, to avoid perforation caution is indicated in treating tortuous and relatively small varicose veins.

Efficacy

Since 2000, several case series have been published showing that RFA can be successfully used in the treatment of lower extremity varicosities.[61-65] The first long-term, large, single-center case series showed that RFA was effective in about 90% of 140 limbs after 2 years.[41] This study also showed that 98% of patients were satisfied with this intervention and would recommend it to a friend. A multicenter study that included 1006 persons (1222 limbs) showed anatomic success rates and patient satisfaction in more than 85% of the people after 4 years of follow-up (see Table II).[40]

Three small randomized clinical trials have compared RFA with vein stripping and demon-strated that the therapies were about equally effective; however, patients treated with RFA reported less postoperative pain and physical limitations, faster recovery, fewer adverse events, and superior HRQOL compared with patients who underwent surgical stripping.[66-68] A retrospective study suggested a significantly higher closure rate for EVLT compared with RFA at 500 days (92% vs 85%).[32]

Safety

The earliest case series of RFA reported serious side effects such as paresthesias, skin burns and DVT, but procedural changes have since been made. With the exception of "a word of caution" by a group who detected DVT in 16% of RFA-treated limbs,[69] the frequency of DVT is less than 1%.[32,39,55,70] Initially, paresthesias were reported relatively frequently, but the incidence decreased significantly after the use of tumescent anesthesia.[32,41] Local RFA-induced

adverse events, such as pain and ecchymosis, are mild compared with EVLT. Skin burns and phlebitis are reported in approximately 2% to 5% of cases (see Table III).[32]

Discussion

Procedure

Each of the minimally invasive therapies can be performed in outpatient settings. EVLT and RFA can be done using local tumescent anesthesia, and UGFS does not require anesthesia. In contrast to UGFS, EVLT and RFA should be performed in a sterile environment. RFA is a patented and standardized procedure. Although the characteristics of the laser (such as wavelength, mode of pulling back, power, and pullback speed) may vary, the procedure is relatively well standardized and it is widely accepted that 60 J/cm or more should be administered. Compared with RFA and EVLT, UGFS seems to vary more between physicians (for example, type and concentration of sclerosant used, the creation of foam, volume of foam needed, localization of injection, and one vs multiple injections, type of compression therapy). Each of the minimally invasive techniques requires US experience, preferably by the physician, but technicians can assist during the procedure. UGFS takes about 5 minutes, whereas the endovenous therapies may last 30 to 45 minutes. Of the 3 therapies, UGFS may be the most cost effective because it is fast, cheap, and easily repeated, but comparative studies are lacking. Although the period of using elastic compression stockings after UGFS is controversial (between 0 and 6 weeks), it seems to be essential in achieving an optimal result.

Efficacy

Small, short-term comparative studies suggest that EVLT and RFA are equally effective compared with vein stripping but are more appreciated by patients.[55] Because none of the minimally invasive techniques seem to be associated with neovascularization, long-term studies are likely to show a clinical benefit for these new procedures compared with ligation and stripping,[56] especially in the treatment of the SSV.[71] UGFS is very promising in the treatment of saphenous recurrences after vein stripping because these veins are tortuous and often have a relatively small diameter, and the anatomic situation is altered. Of the minimally invasive techniques, EVLT may be the best option in veins with very large diameter because UGFS often requires 3 or more treatment sessions and the RFA catheters are designed for a maximum diameter of 12 mm, except for the new fast version of RFA. In small and symptomatic insufficient saphenous veins (diameter <4 mm), UGFS is indicated. A recent meta-analysis reported that the success rates of UGFS, RFA, and EVLT are about 78%, 84%, and 95% after 3 years, respectively (see Table II).[56]

Safety

Because of the destruction and/or irritation of endothelial cells and the ensuing sclerosis (which is different from a thrombus because it is symmetric and causes adherence of the venous walls with no free floating component), the development of DVT is the main concern of each of the 3 minimal invasive techniques. No comparative safety studies are documented but a comparison of the largest case series of each of the treatments suggests that the risk may be highest for RFA (up to 1%), which is comparable to DVT risk after vein stripping.[41,72-74] However, symptomatic and asymptomatic thromboembolic events and methods of diagnosis should be differentiated when comparing thromboembolic outcomes in these treatments. Several preventive measures, such as hypercoagulability screen (for high-risk individuals selected by history and physical examination), preoperative and/or postoperative LMWH (about a week), US control of the junction following treatment after 1 week, localization of the catheter distal from the inferior epigastric vein, ample administration of tumescent anesthesia, avoidance of perforation, and for UGFS limb elevation, immobilization and applying pressure on the junction after injecting the foam, have been suggested to reduce the risk of DVT. However, these measures are controversial and there is no consensus.

Neurologic damage is among the most common serious side effects of saphenous stripping. Saphenous nerve damage occurs in about 7% in short stripping and 40% in long stripping of the GSV.[75-76] Paresthesias have been reported with UGFS, EVLT, and RFA due to extravenous injection of foam or increased perivenous temperature, respectively, but the incidence is significantly lower compared with surgery. As with surgery, the likelihood of saphenous nerve damage may increase with EVLT and RFA procedures of the GSV that start at the ankle. Also, it is recommended that extra tumescent anesthesia be administered in the popliteal fossa in the EVLT and RFA treatment of the SSV to avoid sural nerve damage.

In contrast to surgery, no or minimal scars are created and the risk of wound infection is minimal, but each of the minimally invasive techniques may be associated with local cutaneous side effects. Skin burns have been reported in less than 1% of the EVLT and RFA procedures and can be easily avoided by applying sufficient tumescent fluid. Hyperpigmentation and, to a lesser extent, skin necrosis have been reported after UGFS. Postoperative pain and ecchymoses along the treated vein are very common after EVLT (for about 2 weeks and are controlled by nonsteroidal anti-inflammatory drugs) and, to a lesser extent, after RFA and UGFS.

Recurrence of varicose veins after stripping is thought to be due to neovascularization at the SFJ and occurs in about one fourth of the patients after 5 years.[77] This has been studied using US but has not been documented for UGFS, EVLT, and RFA, probably because these techniques, in contrast to surgery, do not disrupt the endothelial lining and or do not eliminate

other feeding veins into the SFJ. This difference may explain the high long-term success rates of the 3 procedures. Endovenous therapies show anatomic failure in about 10% of patients, with (partial) recanalization of the treated vein, but do not always equal clinical failures.

In conclusion, additional comparative studies are needed among these techniques, standard surgical therapy, and other new therapies. These studies should include patient-reported outcomes and cost-effectiveness analyses so that firm recommendations can be made. However, minimally invasive techniques in the treatment of truncal varicose veins are very promising and challenge surgical vein ligation and stripping as the standard of care. Dermatologists have been pioneers in the development and first clinical studies of each of these new techniques, emphasizing the role of dermatologic surgeons in the therapy for varicose veins. For now, EVLT is probably the most commonly used endovenous therapy because it is less expensive and faster than standard RFA. However, UGFS may be the most cost-effective therapy, but several treatment sessions may be needed.

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Endovenous therapies of lower extremity varicosities: a meta-analysis

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Abstract

Background Minimally invasive techniques such as endovenous laser therapy, radiofrequency ablation, and ultrasoundguided foam sclerotherapy are widely used in the treatment of lower extremity varicosities. These therapies have not yet been compared with surgical ligation and stripping in large randomized clinical trials.

Methods A systematic review of Medline, Cochrane Library, and Cinahl was performed to identify studies on the effectiveness of the four therapies up to February 2007. All clinical studies (open, noncomparative, and randomized clinical trials) that used ultrasound examination as an outcome measure were included. Because observational and randomized clinical trial data were included, both the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) and Quality Of Reporting Of Meta-analyses (QUORUM) guidelines were consulted. A random effects meta-analysis was performed, and subgroup analysis and meta-regression were done to explore sources of between-study variation.

Results Of the 119 retrieved studies, 64 (53.8%) were eligible and assessed 12,320 limbs. Average follow-up was 32.2 months. After 3 years, the estimated pooled success rates (with 95% confidence intervals [CI]) for stripping, foam sclerotherapy, radiofrequency ablation, and laser therapy were about 78% (70%-84%), 77% (69%-84%), 84% (75%-90%), and 94% (87%-98%), respectively. After adjusting for follow-up, foam therapy and radiofrequency ablation were as effective as surgical stripping (adjusted odds ratio [AOR], 0.12 [95% CI, −0.61 to 0.85] and 0.43 [95% CI, −0.19 to 1.04], respectively). Endovenous laser therapy was significantly more effective compared with stripping (AOR, 1.13; 95% CI, 0.40-1.87), foam therapy (AOR, 1.02; 95% CI, 0.28-1.75), and radiofrequency ablation (AOR, 0.71; 95% CI, 0.15-1.27).

Conclusion In the absence of large, comparative randomized clinical trials, the minimally invasive techniques appear to be at least as effective as surgery in the treatment of lower extremity varicose veins.

Introduction

Lower-extremity venous insufficiency is a common medical condition and occurs in about 15% of men and 35% of women.[1-3] The effect of venous insufficiency on patients' health-related quality of life (HRQOL) is substantial and comparable with other common chronic diseases such as arthritis, diabetes, and cardiovascular disease.[4] In 1995 the overall cost associated with deep or superficial venous insufficiency, or both, was about 2.5% of the total health care budget in France and Belgium.[5]

The treatment of varicose veins alleviates symptoms and, hopefully, reduces the complication rate of venous insufficiency. The traditional gold standard in the treatment of varicosity of great saphenous veins (GSVs) is a high ligation at the saphenofemoral junction (SFJ), followed by stripping; conventional treatment of small saphenous veins (SSVs) is ligation at the saphenopopliteal junction (SPJ), often without stripping.

Surgery of varicose veins is usually performed under general or epidural anesthesia and may be associated with neurologic damage (about 7% in short and up to 40% in long stripping of GSVs),[6-7] scars, and postoperative pain. Despite the relatively high incidence, the neurologic damage has often little resultant morbidity. Although surgery is highly effective in the short term, the 5-year recurrence rates are approximately 30% for GSVs and 50% for SSVs, which may be due to neovascularization.[8-9] Only <10% of these recurrences are clinically relevant.

To improve effectiveness and patients' HRQOL and to reduce postoperative downtime, complications, and costs, new minimally invasive techniques such as ultrasoundguided foam sclerotherapy (UGFS),[10] radiofrequency ablation (RFA, VNUS Closure, VNUS Medical Technologies, San Jose, Calif),[11] and endovenous laser ablation (EVLA)[12] are now widely used in the treatment of lower extremity varicosities.

Although case series and comparative studies suggest lower recurrence rates of these minimally invasive interventions compared with surgical stripping, no large, longterm, comparative randomized controlled trials (RCTs) have been performed yet, but some are ongoing.[13] The objective of this analysis is to systematically review and summarize the available studies on the surgical and new therapies and compare the effectiveness of these different options in order to assist physicians and patients in selecting the most appropriate intervention for lower extremity varicose veins in the current absence of well-designed RCTs.

Methods

Because of the heterogeneity of the included studies, both the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) and Quality Of Reporting Of Metaanalyses (QUORUM) guidelines were used.[14-15]

Literature search

We initiated an electronic search of Medline, Cochrane Library, and Cinahl up to February 2007. PubMed was searched by a clinical librarian using the following algorithm: (sclerocompression *or* sclerotherapy) *or* ([{thermal *or* radiofrequency} *and* {ablation *or* obliteration}] *or* VNUS) *or* (laser *or* laser surgery) *or* (endovascular *or* endovenous) *or* (stripping *or* stripped *or* strip *or* strips *or* stripper *or* Babcock) *and* (saphenous *or* saphena *or* varicose veins *or* varicosis) *and* (duplex *or* Doppler *or* ultrasonic *or* ultrasound). To broaden the search, the "related articles" function was also used. Specialty journals such as *Dermatologic Surgery*, *Journal of Vascular Surgery*, *European Journal of Vascular and Endovascular Surgery*, and *Phlebology* were also searched electronically and references of identified studies and reviews were hand-searched. We reviewed all abstracts, studies, and citations, irrespective of language. Clinical trial registries were also searched.

Inclusion criteria

Our meta-analysis included RCTs, clinical trials, and prospective and retrospective case series on the treatment of human lower extremity varicosities by surgical stripping (SFJ ligation and GSV stripping or SPJ ligation [and SSV stripping]), EVLA (all wavelengths and energy parameters were included), UGFS with foam (multiple treatments were allowed and no distinction was made between type or concentration of sclerosant), and RFA. We were unable to differentiate between GSVs and SSVs because most studies that included both did not differentiate the outcomes. Only studies that used US examination as the outcome measure were eligible because US is considered the gold standard in the assessment of venous insufficiency and it increases the homogeneity of the analysis. For comparative studies, the arms of interest were included separately. All follow-up periods were allowed. English, German, French, and Dutch studies were included.

Exclusion criteria

Studies that performed SFJ ligation without stripping were excluded because this approach is considered suboptimal.[16] Studies that explicitly examined combination therapies were excluded. Treatments of nontruncal varicose veins were not included. We excluded UGFS

studies that used liquid sclerosant because it is considered less effective than foam.[17] To our knowledge, there are no comparative RCTs suggesting a type of sclerosant is superior in the treatment of saphenous trunks using UGFS. Moreover, a RCT showed no significant difference between polidocanol and sodium tetradecyl sulphate in the treatment of varicose and telangiectatic veins, suggesting that the effect of the specific sclerosant in our analysis is limited.[18] If multiple articles reported the same study population, the publication with the longest follow-up was included.

Data extraction

The data of all eligible studies were analyzed by two authors (R. v. d. B. and T. N.) independently. The number of patients and treated limbs, the type of veins (GSV or SSV), the treatment procedure, the study type (retrospective or prospective), the duration of follow-up, the type of follow-up (mean follow-up, exact follow-up, or exact with loss of follow-up), the US outcome definitions, and success rate (if possible for GSVs and SSVs separately) were recorded. Because 89% of the included studies were case series, an extensive quality assessment of the studies was not performed, except that a distinction was made between retrospective and prospective data collection. Case series and the arms of interest of RCTs were entered separately in the analysis.

Standardization of outcome measures

All of the eligible studies used US as an outcome, but the definitions of treatment success by US examination varied considerably. Because the technical end point of each of the treatments is obliteration or complete removal (ie, anatomic success) of the insufficient vein, the definitions that closely reflected this objective were grouped by consensus of three authors (R. v. d. B., M. N., and T. N.). Therefore, US-based outcomes that used definitions such as absence of "detectable flow," "recurrence of reflux," "recanalization," "vein reopening," "recurrent or new varices," "closed vein," "occlusion," "obliteration," and "completely stripped vein" were considered to be equally successful. Studies that reported "clinical improvement," "patient satisfaction," "reflux at any site," "varicose veins present anywhere," and others were excluded.

Statistical analysis

After deriving the natural logarithm of the odds of success for all studies, we calculated pooled estimates of success rate and the 95% confidence interval (CI) for all four treatments using SAS PROC MIXED software (SAS Institute Inc, Cary, NC). A random-effect model[19-21] was used because a likelihood ratio test showed that the random-effect model fitted the data significantly better than did a fixed-effect model ($x^2_4 = 32.7$, $P < .001$).

We compared a random-effect model with one general random intercept to a multivariate random-effect model in which each treatment has its own random intercept. Because the latter did not improve the model significantly ($x^2_3 = 3.8$, $P < .28$), we used the random-effect model with one general random intercept only for all treatments. The treatments were used as covariates in the model, and the differences between the estimated log odds of the treatments automatically resulted in the log odds ratios (OR) to compare the treatments with each other.

Because follow-up time varied considerably within and between the four treatment groups and the decline of success percentages over time may differ per treatment, a meta-regression with follow-up time per treatment as a covariate was performed to present success rates for different time intervals (ie, 3 months, 1, 3, and 5 years). Furthermore, we performed subgroup analysis based on the type of study (prospective vs retrospective) and study size (more or less than 60 limbs). The between-study variances of the models with and without these covariates were compared to assess whether heterogeneity in the covariates can explain part of the between-study variances.

Results

Literature search

Of all screened abstracts and titles, 119 reports were reviewed in detail, and 64 studies (with a total of 72 arms) fulfilled the eligibility criteria. Of these, 13 (18%) reported on stripping, 10 (14%) on UGFS, 30 (42%) on EVLA, and 19 (26%) on RFA (Table I). We excluded 55 studies for several reasons (Fig 1).

Study characteristics for included trials

We included 64 studies (72 study arms) with a total of 12,320 treated limbs, of which 2804 (23%) were stripped, 2126 (17%) were treated by UGFS, 4876 (40%) by EVLA, and 2514 (20%) by RFA. The reports were published between January 1994 and February 2007, and 92% in the last 5 years (Table I). Of the 72 study arms, 58 (81%) were prospective. Although follow-up duration ranged from 1 day to 34 years, 51 of the 72 studies had a follow-up of between 3 months and 10 years. The number of included limbs was 12 to 1411. Nine studies reported the separate success rates of SSV and GSV therapy, and seven were RCTs that included two intervention arms. Nine of the 10 UGFS studies used aethoxysclerol (polidocanol), one study only used sodium tetradecyl sulfate, and three studies used both sclerosants.

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│ 570 potentially relevant articles identified │
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                      ├───→│ 451 articles excluded after review of titles │
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│ 119 articles retrieved                       │
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                      │    │ 47 Articles did not meet inclusion criteria        │
                      │    │    15 did not use US examination                   │
                      │    │    2 not described length of follow up             │
                      ├───→│    10 aberrant definition of success               │
                      │    │    4 other languages                               │
                      │    │    16 not fulfilled right treatment procedure      │
                      │    │ 8 Articles met inclusion criteria                  │
                      │    │    8 used same study population                    │
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│ 64 studies (n=72) included in final meta-analysis │
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Figure 1. Schematic flow chart of literature search.

Table I. Characteristics of studies included in meta-analysis

No	First author	Year[†]	Country	Study type*	Total	No GSV	No SSV	Therapy	Follow-up[+]	Total	GSV	SSV	Definition of failure
1	Allegra	2007	Italy	1	1326	862	132	Surgery	60	0.75	0.87	0.7	Recurrent/new varices
2	Bountouroglu	2006	UK	3	30	30	0	Surgery	3	0.78	0.78	NA	Closed/occlusion/ obliteration
3	De Maeseneer	2002	Belgium	1	172	172	0	Surgery	12	0.75	0.75	NA	Recurrent/new varices
4	De Medeiros	2005	Brazil	3	20	20	0	Surgery	1	1.00	1.00	NA	Re-opening
5	Dwerryhouse	1999	UK	1	52	52	0	Surgery	60	0.5	0.5	NA	Recurrent/new varices
6	Fischer	2001	Swiss	2	125	125	0	Surgery	408	0.4	0.4	NA	Recurrent/new varices
7	Frings	2004	Germany	1	500	500	0	Surgery	3	0.95	0.95	NA	Detectable flow/reflux
8	Hartmann	2006	Germany	2	245	220	25	Surgery	168	0.69	0.66	0.88	Recurrent/new varices
9	Hinchliffe	2006	UK	3	16	16	0	Surgery	1.5	0.88	0.88	NA	Incomplete strip
10	Lurie	2005	USA	3	36	36	0	Surgery	24	0.79	0.79	NA	Recurrent/new varices
11	Perala	2005	Finland	3	13	13	0	Surgery	36	0.77	0.77	NA	Recurrent/new varices
12	Sarin	1994	UK	2	43	43	0	Surgery	21	0.51	0.51	NA	Detectable flow/reflux
13	Smith	2002	UK	1	226	189	37	Surgery	12	0.86	0.91	0.62	Detectable flow/reflux
14	Barrett 1a	2004	New Zealand	2	99	79	20	UGFS	23.7	0.69	---[‡]	---[‡]	Closed/occlusion/ obliteration

Table I. (continued)

No	First author	Year†	Country	Study type*	Total	No GSV	No SSV	Therapy	Follow-up†	Total	GSV	SSV	Definition of failure
					No. of included limbs					Success rate			
15	Barrett 1b	2004	New Zealand	2	17	14	3	UGFS	24.5	0.77	---‡	---‡	Closed/occlusion/ obliteration
16	Barrett 2	2004	New Zealand	2	100	98	23	UGFS	22.5	0.77	---‡	---‡	Closed/occlusion/ obliteration
17	Belcaro 1#	2000	Italy	3	39	39	0	UGFS	120	0.81	0.81	NA	Detectable flow/reflux
18	Belcaro 2#	2003	Italy	3	211	211	0	UGFS	120	0.49	0.49	NA	Recurrent/new varices
20	Darke	2006	UK	1	143	115	28	UGFS	1.5	0.88	0.86	0.96	Closed/occlusion/ obliteration
21	Hamel-Desnos	2003	France	1	45	45	0	UGFS	0.75	0.84	0.84	---‡	Detectable flow/reflux
19	Smith	2006	UK	1	1411	886	263	UGFS	11	0.86	0.88	0.82	Closed/occlusion/ obliteration
22	Tessari	2001	Italy	1	24	9	7	UGFS	1	1	1	1	Closed/occlusion/ obliteration
23	Yamaki	2004	Japan	1	37	37	0	UGFS	12	0.68	0.68	NA	Closed/occlusion/ obliteration
24	Agus	2006	Italy	1	1068	1052	16	EVLA	36	0.97	---‡	---‡	Closed/occlusion/ obliteration
25	De Medeiros	2005	Brazil	1	20	20	0	EVLA	2	0.95	0.95	NA	Closed/occlusion/ obliteration
26	Disselhoff	2005	The Netherlands	1	93	93	0	EVLA	3	0.84	0.84	NA	Closed/occlusion/ obliteration
27	Gerard	2002	France	1	20	20	0	EVLA	1	0.9	0.9	NA	Closed/occlusion/ obliteration
28	Gibson	2007	USA	1	210	156	210	EVLA	4	0.96	NA	0.96	Recanalisation
29	Goldman	2004	USA	1	24	24	0	EVLA	8	1	1	NA	Detectable flow/reflux
30	Huang	2005	China	1	19	19	0	EVLA	0.5	1	1	NA	Closed/occlusion/ obliteration
31	Kabnick	2006	USA	1	60	60	0	EVLA	12	0.93	0.93	NA	Detectable flow/reflux
32	Kavuturu	2006	USA	1	66	66	0	EVLA	12	0.97	0.97	NA	Closed/occlusion/ obliteration
33	Kim 1	2006	USA	1	34	34	0	EVLA	12.2	1	1	NA	Recanalisation
34	kim 2	2006	USA	1	60	60	0	EVLA	6.8	0.97	0.97	NA	Closed/occlusion/ obliteration
35	Marston	2006	USA	2	31	31	0	EVLA	0	0.84	0.84	NA	Closed/occlusion/ obliteration
36	Morrison	2005	USA	1	50	50	0	EVLA	12	0.66	0.66	NA	Closed/occlusion/ obliteration
37	Min 1	2001	USA	1	90	90	0	EVLA	9	0.96	0.96	NA	Closed/occlusion/ obliteration

Table I. (continued)

No	First author	Year[†]	Country	Study type*	Total	No GSV	No SSV	Therapy	Follow-up[+]	Total	GSV	SSV	Definition of failure
					No. of included limbs					Success rate			
38	Min 2	2003	USA	1	499	499	0	EVLA	24	0.93	0.93	NA	Closed/occlusion/ obliteration
39	Navarro	2001	USA	1	40	40	0	EVLA	4.2	1	1	NA	Detectable flow/reflux
40	Oh	2003	Korea	1	15	15	0	EVLA	3	1	1	NA	Closed/occlusion/ obliteration
41	Perkowski	2004	USA	1	191	154	37	EVLA	0.5	0.97	---‡	---‡	Recanalisation
42	Petronelli	2006	Italy	1	52	52	0	EVLA	12	0.93	0.93	NA	Recanalisation
43	Proebstle 1	2002	Germany	1	31	31	0	EVLA	1	0.97	0.97	NA	Closed/occlusion/ obliteration
44	Proebstle 2	2003	Germany	1	41	41	0	EVLA	6	0.95	0.95	NA	Recanalisation
45	Proebstle 3	2004	Germany	2	106	106	0	EVLA	3	0.9	0.9	NA	Closed/occlusion/ obliteration
46	Proebstle 4	2005	Germany	1	282	282	0	EVLA	3	0.98	0.98	NA	Closed/occlusion/ obliteration
47	Proebstle 5	2006	Germany	1	263	263	0	EVLA	12	0.96	0.96	NA	Closed/occlusion/ obliteration
48	Puggioni	2005	USA	2	77	77	0	EVLA	0.25	0.94	0.94	NA	Recanalisation
49	Ravi	2006	USA	1	1091	990	101	EVLA	0.5	0.96	0.97	0.91	Recanalisation
50	Sadick	2004	USA	1	30	30	0	EVLA	24	0.97	0.97	NA	Closed/occlusion/ obliteration
51	Sharif	2006	UK	1	145	145	0	EVLA	12	0.76	0.76	NA	Closed/occlusion/ obliteration
52	Theivacumar	2007	UK	1	68	0	68	EVLA	6	0.88		0.88	Closed/occlusion/ obliteration
53	Timperman	2005	USA	1	100	83	0	EVLA	9	0.96	0.96	NA	Detectable flow/reflux
54	Dunn	2006	USA	1	85	85	0	RFA	6	0.9	0.9	NA	Closed/occlusion/ obliteration
55	Fassiadis	2003	UK	1	59	59	0	RFA	3	1	1	NA	Closed/occlusion/ obliteration
56	Goldman	2000	USA	1	12	12	0	RFA	6	1	1	NA	Closed/occlusion/ obliteration
57	Goldman	2002	USA	1	41	41	0	RFA	13	0.68	0.68	NA	Closed/occlusion/ obliteration
58	Hinchliffe	2006	UK	3	16	16	0	RFA	1.5	0.81	0.81	NA	Closed/occlusion/ obliteration
59	Hingorani	2004	USA	1	73	73	0	RFA	0.3	0.96	0.96	NA	Closed/occlusion/ obliteration
60	Lurie	2005	USA	1	46	46	0	RFA	24	0.86	0.86	NA	Recurrent/new varices
61	Marston	2006	USA	2	58	58	0	RFA	0	0.88	0.88	NA	Closed/occlusion/ obliteration

Table I. (continued)

No	First author	Year[†]	Country	Study type*	Total	No GSV	No SSV	Therapy	Follow-up[†]	Total	GSV	SSV	Definition of failure
					No. of included limbs					Success rate			
62	Merchant 1	2002	USA	1	318			RFA	24	0.85	---[‡]	---[‡]	Closed/occlusion/obliteration
63	Merchant 2	2005	USA	1	1222	1154	52	RFA	60	0.87	---[‡]	---[‡]	Closed/occlusion/obliteration
64	Morrison	2005	USA	1	50	50	0	RFA	12	0.8	0.8	NA	Closed/occlusion/obliteration
65	Ogawa	2005	Japan	1	25	25	0	RFA	1	1	1	NA	Closed/occlusion/obliteration
66	Perala	2005	Finland	3	15	15	0	RFA	36	0.67	0.67	NA	Recurrent/new varices
67	Pichot	2004	France	2	63	63	0	RFA	25	0.91	0.91	NA	Closed/occlusion/obliteration
68	Puggioni	2005	USA	2	53	53	0	RFA	0.23	0.91	0.91	NA	Recanalisation
69	Sybrandy	2002	The Netherlands	1	26	26	0	RFA	12	0.89	0.89	NA	Closed/occlusion/obliteration
70	Wagner	2003	USA	2	28	28	0	RFA	3	1	1	NA	Closed/occlusion/obliteration
71	Weiss	2002	USA	1	140	140	0	RFA	0	0.9	0.9	NA	Closed/occlusion/obliteration
72	Welch	2006	USA	2	184	184	0	RFA	0	0.8	0.8	NA	Closed/occlusion/obliteration

EVLA, endovenous laser ablation; GSV, great saphenous vein; NA, nonapplicable; NZ, New Zealand; RCT, randomized clinical trial; RFA, radiofrequency ablation; SSV, short saphenous vein; UGFS, ultrasound-guided foam sclerotherapy; UK, United Kingdom; USA, United States of America.

[†]Year of publication.

*Type 1 is prospective case series, type 2 is retrospective case series, and type 3 is a randomized clinical trial.

[†]Follow-up in months.

[‡]Not documented separately for GSV and SSV.

[#]The surgery arm of this study was not included because only ligation without stripping was performed.

Success rates for each therapy

The crude success rates of each of the four therapies independent of follow-up time according to the random-intercept model suggest that the success rate of EVLA (93.3%; 95% CI, 91.0-95.0) and RFA (87.5%; 95% CI, 82.5-91.3) are higher than for stripping and UGFS (Fig 2). For stripping, UGFS, and RFA, the effectiveness of the therapies decreased over time from ≥80% success rates at 3 months to <80% after 5 years. The success percentages of EVLA remained at ≥92.9% (Table II, Fig 3). The estimated success rates declined significantly for stripping ($P = .004$), but no significant negative trend was detected for UGFS ($P = .08$), RFA ($P = .25$), or EVLA ($P = .61$) over time.

Table II. The pooled proportion of patients with anatomical successful outcome after different time intervals.

Type of intervention	3 months		1 year		3 year		5 year	
	Success rate (%)	95% CI	Success rate (%)	95% CI	Success rate (%)	95% CI	Success rate (%)	95% CI
Surgery	80.4	72.3-86.5	79.7	71.8-85.8	77.8	70.0-84.0	75.7	67.9-82.1
UGFS	82.1	72.5-88.9	80.9	71.8-87.6	77.4	68.7-84.3	73.5	62.8-82.1
RFA	88.8	83.6-92.5	87.7	83.1-91.2	84.2	75.2-90.4	79.9	59.5-91.5
EVLA	92.9	90.2-94.8	93.3	91.1-95.0	94.5	87.2-97.7	95.4	79.7-99.1

CI, confidence intervals; EVLA, endovenous laser ablation; RFA, radiofrequency ablation; UGFS, ultrasound guided foam sclerotherapy.

Table III. Comparisons of four different treatment options for lower extremity varicose veins

Comparisons	Unadjusted for follow-up			Adjusted for follow-up		
	Crude OR	95% CI	P	Adjusted OR	95% CI	P
UGFS vs strip	0.15	-0.49 to 0.80	.64	0.12	-0.61 to 0.85	.73
EVLA vs strip	1.54	1.02 to 2.07	<.0001	1.13	0.40 to 1.87	.006
RFA vs strip	0.87	0.29 to 1.45	.003	0.43	-0.19 to 1.04	.16
EVLA vs UGFS	1.39	0.81 to 1.97	<.0001	1.02	0.28 to 1.75	.013
RFA vs UGFS	0.71	0.08 to 1.34	.03	0.31	-0.29 to 0.91	.27
EVLA vs RFA	0.68	0.17 to 1.18	.009	0.71	0.15 to 1.27	.016

CI, Confidence intervals; EVLA, endovenous laser ablation; OR, odds ratio; RFA, radiofrequency ablation; UGFS, ultrasound guided foam sclerotherapy.

Comparison of therapies

Compared with stripping, UGFS was as effective and EVLA and RFA were significantly more effective in the treatment of lower extremity varicose veins (Table III). After adjusting for duration of follow-up, however, we observed no significant differences between stripping and RFA. Of the three minimally invasive techniques, EVLA was superior to UGFS (P = .013) and RFA (P = .016) after adjusting for follow-up time, but there was no significant difference between UGFS and RFA (P = .27).

Subgroup analysis

Restricting the analysis to the 58 prospective studies confirmed that EVLA was significantly more effective than stripping (P < .0001), UGFS (P <.0001), and RFA (P = .01). However, no
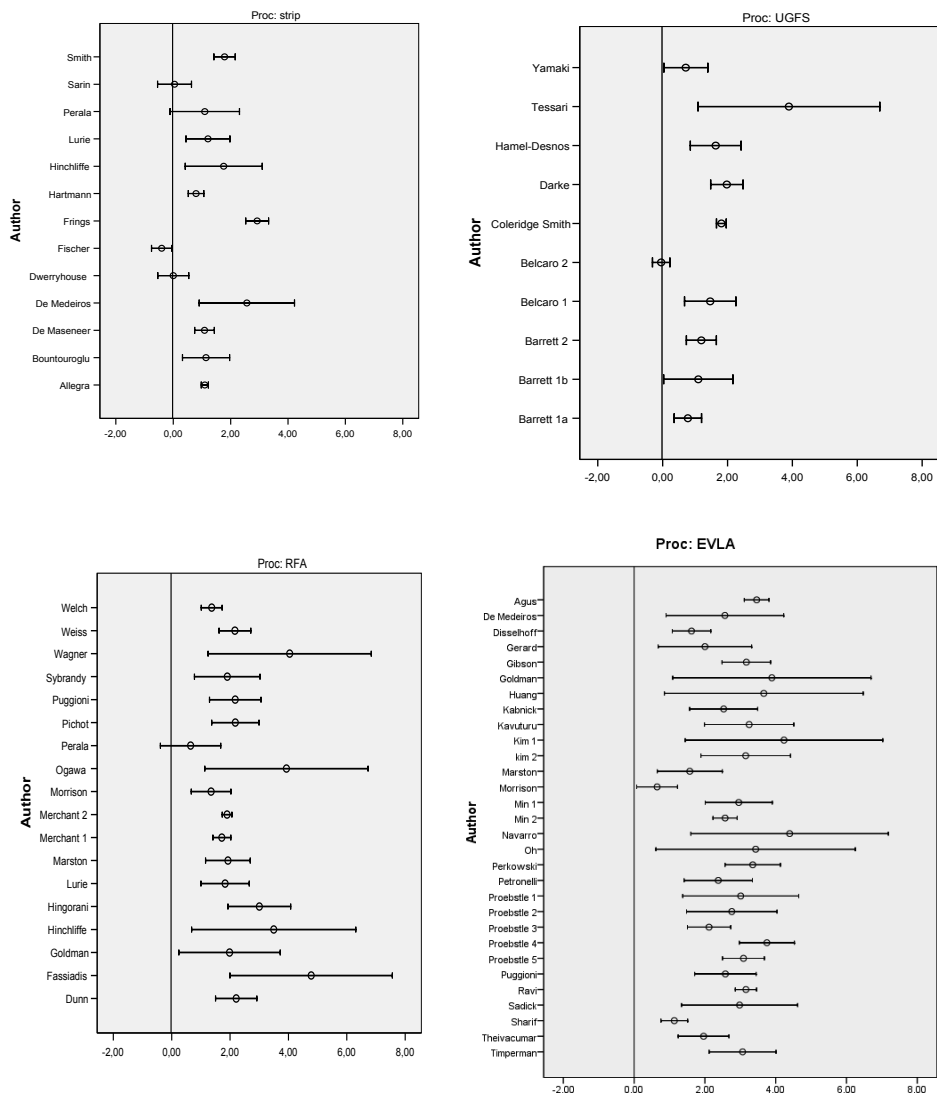
Figure 2. Forest plots with logg(odds) of each study ordered per treatment.

significant differences in effectiveness were observed between RFA vs stripping (P = .14) and RFA vs UGFS (P = .13).

The results of the analyses of the 35 largest studies that treated >60 limbs were comparable with the complete meta-analysis: EVLA remained significantly more successful than stripping (P < .0001), UGFS (P < .0001), and RFA (P = .04); and RFA was superior to stripping (P = .048) and UGFS (P = .04). Excluding the SSV and restricting the analysis to 62 studies that presented success rates for GSVs (separately) confirmed the finding that EVLA was significantly more
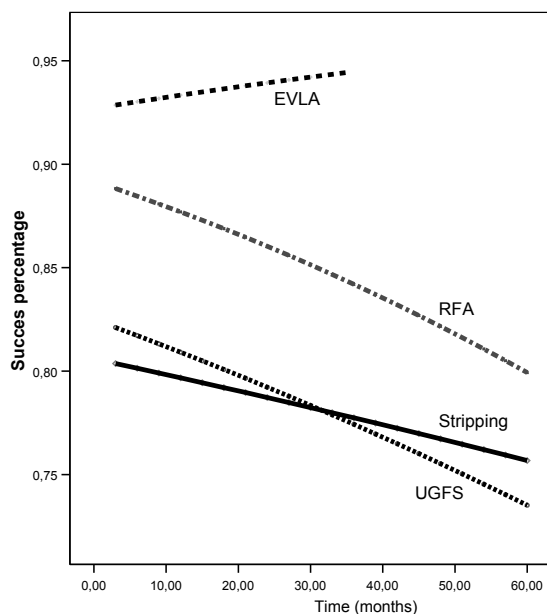
Figure 3. Anatomic success rate for surgical stripping, ultrasound guided foam sclerotherapy (UGFS), endovenous laser ablation (EVLA), and radiofrequency ablation (RFA) in time. The estimated success rates declined significant for stripping (P=.004), but no significant negative trend was detected for UGFS (P=.08), RFA (P=.25), and EVLA (P=.61) over time.

effective than the other therapies ($P < .0001$). Excluding the SSV and restricting the analysis to 62 studies that presented success rates for GSV (separately) confirmed the finding that EVLA was significantly more effective than the other therapies (P < 0.0001).

Discussion

The results of this meta-analysis suggest that endovenous treatments of lower extremity varicosities are better in achieving anatomic success (ie, obliteration or disappearance of veins) than surgery and UGFS. Of the endovenous therapies, EVLA is significantly more effective than RFA to obliterate the insufficient veins. These findings, however, should be confirmed in large, long-term, comparative RCTs.

The estimated success rates of the studied therapies and the comparison between therapies are in agreement with most of the available studies. A small paired analysis[22] and a nonrandomized pilot study that compared EVLA with stripping of the GSV[23] showed that the clinical efficacy parameters were comparable in the short term. A recent RCT showed that EVLA was as effective as stripping after 6 months and was associated with less postoperative pain and bruising.[24] In the long term, however, it is likely that the recurrence rate of surgery is higher

than that of EVLA because of neovascularization, as is confirmed by the findings of the current analysis. One retrospective study suggested that RFA and EVLA were equally effective[25] and another that EVLA was superior.[26] Three small, short-term RCTs showed that RFA and surgery were about equally effective, but RFA-treated patients reported less postoperative pain and physical limitations, faster recovery, fewer adverse events, and superior HRQOL compared with patients who underwent surgical stripping.[27-29] An earlier RCT showed that liquid UGS was less effective than surgical stripping,[30] but that study used liquid sclerosant, which is washed out relatively quickly and induces less vasospasm and sclerous formation than foam sclerosant.[17] Clinical trial registries indicate that several important RCTs of RFA vs stripping and UGFS vs surgery are currently ongoing.[13]

In addition to anatomic success rates, patient-reported outcomes such as HRQOL, treatment satisfaction, symptom relief, and side effects are pivotal in a comparison between invasive and noninvasive therapies for venous insufficiency. Compared with surgery, EVLA-treated patients appreciated EVLA more than surgery because they reported fewer side effects and their HRQOL improved better and faster.[22-23] Patient-reported outcomes are especially important when two therapies are equally effective. For example, this current meta-analysis suggests that the anatomic success rates of UGFS and surgery are comparable, but patients' opinions may differ between these therapies.

Also, cost-effectiveness assessments are lacking and should be included in clinical trials. One study suggested that the RFA procedure was cost-saving from a societal perspective compared with surgery because the patient's physical function was restored faster and endovenous therapies can be performed in an outpatient setting, resulting in lower nonmedical costs.[27]

Minor and relatively common postoperative complications of ligation and stripping are wound infection, hematoma, lymphorrhagia, and hypertrophic scarring. Other complications of surgery are nerve injury (7%) and deep vein thrombosis (<2%).[6-7,31-34] Because the sclerosant enters the deep venous system, UGFS may be associated with several specific complications such as migraine, temporal brain ischaemia, and scotomas, especially among patients with a foramen ovale.[35] As in surgery, most patients will experience ecchymosis and pain (often described as "a pulling chord") for 1 to 2 weeks after endovenous therapies. Dysesthesia, phlebitis, and skin burns have been reported in a small proportion and deep vein thrombosis in <1% of patients after EVLA and RFA.[36-39]

To our knowledge, this is the first meta-analysis and meta-regression analysis comparing different treatment options for lower extremity varicose veins, and the results suggest that there are significant differences between interventions. The detected differences are in ac-

cordance with the few available comparative studies suggesting a good face validity of our findings. More than 60 studies met our inclusion criteria. To increase homogeneity of the comparison, we restricted the analysis to studies that used US as primary end point. Because of the variation in follow-up duration, we adjusted the comparison between the therapies for this difference. Several sensitivity analyses were performed to assess the effects of study design, duration of follow-up, and sample size on our findings and they confirmed our initial results.

Meta-analysis is associated with several limitations. A major limitation of this analysis is that it included a heterogeneous mix of case series and RCTs. This rather unusual but methodologically and clinically sound approach was chosen because of the lack of comparative RCTs in phlebology, as was illustrated by the systematic review. To increase the quality of analysis, both the MOOSE and QUORUM guidelines were followed as much as possible.[14-15] The objective of this study was to inform physicians about four therapies commonly used in the treatment of lower extremity varicose veins and compare their efficacy based on the available data.

An aggregation or ecologic bias, which occurs because group rates may not resemble individual rates, is unavoidable. Because we were unable to precisely describe the heterogeneous study populations, different inclusion criteria may have affected our findings (eg, case series of endovenous therapies may have included more primary, nontortuous, interfascial GSVs than UGFS and stripping, and RFA is limited to veins of <12 mm due to the catheter size). Although we restricted the analysis to studies that used US to increase comparability, the standardization of the different definitions of success, which was based on consensus, may have affected our results.

To minimize the effect of publication bias, an extensive English and non-English literature search was performed, including registries of clinical trials. Small studies were not excluded to reduce publication bias because their impact was weighted and the proportion of total weight of these studies was limited. A subanalysis limited to studies with >60 patients showed findings similar to those presented, confirming that the effect of the smaller studies was not substantial.

The EVLA studies with limited follow-up are likely to reflect the centers' initial experience (ie, learning curve), and the relatively large proportion of these studies may explain the lower success rates after 3 months compared with later intervals. Several studies from the 1970s and 1980s were excluded because US examination was not an outcome measurement. To further increase homogeneity of the analysis, it was restricted to studies that used ligation and stripping because this is the gold standard of surgical care and restricted to foam in

sclerotherapy because it is superior to liquid sclerosant.[17] Also, we did not differentiate between concentration of sclerosant, which varied from 1% to 3%. However, a recent RCT demonstrated that the concentration of sclerosant (1% vs 3%) was not a significant predictor of outcome in UGFS.[40] Because 89% of the studies were case series, a thorough quality assessment was not performed, but subgroup analysis suggests that the results of retrospective and prospective studies were not substantially different.

Conclusion

The results of this meta-analysis support the increasing use of minimally invasive interventions in the treatment of lower extremity varicosities. In the absence of comparative RCTs, it appears that EVLA is more effective than surgery, UGFS, and RFA. However, large, long-term comparative RCTs that include patient-reported outcomes, cost-effectiveness analyses, and safety assessment are needed to achieve the highest level of evidence for these novel therapies.

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A new gold standard for varicose vein treatment?

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The current principles of surgical treatment of varicose veins were established at the beginning of the 20th century by Perthes, Keller, Mayo, Babcock and others. They include ligation of the incompetent sapheno-femoral or sapheno-popliteal junction, stripping of the refluxing saphenous vein and phlebectomy of varicose branches. These principles have been increasingly challenged since the advent of thermal ablation by laser or radio-frequency around the turn of the millennium. Furthermore, sclerotherapy has gained renewed interest due to improved results by ultrasound guidance and the use of foam instead of liquid agents.

Two randomised controlled trials (RCTs) comparing endovenous laser ablation (EVLA) of refluxing saphenous veins with surgical high ligation and stripping were published by Rasmussen et al.[1] and by Darwood et al.[2] Furthermore, Disselhoff et al.[3] published an RCT comparing EVLA with cryosurgery. All studies used laser light with a wavelength of 980 nm. In all trials, abolition of reflux was marginally superior after EVLA, but the differences were not significant. Improvement of symptoms according to AVVSS (the Aberdeen Varicose Vein Symptom Severity Score) or VCSS (the Venous Clinical Severity Score) was similar after EVLA and surgery. Return to normal activities was earlier after EVLA than after surgery, according to the Darwood and Disselhof trials, but not in the Rasmussen study. However, all trials found a tendency towards less pain and bruising after EVLA.

Early in 2009, Van den Bos et al.[4] published a large meta-analysis of results of all current treatment modalities. EVLA, radio-frequency ablation (RFA) and ultrasound-guided foam sclerotherapy (UGFS) were compared with surgical high ligation plus stripping. As many as 64 clinical trials that used ultrasound examination as an outcome measure with a total of 12 320 limbs and an average follow-up of 32.2 months were included. After 3 years, the estimated pooled success rate was highest after EVLA with 94%, followed by RFA (84%), surgery (78%) and foam sclerotherapy (77%). After adjusting for the duration of follow-up, endovenous laser therapy was significantly superior to all other treatments in terms of abolition of saphenous reflux. Foam therapy and radio-frequency ablation were equally effective as surgery. The authors concluded that minimally invasive techniques were "at least as effective as surgery" in the treatment of varicose veins. Superior rates of abolition of saphenous reflux after EVLA using 980-nm technology in the meta-analysis come mostly from non-randomised trials published by enthusiasts of thermal ablation. Moreover, recent studies by Proebstle et al.,[5] Pannier et al.[6] and others suggest that laser light with longer wavelengths may reduce side effects without compromising abolition of reflux. Another recent development provides a fibre with a radial distribution of laser light at its tip (Elves by Biolitec), which may positively affect the balance between desired and undesired effects.

RFA technology has evolved as well. RFA procedures that were included in the meta-analysis[4] used the original VNUS Closure catheter with umbrella-shaped electrodes. They heated the

vein up to barely 90°C in a rather tedious procedure with a slow, continuous withdrawal of the catheter. A more recent variation (Celon by Olympus) features bipolar radio-frequency from a sleek catheter with two integrated electrodes that are 15-mm apart.

A further recent development is named VNUS Closure Fast.[7] The catheter's sleek tip integrates a heating coil of 7 cm length producing temperatures up to 120°C. After a heating cycle of 20 s, the catheter is withdrawn one step of 6.5 cm before the next cycle begins. Large vein diameters are compensated for by double dosage. One small RCT[8] was published earlier this year. It suggests that Closure Fast is superior to the conventional 980-nm laser in terms of post-procedural recovery and quality-of-life parameters. At Klinik Hirslanden, until last April, we have treated 155 patients with 232 refluxing saphenous veins using Closure Fast. All procedures were carried out under tumescent local anaesthesia only and varicose branches were removed by hook phlebectomy in the same session. The outcomes were examined by an independent team from the Zurich University Hospital using questionnaires and ultrasound examination (Amann-Vesti B. et al., publication in preparation). Among the responders (56% to date), patient satisfaction with the procedure was 8.3, on average, using a scale from 0 to 10. Furthermore, 84% of all patients were able to return to work on the next day. Duplex ultrasound at an average follow-up of 13.4 months confirmed abolition of saphenous reflux in 94%. New inventions, such as steam ablation, might find their place among other thermal endovenous therapies in the future.

Based on some evidence from the literature and personal experience, we believe that thermal ablation might become a new standard for the treatment of saphenous reflux. However, what form of thermal ablation? Techniques of the first generation were introduced into clinical practice only a decade ago, and it appears that continuous progress is ongoing ever since. Present and future research may define more clearly what temperatures are required to reach reliable and durable vein occlusion in combination with a minimum of collateral damage. One might speculate that a step-wise application of well-defined doses of energy at moderate temperatures might improve predictability of desired and undesired effects and the balance between them. Notwithstanding, UGFS as an inexpensive and effective treatment modality will play an important role, especially for tortuous, residual and recurrent varicosities. Conventional surgery in the form of hook phlebectomy often remains the best way to remove varicose branches. However, the role of high ligation and stripping as a gold standard for the treatment of saphenous reflux will increasingly be questioned and vascular surgeons are challenged to refine their surgical procedure, for example by performing it under tumescent anesthesia with only a small incision.

Nevertheless is it too early to define a new gold standard. There is an urgent need now for well-performed, sufficiently large RCTs comparing occlusion rates and side effects of surgery

and recent thermal ablation technologies in the long term, as well as safety issues and eco-
nomic viewpoints.

Conflict of Interest

The first author was a medical consultant with ProVena AG, Zurich, representing VNUS Medi-
cal Technologies Inc. in Switzerland until recently.

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Technical review of endovenous laser therapy for varicose veins

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Abstract

Background In the last decade, several new treatments of truncal varicose veins have been introduced. Of these new therapies, endovenous laser therapy (EVLT) is one of the most widely accepted and used treatment options for incompetent greater and lesser saphenous veins.

Objective The objective of this report is to inform clinicians about the EVLT procedure and to review its efficacy and safety in treatment of truncal varicose veins. Also, we discuss some of the underlying theoretical principles and laser parameters that affect EVLT.

Methods We carried out a literature review of EVLT`s efficacy and safety. We included reports that included 100 or more limbs with a follow-up of at least 3 months. The principals and procedure of EVLT are described. Of the laser parameters, mode of administration, wavelength, fluence, wattage and pullback speed are discussed.

Conclusion EVLT appears to be a very effective and safe option in the treatment of varicose veins but large randomized comparative studies are needed.

Introduction

The treatment of varicose veins reduces the symptoms and the complication rate of venous insufficiency and increases the patient's health related quality of life (HRQOL). The classic surgical strategy for incompetence of the great saphenous vein (GSV) is a high ligation and stripping at the saphenofemoral junction (SFJ). Venous insufficiency of the lesser saphenous vein (LSV) is conventionally treated by ligation (and stripping) at the saphenopopliteal junction (SPJ). However, recurrence occurs in approximately one third of cases after 5 years.[1,2] Other disadvantages include the necessity of general anaesthesia and the development of scars and post-operative pain. Adverse events associated with venous stripping are wound infection and saphenous nerve injury. To improve efficiency, HRQOL and to reduce serious side effects, costs and post-operative pain, new minimally invasive techniques, such as ultrasound-guided foam sclerotherapy (UGFS), radiofrequency ablation (RFA) (VNUS closure®) and endovenous laser therapy (EVLT) have been introduced.[3] Although UGFS, RFA and EVLT are likely to fulfil these criteria and will play a prominent role in the treatment of varicose veins in the future, no controlled trials of the three major treatment options have been reported yet. The objective of this review is to inform physicians about EVLT from a practical (i.e. EVLT procedure) and technical (i.e., laser parameters) perspective.

Methods

A literature review of EVLT's efficacy and safety was performed. We carried out an electronic search of Medline, Cochrane library and Cinahl. We searched Pubmed with the following algorithm: (laser OR laser surgery) AND (saphenous OR saphena OR varicose veins OR varicosis OR endovascular OR endovenous) AND (duplex OR doppler OR ultrasonic OR ultrasound). We checked titles and abstracts of the retrieved articles ($n = 237$). To broaden the search we used the "related articles" function. In the evaluation of efficacy and safety, we included reports that included 100 or more limbs with a follow-up of at least 3 months. The mechanism and procedure of EVLT are described. Of the laser parameters, mode of administration, wavelength, fluence, wattage and pullback speed are discussed.

Indications for EVLT

The most common indication for EVLT is an insufficient GSV and to a lesser extent LSV (with or without insufficiency of junction) demonstrated by US examination and/or clinical presentation ('Clinical' stage 2 to 6 of the CEAP classification). In addition to primary truncal varicosities, accessory and perforator veins, recurrent truncal varicosities, varicosities in patients with

postthrombotic or Klippel-Trenaunay syndrome and congenital venous malformations have been treated successfully with EVLT.[4-7]

Practical description of Endovenous Laser Therapy

EVLT can be performed under local tumescent anaesthesia in an outpatient setting. The EVLT procedure varies between centres and we will describe it as reported by Navarro.[8] Venous access is obtained by a needle puncture (incision is rarely needed) under US guidance (Fig. 1). Most commonly, the insufficient GSV is entered at knee level because of its large diameter, linear course and the smaller risk of nerve injury. If possible, identified causes of venous insufficiency, such as paratibial perforator (Boyd's perforator), should be treated concurrently. The treated length of the LSV is usually relatively short (5–20 cm) but an insufficient May's perforator should be included. Stimulation of the varicose vein with the needle may result into local venous spasm, but the vein can be re-punctured about 10 cm proximal of the original site. Otherwise, waiting, applying warm towels, rescheduling, or a surgical incision, are indicated. After entrance to the varicose vein is established, a (metal) guide wire is passed through the hollow needle into the vein. If the varicose vein is tortuous, has a small diameter (due to spasm), large branches, or contains thrombotic or sclerotic fragments (after a phlebitis or prior treatment, respectively), advancing the wire can be difficult. Patients often report pain at the site of obstruction and US may reveal the cause of obstruction. Re-introducing the wire, rotating the U-shaped tip, local massage of the site, surgical incision or intermittent treatment may be helpful, but should be exercised with great caution because of the risk of perforation and inducing embolic events.

**Figure 1.** Access to the vein is obtained by a needle puncture under US guidance.

Figure 2. The tip of the sheath is located 1 to 2 cm distal from the crosse under US guidance.

After the guide wire is in place, the needle removed and a small cutaneous incision of 3 mm is made, an introducer sheath is passed over the guide wire. In some disposable sets, the introducer sheath has a dilator with a sharp point to increase rigidity and enhance venous access. Subsequently, the guide wire (and dilator) are removed when the sheath is at or beyond the junction. Under longitudinal US visualization of the junction, the echo dense tip of the sheath is pulled back till it is located 1 to 2 cm distally from the junction (Fig. 2). This is the most pivotal step in the EVLT procedure.

Subsequently, the laser with red stand-by light and a diameter between 200–600 μm (dependent on the varicose vein and the laser parameters) can be introduced. Depending on the disposable set used, the laser fibre should either be marked before insertion, or will have fixed marks to indicate to what extent the laser has to be advanced. In non-obese patients, position of the laser tip can be confirmed using the red stand-by light of the laser that will be visible transcutaneously.

Local tumescent anaesthesia (5 ml epinephrine, 5 ml bicarbonate and 35 ml 1% lidocaine diluted in 500 ml saline) is administered into the perivenous space under US guidance either using a syringe or pump. The needle tip is positioned near the varicose vein and the tumescent, which will show as a black mass, is injected under a cross sectional US image (Fig. 3). The tumescent remains around the interfascial part of the vein but will diffuse more at the extrafascial part. Therefore, more volume is required at this part. Local tumescent anaesthesia has three functions: (1) reduces pain, (2) protects perivenous tissue by cooling and (3) increases surface area contact between laser tip and vein wall.
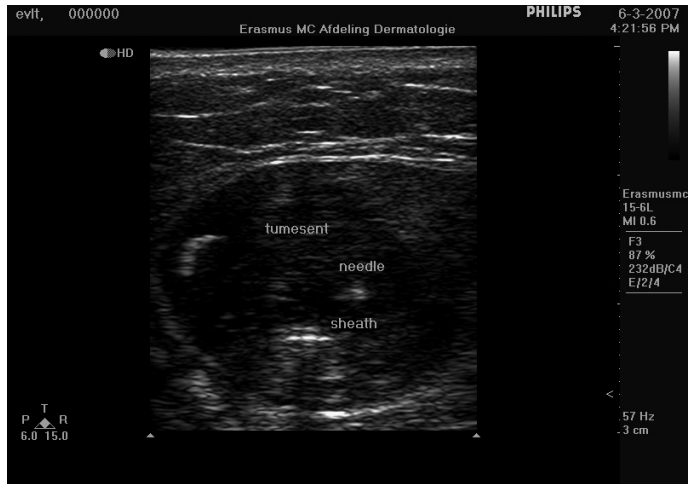
Figure 3. US image of tumescent anesthesia of varicose vein.

Before activation of the laser, individuals in the treatment room should wear protective laser goggles. The parameters used, the velocity and technique in which the laser is pulled back are variable and may be laser dependent, they will be described extensively in the following section.

Mechanisms of EVLT

Laser (Light Amplification by Stimulated Emission of Radiation) creates high-energy, bundled light that is monochromatic (one wavelength), collimated (photons run parallel) and coherent (in phase). The mechanism of EVLT is not entirely clear, but a thermal reaction after laser exposure is likely to be essential. The degree of heat induced cell destruction depends on the temperature and duration of exposure. The temperature of the laser tip increases to 800 °C, direct contact with the venous wall results in local destruction and may lead to (micro) perforation of the vein.[9] Venous compression by tumescent anaesthesia increases contact surface area, which results in more direct laser effects. The intravascular heat decreases to 90 °C at 4 mm of the laser tip due to absorption by venous blood (deoxyhaemoglobin), which is demonstrated by the observation that the penetration of the 940 nm laser is 45 mm in water and 0.3 mm in blood.[10] *In vitro* and *in vivo* studies show that this intense energy absorption results in 'boiling of blood' and the generation of 'steam bubbles' that indirectly, but homogenously affect the varicose vein.[11] The direct and indirect thermal reactions induce scar formation, occlusion and finally absorption of the vein. Histological studies show that EVLT damages the endothelial and intimal layer, internal elastic lamina and media to some degree. The adventitia is affected in a minority of the treatments.[12] In a pig model using EVLT the peak temperature adjacent to the vessel is rarely higher than 50 °C, which is a minimum for collagen degeneration.[13]

**Laser parameters and their practical implications**

The laser induced thermal reaction can be regulated to some extend by adjusting several laser parameters such as wavelength, type of administering laser energy and the amount of energy per surface area (fluence [J/cm^2] or J/cm), which depends on wattage, pulse duration and vessel surface area.

Pulsed and continuous wave

Using the pulsed mode, the blood vessel is exposed to a fixed amount of energy at equal distances. The total amount of administered energy depends on the distance between pulses (0.3–2 cm), pulse duration (0.5–2 s) and energy (10–15 W). During continuous mode, the laser is pulled back constantly and the total energy delivered depends on pullback speed and wattage. In most of the first EVLT studies pulsed mode was used, but the majority of recent studies use continuous mode. This is likely due to practical considerations, such as standardization and duration of treatment (8–10 vs. 1–3 min). Also, presentation of total energy given per unit of length or area is more difficult using pulsed mode and pulsed mode is associated with a higher risk of adverse events such as venous perforation.[14]

Wavelength and absorption spectra

Each chromophore (i.e., target such as haemoglobin or water) has its own absorption spectrum (Fig. 4). The 810, 940 and 980 nm Diode lasers are used because they are absorbed by deoxygenated haemoglobin and the 980 nm also by water. The Nd:Yag lasers (1320 nm) ap-
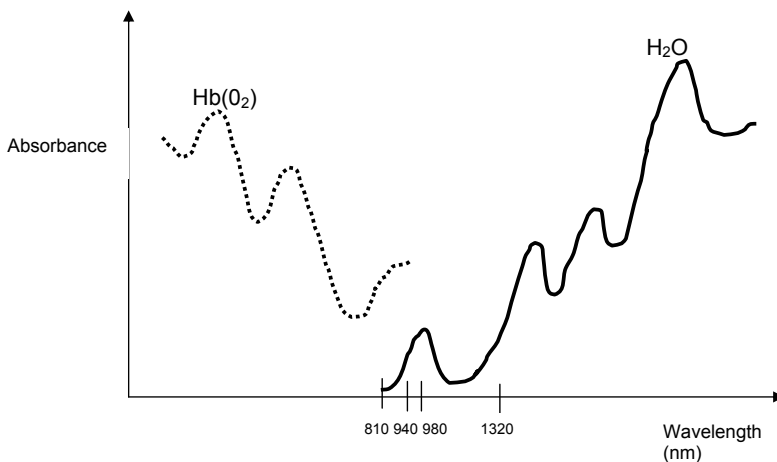
Figure 4. Schematic absorption spectra of water (H_2O) and (deoxygenated) hemoglobin (Hb[O_2]).

pears to be effective for EVLT.[7,15-16] Two comparative EVLT studies demonstrated that patients treated with higher wavelengths reported less postoperative pain, used less painkillers and were less likely to have ecchymosis.[16-17]

Fluence or Joule/cm

In laser therapy, fluence (J/cm^2) is the single most important parameter to quantify the amount of energy given. The amount of Joules depends on the wattage (J/s) and duration of treatment (pullback speed or pulse duration in continuous and pulsed wave, respectively). Because the surface area of the venous wall (cm^2) is difficult to estimate, most studies report J/cm (or linear endovenous energy density) as a surrogate marker of fluence. The length of the varicose vein is estimated either by using a marked catheter or by measuring the distance from the entry site until 1–2 cm caudal of the junction. Proebstle *et al.* have suggested the use of an endovenous fluence equivalent taking the diameter of the vein into consideration.[18-19]

Only very few of the initial EVLT studies reported fluence or J/cm and it ranged between 20–40 J/cm. In a multivariate analysis, Proebstle *et al.* demonstrated that the amount of energy administered in EVLT was an independent predictor of GSV occlusion rate.[18] The same research group confirmed this in two randomized clinical trials, which showed that 60 J/cm was more effective than 25 J/cm[16] and that an endovenous fluence equivalent of 20 J/cm^2 (comparable to about 60 J/cm) or more was associated with durable GSV occlusion after 12 months.[19] Another study suggested that an energy dose greater than 80 J/cm resulted in a success rate of 100%.[20] A mathematical model suggested that 65 and 100 J/cm was needed for varicose veins of 3 and 5 mm respectively, to destroy the intimae irreversibly.[21]

Wattage

Administering high wattage for a short time has a vaporizing effect and low wattage for longer time has a coagulating effect.[12] Besides wattage, the amount of energy also depends on the pullback speed and pulse duration of the laser. Although using 10–15 W is commonly accepted in EVLT, a recent randomized study demonstrates that EVLT using 30 W (63 J/cm) was more effective than 15 W (24 J/cm) with a 940 nm Diode laser (100% vs. 90.3% occlusion after 3 months, respectively).[16] However, a smaller case series using a 980 nm laser suggested that 11 W was as effective as 15 W, but was associated with fewer side effects.[22] It remains unclear whether these studies show a true difference due to wattage (J/s) or whether it is related to fluence (J/cm^2).

Pullback speed

Using a pulsed mode, the pulse duration reflects the exposure time. The pullback speed, however, is an important parameter in continuous mode. If the EVLT is performed with fixed wattage, the energy given per cm^2 depends solely on the pullback speed and can be reported as a function of the wattage (e.g., 5 sec/cm). An alternative is that a laser display shows the cumulative energy (J) administered while pulling back, which enables the clinician to estimate the amount of J/cm given up to a point.

Clinical Studies

Outcomes

Usually, the efficacy of EVLT is expressed in percentage of vessels occluded and/or the absence of flow on US examination. Other studies have used the C of CEAP classification (Clinical, Etiologic, Anatomic, Pathofysiologic) or its derivative VCSS (Venous Clinical Severity Score) as study endpoints.[23] Also, changes in the disturbed hemodynamics of varicose veins using venous fillings index[24] and air plethysmography[25] have been studied. In recent clinical trials, patient reported outcomes such as HRQOL, satisfaction and pain are included because of their importance in the comparison of minimally invasive methods and surgery.[26-27]

Case series

The first cohort studies suggesting EVLT is successful in the treatment of large varicosities were published in 2001.[8,28] Thereafter, multiple case-series (number of treated limbs ranging from 6 to 1250) have been presented and a systematic review has been published in 2005.[29]Table 1 presents a selection of EVLT studies that include at least 100 limbs with at least 3 months follow-up. A success rate of 100% one week after EVLT is reported in most studies. Although success rate decreases with time, it remains at least 90%. In a prospective US study, 93% of 499 GSV were occluded 2 years after therapy.[30] An Italian workgroup reported a success rate of 97% in 1000 patients with a follow-up of 3 years.[26] Another large study with more than 1250 limbs treated, showed a success rate of approximately 95%.[27] Some studies report success rates lower than 90%, which may be due to the characteristics of the varicose veins they treated e.g. very large or tortuous, or associated large insufficient perforator of Dodd or Hunter.[5,31]

Combined treatment studies

Because the management of varicose veins is usually a combination of different types of interventions, several studies have investigated the use of EVLT combined with other therapies, such as ambulatory phlebectomy,[32] UGFS of the accessory vein and smaller varices[30] or UGFS and surgical stripping.[33]

Comparative studies

Three studies have compared EVLT with other treatments of varicose veins. A small paired analysis of 20 patients showed one recanalization after EVLT and none after junction ligation followed by a short strip.[25] Although no differences were noted in treatment related pain, less swelling and bruising were noted after EVLT compared to surgery. A retrospective study suggested that RFA and EVLT were equally effective, but three DVT were reported after EVLT.[34] A nonrandomised pilot study compared EVLT (*n* = 70) with inversed stripping of the GSV (*n* = 62).[35] The clinical efficacy parameters were comparable, but EVLT had significant superior effect on the short and long term HRQOL. Although cost-effectiveness studies are lacking, EVLT is likely to reduce costs because it has less down-time and is an outpatient therapy.[36]

Adverse events

EVLT induces sclerosis and micro perforations of the venous wall that often results in pain and ecchymoses, which will disappear in one to two weeks, and can be reduced by elastic stockings and pain killers. The frequency and intensity of these symptoms may be less for higher wavelengths and in continuous than pulsed mode.[16,37]

Although minimally invasive techniques may reduce classical surgical side effects (e.g., wound infection and scarring), it may be associated with specific adverse events such as DVT and skin burns (Table 1). One day after EVLT, D-dimers were elevated in about half of the patients and especially in those who had a bilateral procedure.[11] Due to the theoretical chance of DVT, most studies carefully examined DVT incidence after EVLT. Among three case series that included 2750 limbs, only one lung emboli was found.[26-27,30] Two smaller studies detected several EVLT induced DVTs (3/77 and 3/56), which may be due to their retrospective design and/or is a reflection of a learning curve.[34,38] Proebstle reported on a patient with polycythemia vera who developed a DVT after EVLT.[4] Some authors advise US examination one week after EVLT to exclude DVT and others use LMWH for 5–7 days post-operative.[34] The incidence of DVT seems to be at most comparable with surgical treatment (about 2%). Low-risk patients do not need thromboprophylaxis after treatment. Prophylaxis with 20 mg enoxaparin did not guarantee against developing a DVT in "high-risk" patients either.[39-41] Of special concern in

EVLT is the induction of emboli in previously treated veins because inserting the sheaths and fibres may induce detachment of thrombus.

Skin burns are another possible EVLT associated adverse event and may occur if the administered energy is too high or the cooling effect of tumescent anaesthesia is insufficient. None of

Table 1. Characteristics of included Endovenous Laser Therapy (EVLT) studies

Author	Year	Type study	Type laser (nm)	No. of limbs	Type (No.) of varicose veins	Inclusion	Duration of follow-up	Complete response (partial)[#]	Major complications (No.)*
Min et al.	2003	Prospective case series	Diode (810 nm)	499	GSV (499)	GSV and SFJ insufficiency on US	2 years	93.4% (GSV)	No
Perkowski et al.	2004	Prospective case series	Diode (940 nm)	165	GSV (154) SSV (37) Accessory vein (12)	C4 or more: 62% Ulcer: 8.9%	2 weeks	97.0% (all)	No
Huang et al.[Ŧ]	2004	Prospective case series	Diode (810 nm)	230	GSV (230)	C2: 37% C3: 11% C4: 47% C5: 0.4% C6: 3.9%	2 weeks	100%	Skin burns (2)
Proebstle et al.	2004	Retrospective case series	Diode (940 nm)	106	GSV (106)	C2-C6[@]	3 months	90%	No
Proebstle et al.	2005	RCT	Diode (940) vs. Nd:Yag (1320)	282	GSV (282)	C2-C6[@]	3 months	Average 98%	No
Sharif et al.	2006	Prospective case series	Diode (810 nm)	145	SSV (145)	Primary and relapsing isolated SSV insufficiency	1 year	76%[$] (18%)	Saphenous nerve injury (1) Skin burns (1)
Ravi et al.	2006	Prospective case series	Diode (940 nm)	1091	GSV (990) SSV (101)	C2: 29% C3: 11% C4: 46% C5: 9% C6: 5%	2 weeks and 200 for 1 year	96.7% (GSV) 91.0% (SSV)	Lung emboli (1)
Agus et al.	2006	Prospective case series	Diode (810 & 980 nm)	1076	GSV (1052) SSV (16) Accessory vein (8))	C2: 82% C3: 10% C4-6: 8%	3 years	97% (all)	No

[#] By US.

* Major complications: nerve injury, deep venous thrombosis (± emboli), and skin burns, but not pain and ecchymosis.

[Ŧ] From ankle to groin and in 10 patients in combination with surgical approach.

[@] C-classification not specified in number of patients.

[$] Of 21 `failures`: 12 passage of wire, 4 failed cannulation, 3 patient discomfort, 1 syncope, and 1 technical laser problem.

the major case series reported skin burns and only a few smaller studies reported superficial skin burns (Table 1).

A major disadvantage of stripping is the risk of damaging the saphenous nerve (about 7% in short to 40% in long stripping).[5] As in surgery, the likelihood of neurological damage is likely to be higher in 'long' EVLT that start at ankle level than in 'short' EVLT procedures. Several other side effects of EVLT, such as superficial thrombosis (5%),[30] haematoma at entry site (rare), cellulitis (especially with incisions and less with needle punctures) and one case of an arteriovenous fistula have been reported after EVLT.[42]

Conclusion

About a decade after its introduction, EVLT appears to be a very effective and safe option in the treatment of varicose veins. Although thousands of patients treated with EVLT with several years of follow-up have been reported, no large randomized clinical trials comparing EVLT with UGFS, RFA and surgery have been performed yet. There is an urgent need for comparative studies to assess long term clinical efficacy, safety, patient reported outcomes (i.e., HRQOL, symptoms and treatment satisfaction), and costs of the available treatment modalities in order to make informed medical decisions and to optimize care of patients with varicose veins. Currently, at least four RCT's on the treatment of varicose veins are 'ongoing' (www.controlled-trials.com) and the preliminary results of meta-analysis suggest that EVLT is significantly superior in achieving anatomical success using ultrasound criteria compared to RFA, UGFS and surgery (personal communication by RRVDB).

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Endovenous laser ablation–induced complications: review of the literature and new cases

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Abstract

Background In the last decade, minimally invasive techniques have been introduced in the treatment of lower extremity varicosities. Of these therapies, endovenous laser ablation is the most widely accepted and used treatment option for insufficient great and short saphenous veins.

Objective To present a review of reported common and rare and minor and major complications associated with endovenous laser ablation.

Methods A systematic review of studies and case reports on endovenous laser ablation–induced complications. The complications were classified as minor or major according to the Society of Interventional Radiology Standards of Practice Committee guidelines on reporting complications. A case-series of complications after endovenous laser ablation is presented.

Results Ecchymoses and pain are frequently reported side effects of endovenous laser ablation. Nerve injury, skin burns, deep vein thrombosis and pulmonary embolism seldom occur. An exceptional complication is a material or device that by accident remains inside the body after the procedure. Ecchymosis, pain, induration, skin burns, dysesthesia, superficial thrombophlebitis, and hematoma were classified as minor complications. Deep vein thrombosis and nerve injury were classified as major complications.

Conclusion Endovenous laser ablation may be considered a safe treatment of lower extremity varicosities. The incidence of common side effects may decrease with better laser parameters.

Introduction

Minimally invasive techniques such as endovenous laser ablation (EVLA), endovenous radiofrequency ablation (RFA), and ultrasound-guided foam sclerotherapy (UGFS) are now widely used in the treatment of varicose veins of the lower extremities. Of these relatively new techniques, EVLA is probably the most commonly used.[1-4] It is used for treating the great saphenous vein (GSV) and to a lesser extent the short saphenous vein (SSV), with average occlusion rates of more than 90%.[5] Less common indications are accessory veins, varicose veins in patients with Klippel-Trenaunay syndrome, perforator veins, and congenital venous malformations.[6-9] The popularity of these minimally invasive techniques has even led investigators to amend their study protocols to circumvent difficulties with patient recruitment.[10]

Because most authors consider EVLA to be a safe therapy, to our knowledge no recent comprehensive review of adverse events after EVLA has been published. Mundy and colleagues reported adverse events associated with EVLA from a number of studies published before 2004.[11] Many studies have been published since, and we felt that an update on this topic was needed. In this study, we present a review of the literature of EVLA-induced complications. In addition, we report rare and exceptional complications that occurred in our or nearby centers.

Methods

Clinical trials of EVLA that were included in a recent systematic review[12] were screened for adverse events. An additional search (of articles published until July 2008) specifically for complications was performed using the following search terms: (endovenous laser OR endovenous ablation) AND (saphenous OR saphena OR varicose veins OR varicosis) AND (complications OR adverse events OR side effects). Only studies that used EVLA were included, combined treatments (such as ligation and concomitant phlebectomies) were excluded. Studies that were not in English, German, or Dutch were excluded. The reported complications were categorized as minor or major complications according to the guidelines of the Society of Interventional Radiology Standards of Practice Committee.[13] Minor complications were categorized as A (no therapy needed, no consequence) or B (nominal therapy needed, no consequence; includes overnight admission for observation). Major complications were divided into four groups: C (require therapy, minor hospitalization (<48 hours), D (require major therapy, unplanned increase in level of care, prolonged hospitalization (>48 hours), E (have permanent adverse sequelae), and F (result in death). A description of our center's experience with EVLA-induced complications is presented, as well as personal communications from affiliated colleagues.

Review of the literature

In 2001, Navarro and colleagues[14] reported on a case series of 33 patients (40 limbs) treated using EVLA. No complications, apart from mild ecchymoses, were reported. Systematically studying all publications on EVLA showed that the most common side effects were ecchymoses and pain with or without induration (100%) and that skin burns (<1%), dysesthesia (0-22%), superficial thrombophlebitis (0-25%), deep vein thrombosis (DVT) (0-6%), nerve injury (<1%), and hematoma were reported much less. The reported frequencies vary considerably between studies (Table 1). Some studies suggest that wavelength of the laser is related to the frequency and intensity of minor side effects such as ecchymosis and pain,[4]

Table 1. Overview of different studies reporting on complications after Endovenous Laser Ablation (EVLA)

Author	Year	No Limbs	Wave Length, nm	Skin burns	Ecchymoses or Bruising	Dysesthesia	Phlebitis	Deep-vein Thrombosis	Other
Agus[¶]	2006	1076	810, 980	0.2%	39%	0.8%	1%	0%	0%
De Medeiros	2005	20	810	0%	100%	0%	0%	0%	0%
Darwood	2008	71	810	0%	†	1.4%	12.7%	0%	Pruritis 1.4%, Transient discolouration 1.4%
Disselhoff	2005	93	810	0%	31%	0%	2%	0%	Tightness 17%, Induration 2%, Pain 14%
Elmore	2008	516	810	0.4%	†	2.1%	†	0%	0%
Gibson[¶]	2007	210	980	0%	0%	1.6%	0%	5.7%	0%
Goldman	2004	24	1320	†	0%	†	†	†	†
Gonzales-Zeh	2008	45	980	†	64.4%	4.4%	22.2%	0%	Induration 68.9%
Huang	2005	230	810	1%	0%	7.2%	0%	0%	Pain +, Induration +
Kabnick	2006	60	810, 980	0%	+	0%	22%	0%	Pain +, Itching +
Kim1	2006	34	980	0%	24%	2.9%	2.9%	0%	Hematoma
Kim 2	2006	60	980	0%	27%	0%	3.3%	0%	Hematoma, Tenderness 28%
Marston	2006	31	810	†	†	†	†	3.2%	†
Min 1	2001	90	810	0%	+	1.1%	0%	0%	0%
Min 2	2003	499	810	0%	24%	0%	5%	0%	Pulling cord sensation 90%
Myers[¶]	2006	404	810	0%	+	0%	0%	1.9%	Pulm embolism 0.25%, Sural nerve palsy 0.25%
Navarro	2001	40	810	0%	+	0%	0%	0%	0%
Oh	2003	15	980	0%	100%	†	6.7%	0%	Induration 60%
Park[§]	2007	21	980	9%	60%	9%	†	0%	Tightness 33.3%
Park	2008	390[‡]	980	0%	83%	2%	2.3%	0%	Pain 87%
Perkowski[¶]	2004	165	940	0%	+	0%	†	0%	0%

Table 1. (continued)

Author	Year	No Limbs	Wave Length, nm	Skin burns	Ecchymoses or Bruising	Dysesthesia	Phlebitis	Deep-vein Thrombosis	Other
Pleister	2008	50	980	†	†	†	†	0%	†
Proebstle	2003	41	940	0%	49%	11%	8%	2.8%*	0%
Proebstle	2005	264	940, 1320	0%	61-81%	5-14%	10%	0%	Pain50-80%, Induration 45-64%
Proebstle	2006	252	940	0%	80%	9%	12%	0%	Pain 80%, Induration 63%, Hyperpigmentation 2%
Puggioni	2005	77	810	0%	†	†	5.2%	0%	Cellulites 2.6%, Urine retention 1.3%, Excessive pain 3.9%, Hematoma 1.3%, Edema 2.6%
Ravi[¶]	2006	1091	940	0%	+	0%	0%	0%	0%
Sharif	2006	145	810	0.8%	83.1%	0%	0%	0%	Saphenal nerve injury 0.8%
Theivacumar[¶]	2007	68	810	0%	+	4.4%	4.4%	0%	0%
Theivacumar	2008	644	810	†	†	1.1%	10.2%	0.2%	†
Timperman[¶]	2004	111	810	0.9%	†	†	†	0.9%	†
Timperman	2005	100	810	0%	0%	1%	0%	0%	Spider veins 1%
Viarengo[¶]	2007	27	980	3.7%	62.9%	22.2%	0%	0%	Pain 33.3%, Induration 18.5%, Thrombus extending to femoral vein 7.4%, Lipoid necrosis 3.7%
Yang	2006	71	1320	0%	†	2.8%	†	0%	Thrombus extending to common femoral vein 1.4%

*Patient with polycythemia vera. †Was not reported. ‡Only short saphenous vein (SSV). §Side branches were also treated using EVLA. ¶Studies in which either the GSV or the SSV was treated.

but the comparisons in this study are not optimal because other parameters such as power and pullback speed varied substantially between the different wavelengths. According to the guidelines on complications of the Society of Interventional Radiology Standards of Practice Committee, the complications after EVLA were classified into: ecchymosis (minor A), pain (minor A/B), induration (minor A), skin burns (minor B), dysesthesia (minor A), superficial thrombophlebitis (minor A), DVT (major C/D/E), nerve injury (major C), and hematoma (minor A). In summary, most adverse events associated with EVLA are minor, except DVT and nerve injury, which occur in approximately 1% of patients.

Case reports in the literature

The most minor complication of EVLA-induced complications was persistent hyperpigmentation.[15] In one patient, cutaneous thermal injury that resulted in pain and blistering was reported 8 days after EVLA.[16]

Two cases of arteriovenous fistula after EVLA have been reported.[17-18] One week after treatment of the SSV, a high-flow fistula from a branch of the popliteal artery to the stump of the SSV was observed using ultrasound. The popliteal fossa is at particular risk because of the close proximity of the superficial sural artery and the SSV.[17] In the second case, multiple small arteriovenous fistulas between superficial femoral artery muscle branches and the GSV developed after EVLA. Ultrasound examination showed arterialized flow in the GSV 1 week after therapy.[18] Diffuse phlegmonous phlebitis after EVLA of the GSV was seen on the fifth postoperative day in another report. The treated leg became increasingly painful, and the patient's temperature increased to 40°C.[19] The treated leg was diffusely infected by *Staphylococcus aureus* resulting in spontaneous drainage of pus. The authors suggest that the presence of a foreign body in necrotic venous tissue may have caused this complication, although this patient had a venous ulcer and underwent multiple stab avulsion phlebectomies concurrently. Seroma after EVLA has been reported once. One week after EVLA, local pain, redness, and swelling around the access site were present, and ultrasound revealed subcutaneous fluid collection. Needle aspiration of the collection allowed complete evacuation of the clear yellowish fluid, which was negative on bacterial culture.[20]

Device-related complications after EVLA have been reported twice.[21-22] During a procedure, the laser fiber broke because of significant bending, and the proximal 28-cm-long part of the laser fiber was retained in the ablated GSV. Seven days after treatment, the fiber was noted on ultrasound examination and removed surgically.[21] Recently, a guide wire was retained without the knowledge of the physician. One year after EVLA, the patient reported chronic dyspnea and chest pain. Parts of the guide wire were visualized on X-ray and removed using percutaneous transluminal intervention.[22]

Our experience

We have performed approximately 500 EVLAs in our center using a 940-nm diode laser. All patients experienced ecchymoses at the treated site. Degree of pain is much more variable than degree of ecchymoses between patients after EVLA. Most patients report pain (or sensation of "pulling cord") for 1 to 2 weeks that is mild and can be controlled with medical elastic stockings and analgesics. Some patients do not report any pain, and approximately 5% to

10% experience a high-intensity pain that sometimes results in work absence or functional impairment for 1 or 2 weeks. In general, EVLA of the SSV is more often painful than of the GSV. Several patients have experienced superficial thrombophlebitis, especially those with large side branches of the treated varicose vein, such as the accessory veins or the distal parts of the GSV. Performing phlebectomy before or during the EVLA procedure can reduce the occurrence of this side effect. In one obese patient, we experienced difficulty gaining access to the GSV at knee level because of the thick layer of adipose tissue. The angle at which access was finally gained was too sharp to allow smooth passage of the rigid sheath. The procedure was discontinued. The patient returned with thrombophlebitis of the GSV after 1 week that was most likely due to iatrogenic damage of the vessel wall. A few patients have reported transient paresthesia, but we have not seen any serious neurological damage. Injury of the saphenal nerve is a possible risk of treating the SSV, but it can be prevented by ample use of tumescent anaesthesia near the saphenopopliteal junction. The use of tumescent anesthesia is also pivotal in the prevention of skin burns. No skin burns have occurred in our center. Three of our patients developed DVT after EVLA of the GSV, one of which resulted in pulmonary embolism. The patient who developed an embolism was diagnosed with a coagulation disorder retrospectively. Within a week after the procedure, she travelled by car for more than 10 hours, which in combination with her coagulation disorder may explain this thromboembolic event. This case prompted us to warn patients against periods of immobilization, such as travelling, within a month after EVLA. Another patient developed a thrombosis of the common femoral vein probably caused by a technical error (disposition of the laser tip beyond the saphenofemoral junction that may have been related to the patient's obesity because it complicates the ultrasound visibility of the saphenofemoral junction). Our last case of DVT after EVLA can be considered classical; the patient reported acute and intense pain 2 days after therapy. Ultrasound examination showed a partly floating thrombus that originated from the occluded GSV and crossed the saphenofemoral junction into the deep venous system. One affiliated colleague (K-P De Roos, personal communication) reported on a 41-year-old female patient who presented with shortness of breath and stinging pain on the right side of the chest. One month before, her right GSV and 1 week after that her left GSV had been treated using EVLA in a center elsewhere. She had been mobilized immediately after EVLA. There was no medical history and no family history of thrombotic events. Computerized tomographic angiography of the thorax confirmed the clinical diagnosis of pulmonary embolism (right pulmonary artery). Ultrasound examination of the leg veins did not reveal any DVT. Treatment consisted of warfarin and nonsteroidal antiinflammatory drugs, and she continued to wear compression stockings for the following 6 months. She recovered without any sequelae.

Other unusual cases

After EVLA of the right GSV, a 64-year-old male patient developed therapy-resistant cardiac arrhythmia. Four months after the procedure, heart echography revealed a foreign body that had perforated the right ventricle into the septum (Figure 1). Thoracotomy was performed, and the 6-cm end of the catheter used in the EVLA procedure was removed (DA Groeneweg, personal communication). The physician who performed the procedure hypothesized that the laser tip was not introduced beyond the plastic sheath and that the activation of the laser disconnected the tip from the sheath. In an in vitro experiment, the heat of the laser tip melted and disconnected the proximal end of the catheter immediately, confirming his hypothesis. This experiment showed that melting of the catheter occurred only in blood and not in saline, suggesting an essential role of blood in the heating effect of EVLA. This complication stresses the need to ensure that the laser tip lies beyond the end of the catheter before activating the laser. Some manufacturers of disposable catheters try to ensure this by introducing an additional step in the procedure; after the sheath is positioned, instead of the laser fiber being blindly introduced, it is pushed into the sheath to a first mark, and than the sheath is pulled back to a second mark a fixed distance from the first mark. In this way, the laser fiber tip is placed beyond the sheath without the risk of the fiber perforating the venous wall.

Another exceptional case, similar to the one reported by Kichari and colleagues,[22] concerned a patient, treated in a center that had performed more than 1,500 EVLAs, in which the entire guide wire entered the systemic circulation and caused cardiac problems. Because of shear stress in the right ventricle, the metal guide wire broke into multiple pieces that spread across the major vessels of the body (Figure 2). Endovascular and one open procedure were needed to remove these pieces of guide wire (EFC Duponselle, personal communication). This techni-
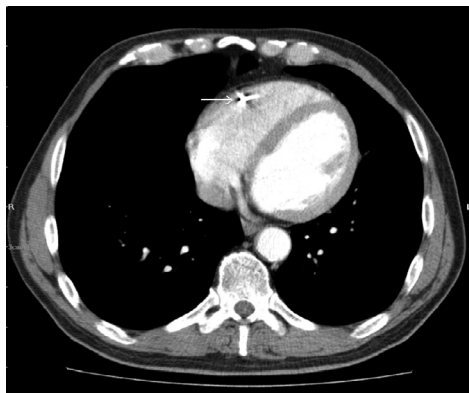
Figure 1. Computed tomography of the chest. White "star-like" structure (end of the catheter) visible in right ventricle.
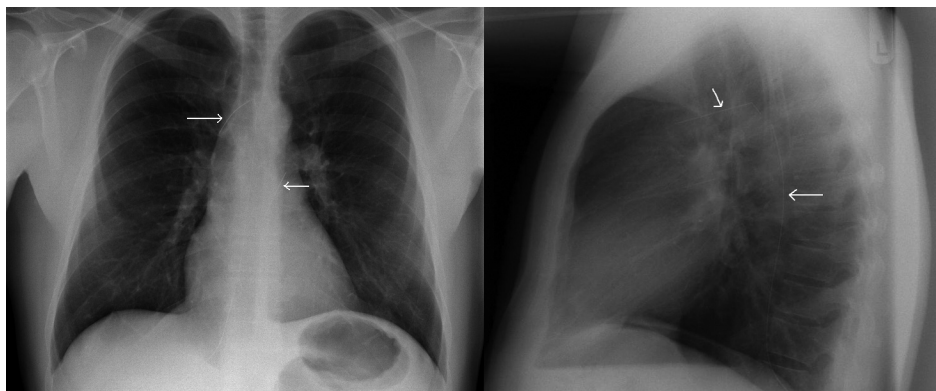
Figure 2. Chest X-ray. (A) Anteroposterior view, (B) lateral view. Pieces of guide wire indicated by white arrows.

cal error occurred because the guide wire was blocked in the lumen, probably because of a slight nick in the sheath, and because the sheath was pushed further over the guide wire, the latter could enter the circulation. This can be prevented if the guide wire is at least twice as long as the sheath because the guide wire is visible at all times during the procedure. These device-related complications highlight the importance of routinely inspecting the disposables that are used, such as the sheath and the laser fiber, after withdrawal to ensure that they are present and undamaged. These extraordinary complications have not been published in the medical journals, but the Food and Drug Administration Website contains several reports of EVLA-related complications that have required additional surgical procedures to remove retained laser fibers and sheaths.[23] The loss of guide wires that are used in many endovascular procedures has been reported previously and is not restricted to EVLA.[24] Holdstock and colleagues performed an in vitro experiment that suggests that it is possible to cause sufficient needle damage to fracture a laser fiber when fired. In the experiment, it was shown that the needle used for tumescent anesthesia could damage the sheath and the laser fiber, even leading to complete severance. The authors recommend administration of tumescent anesthesia before introduction of the laser fiber.[25]

Another patient experienced anaphylactic shock during the procedure, which was retrospectively diagnosed as an allergic immune response to lidocaine (W Roest, personal communication).

Discussion

Minimally invasive techniques such as EVLA are a popular choice for patients and doctors because of the low risk of complications, short "downtime," and excellent cosmetic results.

When applied properly, these techniques also seem to be effective and safe. For efficacy and safety, it is essential that professionals well trained in phlebology and ultrasound examination perform these complex procedures, but pain and ecchymoses seem to be inherent to all (minimally invasive) procedures of varicose veins including EVLA. In EVLA, the frequency and intensity of these minor complications can be reduced by administering ample tumescent anesthesia and possibly by optimizing the laser power and pullback velocity. Several clinical trials have compared the different laser wavelengths, but important parameters such as laser power and pullback velocity were not standardized, making it difficult, if not impossible, to assess the effect of different wavelengths in the complication rate of EVLA. Major complications such as skin burns, nerve injury, DVT, and embolism occur rarely (<1%), but patients should be informed about the potential risks associated with EVLA and instructed to return if they develop symptoms that are suspicious of DVT, such as acute swelling and pain. Major complications are reported rarely, which may be due to diagnostic bias (e.g., subclinical DVT) or studied outcomes. However, the proportions of serious adverse events did not differ considerably between most studies, including the studies designed to detect complications such as DVT. It is suggested that incorrect positioning of the laser tip; using general or epidural anesthesia instead of tumescent anesthesia, which disallows immediate ambulation after the procedure; and preexisting coagulation disorders increase the risk of DVT.[26] Although we do not routinely administer low-molecular-weight heparin (LMWH) before or after EVLA, some have suggested its routine use, and others administer LMWH postoperatively in high-risk patients.[27-28] Performing a limited coagulopathy screen preoperatively (at least an activated protein C resistance) has been suggested for any patient with a history of thrombophlebitis or DVT or a family history of DVT.[28] Of all included studies (Table 1), only the case series by Proebstle and colleagues and Navarro and colleagues reported the routine use of LMWH prophylaxis. The risk reduction of LMWH has not been studied in a randomized controlled trial. Because of the low incidence (<1%), the number of "healthy" low-risk patients needed to treat with LMWH to avoid the development of one DVT is likely to be high and not cost effective. The overwhelming majority of eligible studies used local tumescent anesthesia. The small number of studies that administered epidural or general anesthesia and the low incidence of DVT enable us to indirectly estimate the effect of type of anesthesia on DVT development. The National Institute for Clinical Excellence's guidelines on the use of routine preoperative tests for elective surgery recommend testing hemostasis (including prothrombin time, activated partial thromboplastin time, and international normalized ratio) only in specific patients.[29] There is no consensus as to follow-up after EVLA, some authors check for DVT within 1 week after the procedure,[28] others within 1 month.[30] In our center, patients are routinely checked after 3 months with ultrasound examination for success of the procedure. The cases of retained devices emphasize the need to carefully check the presence and status of disposables after the procedure. Patients should leave the clinic only when all materials used are accounted for. Several laser manufacturers have introduced technical adjustments,

Table 2. Prevention and therapeutic options for complications after endovenous laser ablation

Complication	Prevention	Therapy
Ecchymosis	Correct energy dose*	Compression (elastic stockings)
Pain	Tumescent anesthesia, correct energy dose	Compression (elastic stockings) NSAIDs
Skin burn	Tumescent anesthesia, correct energy dose, stop laser activation at entry site, caution at extrafascial part	Post-operative cooling
Superficial thrombophlebitis	Prior or simultaneous phlebectomy	Compression (elastic stockings) NSAIDs
Nerve injury	Tumescent anesthesia (especially at short saphenous vein junction), knowledge of anatomy	None
Deep vein thrombosis	Correct positioning laser tip, immediate mobilization, screening for coagulating disorder in selected patients, avoid postoperative immobilization	Low-molecular-weight heparin Compression (elastic stockings)
Hematoma	Correct energy dose, prior phlebectomy	Incision Compression (elastic stockings)

*Not too high (depends on wattage and pullback speed). NSAID, nonsteroidal antiinflammatory drug.

such as prevention of laser fiber activation extravenously, to minimize complication rates. Table 2 shows the therapeutic options for the most common complications after EVLA.

Conclusion

Because most of the side effects are minor, and major complications are rare, EVLA is a safe and minimally invasive procedure with excellent efficacy in the treatment of varicose veins. Because optimizing laser parameters and the EVLA procedure may reduce the incidence and severity of complications associated with EVLA, additional research is warranted.

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Laser fiber stabs the catheter: a serious complication of EVLA

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Abstract

An 82-year-old woman was treated with Endovenous Laser Ablation for insufficiency of the right Great Saphenous Vein. Because of a very thick layer of subcutaneous fat, puncturing the vein and introducing the laser fiber was difficult. The patient reported pain after activation of the laser. Subsequently, the procedure was discontinued and the catheter was removed. Inspection of the disposables showed that the laser fiber had punctured the catheter and was therefore located outside the lumen. Fortunately, there were no harmful sequelae in this case, but as device-related complications of EVLA are serious, reporting them is important.

Case

An 82-year-old woman presented at a nearby clinic for investigation of her varicose veins. Her venous insufficiency had resulted in venous dermatitis at the distal part of the right leg. She was otherwise healthy and only used benzodiazepines for sleep disturbance occasionally. She was treated with liquid sclerocompression therapy for telangiectasias on both legs years ago. Ultrasound examination of the deep and superficial venous system showed only an insufficient great saphenous vein (GSV) of the right leg which was 6 mm in diameter. The proximal 15 cm of the GSV was linear and located in the fascial compartment; distally a tortuous tributary was located extrafascially. The patient consented to an endovenous laser ablation under tumescent anesthesia in an outpatient setting.

The GSV was accessed at the upper half of the thigh, where it was located relatively deep in the subcutaneous fat (ca 4 cm) due to extreme obesity. The catheter was introduced very easily over the guide wire. Subsequently, the laser fiber was introduced into the catheter. Introducing the fiber was initially slightly difficult, but further on it glided easily. After laser activation and subsequent withdrawal of the catheter the patient reported some pain for which additional tumescent anesthesia was administered under ultrasound guidance. This did not reduce the pain, and therefore it was decided to stop the procedure and withdraw the catheter. Inspection of the disposables showed that the laser fiber had punctured the catheter and was therefore located outside the lumen. (Figure 1). The patient had a little pain afterwards, but fortunately this resolved entirely in the following hours. Immediate post-procedure ultrasound examination and 5 days later showed a normal deep vein system and an open GSV and no other abnormalities. Whilst seeing this patient every few days after the failed procedure she did not report any complains.
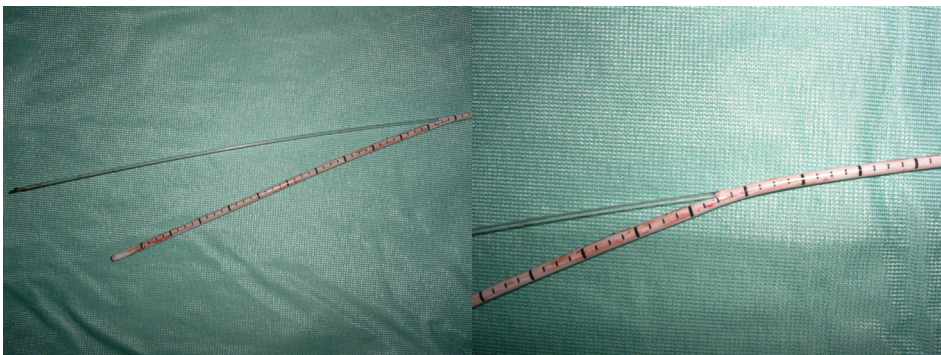
Figure 1. A. Catheter punctured by the laser fiber. B. Detail.

Discussion

Perforation of the catheter by a laser fiber has not been reported yet.[1-3] As device related complications are serious, we felt that reporting this one is of great value. It is important to realize that only the catheter and barely the fiber itself can be visualized clearly on ultrasound examination. We hypothesized that the thick layer of adipose tissue resulted in almost a right angle between introduction site of the catheter and stretch of the GSV. This may be encountered when the GSV is located fairly deep (for example when punctured at mid-thigh level instead of knee level) in obese patients. The catheter, which is quite flexible, must have bended too much due to this angle. This could have resulted in puncturing of the bended catheter by the rigid laser fiber during its introduction. (Figure 2) As a consequence, the laser fiber was activated whilst being extravenously. This exceptional complication should urge practitioners to take patients serious who report pain during the procedure, and they should refrain from excessive bending of the catheter and the laser fiber which may happen more easily in adipose patients. Also, it is important to visualize the fiber tip protruding beyond the catheter before activating the laser fiber to make sure the fiber is in its correct position. In general, the disposables should be checked for holes or kinks prior to each venous insertion, when the same catheter and fiber are being used to treat more than one venous segment.

GSV
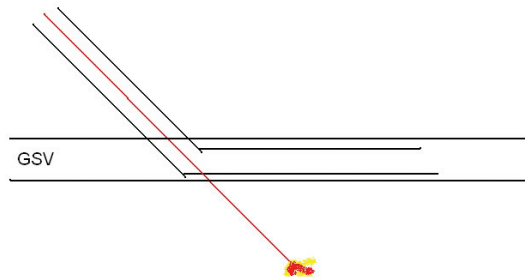
Figure 2. Schematic drawing. The extravenous position of the laser fiber after puncturing the catheter.

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Heat conduction from the exceedingly hot fiber tip contributes to the endovenous laser ablation of varicose veins

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Abstract

Lower-extremity venous insufficiency is a common condition, associated with considerable health care costs. Endovenous laser ablation is increasingly used as therapy, but its mechanism of action is insufficiently understood. Here, direct absorption of the laser light, collapsing steam bubbles and direct fiber-wall contact have all been mentioned as contributing mechanisms. Because fiber tips have reported temperatures of 800–1,300°C during endovenous laser ablation, we sought to assess whether heat conduction from the hot tip could cause irreversible thermal injury to the venous wall. We approximated the hot fiber tip as a sphere with diameter equal to the fiber diameter, having a steady state temperature of 800°C or 1,000°C. We computed venous wall temperatures due to heat conduction from this hot sphere, varying the pullback velocity of the fiber and the diameter of the vein. Venous wall temperatures corresponding to irreversible injury resulted for a 3 mm diameter vein and pullback velocities <3 mm/s but not for 5 mm and ≥1 mm/s. The highest wall temperature corresponded to the position on the wall closest to the fiber tip, hence it moves longitudinally in parallel with the moving fiber tip. We concluded that heat conduction from the hot fiber tip is a contributing mechanism in endovenous laser ablation.

Introduction

Chronic venous insufficiency has a great impact on the quality of life of patients and is associated with considerable health care costs (up to 1% of total budget).[1] This common medical condition is now increasingly being treated by minimally invasive endovenous laser ablation (EVLA) because of excellent outcomes and low rates of complications and recurrences.[2] Although EVLA has demonstrated occlusion rates of 90% or more after several years of follow up studies,[3-7] multiple laser wavelengths, laser powers and pullback velocities are currently in use. Most likely, this wide variation of commercially introduced laser parameters is a consequence of the current uncertainty in the mechanism of action of EVLA. Despite consensus on the requirement of a thermally injured venous wall, the uncertainty relates to the mechanism or mechanisms that cause the thermal injury. Here, direct absorption of the scattered laser light by the venous wall,[8-9] steam bubble generation at the fiber tip and their subsequent propagation to, and distal collapse at, the wall,[10-11] and direct contact of the fiber tip with the wall,[12] have been suggested as contributing mechanisms. Notably, however, exceedingly high temperatures of the fiber tip during laser irradiation in blood have also been reported, at 810 nm,[9,13] 980 nm,[10] and 1,064 nm.[14] For a wavelength of 1,320 nm, such information is not available; however, the recent description of a serious complication[15] strongly supports the conclusion that very high temperatures had occurred. Briefly, an EVLA at 1,320 nm caused perforation of the right ventricle of the patient's heart by a 6 cm end of the catheter, identified because of therapy-resistant cardiac arrhythmia and subsequent removal by a thoracic surgeon. The treating physician's hypothesis was that the laser tip had been erroneously located inside—rather than outside—the catheter and that laser activation had explosively disconnected the tip of the catheter distal to the position of the fiber tip. Explosive disconnection was confirmed in an in vitro experiment in blood, but not in saline solution.[15]

Because the hot fiber tip has not been considered as a contributing mechanism in EVLA, we sought to evaluate whether heat conduction from the hot tip could cause irreversible thermal injury of the venous wall.

Methods

Hypothesis

Laser irradiation through a fiber held in blood causes the temperature of the laser tip to increase rapidly to temperatures of 800–1,300°C.[9-10,12-14] These high temperatures sometimes cause melting of the tip.[9] Such temperatures cause the generation of steam bubbles. These bubbles propagate towards the venous wall for several seconds, opposite to the direction

of fiber pullback, and collapse at the wall, centimeters distal to the tip. Further, such high temperatures also cause carbonization and even perforation of the venous wall when the fiber tip touches the wall.[9-12,14]

Thus, four mechanisms potentially contribute to EVLA efficacy. First, direct absorption of the laser light transmitted through the fiber tip, scattered by the blood and reaching the venous wall, which was previously discussed by Mordon and colleagues.[8] Second, heat diffusion from the hot fiber tip towards the venous wall, which consequences have not been considered so far. Third, steam bubbles propagating away from the fiber tip and subsequently collapsing at the venous wall. And, fourth, direct contact between the hot tip and the wall. In this paper we focus on the second mechanism of heat conduction from the hot fiber tip and show that it leads to irreversible injury of the (peri)venous wall at typical pullback velocities and vein diameters following tumescent anesthesia.

Heat conduction from a very hot fiber tip

We calculated the increased venous wall temperature resulting from heat conduction from the fiber tip. We assumed that this very hot tip could be represented by a sphere with diameter equal to the fiber diameter, which instantaneously reached steady state temperatures of up to 1,300°C[9-10,12-14] following the switching on of the laser power. The analysis was based on the following result from the standard textbook by Carslaw and Jaeger, describing known analytical solutions of problems of heat flow.[16] In the situation of a non-moving fiber tip, the temperature in a tube of venous blood with thermal diffusivity κ, at point A (representing any point on the venous wall), at distance R from the center of a sphere of radius a, t seconds after the switching of the surface of the sphere to V degrees K above 37°C, is

$$T(R,t) = 37 + \frac{aV}{R} \; erfc \left[\frac{R - a}{2 \sqrt{\kappa t}} \right] \tag{1}$$

where *erfc* is the complementary error function.

In the situation of a moving fiber tip with a pullback velocity of v mm/s, distance R is time dependent. At $t = 0$, we used the notion that the fiber tip starts at distance L_0 cm from point A (Fig. 1). Further, because the vessel wall now experiences a spatial–temporal varying temperature, heat conduction along the vessel wall takes place as well. However, because the time constant for heat conduction is quite long, estimated to be approximately 80 s (see Appendix), we neglected axial heat conduction along the vessel wall for this analysis.

Figure 1. Artist's impression of a fiber of radius a, inside a vein of radius r, pulled back with velocity v. "A" is an arbitrary point at the vessel wall at distance R from the centre of the fiber tip. The distance to the fiber tip from a certain position on the vein wall, R(t), which started at position L_0 at t = 0, relates to r and distance ($L_0 - vt$) as

$$R(t) = \sqrt{r^2 + (L_0 - vt)^2}$$

Results

Figure 2 shows some results for $\kappa = 1.4 \times 10^{-7}$ m²/s, a typical value for blood,[8] a = 0.2 mm, i.e., taken as equal to the radius of the fiber, $L_0 = 1$ cm, V = 1,073 K (800°C) or 1,273 K (1,000°C), a venous radius of r = 1.5 mm (assuming that the diameter of the treated vein is the diameter of the catheter, in our case 3 mm, caused by the tumescent anesthesia that increases the perivenous pressure), but also 2.5 mm (Fig. 3), the vein radius used in the experiments by Disselhoff et al.,[9] and close to the tube radius of 3 mm used by Proebstle et al.,[11] and v = 1 mm/s, 2 mm/s, and 3 mm/s. As an example (Fig. 2), at a velocity of v = 1 mm/s it takes 10 s for the fiber tip to propagate from the 1 cm starting distance to reach the minimum radial distance to point A, causing the maximum wall temperature at point A to be reached. For larger pullback veloci-
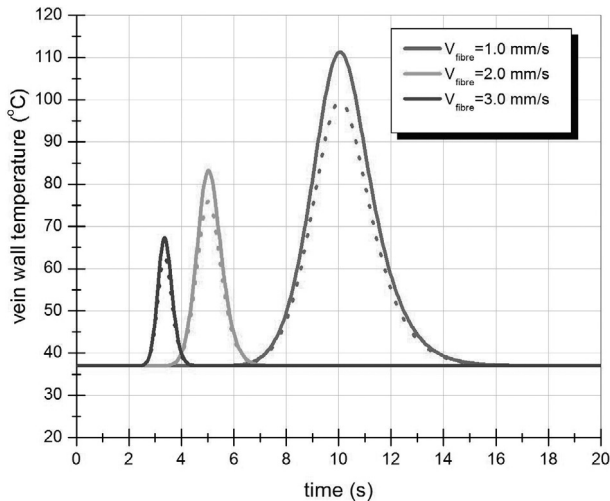
Figure 2. Vein wall temperatures due to heat conduction from the fiber tip, according to Eq. 1, plotted for various pullback velocities. Vein radius r = 1.5 mm. *Solid line T_tip = 1,000°C, dotted line T_tip = 800°C*
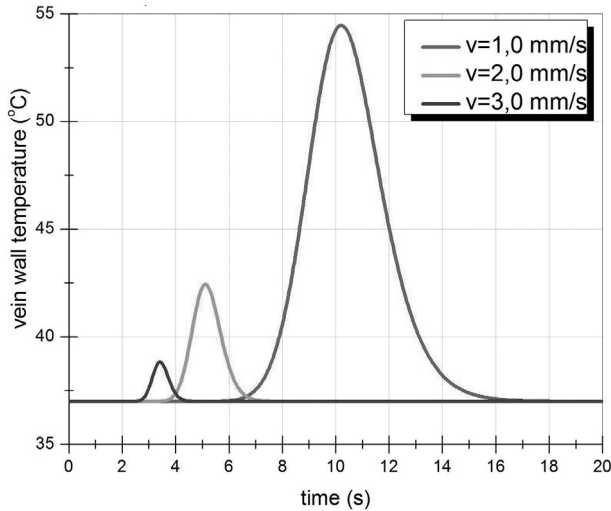
Figure 3. As Fig. 2, but now for a vein radius of $r = 2.5$ mm and $T_{tip} = 1,000°C$

ties, the time period that the hot sphere is closest to point A becomes increasingly shorter; thus, the maximum temperature becomes increasingly lower.

This mathematical model confirms the suggestion that the heat of the hot tip that diffuses to the vessel wall is sufficient to cause irreversible injury of the (peri)venous wall, reaching temperatures up to and above 70°C, provided that both the radial distance between fiber and wall and the pullback velocity are not too large (Figs. 2 and 3). It also suggests that the actual temperature of the hot tip is not very critical, provided sufficient laser power is used to reach at least 800°C.

Discussion

We have shown that heat conduction from a very hot tip kept in the center of the vein with realistic temperatures of 800–1,200°C causes irreversible injury of the venous wall under typical EVLA clinical conditions. These exceedingly high temperatures have been measured, or estimated, based on impressive events such as melting of the fiber tip[9] or explosive removal of the distal end of a catheter[15] and comprise the wavelength range of 810–1,320 nm. Although no information is currently available for wavelengths of 1,450 nm, we hypothesize that similar high temperatures are likely to occur, although at lower laser powers, based on the higher blood absorption coefficient (a factor of more than 10 higher than that at 1,320 nm).[17] Importantly, this mechanism achieves the highest wall temperature at the shortest distance between tip and wall (Figs. 2 and, 3), thus in radial direction perpendicular to the (moving) fiber tip. In contrast, steam bubbles generated at the hot tip move opposite to

the direction of fiber pullback over a distance of centimetres before collapsing at the venous wall (personal observation). Importantly, therefore, the moving bubbles do not interfere with radial heat conduction, and, in addition, the moment that steam bubbles collapse against the wall is significantly delayed (seconds) when compared with the moment of maximum venous wall temperature by heat conduction. In addition, the rate of steam bubble condensation is proportional to the temperature difference between the steam content of the bubble and the environment, and the significantly elevated wall temperature for a duration of seconds (Figs. 2 and 3) may explain the rather long life time of these bubbles (Dr. Cees W.M. van der Geld, Faculty of Mechanical Engineering, Eindhoven University of Technology, personal communication). Consequently, steam bubbles may be of secondary importance for EVLA efficacy. Nevertheless, it cannot be excluded that they are another contributing EVLA mechanism. Although Mordon et al.,[8] Disselhoff et al.[9] and Fan and Anderson[12] provided arguments against the thermal efficacy of steam bubbles, the further unravelling of the complex mechanisms of EVLA calls for identification of the thermal consequences of propagating and collapsing steam bubbles, a project in progress in our group.

Direct contact between vein wall and hot fiber tip certainly occurs, proposed to cause wall perforations and showing as carbonized particles on the wall, as was clearly demonstrated by, e.g., Disselhoff et al.,[9] Meissner et al.,[10] Proebstle et al.[11] and Weiss.[13] It was recently proposed as the primary mechanism of action by Fan and Anderson.[12] Nevertheless, we hypothesized that accidental contact alone cannot produce sufficient wall damage for subsequent closure of the total length of the vein. However, some clinicians include manual compression of the vein during laser therapy stimulating the draining of blood out of the vein as well as direct contact between fiber tip and venous wall. In such cases it is unclear whether enough blood is present to produce severe heating of the tip, and, also, direct interaction of the wall with the laser light may occur to a larger extent than without compression. In any case, our model was not intended to describe such procedures.

The mechanism of heat conduction explains why saline solution-filled vessels only showed injury at sites of direct laser light versus wall impact, whereas a homogeneously injured wall occurred in blood-filled vessels now caused by heat conduction from the very hot tip.[18] Our results in Fig. 3 imply that a vein radius of 2.5 mm and a pullback velocity of 2 mm/s, the experimental conditions used by Disselhoff et al., would produce insufficient temperatures at the vein wall, reproducing their observation that "the diffusion of heat into the surrounding tissue was minimal".[9] Laser power may be less critical, provided it is sufficient to reach tip temperatures of at least 800°C (Fig. 2). Unfortunately, however, the relation between laser power and resulting steady state tip temperature and to what extent tip blackening is involved[9-10,12] is currently incompletely understood.

In conclusion, heat conduction from the very hot fiber tip causes thermal injury of the venous wall under typical clinical conditions of pullback velocities and vein diameters. This mechanism thus is another contributing factor in EVLA. Steam bubbles moving away from the fiber tip have a delayed distal impact on the venous wall, implying that their potential efficacy may be secondary to the mechanism of heat conduction from the hot tip.

Appendix: time constant of axial heat conduction along the vessel wall

In a coordinate system that moves with the temperature profile, we have found, approximately, that heat conduction, proportional to the second spatial derivative of the temperature distribution, can be approximated as

$$\kappa \cdot \frac{\partial^2 \Delta T(x, t)}{\partial x^2} \approx - \frac{\Delta T(x, t)}{\tau} \tag{2}$$

where ΔT is the temperature increase above 37°C and τ is the time constant of heat conduction, which is given by

$$\frac{1}{\tau} \approx \kappa \cdot \left(\frac{\pi}{2} \cdot \frac{l}{x_0} \right)^2 \tag{3}$$

Here, x_0 is the width of the temperature profile along the vessel wall axis. This estimate implies that the temperature profile in the x-direction is approximated by a cosine function, i.e., $\cos[(\pi/2)(x/x_0)]$. From Fig. 2, we have $x_0 \approx 6$ mm, and with $\kappa \approx 1.8 \times 10^{-7}$ m^2/s, we find $\tau \approx 80$ s.

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Carbonized blood deposited on fibres during 810, 940 and 1,470 nm endovenous laser ablation: thickness and absorption by optical coherence tomography

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Abstract

Endovenous laser ablation (EVLA) is commonly used to treat saphenous varicosities. Very high temperatures at the laser fibre tip have been reported during EVLA. We hypothesized that the laser irradiation deposits a layer of strongly absorbing carbonized blood of very high temperature on the fibre tip. We sought to prove the existence of these layers and study their properties by optical transmission, optical coherence tomography (OCT) and microscopy. We analysed 23 EVLA fibres, 8 used at 810 nm, 7 at 940 nm and 8 at 1,470 nm. We measured the transmission of these fibres in two wavelength bands (450–950 nm; 950–1,650 nm). We used 1,310 nm OCT to assess the thickness of the layers and the attenuation as a function of depth to determine the absorption coefficient. Microscopy was used to view the tip surface. All fibres showed a slightly increasing transmission with wavelength in the 450–950 nm band, and a virtually wavelength-independent transmission in the 950–1,650 nm band. OCT scans showed a thin layer deposited on all 13 fibres investigated, 6 used at 810 nm, 4 at 940 nm and 3 at 1,470 nm, some with inhomogeneities over the tip area. The average absorption coefficient of the 13 layers was 72 ± 16 mm-1. The average layer thickness estimated from the transmission and absorption measurements was 8.0 ± 2.7 µm. From the OCT data, the average maximal thickness was 26 ± 6 µm. Microscopy of three fibre tips, one for each EVLA wavelength, showed rough, cracked and sometimes seriously damaged tip surfaces. There was no clear correlation between the properties of the layers and the EVLA parameters such as wavelength, except for a positive correlation between layer thickness and total delivered energy. In conclusion, we found strong evidence that all EVLA procedures in blood filled veins deposit a heavily absorbing hot layer of carbonized blood on the fibre tip, with concomitant tip damage. This major EVLA mechanism is unlikely to have much wavelength dependence at similar delivered energies per centimeter of vein. Optical–thermal interaction between the vein wall and the transmitted laser light depends on wavelength.

Introduction

Endovenous laser ablation (EVLA) is now commonly used as a minimally invasive technique to treat saphenous varicose veins. EVLA has a high success rate of over 90% after several years of follow-up studies and a minimal complication rate compared with traditional ligation plus stripping.[1] Despite the excellent performance of EVLA the exact mechanism of action is still not fully identified. This uncertainty may have stimulated the current, commercially driven proliferation of different laser wavelengths (810 nm, 840 nm, 940 nm, 980 nm, 1,064 nm, 1,320 nm, 1,470 nm), powers and pullback velocities. We hypothesized that improved knowledge of the mechanism of action of EVLA would stimulate the achievement of a consensus on the best laser method. This would reduce costs and improve clinical outcomes.

Several potential mechanisms of EVLA have been proposed: first, the optical–thermal response of the vein wall to scattered laser light;[2] second, the thermal response of the vein wall to condensing steam bubbles;[3] third, the direct contact between the hot fibre tip and the wall;[4-5] and fourth, the thermal response of the vein wall to heat diffusion from the hot fibre tip. The last of these mechanisms, recently proposed by our group,[6] is based on measured tip temperatures close to or exceeding 1,000°C,[7-8] sometimes causing melting of the tip.[5] We hypothesized that such high temperatures can only occur when a strongly absorbing layer of carbonized blood is deposited on the fibre tip -and thus concomitantly heated by the laser irradiation- during EVLA procedures.

To date, such layers have not been described, let alone their properties such as thickness, homogeneity, and transmission and absorption measured. We sought to show the existence of these layers, examine their properties and derive the relationships with EVLA parameters.

Materials and methods

Clinical laser procedures

The EVLA wavelengths used were 810 nm (Diomed), 940 nm (Diomed) and 1,470 nm (BioLitec ELVeS). All catheters used a bare fibre of 0.6 mm core diameter. The clinical EVLA procedures were performed in accordance with the standard protocols used in our clinic, including tumescent anaesthesia. Laser parameters (pullback velocity, power) were such that on average 50–60 J/cm vein was administered. At the end of the procedure, the fibre was carefully withdrawn out of the treated vein and stored in a box. No contact was made between the fibre tip and the wall of the box. The next day, the fibre was transported from the clinical site (Rotterdam) to the laboratory (Amsterdam) for the optical measurements.

Optical transmission measurements

The transmission coefficient (T) of the clinical fibre was defined as the light intensity transmitted by the fibre divided by the light intensity transmitted by an identical but unused clean fibre. Fibre transmission was measured over two wavelength bands (450 to 950 nm and 950 to 1,650 nm) using two different set-ups available in our laboratory. To measure the transmission between 450 and 950 nm a tungsten-halogen light source (Ocean Optics, DH-2000) was used. A commercial CCD spectrometer (Ocean Optics, USB4000) was used for wavelength selection and photo detection. To measure the transmission between 950 and 1,650 nm another halogen light source (Dolan Jenner, PL800) with a wavelength range of 400 nm up to 2,000 nm was used. Wavelength selection was achieved by a monochromator (Oriel Monochromators, Cornerstone 130 1/8 m) with a spectral resolution of 10 nm. A long-pass filter (Thorlabs, FEL0950) with a cut-on wavelength of 950 nm was implemented in front of the monochromator input slit to minimize the effect of high-order diffraction. The light intensity was detected by a photoreceiver (New Focus, model 2011) and the output signal of the photoreceiver was captured by a data acquisition card (National Instrument, USB-6009) and stored on a personal computer (Dell).

OCT imaging

A Santec swept source optical coherence tomography (OCT) system was used in this study (HSL 2000). The system is based on a Michelson interferometer that measures the amplitude
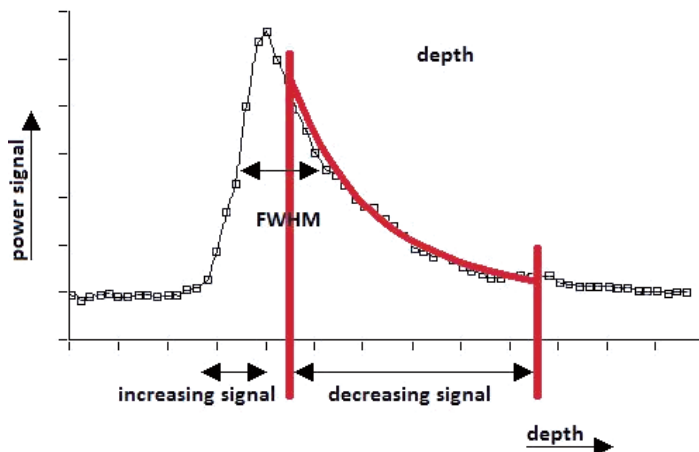
Figure 1. A typical deconvoluted OCT signal versus depth of a layer deposited on a fibre tip. The vertical axis is the amplitude signal and the horizontal axis is the depth. The red lines indicate the region of interest of the fit to Eq. 1. The maximum layer thickness, d_{max}, was determined from the full-width at half-maximum (FWHM). The distance between the pixels (white squares) is 4.3 μm, based on a layer of assumed refractive index of 1.5

of the light back-scattered from the sample.[9] The swept light source has a central wavelength of 1,310 nm and a wavelength band of 110 nm. The scan speed is up to 50 kHz. The axial resolution is determined by the coherence length of the source, which was 11 µm in air. The lateral resolution is determined by the confocal image properties of the system and was about 10 µm. A three-dimensional scan had $155 \times 400 \times 249$ pixels. Three-dimensional scans of the fibre tips were made to image the structure of the layers. A two-dimensional B-scan had $1,019 \times 4,000$ pixels. Two-dimensional scans where performed along lines over the fibre tip area versus depth to determine the attenuation coefficient and the thickness of the deposited layer. The attenuation coefficient of the layer was derived from the OCT data by fitting Beer's law to the averaged A-scan within the region of interest in the OCT image (Fig. 1). The starting point was chosen as three pixels past the specular reflection peak.

OCT signal analysis

The OCT signals were corrected for the noise level, defined as the average signal between pixels 10 and 30 before the specular reflection peak. Prior to fitting, all A-scans were aligned. We assumed that the spatial curve decay followed the first-order scattering approximation

$$A(z) \propto \exp(-\mu_a z) \tag{1}$$

Here, $A(z)$ is the back-scattered amplitude from depth z and μ_a is the absorption coefficient, here expected to be virtually equal to the attenuation coefficient (but see Discussion).

Deconvolution and absorption coefficient

Because the thickness of the layers was in the order of or only a few times greater than the axial resolution of the OCT system, deconvolution processing was considered necessary. The measured OCT signal (m[p], p denotes pixels, see Fig. 1) of the clinical fibre is the convolution of the "true" nondistorted signal (x[p]) and the impulse response (y[p]) of the system; hence, m[p] = x[p]*y[p], where "*" denotes the convolution integral operator. The impulse response was the OCT signal of the clean fibre. We implemented discrete deconvolution, deriving x[p] from the inverse Fourier transform of m[ω]/y[ω] where m[ω] and y[ω] are the Fourier transforms of m[p] and y[p], respectively.

To determine the absorption coefficient, an average of 4,000 A-scans was performed over a tissue depth of 100 µm of the fibre tip. For each fibre, an average of three scans, from different positions on the fibre tip area, was used to determine the absorption coefficient by fitting the decreasing deconvoluted part of $A(z)$ to Eq. 1 (Fig. 1).

Microscopy

Tips were detached from the fibre at a length of about 1.5 cm. They were cleaned for about 30 min in a strong acid and remains of the carbonized blood were manually removed by rubbing with paper tissues. The tip surfaces were viewed under a microscope and photographed.

Statistical analyses

ANOVA was used to compare the transmissions at the three EVLA wavelengths, and total energy administered versus wavelength and power. We used a multiple linear regression model to estimate the association between transmission and cumulative Joules administered after adjusting for wavelength. The Pearson correlation coefficients (r) were calculated between, respectively, mean thickness and maximum thickness of the layer and wavelength, total energy administered, and transmission. Significance was assumed if $p < 0.05$.

Results

A total of 23 clinical fibres were analysed. Table 1 shows the fibre number corresponding with EVLA wavelength, power, total delivered energy and transmission at 1,310 nm. Not all 23 fibres could be used for all optical measurements because not all equipment was always available the day after therapy.

Transmission measurements

Figure 2 shows the transmissions in the 450–950 nm wavelength band of 13 fibres, 4 used at 810 nm, 2 at 940 nm and 7 at 1,470 nm. The transmission spectra increased slightly with wavelength, in a manner quite similar for each EVLA wavelength. Of the 13 transmission spectra, 3 (fibres 12, 17 and 21) showed signs of oxyhaemoglobin absorption at 542 nm and 577 nm. We hypothesized that this behaviour was caused by deposited blood that remained on the tip, either from noncoagulated blood still present in the vein or from leakage onto the sheets covering the patient's leg during EVLA. Vaporization of the water out of the red blood cells between withdrawal and measurement the next day may have been the reason for the lack of the typical water absorption peaks at 1,230 and 1,450 nm.[10]

Figure 3 shows the transmissions in the 950–1,650 nm wavelength band of all 23 fibres. Each of the three EVLA wavelengths used showed virtually wavelength-independent transmission, with values between 0.33 and 0.72 at 1,310 nm, or 0.57 ± 0.10 (average ± SD).
Figure 3

**Table 1.** Fibre number, EVLA wavelength, laser power, total delivered energy, and measured transmission at 1,310 nm

Fibre number/patient	EVLA wavelength (nm)	Laser power (W)	Total delivered energy (J)	Transmission at 1,310 nm
1/18	810	14	1,700	0.46
2/17	810	14	519	0.71
3/16	810	14	1,097	0.58
4/15	810	14	508	0.58
5/25	810	14	446	0.72
6/26	810	14	2350	0.63
7/27	810	14	1963	0.57
8/28	810	14	1270	0.48
9/21	940	20	626	0.70
10/20	940	20	2,515	0.56
11/14	940	20	1,898	0.57
12/13	940	20	2,178	0.33
13/5	940	20	1,640	0.57
14/4	940	20	2,108	0.44
15/2	940	20	1,886	0.67
16/23	1,470	8	1,450	0.61
17/12	1,470	8	1,144	0.65
18/11	1,470	8	1,140	0.69
19/10	1,470	8	1,880	0.56
20/9	1,470	8	817	0.55
21/8	1,470	8	2,105	0.46
22/7	1,470	8	1,103	0.40
23/6	1,470	5	1,746	0.53
Average ± SD			1,482 ± 627	0.57 ± 0.10

Three-dimensional OCT scans

Three-dimensional OCT scans were made of 13 fibres, 6 used at 810 nm, 4 at 940 nm, and 3 at 1,470 nm. Figure 4 shows scans of fibres used at 810 nm (Fig. 4a, b), at 940 nm (Fig. 4c, d), at 1,470 nm (Fig. 4e, f), and of an unused clean fibre (Fig. 4g, h). Some OCT scans showed inhomogeneous structures.

Thickness and absorption coefficient of layers

The results for the 13 fibres are presented in Table 2. For convenience, we assumed a refractive index n of 1.5, first because the OCT scans lack clear Fresnel reflected peaks at layer–glass transitions, so the refractive index is probably close to the value of glass and second because
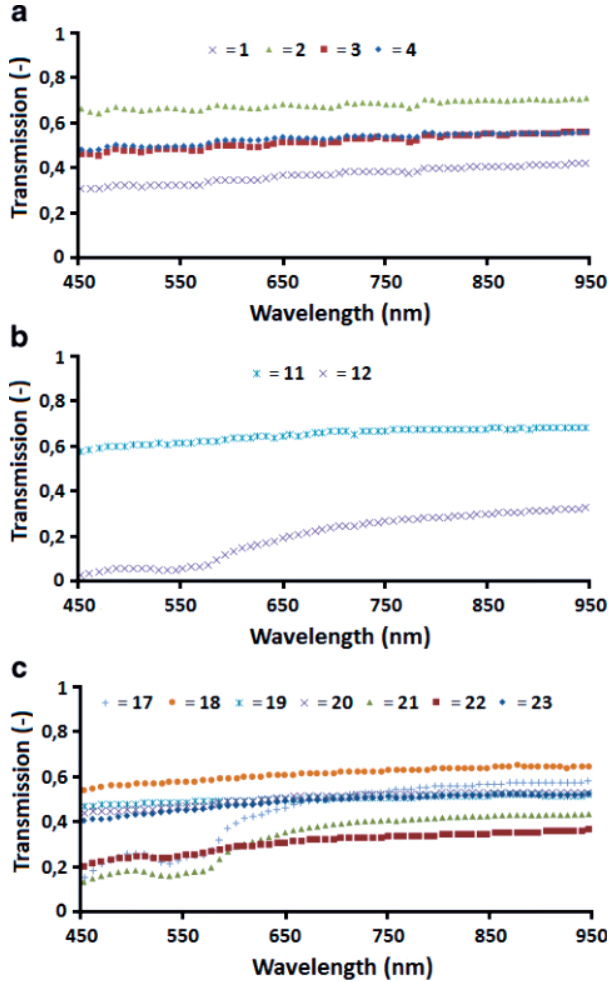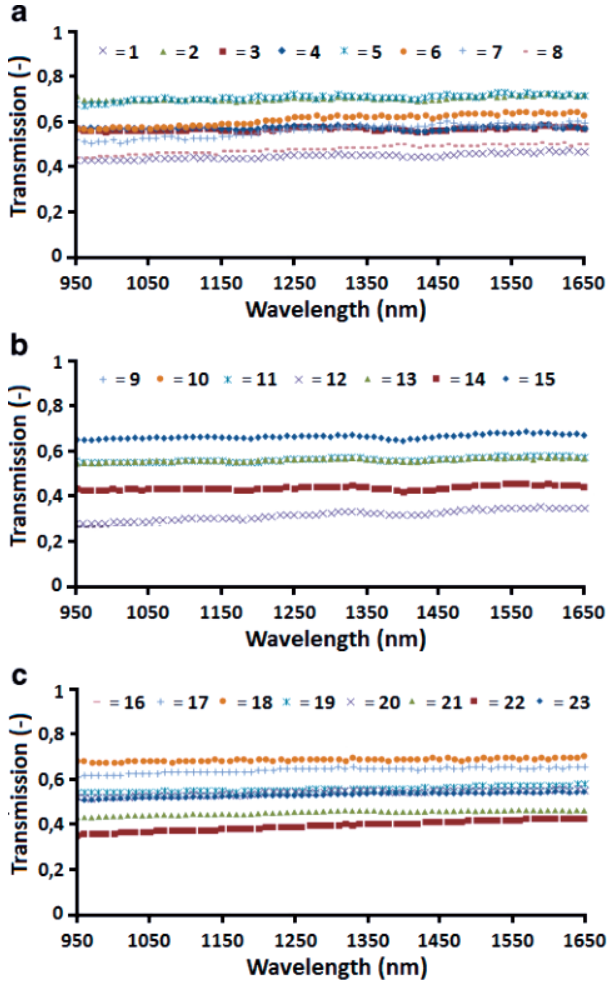
Figure 2. Transmission of 13 fibres in the 450 to 950 nm band. a Fibres 1–4 were used clinically at 810 nm. b Fibres 11 and 12 were used clinically at 940 nm. c Fibres 17–23 were used clinically at 1,470 nm

refractive indices of tissues with a low water content are about 1.5.[11] Then we obtained absorption coefficients between 36 mm^{-1} and 98 mm^{-1}, or μ_a=72±16 mm^{-1} (average ± SD). Due to the inhomogeneous structure of some of the layers, layer thickness was not always constant. For example, the layer depicted in Fig. 4e shows variable transparency, indicating variable thickness. The average thickness $\langle d \rangle$ of the layer can be calculated, because the measured transmission, T, and the measured absorption coefficient, μ_a, both at 1,310 nm, are related by Beer's law, i.e.

$$T = \exp(-\langle d \rangle \mu_a) \tag{2}$$

Hence,

Figure 3. Transmission of 23 fibres in the 950 to 1,650 nm band. a Fibres 1–8 were used clinically at 810 nm. b Fibres 9–15 were used clinically at 940 nm. c Fibres 16–23 were used clinically at 1,470 nm

$$\langle d \rangle = \ln(T^{-1})\mu_a \tag{3}$$

The average thickness $\langle d \rangle$ was between 4.4 and 13.5 µm, or $\langle d \rangle = 8.0 \pm 2.7$ µm (average ± SD). Due to the lack of a good criterion, the maximum thickness of the layer, d_{max}, was defined as the full-width at half-maximum of the two-dimensional OCT images (Fig. 1). The d_{max} was between 17 and 36 µm, or $d_{max} = 26 \pm 6$ µm (average ± SD).
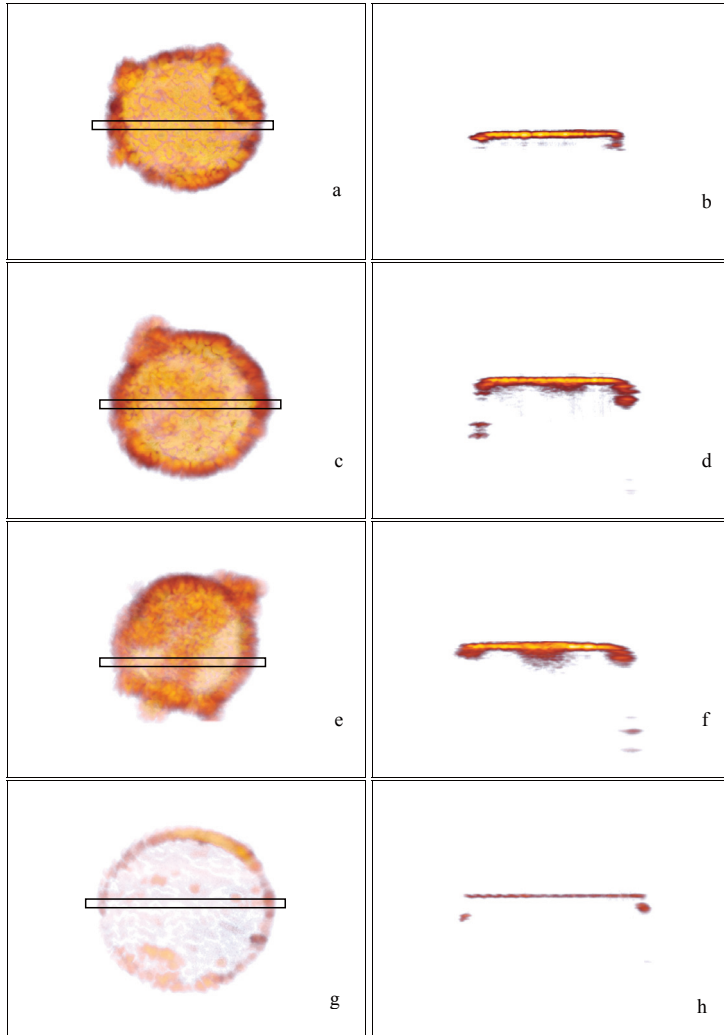
Figure 4. Three-dimensional OCT scans of clinical fibres: left column top views, right column cross sections (location indicated by the rectangles in the left images). a, b Fibre 3 used at 810 nm. c, d Fibre 6 used at 940 nm. e, f Fibre 13 used at 1,470 nm. g, h Unused fibre. The thickness (h) equals the OCT resolution of about 11 μm. The darker areas (left), corresponding with the deeper parts of the layers (right) are likely holes (as in Fig. 5), here filled with carbonized blood. These holes are the sites where d_{max} was measured

Microscopy

Three fibre tips were investigated, one for each EVLA wavelength. All showed a damaged, cracked irregular surface, two with clear depth irregularities. Figure 5 shows, as an example, an EVLA fibre used at 1,470 nm (fibre 20), with a severely damaged tip surface.
Figure 5
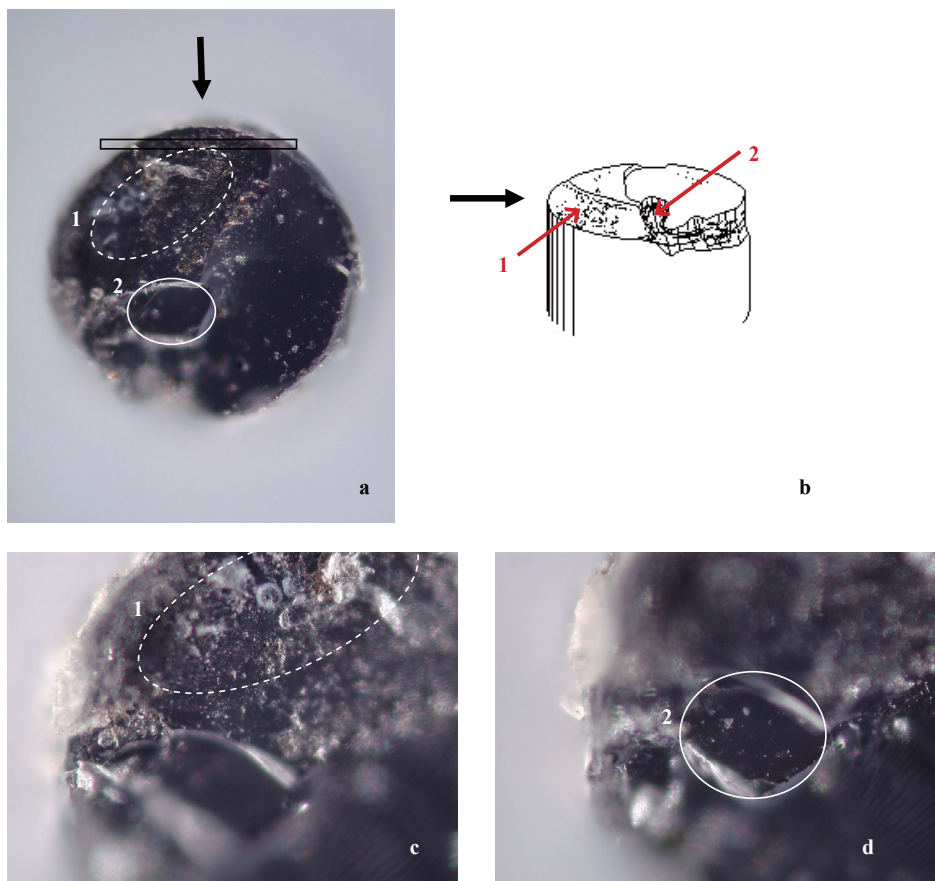
Figure 5. Tip of EVLA fibre 20 used at 1,470 nm photographed through a microscope; the fibre diameter is 0.6 mm. a Overview (×10). Two damaged areas (1 and 2) are indicated. b Artist's impression. Black arrow indicates the direction of view indicated in a. The red arrows point to areas 1 and 2. c Image focused on irregular and cracked area 1 (×20). d Image focused 29 µm lower than c on area 2 (×20)

Correlation between parameters

The 23 transmissions measured at 1,310 nm (Table 1) showed no difference between the three EVLA wavelengths studied (ANOVA, p=0.71). However, transmission was significantly negatively associated with cumulative Joules after adjusting for wavelength (β=−0.47, p=0.028). Total delivered energy showed no correlation with wavelength (β=0.003), nor with laser power (β=−0.24). This implies an approximately inverse relationship between power and irradiation time (r=−0.55). In the 13 OCT measurements, mean thickness was not correlated with EVLA wavelength (r=−0.08), but was correlated moderately with cumulative Joules (r=0.61) and excellently with transmission (r=−0.77). For the maximum thickness versus wavelength, Joules and transmission, the r values were similar (r=−0.08, 0.45 and −0.65, respectively). The absorption coefficient was not correlated with EVLA wavelength (r=−0.03). Further, mean

Table 2. Fibre number, EVLA wavelength, average absorption coefficient, μ_a, of three measurements per fibre, the average value of the layer thickness, $\langle d \rangle$ determined from Eq. 3, and the maximal thickness, d_{max}, determined from two-dimensional OCT images

Fibre number	EVLA wavelength (nm)	μ_a (mm^{-1})	$\langle d \rangle$ (µm)	d_{max} (µm)
3	810	72	7.6	19
4	810	80	6.8	23
5	810	52	6.3	27
6	810	44	10.5	28
7	810	90	6.2	31
8	810	74	9.9	31
9	940	78	4.6	17
10	940	66	8.8	23
11	940	80	7	25
12	940	82	13.5	36
16	1,470	72	6.9	22
17	1,470	98	4.4	26
19	1,470	52	11.2	28
Average ± SD		72±16	8.0±2.7	26±6

thickness was slightly negatively correlated with absorption coefficient ($r=-0.42$), which may suggest that a thinner layer has a more compact structure, but maximum thickness was not correlated with absorption coefficient ($r=0.02$).

Discussion

All 13 fibres available for OCT, from all three EVLA wavelengths used, had a thin layer of deposited carbonized blood, and neither the thickness nor the absorption coefficient of the layers correlated with the EVLA wavelength used. Further support for lack of EVLA wavelength dependence comes from the transmission spectra of all 23 fibres which also did not correlate with the EVLA wavelength. This strongly supports the assertion that the other ten fibres, also from the three EVLA wavelengths, had very similar deposited layers of carbonized blood on their tips. Even following EVLA at 1,470 nm (commercially introduced because of the hypothesized but unproven advantage of a very high absorption of the water component in blood and vein wall) a deposited layer was present with the same properties as the layers formed during EVLA at 810 and 940 nm. Some layers showed an inhomogeneous structure, implying that the average thickness, $\langle d \rangle = 8.0 \pm 2.7$ µm, differs from the maximal thickness, $d_{max} = 26 \pm 6$ µm.

The average absorption coefficient of the layers was μ_a=72±16 mm^{-1}. When irradiated with 5 to 20 W from 0.6-mm diameter fibres (irradiances, I, between 1,770 and 7,080 W/cm^2), such very high absorptions would indeed be expected to cause the very high tip temperatures reported, i.e. at 810 nm,[5,8] 980 nm,[12] and 1,064 nm.[7] At 1,320 nm, in vitro simulation of a serious complication of EVLA at 1,320 nm[13] strongly supports the conclusion that very high temperatures also occur during EVLA at 1,320 nm. Here, when the laser tip was located inside -rather than outside- a blood-filled catheter, explosive disconnection of the catheter occurred, whereas nothing happened when the catheter was filled with saline. Combining this observation with our findings that the layers deposited during EVLA at 1,470 nm are not different from the layers deposited at 810 and 940 nm warrants the conclusion that EVLA at 1,470 nm also causes very high temperatures at the fibre tip.

Consequences of these high temperatures were demonstrated by microscopy of some of the fibre tips. For example, Fig. 5 shows the severely damaged tip of an EVLA fibre used at 1,470 nm, with a large and very rough surface part and a smaller rather flat part where focusing required a 29 μm upward movement of the tip area, implying that this tip volume was probably ejected during the EVLA procedure. Similar surface pictures of the two other fibres were obtained (not shown). We therefore hypothesize that the darker regions in the left parts of Fig. 4, which correspond to the deeper dark parts in the right pictures, indicate holes in the tip surface, as in Fig. 5, but filled with carbonized blood. In these holes the maximal thickness, d_{max}, was measured.

The OCT scans and fits to Eq. 1 basically give the attenuation coefficients $\mu_t=\mu_a+\mu_s$, with scattering coefficient μ_s, implying that the true absorption coefficients are smaller than those given in Table 2. Unfortunately, we had no means available to determine the scattering coefficient of the layers. However, assuming that our layers can be compared with compacted soot which has approximately the density of charcoal, our data agree reasonably well with the 30 mm^{-1} at a wavelength of 10 μm quoted under such circumstances by McKenzie.[14] Scattering coefficients of carbonized tissue are not available to the best of our knowledge but a scattering coefficient of about 21 mm^{-1} has been reported for coagulated bovine liver at a wavelength of 980 nm.[15] If carbonized blood can be assumed to have a similar value, which however is not certain, then our absorption coefficients would be smaller by about 30%.

Several candidate mechanisms have been proposed for EVLA. First, our transmission measurements prove that laser irradiation remains available for direct heating of the vein wall by absorption of light as analysed by Mordon et al.[2] However, this mechanism can only account for a small proportion of EVLA efficacy because the layer of carbonized blood absorbs between 30% and 70% of the light exiting the fibre tip, except perhaps for veins emptied of blood (see next paragraph). Second, the presence of a thin, heavily absorbing layer on

the fibre tip during EVLA, shown in this study, strongly suggests that measured fibre tip temperatures of up to 1,200°C occur for any EVLA wavelength clinically in use. Thus, a major EVLA mechanism of action is the vein wall's thermal response to heat diffusion from the hot fibre tip, as we have previously proposed.[6] The remaining two mechanisms are consequences of these high tip temperatures. Third, steam bubbles developing at the tip which damage the vein wall centimeters away when condensing.[3,5] The importance of this mechanism remained unproven until recently, when our group identified the underlying physics of the exceptional efficacy of boiling vapour bubbles in transferring the heat from the hot fibre tip to the vein wall (van der Geld et al., submitted for publication). Finally fourth, direct contact between the hot fibre tip and the wall,[4-5] actually also contributing to the development of the black layer on the fibre tip.[16] The wall perforations resulting from this contact are thus likely with all EVLA wavelengths in use.

Recently, Mordon and associates advocated that EVLA should be performed in a vein lumen drained of its blood by, for example, leg elevation and manual compression.[17] Obviously, our results only apply to EVLA performed in blood-filled veins.

In conclusion, we found strong evidence that all EVLA procedures in blood-filled veins deposit a heavily absorbing and thus exceedingly hot layer of carbonized blood on the fibre tip, causing concomitant tip damage. This major EVLA mechanism is not likely to have much wavelength dependence at similar delivered Joules per centimeter of vein. Optical–thermal interaction between the vein wall and the transmitted laser light depends on wavelength.

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Endovenous simulated laser experiments at 940 nm and 1470 nm suggest wavelength independent temperature profiles

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Abstract

Background EVLA has proven to be very successful, but the exact working mechanism is still not fully identified. A better understanding of the mechanism of action may contribute to achieving a consensus on the best laser method and the most effective use of laser parameters, resulting in optimal clinical outcomes, maintaining high success rates with minimal adverse events. The aim of this study is to assess the impact of wavelength, pullback speed and power level on the endovenous temperature profile in an experimental setting.

Methods In an experimental setting, temperature measurements were performed using thermocouples. The experimental set-up consisted of a transparent box in which a glass tube was fixed. Different laser parameters (wavelength and power) and 2 different pullback speeds (2 and 5 mm/s) were used. Thermocouples were placed at different distances from the fiber tip. Validity of the experimental setting was assessed by performing the same temperature measurements using a stripped varicose vein. The maximal temperature rise and the time span that the temperature was above collagen denaturation temperature were measured.

Results The experiments showed that decreasing the pullback speed (2 mm/s) and increasing the power (up to 14 W) both cause higher maximal temperatures. The use of different laser wavelengths (940 or 1470 nm) did not influence the temperature profile.

Conclusions The results of our experiments suggest that the heat induction, which is responsible for vein occlusion in EVLA, is independent of laser wavelength.
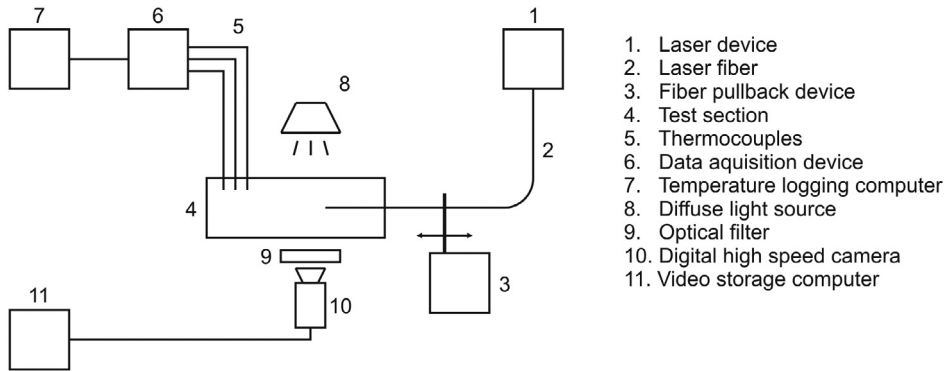
Introduction

Endovenous laser ablation (EVLA) is most frequently used as thermal therapy for saphenous varicose veins. EVLA is challenging traditional surgery as the gold standard for varicose vein treatment because of its very high success rate (>90%)[1], low rates of complications[2] and recurrences. Although EVLA has proven to be very successful, the exact working mechanism is still not fully identified, and the procedure is, therefore, not yet standardized (i.e., wavelength, pullback speed, and power). This lack of knowledge may have contributed to the commercially driven proliferation of different laser wavelengths and modifications such as fiber tips with radial emission of laser light.

Thermal injury to the venous wall is thought to be responsible for vein occlusion in endovenous thermal treatments. However, the exact mechanism of EVLA induced temperature rise is not well documented. Four main theories on the heat induction of EVLA have been proposed: (1) direct absorption of the scattered laser light by the vein wall[3-4], (2) heat transport by steam bubbles emerging from the hot fiber tip and heat release associated with their condensation[5-6](3) direct contact of the laser fiber with the vein wall[4,7] and (4) heat diffusion from the hot fiber tip.[8]
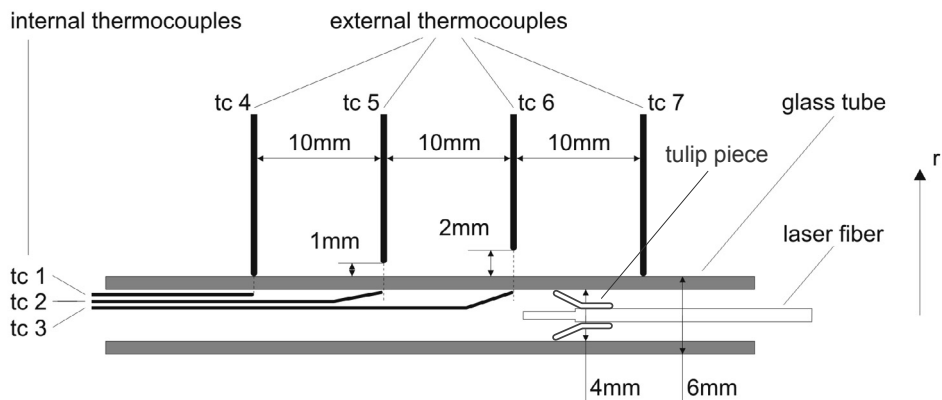
Knowledge about heat generation and heat transport is important. Two studies measured intravenous temperatures during EVLA (810 and 980 nm) of 61-140 °C and perivenous temperatures of 35-48 °C. [9-11] The effect of the various laser parameters that may affect the rise in temperature, such as wavelength, power level and pullback speed (which are not standardized in EVLA) is poorly documented. The aim of this study is to assess the impact of wavelength, pullback speed and power level on the endovenous temperature profile in an experimental setting.

Methods

The experimental set-up consisted of a transparent box in which a glass tube was fixed. From two sides the glass tube could be entered, so that the laser fiber and some thermocouples were introduced from opposite sides. The box was filled with water (room temperature) and the tube was filled with heparinized pig blood. Three thermocouples were positioned within the tube (tc 1, 2, 3) and 4 thermocouples were positioned at the outside of the tube and at different distances from the tube wall (tc 4, 7: 0mm, tc 5: 1mm, tc 6: 2mm) (Figure 1, 2). The internal thermocouples inside the tube were placed at three different positions because it was expected that the temperature profiles would differ for various axial positions due to development of the heat caused by the laser fiber moving from left to right. To assess

1. Laser device
2. Laser fiber
3. Fiber pullback device
4. Test section
5. Thermocouples
6. Data aquisition device
7. Temperature logging computer
8. Diffuse light source
9. Optical filter
10. Digital high speed camera
11. Video storage computer

Figure 1. Schematical representation of the experimental setup.

Figure 2. Position of the thermocouples and fiber with definition of the radial distance, r.

the validity of the experimental setting, a stripped great saphenous vein (GSV) was used for similar temperature measurements. In these experiments thermocouples were placed inside the vein and at the outer surface of the vein. This was done since positioning thermocouples at a certain distance from the outer surface was not possible due to flexibility of the vein.

Two laser wavelengths were used: 940 nm (Diode) and 1470 nm (BioLitec, ELVeS). To assure a centered position of the laser fibers in the tube (i.e., fixed distance to the thermocouples), the laser fibers (core diameter of 0.6 mm) were centered in the tube using a 'tulip' piece attached to the fiber tip.[12] We used a new fiber after two experiments, after one experiments the tip was cleft. The temperature experiments were repeated for two pullback speeds, v, (2 and 5 mm/s), two laser wavelengths, λ, (940 and 1470 nm) and several values for laser power, P (continuous mode). The measured output was different from the power setting. At 940 nm the measured power was 4 W at a power setting of 5 W, 10.5 W (setting 14 W), and 14.3 W (setting 20 W). At 1470 nm measured output was 3 W (setting 5 W) and 8 W (setting 14 W). An additional comparison was made using a measured power output of 8 W for both lasers.

Data for the 1470 nm laser were readily available at this power and for the 940 nm laser linear interpolation between measured data at 4 W and 10.5 W was applied. For each of the 10 possible combinations of parameters temperature measurements were repeated 5 times. To assess the endovenous temperature profile, ΔT_{max} and Δt_{den} were calculated from this graphical representation. ΔT_{max} was defined as the maximal temperature increase above the initial temperature (about 20°C), and Δt_{den} was defined as the time span that the temperature was above 50°C (i.e., temperature at which collagen denatures). This time span reflects the damage to the collagen of the vein wall, which is assumed to be required for successful thermal ablation.[13-15] Mean outcomes and standard deviation (SD) were calculated for ΔT_{max} and Δt_{den} for the measurements of the experiments that were 5 times repeated. The SD in figures 3 and 4 are presented with vertical error bars, the horizontal error bars indicate uncertainty in measurement location.

Statistical analyses

Continuous variables are presented as means with a standard deviation and were compared between groups using a Student t-test. We used SPSS 15.0 software (SPSS Inc, Chicago, Ill) and two-sided p-values were considered significant if <0.05.

Results

The results for ΔT_{max} are graphically depicted per wavelength (Figure 3) and per pullback speed (Figure 4). The time span that the temperature was above the threshold value for collagen denaturation (Δt_{den}) is listed in Table I.

Increasing the speed from 2 to 5 mm/s resulted in a decrease in ΔT_{max} for both wavelengths. In addition, higher pullback speed resulted in lower Δt_{den}. Increasing the power level from 4 W to 10.5 W resulted in higher ΔT_{max}, but only a minor effect on ΔT_{max} was observed for a further increment to 14.3 W in the 940 nm laser wavelength. However, Δt_{den} increased nearly linearly with increasing power (Table I).

Since the measured power value at the fiber output proved to be lower than the set values during the experiments (power measurements: sensor Ophir 30A (power accuracy ±3%), meter Ophir Nova), with differences depending on the laser used, an additional comparison was made using a measured power output of 8W for both lasers. Data for the 1470 nm laser were readily available at this power and for the 940 nm laser linear interpolation between measured data at 4 W and 10.5 W was applied. Figure 5 shows that variations in ΔT_{max} due to wavelength variation can only occur within a distance of about 2 mm from the line over
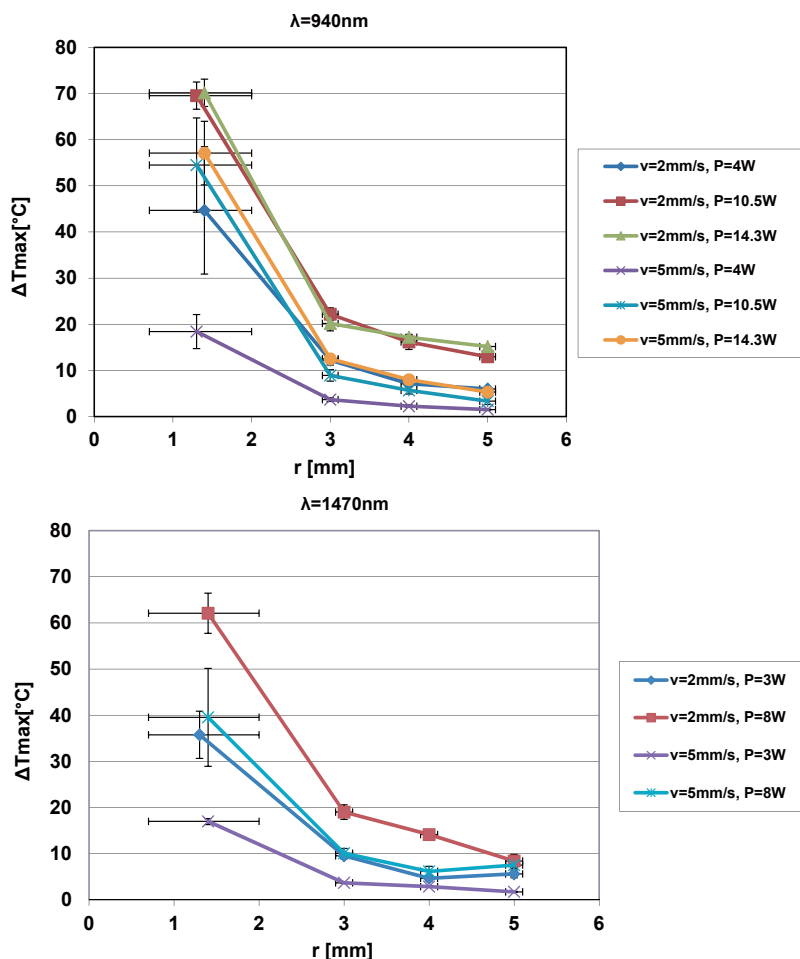
Figure 3. ΔT_{max} as a function of distance from the fiber tip for combinations of power (output) and pullback speed, left for 940 nm and right for 1470 nm.
P, Power; W, watt; v, speed; r, radial distance.

Table I. Values for Δt_{den} (seconds), mean ± SD for three different power outputs* and two pullback speeds.

	4W[+]	3W[+]	10.5W[#]	8W[#]	14.3W[^]
			v = 2 [mm/s]		
r[mm]	940	1470	940	1470	940
2	2,6±2,9	2,3±1,5	8,3±1,4	9,7±0,8	9,6±1,8
			v = 5 [mm/s]		
	4W[+]	3W[+]	10.5W[#]	8W[#]	14.3W[^]
r[mm]	940	1470	940	1470	940
2	0,1±0,1	0,0±0,1	2,4±1,5	1,5±1,4	3,7±1,5

*Power output differed from power setting:
[+] power setting 5W; [#] power setting 14W; [^] power setting 20W

v=2[mm/s]

Legend:
- λ=940nm, P=4W
- λ=940nm, P=10.5W
- λ=1470nm, P=3W
- λ=1470nm, P=8W

y-axis: ΔT_{max}[°C]
x-axis: r[mm]

v=5[mm/s]

Legend:
- λ=940nm, P=4W
- λ=940nm, P=10.5W
- λ=1470nm, P=3W
- λ=1470nm, P=8W

y-axis: ΔT_{max}[°C]
x-axis: r[mm]
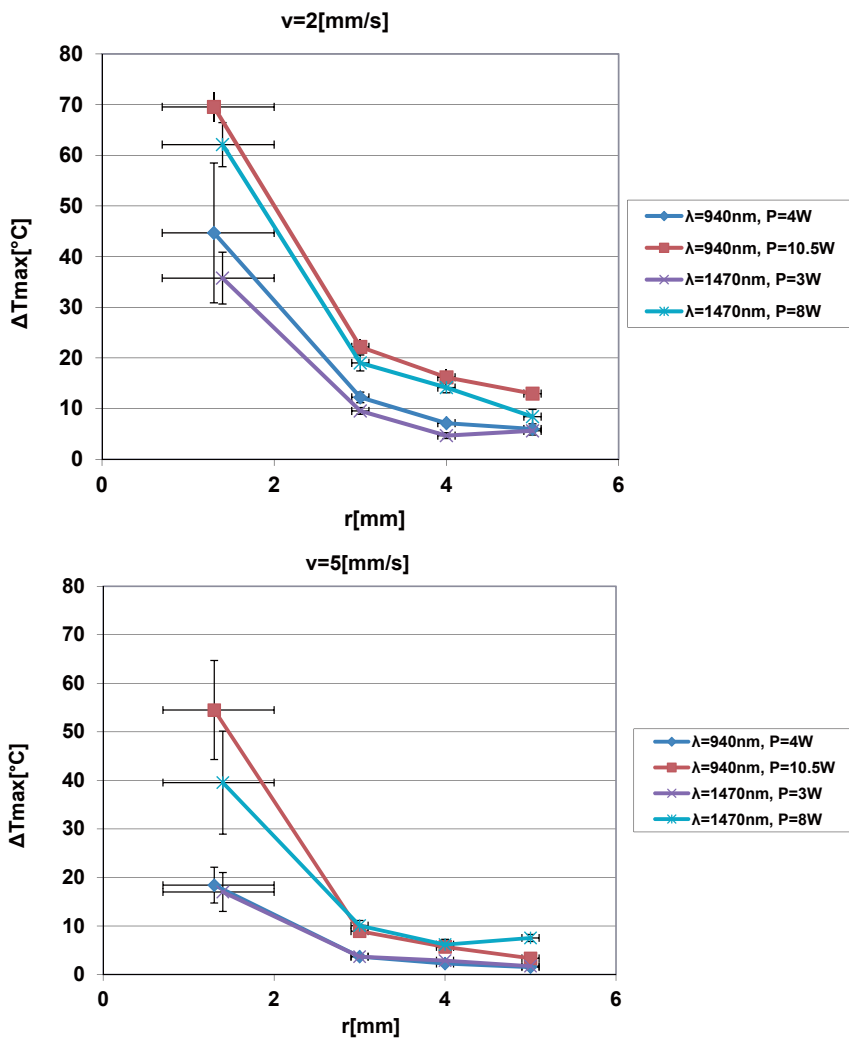
Figure 4. Comparison between wavelengths of ΔT_{max} at various power (output) levels and pullback speeds (v=2mm/s and v=5mm/s).
P, Power; W, watt; v, speed; r, radial distance.

which the laser tip is moving. More and more accurate measurements are required to give conclusive results regarding the wavelength dependency of the time-dependent temperature field around the fiber. The applied laser wavelength (940 nm or 1470 nm) had only little effect on ΔT_{max}.

Figure 6 shows the temperature results using a varicose vein (GSV). Although the obtained maximum temperatures were higher than the temperatures in the glass tubes, the differ-
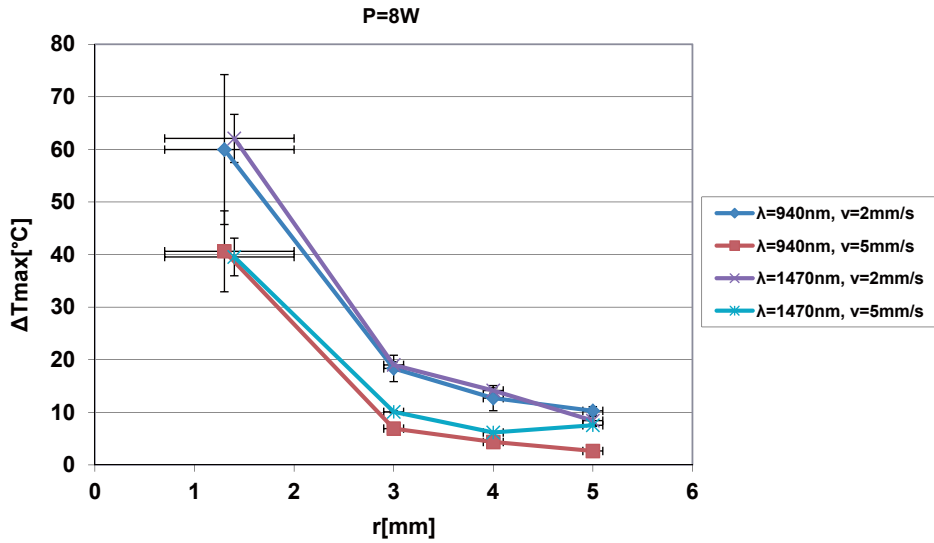
Figure 5. Peak temperature values interpolated at 8 W.
P, Power; W, watt; v, speed; r, radial distance.
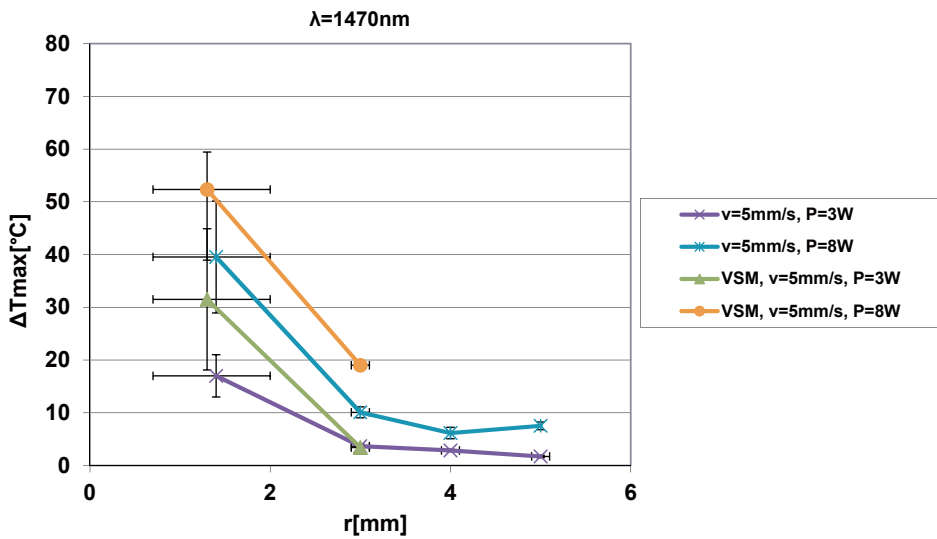
Figure 6. Comparison of ΔT_{max} for experiments with a great saphenous vein and a glass tube.
P, Power; W, watt; v, speed; r, radial distance.

ences were not statistically significant for the combinations of different laser settings and distances to the laser tip, except for the 8 W, 5 mm/sec at a distance of 3 mm (p=.02).

Discussion

Our simulated experiments of EVLA confirmed that pullback speed and power level both influence the temperature profile. We showed that only combinations of laser power and pullback speed that supply a relatively high administered energy per cm resulted in substantial Δt_{den} values. At 940 nm, ΔT_{max} and Δt_{den} increased when the power was increased from 4 W to 10.5 W and at 1470 nm, ΔT_{max} and Δt_{den} increased when the power was increased from 3 W to 8 W. However, at 940 nm, when further increasing the power to 14.3 W, only the Δt_{den} further increased and ΔT_{max} did not. This means that further increasing the power to 14.3 W at 940 nm may cause more damage to the vein wall. At 1470 nm, this experiment could not be performed because the power setting was limited to 14 W. The stagnation in maximum temperature is explained by noting that the maximum temperature approaches the boiling point, which limits further increase of temperature. Only combinations of power level and pullback speed that supply a relatively high administered energy (approximately >40 J/cm) per cm result in substantial Δt_{den}. It was not our aim to propose the appropriate energy dosing based on our experiments. Ideally, this should be based on a comparative randomized trial using different laser parameters studying effectiveness and side-effects. However, based on our experimental data, we could hypothesize that for effectiveness at least 8 W in combination with a pullback speed of 2mm/s should be administered independent of laser wavelength. To prevent side-effects it seems logic to prevent vein wall perforations by preventing direct contact of the laser tip with the vein wall, for example by using a tulip piece around the tip.

The most important conclusion drawn from the experimental results is that the temperature profiles of 940 and 1470 nm laser wavelengths are virtually identical at equal pullback speed and power. The wavelengths used in this study cover the clinically applied range of wavelengths to a large extent. Light at 940 nm is primarily absorbed by hemoglobin with about 0.16 mm^{-1} blood absorption coefficient, very comparable to the 0.12 to 0.17 mm^{-1} blood absorption coefficients between 810 and 1064 nm[16], and light at 1470 nm primarily by water. Since the resulting temperature profiles are virtually identical, this suggests that EVLA treatments are virtually wavelength independent at equal powers and pullback speeds. Consequently, possible differences between different EVLA studies can unlikely be explained by different laser wavelengths but rather by differences in other laser parameters such as pullback speed and power.[17]

In addition to virtually identical ΔT_{max} and Δt_{den} for equal power and pullback speed for both 940 nm and 1470 nm laser wavelengths, the extreme temperature near the laser fiber tip is likely to be comparable as well. In a recent study, the tips of fibers used for 940 nm and 1470 nm were both damaged suggesting temperatures of more than 800°C.[18]

In the experiments with a varicose vein, peak temperatures were higher, but not statistically significant, than these measured in the glass tube. We hypothesize that the thermocouples were located closer to the fiber tip in the varicose vein because the vein might have been compressed and contracted during the experiments. A thermocouple location of only 0.5 mm closer to the fiber tip would already explain the increase in maximum temperatures in figure 6. Subcutaneous tissue and water have similar heat diffusivity. More importantly, also the tube material has a heat diffusivity of about 0.16×10^{-6} m²/s. Two significant transport mechanisms of heat, diffusion and radiation, are therefore virtually the same in actual veins and in the mock-up we employed. Altogether, the findings in the varicose vein and glass tube were very comparable confirming the validity of the experimental setting of a glass tube. The latter is also more suitable for the performed measurements because of its constant shape and position, yielding better reproducible measurement conditions.

Our results are in line with a previous study in which we showed that fiber tips after EVLA had a carbonized layer of blood on the tip and destruction of the fiber glass was visible, suggesting that the temperature rise close to the fiber tip is high. These results were also independent of laser wavelength. The carbonized layer on the fiber tip absorbed between 30% and 70% of the laser light emission suggesting that heat diffusion is a major mechanism for EVLA, independent of wavelength.[18] This observation also supports two other temperature-related mechanisms, namely steam bubble formation and direct contact of the fiber tip with the vein wall, since both mechanisms are based on exceedingly high fiber tip temperature.

Conclusions

The findings of this study are that increasing power (up to 14 W) and decreasing pullback speed (2 mm/s) result in higher peak temperatures. Only a relatively high administered energy per unit length results in high enough temperatures to cause collagen denaturation. In addition, wavelength is not important for the temperature profile in EVLA. These observations suggest that the working mechanism of EVLA is independent of laser wavelength and thus independent of the target (Hb or water) of the laser. In future studies, standardized clinical parameters based on this study could be applied and tested in a randomized clinical trial. A better understanding of the mechanism of action may contribute to achieving a consensus on the laser settings resulting in an optimal risk-benefit ratio (high effectiveness, with minimal adverse events).

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Treatment of incompetent perforating veins using the radiofrequency ablation stylet: a pilot study

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Abstract

Background Although the role of incompetent perforating veins (IPV) in chronic venous insufficiency remains controversial, they are often treated by surgical or by minimal invasive techniques.

Objectives To describe the procedure of radiofrequency ablation (RFA) of IPV and to evaluate its short-term effectiveness and safety.

Methods In a clinical pilot study, 14 IPV in 12 patients were treated with a radiofrequency stylet. After three months, ultrasound (US) examination was used to assess anatomical success rate and exclude deep venous thrombosis. Also, self-reported side-effects were investigated.

Results Of the 14 treated IPV, nine (64%) were obliterated on US examination and the others showed remaining reflux. Two patients reported localized paresthesia, but no deep venous thrombosis was recorded.

Conclusion RFA of IPV may be a promising procedure, but patient and incompetent perforator vein selection is important and further standardization of the procedure is required. Comparative clinical trials between RFA and other therapies are warranted.

Introduction

By perforating the fascia generalis, about 150 perforating veins (PV) in the lower extremity connect the superficial with the deep venous system (reviewed by Van Neer *et al.*).[1] PV larger than 1 mm diameter have valves and appear to function as pressure valves when high pressures occur in the muscular compartment and avoid an outward flow from the deep to superficial system. Incompetent PV (IPV) show reflux on ultrasound (US) examination of more than 0.5 second and often have a larger diameter (Figure 1). Because of its close association with deep or superficial venous incompetence, it is difficult to assess the contribution of isolated IPV in the development of chronic venous insufficiency (CVI).

Because of the controversial role of IPV in CVI, the need to treat IPV remains somewhat unclear.[1-2] Some authors suggest that PV are part of a compensatory mechanism in venous return and have shown that selective ligation of IPV did not improve venous haemodynamics. The increased venous limb volume diameter is correlated with the largest IPV diameter and may be responsible for and precede IPV development.[3] In clinical practice, IPV have often been treated in conjunction with the treatment of the superficial venous system.[4-5] The most traditional therapy of IPV is surgical subfascial ligation or subfascial endoscopic perforator surgery (SEPS).[1,6-8] Surgical ligation and, even more, Linton's procedure and its modifications leave a noticeable scar and have a high complication rate such as wound infection, nerve injury and postoperative pain, especially in patients with CVI-induced skin changes (≥C4 level of clinical, aetiological, anatomical and pathological elements [CEAP] classification).[9] Because the incision made in SEPS is remote from the affected skin, wound infections are
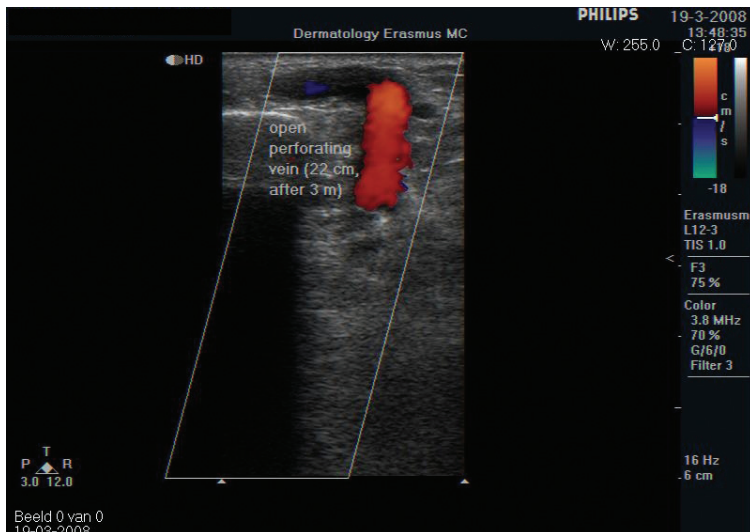
Figure 1. Incompetent perforator vein on ultrasound

less frequent; however, this technique has a slow learning curve and paratibial IPV and those of the upper leg are not eligible for this technique, which may explain why SEPS is not commonly accepted after its introduction. The percutaneous ablation of perforators (PAP) comprises techniques that are minimally invasive (i.e. no skin incision, local aesthesia and performed in an outpatient setting), are US-guided and can be easily repeated if necessary.[10] For more than 30 years, liquid sclerosant and more recently foam sclerosant have been used in the treatment of IPV with or without US guidance. US-guided sclerocompression therapy (UGST) of IPV (with foam) is a straightforward, swift and inexpensive procedure and open clinical studies suggest an efficacy of about 75–90%.[11-12] The disadvantages of UGST of IPV are the lack of standardization (e.g. percentage and volume of sclerosant and type and duration of compression after treatment) and uncontrollable distribution of the injected sclerosant. Therefore, in addition to the IPV, it is likely that the superficial venous system may occlude. Another complication of UGST may be the inadvertent injection of foam in a satellite artery with subsequent necrosis. Two more controlled PAP options are endovenous laser ablation (EVLA) and radiofrequency ablation (RFA). EVLA has been reported to be successful in the treatment of IPV in several small case series.[13] To our knowledge, laser fibres and disposables used to treat saphenous varicose veins were used and no proprietary EVLA catheter or system to treat IPV is available yet. In a venous forum abstract, Whiteley *et al.*[14] have performed many IPV ablations by using the saphenous RF probe and reported a 93% occlusion rate after one year. Subsequently, VNUS Closure® developed the radiofrequency stylet (RFS), which is a rigid RF catheter designed to treat IPV.[15] Although the Food and Drug Administration approved this device in 2004, relatively few studies have reported on its use, except for abstracts of the Society for Clinical Vascular Surgery (SCVS) and unpublished case series.[16-17] One study showed 100% procedural success, a decreasing occlusion rate in time (91% were reflux free but 56% were patent after 1 year) and no complications in less than 40 IPV treated with RFS. Another open VNUS sponsored study demonstrated that 31/34 of the IPV that were treated with 'intravascular' RFS were occluded after three weeks. 'Extravascular' treatment of 63 IPV yielded 'a significantly lower occlusion rate'. Two tibial vein thromboses occurred.

In this pilot study, the RFS procedure is described and its short-term efficacy and safety in 14 IPV after three months are reported.

Methods

Patients

In this pilot study, patients with one or more symptomatic (e.g. painful) IPV (reflux on US >0.5 second) with a diameter of at least 4 mm, with C2–4 according to the CEAP classification,

Table 1. Demographic and clinical characteristics of study population

Identification		Demographics		Phlebological status	Incompetent perforating vein (IPV)		Outcomes after 3 months		
Patient no.	Vein no.	Gender	Age (years)	'CEAP' Classification	Localization: Distance (cm) and site	Diameter (cm)	Anatomical success†	Symptom reduction	Self-reported side-effects
1	1*	Female	67	C2	33 Right	0.5	+	+	Paresthesia
2	2*	Female	28	C3	37 Right	0.4	+	+	-
3	3*	Female	57	C4	23 Right	0.4	-	-	Paresthesia
4	4*	Female	66	C3	13 Left	0.4	+	-	-
5	5*	Female	53	C5	67 Left	0.6	+	+	-
6	6	Male	74	C2	22 Left	0.5	-	+	-
7	7	Male	77	C3	21 Right	0.4	-	-	-
8	8	Male	83	C3	37 Left	0.5	-	+	-
	9			C3	24 Left	0.7	+	+	-
9	10	Female	67	C2	20 Left	0.4	+	-	Localized pain
10	11	Female	35	C2	18 Right	0.4	+	+	-
11	12	Female	49	C4	18 Left	0.5	+	+	-
12	13	Male	75	C4	39 right	0.4	-	-	-
	14			C4	32 Left	0.4	+	+	-

*4 cc anesthesia and turning 90 degrees every minute and the remaining IPV (vein no. 6 to 14) were treated using 8 or more cc anesthesia ultrasound-guided and without turning every minute
†Obliteration and absence of flow on ultrasound examination
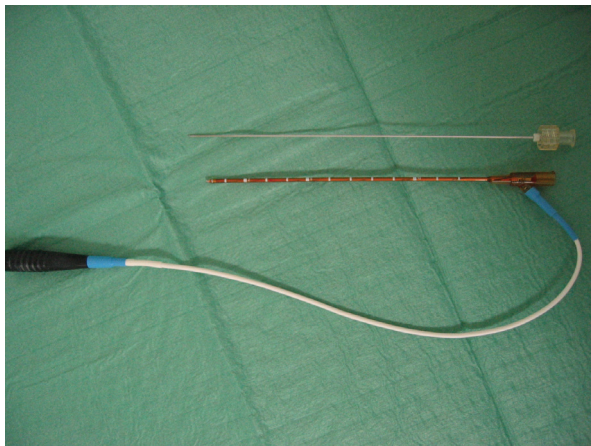

Figure 2. Diameter of incompetent perforator vein on ultrasound

were included (Table 1, Figure 2). Of the leg to be treated, the great saphenous vein (GSV) and small saphenous vein (SSV) had to be competent or successfully treated prior to the RFS procedure.

Procedure

The procedures were performed in an outpatient setting in an academic, tertiary hospital by dermatologists specialized in (minimal invasive) phlebological procedures. The rigid RFS catheter, which has two electrodes on the distal part of the shaft (with a thermocouple) and a removable needle trocar, was used (Figure 3). Before inserting the probe, the functionality of the RFA electrodes was tested by measuring an impedance of about 100 ohm of an activated catheter in physiological water. US guidance (Phillips EnVisor HD) was used to locate and select a non-tortuous part of the IPV, which are often curvilinear and angulated, in standing position. After local lidocaine anaesthesia, with the patient now in the horizontal position, a small skin incision of about 2 mm was made to directly puncture the IPV and the tip was positioned endovenously at or just below the level of the fascia generalis (>0.5 cm from the deep venous system) under US guidance in longitudinal view (Figure 4). At 4 W power, the thermocouple on the electrodes was at about 37°C and the level of impedance was between 250 and 400 ohm. Using a syringe, (tumescent) anaesthesia was administered. In the first four sessions, we followed VNUS Closure's protocol and applied 4 cc of lidocaine solution blind around the tip of the catheter, which caused a temperature drop to about 30°C as the solution was administered around the tip. The activated RFS was rotated to four different positions, each for one minute of treatment (total treatment time of 4 minutes at 85°C), while local pressure was administered with the US probe. In subsequent sessions, this protocol was changed. Instead, after administering 8–12 cc of local anaesthesia under US guidance, the RFS remained fixed for four minutes in the same position under local pressure (Figure 5). In some cases, it was possible to repeat the procedure in the same IPV after withdrawing the catheter 1 cm. The rationale of these two deviations from the original protocol was the observation that two-fourths of patients treated in the first session presented with localized paresthesia just below the RFS-treated PV. The cause of this RFS-induced nerve injury might have been insufficient volume of tumescent anaesthesia, which should also protect the perivenous tissue by cooling it and the frequent manipulation of the catheter during the procedure. In the first sessions, we noted that the impedance relatively often increased to values above 500 (somewhere in the range of 2000) suggesting that the tip of the catheter was positioned extravascularly. When the latter occurred, the RF was inactivated and the tip was repositioned under guidance of the US and the impedance level. However, this may have played a role in the development of the observed neurological damage. After the procedure, local manual pressure was applied at the treated site for about one minute and medical elastic compression stockings were not advised.

Figure 3. Radiofrequency ablation stylet

Figure 4. Visualization of the needle inside the incompetent perforator vein

Figure 5. Ultrasound visualization during treatment

Outcomes

After three months, US examination was performed to assess anatomical success (i.e. obliteration of the PV and absence of flow) of the procedure. Patients were asked to rate whether their symptoms related to the treated PV had remained the same, increased or decreased. Self-reported side-effects were documented.

Results

The demographic and clinical characteristics of the study patients are presented in Table 1. Four patients were classified as C2 of the CEAP classification, four as C3, three as C4 and one as C5. Of the included patients, six had a history of GSV therapy and four of SSV therapy prior to the RFS procedure. Of the included IPV, most connected the posterior accessory GSV with the posterior tibial veins (Cockett's PV) but paratibial PV and a Hunter's PV of the thigh were also included. All included IPV were treated using RFS (i.e. 100% procedural success, defined by a technically correct procedure with the perforator not showing flow directly after the procedure). During the procedure, patients did not report any discomfort. After three months of follow-up, nine of 14 treated IPV were occluded (64%) and the other five showed reflux on US examination. Three months after therapy, the effect of RFS on patients' symptoms varied considerably (Table 1). No deep vein thrombosis (DVT) was noted. Two patients reported localized paresthesia in the lower leg; this paresthesia entailed loss of sensibility in a 1–4 cm^2 area around the place of needle puncture. Six months after the procedure, these two patients reported a continuation of their paresthesia by telephone.

Discussion

RFA and EVLA are promising new techniques for the controlled ablation of IPV, but have not yet been well standardized, documented and studied. In this pilot study, a success rate of 64% of RFS in the treatment of IPV is low compared with previous open studies.[14,16-17] Because of the relative poor reporting of the available case series, which were often abstracts, it is difficult to explain the observed difference.[14,16-17] However, better results may be expected, due to a learning curve, as these were the first patients we treated with the RFS. In most patients, we were unable to treat IPV at two locations 1 cm apart because of the tortuous tract of the included IPV, which may explain some of the failures, and suggest that an optimal patient and IPV selection increases the success rate.

Although some surgical complications can be avoided by PAP, these techniques may be associated with specific complications such as DVT and cutaneous paresthesia, and have a relatively long learning curve.[10,16-17] Although dermatologists who were experienced in obtaining percutaneous access to varicose veins including IPV performed the RFA procedures in this pilot, it was challenging to position the stylet because of the relatively small size and the angulated tract of the IPV and the large size of the catheter (6 French). From our experience, it seems important to pass the RFS at least a few centimetres in the IPV, to avoid the fixed electrodes being 'pushed' extravascularly by the contracting IPV after generating the heat. Positioning the RFS tip extravascularly and/or above the fascia decreases the likelihood of success and may increase the risk of nerve injury.[17] In 2/14 cases paresthesia was reported, which is in accordance with the available literature that suggests that between 9% and 19% of patients develop (transient) paresthesia.[16] In accordance with our observation, the likelihood of this complication is higher in the treatment of IPV below the knee because the saphenous nerve travels superficial of the saphenous compartment and is thus more susceptible to heat-induced injury. Also, along with PV run a small artery and a nerve. Ample and well-positioned tumescent anaesthesia, a long enough intravascular part of the RFS and a minimum of RFS manipulation may decrease the risk of RFS-induced paresthesia.

Indications to treat IPV are that they are symptomatic, contribute to CVI and/or induce skin changes in their close proximity. Although the role of IPV in CVI is somewhat controversial, studies showed that about two-thirds of recurrent varicose veins and limbs with skin changes have IPV in conjunction with superficial or deep venous insufficiency. In addition, several studies showed benefit of interruption of IPV.[6-7,18] Unfortunately, there are no randomized clinical trials that assess the effect of IPV therapy compared with conservative therapy or compare different (minimally invasive) treatment options. Compared with surgery, the PAP procedures are especially indicated in patients with IPV with overlying skin changes due to CVI such as lipodermatosclerosis and leg ulcers. It could be argued that EVLA and RFA of the IPV are more likely to spare the saphenous veins because of their controlled approach compared with UGST. But because UGST is swift, inexpensive and has a low complication risk, large randomized trials are warranted to compare these three percutaneous therapies of IPV.

Acknowledgements

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Proof-of-principle study of steam ablation as novel thermal therapy for saphenous varicose veins

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Abstract

Introduction During the last decade, thermal ablation techniques such as endovenous laser ablation have been challenging the position of traditional surgery for the treatment of saphenous varicose veins. The newest method of thermal ablation is pulsated steam, which works by heating the vein with steam at 120°C. This study assessed the effectiveness of steam ablation of varicose veins in sheep and in humans.

Methods The safety of the procedure in sheep was assessed by cardiovascular monitoring during treatment. We used ultrasound imaging to examine occlusion of the veins. Changes in treated veins were examined microscopically. In a pilot study, 20 veins in 19 patients with insufficiency of the great or the small saphenous vein were treated with pulsated steam ablation. Anatomic success, patient satisfaction, and complications were investigated for 6 months after the procedure.

Results All veins in the sheep were occluded. No cardiovascular changes occurred during treatment. Histologic examination of treated veins showed typical changes of the vein wall, such as disappearance of the endothelial layer, fibrotic thrombosis, and major alterations in collagen fibers in the media. Steam ablation was effective in the 19 patients: 13 of 20 veins were completely closed, and 7 showed a very small segment of recanalization after 6 months of follow-up that did not seem to be clinically relevant. Nine patients had some ecchymoses at the puncture site, and one patient had a transient superficial phlebitis. A median maximal pain score of 1 (range, 0-10) was reported. No serious side effects, such as deep vein thrombosis, nerve injury, skin burns, or infections, were reported. Patients were very satisfied with the treatment, with a median satisfaction score of 9.25 (range, 0-10).

Conclusions In this proof-of-principle study, pulsated steam ablation was an effective treatment for saphenous varicose veins.

Clinical Relevance This article describes a proof-of-principle study on the newest thermal endovascular treatment, steam ablation. It describes the first group of patients treated with hyperheated steam of 120°C for ablation of saphenous varicose veins. It also reports basic experimental data of this treatment on sheep to investigate the safety profile and the morphologic and histologic changes resulting from steam ablation. Steam ablation in the patients was effective, safe, and very well appreciated by the patients. This article describes the steam ablation procedure in humans, shows the first results, and provides basic background information received from animal experiments.

Introduction

For more than a century, saphenous varicose veins have been treated surgically with ligation and stripping of the saphenous veins. During the last decade, however, minimally invasive therapies for treating saphenous veins have been replacing traditional surgery, because they produce a lower recurrence rate, higher health-related quality of life, higher treatment satisfaction, and a lower complication rate.[1] A comparative meta-analysis of four different therapies showed that endovenous laser ablation (EVLA) was superior, followed by nonsegmental radiofrequency ablation (RFA), ultrasound (US)-guided foam sclerotherapy, and stripping, with success rates of 95%, 80%, 74%, and 76%, respectively, after 5 years of follow-up.[2]

The mechanism of ablation in endovenous thermal therapies such as EVLA and RFA is based on heating the venous structure, and in EVLA, creating intravascular "steam bubbles."[3] The rise in temperature during EVLA is very high, inducing blood carbonization, evaporation of the laser fiber tip, and perforation of the venous wall.[4] Patients also report the taste of burned blood during EVLA. These observations hypothesize that foreign material may stay within the body and justify our search for other treatment modalities.

Steam ablation is a new method of thermal vein ablation. Its objective is to achieve a safer and easier method of thermal ablation that has fewer side effects. No studies have reported on steam ablation yet. The present article describes a proof-of-principle study in which we assessed the effectiveness and safety of steam ablation in animal experiments and in a pilot study involving 19 patients with varicose veins. The purpose of our studies was to assess safety and effectiveness of steam ablation, first in animals and then in patients, in a proof-of-principle study and to investigate patient satisfaction of the steam treatment.

Materials and methods

For the steam ablation, the Steam Vein Sclerosis (SVS) system (CERMA SA, Archamps France) was used. The SVS system consists of a steam generator and a handpiece that injects micropulses of steam into a catheter that delivers the steam into the vein to be treated (Fig 1). A more detailed description of the steam ablation procedure is given in "Procedures" of the pilot study in patients. The procedure in sheep was very similar to the procedure in humans.

Experiments in sheep

The sheep used in this study received care in compliance with the FDA Good Laboratory Practice (GLP) regulations 21 CFR 58 (revised April 1, 2005).
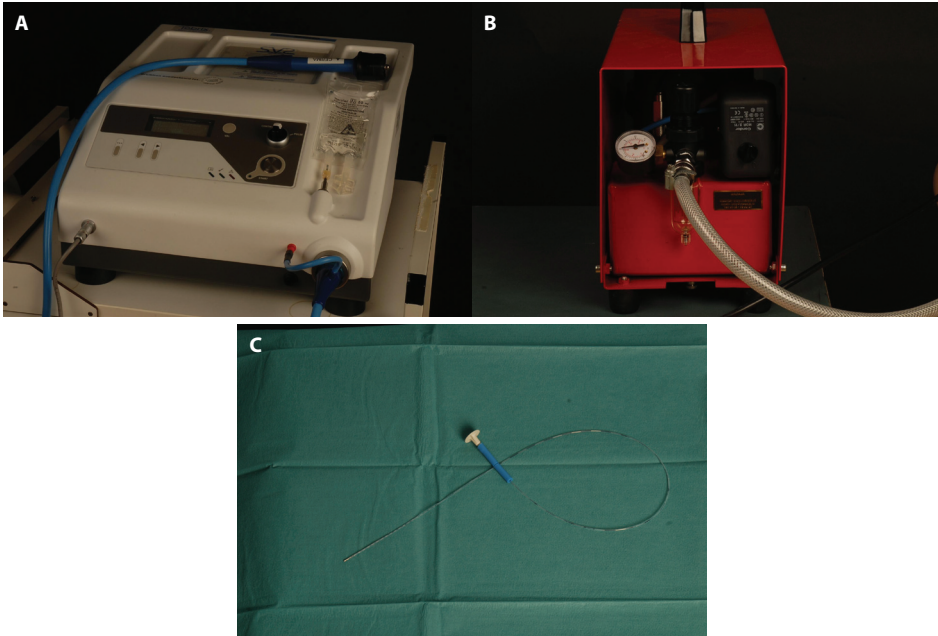
Figure 1. Photographs show (A) the Steam Vein Sclerosis device, (B) the steam generator, and (C) the steam catheter.

The experiments in sheep consisted of two parts. The first was a safety assessment during steam ablation by caval vein blood temperature measurement, subcutaneous temperature measurement, and monitoring of hemodynamic parameters. The second part consisted of measurements of the vein diameter by US imaging for 3 months after the steam treatment and microscopic investigation of treated veins after euthanasia of the sheep.

Steam ablation procedure
The steam ablation in six sheep was performed under general and tumescent (sterile saline with 1% lidocaine) anesthesia. To measure perivenous temperature, sensors were inserted under the skin close to the saphenous vein. Sensors were placed inside two veins to measure initial and final intravascular temperatures. During treatment, electrocardiography, arterial blood pressure, heart rate, and oxygen saturation were monitored. In one sheep, a temperature-monitoring catheter was inserted into the contralateral saphenous vein and threaded up into the inferior caval vein to measure blood temperature during steam ablation.

A US examination was performed to measure the vein diameter before, immediately after, and at 1 and 3 months. Macroscopic examination was performed immediately, >20 days after, or 3 months after the treatment.

On four of the six sheep undergoing the steam ablation procedure, we performed US exami-
nation to measure diameter shrinkage; two of these four sheep were used for intravascular
temperature measurement, two were used for perivenous temperature measurement, and
all four sheep were used for macroscopic examination. These four sheep were euthanized 3
months after steam ablation. Two other sheep (2462 and 41083) were used for macroscopic
examination (one with excision of a small part of the vein immediately after treatment) for
perivenous temperature measurements and one also for caval vein temperature measure-
ment. These two sheep were euthanized 20 days after treatment. Hemodynamic parameters
were measured in all six sheep. To test the validity of the animal study, two veins from two of
the sheep were treated with RFA in a standard fashion.

Pilot study

Patients
The pilot study included 20 veins of 19 consecutive patients presenting at our Department
of Dermatology with primary insufficiency of the great saphenous vein (GSV) or short saphe-
nous vein (SSV) with typical complaints such as tired legs and heaviness, defined by reflux
time >0.5 seconds and a vein diameter >5 mm. The exclusion criteria for patients included age
<18 years, acute deep or superficial vein thrombosis, agenesis of deep vein system, vascular
malformations or syndromes, occlusive postthrombotic syndrome, pregnancy, immobility,
allergy to lidocaine, and arterial insufficiency (ankle-brachial index <0.9). In the Netherlands,
the introduction of a new medical device with a CE registration number, such as the SVS
system, does not require permission of the medical ethical committee.

Procedure
The procedure of steam ablation is very similar to EVLA. Steam ablation was performed with
the patient under local tumescent anesthesia in an outpatient setting. The vein was punc-
tured with a 16-gauge infusion needle under US guidance. The insufficient GSV was mostly
entered at or just above knee level because access is easy at that site and the risk of nerve
injury is small. The SSV was entered halfway or at the distal third part of the calf, depending on
vein diameter. After puncturing the vein, the steam catheter (1.2-mm diameter) was passed
through the hollow needle into the vein until positioned 3 cm below the junction. The most
pivotal step in the procedure is positioning the echo-dense tip of the sheath approximately
3 cm distally from the junction under longitudinal US visualization.

About 150 to 300 mL (depending on the length of vein treated) of tumescent anesthesia (5
mL epinephrine [5 mL bicarbonate] and 35 mL lidocaine 1% diluted in 500 mL saline solution)
was administered into the perivenous space under US guidance using a mechanical infusion

pump. Tumescent anesthesia is necessary because it reduces pain, cools perivenous tissue, and decreases the venous diameter.

After activation, the catheter releases small "puffs" of steam, and the catheter was pulled back stepwise. With the first activation 3 cm below the (saphenofemoral or saphenopopliteal) junction, four puffs of steam were administered, meanwhile with manual pressure on the junction. Two puffs of steam were administered at 1-cm intervals. During the first 4 cm of treatment, manual compression on the junction was still applied. After the first 12 treatments, we reduced the amount of administered energy to one puff per further cm in patients with a vein diameter <8 mm. This was because a few patients reported the sensation of feeling heat during the treatment and because good results with using less energy in smaller veins was observed during the evolution of the method.

A physicist calculated that approximately 2258 J is released when 1 g of steam condenses. In EVLA, it is considered consensus to apply about 50 to 60 J/cm. To occlude 30 cm of vein with steam ablation, theoretically, 1 to 1.5 mL of water is needed. In practice, 2 to 5 mL of water is likely to be required, because not all steam condenses at the vein wall.

The steam is produced by means of piston pressing a fixed amount of water (76 µL = diameter piston × stroke) through a heated element located just before the catheter. By keeping the lumen diameters very small and the exit holes even smaller, pressure is maintained and loss of energy is limited. The volume of the steam depends on the pressure and temperature. As the energy is transferred to the vein, the steam cools and condenses to the same volume of water used to produce the steam. The steam starts to cool and condense when it leaves the catheter due to the drop in pressure and the exchange of energy with the surroundings. This process is dynamic. The theoretic amount of energy of one pulse of steam is 174 J. The measured amount released at the tip of the catheter is 60 J per pulse. However, additional dose-finding studies are warranted.

After the procedure, patients were advised to wear thigh-length medical elastic compression stockings (pressure range, 25-35 mm Hg) for 1 week and to mobilize immediately after the treatment.

Statistical analysis
Variables were presented in means with standard deviation (SD) if distributed parametrically, or as median with the 25th and 75th percentile value (interquartile range [IQR]) if distributed nonparametrically. We compared the scores of the EuroQol quality-of-life questionnaire (EQ-5D) index and visual analog scale (VAS),[5] Aberdeen Varicose Vein Questionnaire (AVVQ),[6] and Venous Clinical Severity Score (VCSS)[7] before and 3 months after therapy using the Wilcoxon

signed-rank test. We performed statistical analysis with SPSS 15.0 software (SPSS Inc, Chicago, Ill) and assigned significance at P < .05 (two-sided P).

Results

Experiments in sheep

Safety
The treatment parameters for four treated limbs are summarized in Table I. No temperature rise was observed at the level of the vena cava inferior in sheep 41083. In sheep 2462, a temperature rise from 30° to 59°C was observed with the subcutaneous thermocouple in the left limb and from 30° to 32°C in the right limb. The temperature rise was from 30° to 38°C in the right and left limb of sheep 41083. Noninvasive arterial blood pressure, heart rate and oxygen saturation remained stable during treatment in all sheep. Only transient lower oxygen saturation was observed in the right limb of sheep 41083. The intravascular temperature increased at the end of the procedure in one of two veins from 36.4° to 40°C.

Table I. Steam ablation in sheep, treatment parameters

Sheep No.	Limb	Puffs/cm	Withdrawal (cm)	Total puffs (No.)	Total energy (J)	Energy (J/cm)
					Mean (SD)	Mean (SD)
2462	Right	3	1	42	1592 (67)	114 (4.8)
2462	Left	1	1	24	910 (38)	38 (1.6)
41083	Right	3	1	39	1474 (35)	59 (1.4)
41083	Left	2	1	42	1588 (38)	76 (1.8)

SD, Standard deviation.

Morphologic changes in vein diameter
Before treatment, the diameters of the veins varied between 0.28 and 0.35 cm. US examination demonstrated that all veins were occluded and that the diameter of each vein decreased directly after the steam ablation. The diameters continued to decrease over time, with a mean decrease in initial diameter of 56% (SD, 4.8%) after 3 months (Table II).

Microscopic examination
Microscopic examination of veins immediately after the steam ablation showed disappearance of the endothelial layer, with negative marking for factor VIII and a few cleavage zones in the media (Fig 2, A) Microscopic examination of treated veins that were removed 20 days after the steam ablation showed endothelial destruction, fibrotic thrombosis with inflammatory reaction of the media, major alterations of elastic and collagen fibers in the media,
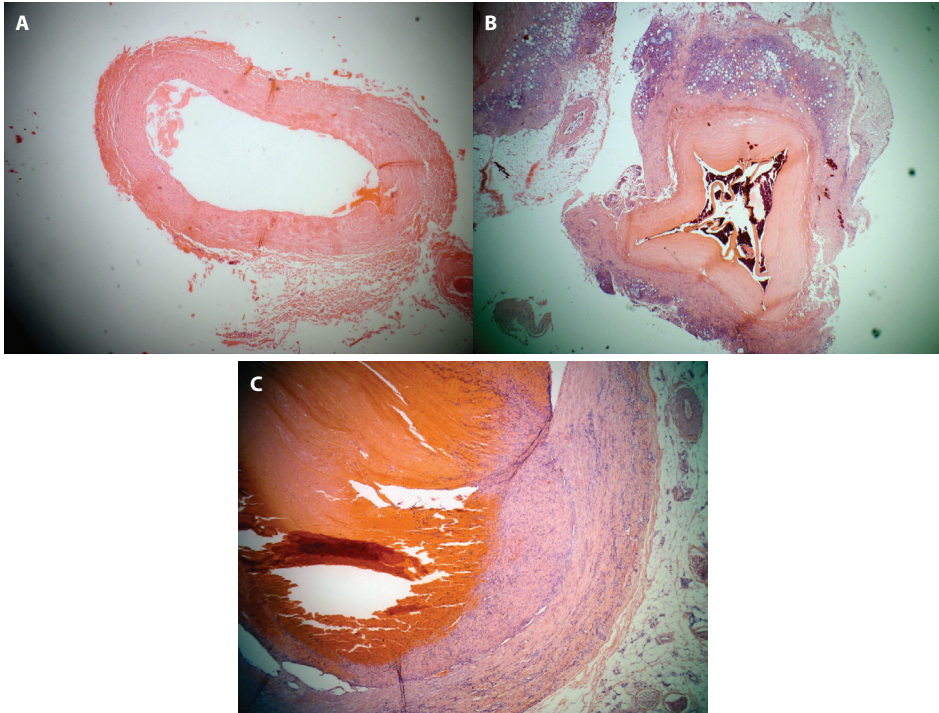
Figure 2. Photomicrographs show a vein (A) immediately after treatment with steam ablation and (B) at 20 days after treatment with steam ablation (both hematoxylin-eosin stain, original magnification ×40). C, Detail (hematoxylin-eosin stain, original magnification ×200). D, Photomicrograph shows a vein 3 months after treatment with steam ablation (hematoxylin-eosin stain, original magnification ×40).

Table II. Morphologic changes measured by ultrasound examination

Sheep No.	Limb	Energy (J/cm)	Vein diameter, cm				
			Before Tx	After Tx	At 1 mon	At 3 mon	Difference after 3 mon
2872	Right	40	0.28	0.25	0.17	0.15	0.13
3347	Left	80	0.32	0.28	0.28	0.18	0.14
2343	Right	40	0.34	0.29	0.21	0.22	0.12
2343	Left	80	0.35	0.27	0.23	0.15	0.20
1481	Right	80	0.31	0.28	0.18	0.18	0.13
1481	Left	40	0.33	0.25	0.20	0.19	0.14
Mean (SD)		NA	0.32 (0.18)	0.27 (0.13)	0.21 (0.29)	0.18 (0.19)	0.14 (0.19)

NA, Not applicable; SD, standard deviation; Tx, treatment.

and lesions in the adventitia with liponecrosis and lipogranuloma (Fig 2, B and C) Locally, the inflammatory reaction extended to the adventitia. Three months after the steam ablation, microscopic examination showed (major) thickening of the vein wall with fibrosis and inflammation, destruction of endothelium, alterations of elastic and collagen fibers, numer-

ous pigmented histiocytes, a significant reduction of the lumen, and capillary neovessels. There were also focal areas in which the endothelium was preserved (Fig 2, D). The observed histologic changes were similar to those found after treatment with RFA.

Pilot study

Study population
The study comprised 19 patients (7 women) who were a mean age of 53 years (Table III). Of the 20 veins treated, 17 were GSV and 3 were SSV. More than half of the treated patients were considered clinical class 2 of the CEAP classification.

Outcomes

The mean treated length of the veins was 25 cm, and an average of 50 pulses of steam were administered per treated vein (Table III). All treated veins were occluded on US examination at 1 week. At 3 months, 1 of the 20 treated varicose veins showed a small segment of several centimetres with minimal blood flow. At 6 months, flow was observed on US examination in 7 of 20 treated saphenous veins, but this was a small string (never filling the entire venous diameter) over a tract of <10 cm. In only two of seven cases did the strings of flow show

Table III. Patient characteristics

Variable	No. or Mean (SD)
Patients	19
Legs	20
GSV	17
SSV	3
Age, y	53 (15)
Sex	
Female	12
Male	7
CEAP	
C2	11
C3	2
C4	4
C5	2
C6	0
Treated length, cm	25 (7)
Pulses, No.	50 (19)

GSV, Great saphenous vein; SD, standard deviation; SSV, small saphenous vein.
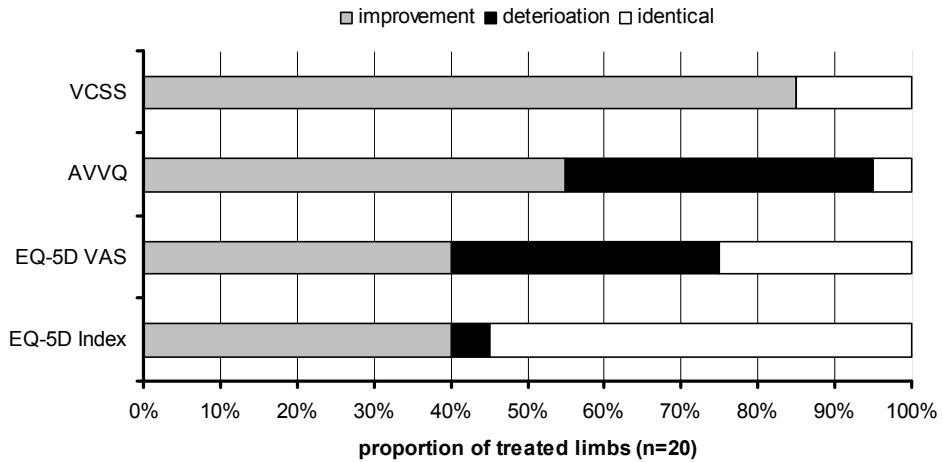
Figure 3. The positive, neutral, and negative impact of steam ablation is shown on the Venous Clinical Severity Score (VCSS), Aberdeen Varicose Vein Questionnaire (AVVQ), and the EuroQol quality-of-life questionnaire (EQ-5D) index and visual analog scale (VAS), four measures of clinical and health-related quality-of-life.

minimal reflux. At the 1-week follow-up, there were no cases of deep vein thrombosis, skin burns, nerve injury, infections, or hyperpigmentation. One patient had transient superficial phlebitis distally from the treated part, and nine patients had some ecchymosis only at the puncture site, but not along the treated vein. No complications were reported by the patients or were detected with US at 3 and 6 months of follow-up.

The median VCSS decreased significantly from 5.0 (IQR 3.3, 9.3) to 2.5 (IQR 1.0, 5.0) 3 months after the treatment (P < .001; Fig 3). Of the three patients in whom the VCSS remained identical, the absolute scores were 2, 10, and 14. The AVVQ improved significantly from 12.6 (IQR 6.9, 25.1) to 9.8 (IQR 2.1, 17.9; P = .027). Although the EQ-5D index improved 3 months after the treatment in eight patients and deteriorated in one, the difference was not significant (P = .11). The VAS of the EQ-5D did not change considerably after steam ablation (median remained 80 of 100, P = .56). Median satisfaction of the treatment was 9.25 (IQR 8.6, 10.0) and median maximal pain after steam ablation was 1 (IQR 0, 2) on a 10-point VAS. Four patients used four to six analgesics (500 mg paracetamol or a nonsteroidal anti-inflammatory drug) daily 1 or 2 days after the treatment.

Discussion

In this study, we have described the first results of a new technique to ablate varicose veins using high-temperature steam, which appears to be safe, effective, and appreciated by patients.

In sheep veins treated with steam ablation, fibrosis and destruction of the vein was confirmed by histology, and ongoing fibrotic contraction was confirmed by shrinking of vein diameter on US imaging. The similar histologic changes found after heating using the RFA technique show that our study design was valid and very much in line with previous observations.[8]

In the 20 veins treated in the patients, 13 were completely occluded and 7 showed minor recanalization on US examination at 6 months of follow-up. Although the number of partial recanalizations increased from 1 to 7 between 3 and 6 months of follow-up, the clinical relevance of this finding is unclear. The observed flow on US examination was limited and may reflect a process of venous remodelling as is observed after RFA. This deterioration emphasizes the need for clinical dose-finding studies in SVS (ie, number of steam pulses/cm).

Many observational studies—but few randomized controlled trials—have shown the high efficacy of EVLA, and a recent meta-analysis of all available data after an adjustment for follow-up demonstrated that EVLA was more effective than stripping, RFA, and US-guided foam sclerotherapy.[2] Only two publications have reported radiofrequency-powered segmental thermal ablation, which has a heating element of 7 cm. The first was a case series that showed occlusion rates of 99% after 6 months of follow-up.[9] The second was a randomized controlled trial that compared EVLA with radiofrequency-powered segmental ablation measuring post treatment recovery and quality-of-life parameters, in which the authors concluded that the radiofrequency-powered segmental ablation was superior.[10] Because thermal endovenous treatments are very effective, the challenge is now to search for the one that is the safest, cheapest, and most appreciated by patients and physicians (optimal risk-benefit ratio).

Our second finding concerned the safety of steam ablation, which was demonstrated by stable hemodynamic parameters and low perivenous temperatures in the sheep during steam ablation, and neither did the 19 patients have any major complications, such as DVT or nerve injury. Two other features that might be advantageous compared with EVLA are that steam ablation is performed with a very small volume of sterile water (approximately 2 mL per treated vein) and that the temperature is relatively constant, with a maximum of 120°C. Carbonized blood is released during EVLA, and the temperature is very variable, rising to 600° to 1000°C, and sometimes even melting the fiber tip.[11] The steam catheter, in contrast, is introduced directly through the puncturing needle, without the need for a guidewire or

sheath, resulting in an easier and safer procedure. There is less risk of device-related complications, such as the retention of a guidewire inside the body, which has been reported in EVLA.[12-13]

The patient-reported outcomes suggest that steam ablation was very well tolerated. The pain scores were low, and patients were very satisfied with the treatment. The clinical disease severity, as measured by the VCSS, improved significantly, and the AVVQ disease-specific questionnaire showed a significant improvement after steam ablation. Whether these patient-reported outcomes are better than with EVLA and RFA has to be assessed in a comparative study.

An advantage of the steam-ablation procedure is that the catheter is minute and very flexible. The diameter of the SVS steam catheter (1.2 mm) is almost 50% smaller than that of the segmental RFA (2.33 mm). The flexibility may facilitate placement of the catheter into branches, tortuous vessels, and perforator veins, which are sometimes difficult to access with the more rigid catheters used in RFA and the stiff glass fibers used in EVLA. The steam is released from two small areas at the tip of the catheter, allowing treatment of any length of vein, which is not possible with the segmental RFA with a 7-cm-long stiff heating tip. The steam is released under pressure and, therefore, disperses over a distance of at least 2 cm. This may be of additional benefit in the treatment of short perforator veins and short segments of meandering veins.

The limitations of this study were the limited number of treated limbs and the lack of comparison with established methods. The main objective was, however, not to prove superiority over another method but to show that the steam ablation of the saphenous veins is feasible to perform safely in animals and humans with satisfactory short-term results. Larger comparative studies are needed to compare the long-term efficacy and the risk-benefit ratio of steam ablation with those of existing endovenous techniques.

Conclusion

Steam ablation of the saphenous vein using the SVS is a novel method of endovenous thermal ablation. It appears to be safe, effective, and highly appreciated by patients. It may potentially have advantages over currently available thermal therapies.

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Temperature measurements for dose-finding in steam ablation

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Very recently, we have demonstrated the safety and efficacy of steam ablation for varicose veins in sheep and human in a pilot study.[1] The effectiveness of endovenous thermal ablative treatments (using laser, radiofrequency of steam) depends primarily on the amount of energy delivered to the venous wall.[2-3] Previously, it was estimated that one 'puff of steam' in steam ablation equalled approximately 56 joules, suggesting that one to two puffs per cm vein would be sufficient to occlude the vein.[1] However, in the first 20 patients treated it was shown that one pulse/cm was not optimal and the pulse dose was subsequently doubled. The objective of our experiment is to better understand the heat profile induced by steam and to investigate the heat induction of 1, 2 and 3 puffs/cm using steam ablation.

In a sealed glass beaker filled with demineralised water, analysis of the number of frames of a high speed camera demonstrated that a steam pulse of the Steam Vein Sclerosis (SVS system; CERMA SA, France) lasts 0.99 sec. Also, using a balance (with a precision of 0.01 g), we estimated that the water mass of one steam pulse was on average 0.08 grams.

In an experimental set-up, previously used to study thermal effects of endovenous laser ablation,[4] we measured the temperature profiles induced by steam ablation using three thermocouples located in the wall of the tube, 1 cm apart and intratubulair thermocouples fixed at the top, bottom and sides at 2 mm distance of the centre of the catheter, which is moving in the centre of the tube. The main parameter controlling the unsteady heat transfer process is the heat diffusivity, which is around 0.14×10^{-6} m^2/s. The process of expansion and subsequent collapse and segregation of induced steam is that fast that the effect of heat transfer through the bounding wall is minimal. The inner and outer diameter of the tube was 4 and 6 mm, respectively. Because of the fast spreading of injected steam in the vein, conclusions regarding differences between the number of puffs given is likely to be comparable for other diameters. The circumferential locations were selected in order to assess the homogeneity of the temperature distribution caused by the steam delivered through a catheter with two opposite holes. Each of the measurements was repeated 5 times and presented as mean with standard deviation (SD). The maximum temperature rise (ΔT_{max}) at the wall of the plastic tube was modest for 1 pulse and increased considerably with increasing number of pulses/ cm (Table I). One steam pulse/cm showed inhomogeneous ΔT_{max} compared to 2 or 3 pulses/ cm for which the temperature rise was similar at the top, bottom and sides at 2 mm radial distance from the steam catheter. At 1 mm outside the tube, ΔT_{max} was less than 5 °C. At 2 mm distance from the catheter, the duration that the temperature was above 50 °C (inducing denaturation of collagen; t_{den}) was zero for one pulse/cm (Table I). For 2 pulses/cm the Δt_{den} varied between locations but was >10 s at the top and bottom and for 3 pulses/cm it was higher (>20 s) and more homogenous compared to 2 pulses. Compared to EVLA (940 nm; 20 W; 2 mm/s), the ΔT_{max} was considerably lower, but the t_{den} was longer for steam ablation (data not shown). The loss of homogeneity using 1 pulse/cm is due to increased convection

Table I. The mean maximum temperature rise (ΔT_{max}), the actual maximum temperature (T_{max}), and time above 50 °C (Δt_{den}) at different distances and locations inside the plastic tube for 1, 2 and 3 pulses/cm.

Outcome	Distance from centre steam catheter tip C (mm)			
	2 mm	3 mm	4 mm	5 mm
1 pulse/cm				
ΔT_{max}	16.7±3.3	3.0±0.4	2.1±0.2	1.6±0.2
T_{max}	36.7±3.3	23.0±0.4	22.1±0.2	21.6±0.2
2 pulse/cm				
ΔT_{max}	33.9±1.7	5.4±0.3	3.8±0.2	3.1±0.2
T_{max}	53.9±1.7	25.4±0.3	23.8±0.2	23.1±0.2
3 pulse/cm				
ΔT_{max}	47.6±4.4	6.9±0.3	4.8±0.3	4,2±0.3
T_{max}	67.6±4.4	26.9±0.3	24.8±0.3	24,2±0.3

	Circumferentially distributed thermocouples at 2 mm distance from C		
	Top	Bottom	Lateral
1 pulse/cm			
ΔT_{max}	20.9±4.1	16.5±2.4	12.7±3.3
T_{max}	40.9±4.1	36.5±2.4	32.7±3.3
2 pulse/cm			
ΔT_{max}	33.8±1.6	33.8±2.0	33.7±1.4
T_{max}	53.8±1.6	53.8±2.0	53.7±1.4
3 pulse/cm			
ΔT_{max}	47.0±4.3	47.4±4.7	48.3±4.1
T_{max}	67.0±4.3	67.4±4.7	68.3±4.1

Δt_{den} (seconds, mean ± SD)			
1 pulse/cm	0.0± 0.0	0.0± 0.0	0.0± 0.0
2 pulse/cm	13.0±30.1	10.4±4.5	4.8±3.7
3 pulse/cm	29.0±7.5	27.3±8.1	24.0±10.0

ΔT_{max}, temperature rise (°Celsius, mean ± SD)

T_{max}, maximal temperature -baseline is considered 20 °C- (°Celsius, mean ± SD)

of the liquid and migration of vapour bubbles. The catheter releases the steam puffs at two opposite sites of the distal end. In a restricted area, the administered steam first expands quickly and occupies the entire volume available in its vicinity leading to a homogenous heat distribution over the inner but not over the outer side of the venous wall.

In summary, these experiments suggest that the temperature induced by 1 steam pulse/cm is insufficient whereas at least 2 pulses/cm seems adequate to ablate varicose veins.

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CHAPTER 13

General discussion

General discussion

The "gold standard" for the treatment of insufficient saphenous veins has been ligation plus stripping for the last 100 years. In the last decade the introduction of endovenous thermal ablation (EVTA) techniques has changed this concept. EVTA techniques, always performed under duplex guidance, appeared to be very effective treatments with high success rates at short-term follow-up. EVTA techniques were therefore implemented almost immediately after their introduction in several countries including the Netherlands.

Endovenous thermal ablation: the lack of evidence

Regarding endovenous treatment, several issues are still not fully understood. Compared to other new medical treatments, such as pharmaceutical drugs, surgical and endovenous treatments are not studied that well. In dermatology, as in other specialties, the implementation of new pharmaceutical treatments always needs to meet strict requirements. Contrarily, for the introduction of endovenous treatment methods in dermatologic and surgical practice, this was not the case. The only requirement for the implementation of medical devices in the Netherlands is obtaining a CE-certification. Once this CE certificate has been obtained, the device can be used in human subjects. Unfortunately manufacturers of medical devices have relatively little interest in research concerning dose-finding, mechanism of action and setting up randomized controlled trials (RCTs). Companies manufacturing endovenous devices differ from pharmaceutical companies which spend a lot of financial resources for clinical drug research. For new developments, research is classically divided into phase 0 to phase 4 studies. Fase 0 are exploratory, first-in-human studies. Phase 1 studies are the first stage of testing in human subjects. Phase 2 is divided into safety, dosing and efficacy assessment. Phase 3 studies are RCTs and phase 4 studies are post marketing surveillance trials which assess safety as well as cost-effectiveness. It is remarkable that these stages of investigation are not always followed for endovenous treatments.

Early in vitro and animal studies of EVTA techniques may have been performed, but are often not available for researchers and physicians. Only after these treatments had already been implemented, the first RCTs and case-series were published. EVTA techniques underwent considerable changes since their introduction. For example, the temperature applied during radiofrequency ablation (RFA) changed from 85°C (VNUS Closure Plus) to 120°C (VNUS Closure Fast). The RFA protocol for the VNUS Closure Fast system prescribes double heating of the most proximal segment of the vein, near the junction. These characteristics and instructions

are not based on a phase 2 (dose finding) study, but seem to be based on empirical evidence (or data leading to potential evidence are not readily accessible). Equally, the changes that occurred in endovenous laser ablation (EVLA), such as wavelength, fiber design, and power settings were not based on phase 2 studies neither. In particular the introduction of higher wavelengths after the initial 810 nm (e.g., 940, 980, 1320 and 1470 nm wavelength) was not the result of phase 2 studies. Proebstle et al did perform phase 2 studies on energy dosing (J/cm). They performed a clinical study that showed that there is a pronounced dose-response relationship between the administered energy and the durability of success after EVLA.[1] In another study, using multiple regression analysis, Proebstle et al showed that low laser fluence was the relevant risk factor for EVLA failure or recanalization.[2] A small number of studies that tried to investigate the working mechanism of EVLA and RFA (by microscopy or by temperature measurements) were published much later than the first case-series. The first RCT of EVLA versus stripping was published in 2007,[3] whereas first case-series of EVLA were already published in 2000.[4-5] Only in 2009 a first RCT on segmental RFA was published,[6] while this is probably the most frequently used EVTA treatment in the Netherlands nowadays. It is quite remarkable that very few RCTs are available for EVTA treatment while it has become so popular. Because of the lack of RCTs, reimbursement of EVTA was even temporarily on hold in the Netherlands and is still in Belgium.

Very recently, the Lancet dedicated an issue to surgical research, quoting that surgical re-search is a "scientific desert", and proposing the rationale for the IDEAL (Idea – Development – Exploration – Assessment – Long term study) framework to advance surgical knowledge. This framework recognizes that at different stages of innovation, different study designs will be appropriate.[7] In 1923 Greenwood collected uncontrolled low-quality data and compared it to a "comic opera". This remark caused indignation when republished in 1996.[8] However, un-fortunately the proportion of RCTs in surgery remains low and poor-quality research without benefit to surgeons or patients continues to go on. Applying the IDEAL framework to EVTA, we can conclude that too little attention has been given to the exploration and assessment phase in particular. Hopefully in the future long term follow-up will be better monitored, especially when registries and routine databases are introduced.

When EVLA was started in our clinic, very few comparative studies were available. Therefore, we started a RCT in 2006 (MAGNA -Trial) which compares stripping with ultrasound guided foam sclerotherapy (UGFS) and EVLA for the treatment of the insufficient great saphenous vein (inclusion completed, n=240). We have also tried to contribute to evidence-based phlebology by performing a systematic review and a meta-analysis. Therefore we compared different treatments by studying all the published literature and evaluated selected studies in a meta-analysis. A systematic review shows the gaps in the available evidence and a com-parative meta-analysis is indicative when RCTs are lacking. This analysis showed that EVLA

has a higher success rate than stripping, UGFS and non-segmental RFA. One disadvantage of meta-analysis is the heterogeneity of the included studies. However, we have tried to minimize this heterogeneity by using several selection criteria (such as ultrasound based outcomes). Because of these criteria, and because all the individual data have been pooled, biases of individual studies are minimized.

Towards increased standardization of EVTA

As for many surgical and interventional procedures there is lack of standardization for EVTA. This lack is notorious for EVLA and UGFS. RFA is actually the only endovenous treatment that has a standardized procedure. Although also with segmental RFA, treatment parameters such as additional manual compression and amount of treatment cycles may vary. A variety of different energy settings and parameters are used in EVLA studies, all based on expert opinion but not on scientific evidence.

In an attempt to understand the impact of the different laser variables, such as power, pull-back speed, energy dosing, and wavelength on the effectiveness and side-effect profile of the EVLA procedure, we wanted to give an overview of technical aspects of EVLA. A thorough description of the technique, as well as the documentation of laser parameters such as energy dosing and wavelength was performed (chapter 5). This review also demonstrated the lack of knowledge concerning the optimal use of the different laser variables. Subsequently, in collaboration with physicists, we performed experiments to assess the influence of several parameters on the temperature profile during EVLA (these experiments are described in chapters 7,8,9).

There are a few studies (which may be considered phase 2 studies) that aimed to compare different laser wavelengths on efficacy and tolerability (e.g., pain, bruising). Some authors claim a better side-effect profile using higher wavelengths. In fact, these studies often not only used two different wavelengths, but also different energy levels. The comparative results are therefore difficult to interpret, and alleged differences may actually be the result of lower energy dose than higher wavelength.[9] One study compared 810 and 980 nm with similar energy dosing. There was no significant difference in pain intensity after 72 h and 3 weeks, but there was a small difference in pain intensity after 4 months favoring 980 nm. Itching was not statistically different after 72 h and 4 months, but was different at 3 weeks. It is unclear whether these outcomes are relevant in terms of post-procedural complications, and one could question whether itching at 3 weeks and pain at 4 months has something to do with the initial procedure.[10]

Potential complications after EVTA

We continued looking for evidence by investigating the frequency and seriousness of complications that occur in EVLA (phase 4 study). These complications were divided into minor, major and exceptional cases (device-related complications). Severe complications, such as device-related ones may injure the patient seriously, but fortunately these are very rare. We found that minor complications such as ecchymoses and pain are common and are reported in variable degrees. Pain is always subjective and difficult to measure. Many parameters of evaluation after treatment are not standardized (e.g., number of days to return to normal activities, number of analgesics used, VAS-score etc.).

Deep vein thrombosis (DVT) is an important complication that occurs in less than 1% after endovenous procedures. Some controversy exists concerning prophylaxis with low-molecular weight heparin (LMWH). Although the reported incidence of DVT is very low, physicians feel uncomfortable with this thrombotic risk. Therefore some authors have suggested the routine use of LMWH after EVTA, while others suggest administering LMWH only in high-risk patients.[11-12] At our centre we have chosen not to administer LMWH routinely, but only in high-risk patients. However, the definition of a high-risk patient is not always well defined.

The diagnosis of DVT after EVTA is also controversial somehow and the clinical importance of what has been called 'endothermal heat induced thrombosis' (EHIT) is still unclear. Duplex ultrasound findings will be different at different time intervals after EVTA. Thrombus extension into the deep venous system, sometimes even a floating thrombus, is more often seen the first few days after EVTA procedures. After 1 or 2 weeks, such thrombus extension is dissolved and hence not visible any longer on ultrasound examination. Physicians who investigate their patients routinely shortly after the endovenous procedure report more often DVT and will more often treat these patients with LMWH. This problem of definition (which may result in bias) might have occurred in one study which reported an exceptionally high number of DVT (5.6%). In this study DVT was defined as "a tail of thrombus protruding into the popliteal vein" at the 1-week follow-up duplex examination.[13] In fact, such thrombus usually disappears quickly, and is therefore different from a true DVT.

How does EVTA really work?

As mentioned before, the mechanism of EVLA and RFA was also a relatively unexplored domain (lack of phase 0 studies). In the years after its introduction, physicians – sometimes stimulated by manufacturers of lasers - started using other wavelengths, other fiber designs and varied the laser parameters to obtain better results in terms of efficacy, adverse events

and patient satisfaction. However, understanding the exact working mechanism should be the basis for this research. Only after understanding the mechanism of EVLA, physicians should start searching for optimization of the laser parameters. Lasers using standardized optimal settings should then be compared to other endovenous techniques or to laser techniques using different variables.

Three main theories on heat induction of EVLA have been proposed: (1) direct absorption of the scattered laser light by the vein wall[14-15], (2) heat transport by steam bubbles emerging from the hot fiber tip and heat release associated with their condensation[16]; and (3) direct contact of the laser fiber with the vein wall[15,17]. We suggested a fourth contributing mechanism: heat diffusion from the hot fiber tip.[18]

Many studies are performed with the aim of finding out which laser parameters influence efficacy rate and side-effect profile of EVLA. Although it has been proposed that the use of higher wavelengths may result in a better side-effect profile, this observation is not endorsed by well-performed RCTs. Most studies that aimed at comparing the effect of different wavelengths also varied the energy or the pullback speed.[9] To assess the impact of one variable (e.g. wavelength), the other variables should be kept constant. So whether these alleged effects were wavelength or energy dependent cannot easily be defined. In contrast to the in the literature proposed idea that wavelength is important, we found that the temperature profiles are identical using different wavelengths, suggesting that EVLA treatments are virtually wavelength independent at equal power and pullback speed.[19] These observations suggest that the working mechanism of EVLA is independent of laser wavelength and thus independent of the target (Hb or water) of the laser light.

Latest development: steam ablation

A nuclear medicine specialist in France proposed to use steam as a vector for injecting radioactive nanoparticles in tumor lesions and developed a steam generator. As an unexpected side-effect, steam killed cancer cells by heat. René Milleret, a French vascular surgeon, with extensive experience in EVTA for varicose veins, introduced steam ablation as an alternative for the treatment of varicose veins. The existing steam generator was adapted and a suitable catheter was developed. The experiments, first in living animals, and later in human patients started in 2006. For this research we have tried to follow all the different phases of investigation for the introduction of steam ablation. The studies that we performed on sheep are the phase 0 studies, and the pilot study in humans may be considered a phase 1 study. Then we performed a phase 2 study which was a dose-finding study, and finally, we started a RCT which is a phase 3 study.

Because effectiveness of the current EVTA treatments is excellent (>90%), side-effects are mild and serious complications are rare, a new EVTA technique should at least perform equally or preferably have some advantages over the existing ones. The hypothesis is that endovenous steam ablation (EVSA) is at least as effective as RFA or EVLA. The advantage of steam should be sought in terms of better patient tolerance, a safer, faster and easier procedure, and lower costs. First EVSA was investigated in animals and in human patients (phase 0-1 study). In sheep experiments, in close collaboration with Dr Milleret and the manufacturer of the device, we showed that it was effective and safe. In a pilot study (phase 1), we found a very mild side-effect profile in 19 patients. Whether the patient reported outcomes of EVSA are better than with EVLA will be investigated in a (phase 3) randomized controlled trial (LAST-Trial) including 240 patients that is currently ongoing. Preliminary results suggest that EVSA is associated with lower pain scores after treatment and lower amount of days off work or quicker return to normal daily activities.[20] The catheter used in EVSA is about 50% cheaper than the catheter used in segmental RFA. The prices of EVLA sets vary, the cheapest sets are cheaper than the EVSA sets. In line with RFA, there is no need for a guide-wire in EVSA, and also no sheath is used. This may be an advantage compared to EVLA, where the introduction is (often) performed in three steps. This saves time and because it is more straightforward than the EVLA procedure, it might help to prevent rare and serious complications such as leaving the guide-wire inside the body or burning the sheath.[21-22]

In addition, new indications may also justify the development of a new EVTA therapy. It is imaginable that EVSA could be used for treating perforator veins and tributaries. For perforator veins, steam may have an advantage, because of the flexibility of the catheter and because the heat induced by the condensation of steam puffs reaches a few centimeters. Because of this way of heat distribution, the catheter does not have to be pulled back or repositioned, which is one of the difficult steps in perforator treatments. The radiofrequency mini-stylet (chapter 10) is quite difficult to use for perforator veins because of its rigidity and relatively long heating segment. A new stylet with a 4 cm RFA segment is currently being investigated (no results have been published so far). We do not have enough experience yet in treating perforator veins with EVSA to assess these alleged advantages. We did treat some tributaries with steam ablation and introducing the catheter was relatively easy. However, it was difficult to administer enough tumescent anesthesia, and therefore the procedure was sometimes painful. It would certainly be interesting to assess the outcomes of perforator vein treatment in a trial comparing steam ablation with UGFS.

During our pilot study on EVSA (chapter 11), we found that administering 1 puff of steam per cm might not be sufficient to close the vein. Therefore we amended our protocol to administering 2 steam puffs/cm. Adequate dosing was indeed one of the key questions during the discussion at the European Venous Forum 2010 in Antwerp, where we presented

the first results of our steam study. In response to this observation and the questions raised by experts, we performed additional ex-vivo temperature measurements to compare the temperature profiles induced by administering 1, 2 and 3 steam puffs/cm in an experimental setting (chapter 12). We found that administering 1 steam puff per cm did not lead to high enough temperatures indeed. Two and three steam puffs do lead to temperatures above 50 °C (temperature of collagen denaturation) for a reasonable time span. This experiment, therefore, confirmed our "clinical" assumption that 1 puff may not be enough for closing the vein. An additional dose-finding study in human subjects may be valuable to assess optimal dosing.

Future

Several publications support the hypothesis of ascending or multifocal development of varicose disease starting from the distal superficial venous network.[23-25] The surgical approach focusing on the treatment of the so called 'varicose reservoir' by means of phlebectomies with conservation of a refluxing saphenous trunk is enjoying renewed attention. Treating insufficient tributaries of the insufficient saphenous vein may lead to abolition of the saphenous reflux in the trunk, which means the saphenous vein itself can be saved.[26] This concept challenges the current approach to treatment of venous insufficiency, which usually focuses on the treatment of the refluxing saphenous trunk. Choosing to treat tributaries first may become the preferential approach. The treatment of tributaries by phlebectomies and UGFS has been practiced for many years. The question is whether the current EVTA therapies are as useful for treating tributaries as they are for saphenous veins. EVLA and segmental RFA are usually not indicated because of tortuosity of the tributaries. EVSA, however, may be very useful for treating tributaries for several reasons. The catheter is very flexible, steam reaches several centimeters, there may be less neovascularization than with phlebectomies, and EVSA can be used for more deeply situated veins.

When saphenous insufficiency remains after the treatment of tributaries, the saphenous vein may be treated in a second stage. In patients presenting with extensive varicose veins and a clearly dilated refluxing saphenous trunk ($\geq 7 – 8$ mm) it might be wiser to treat the refluxing trunk with concomitant phlebectomies of large tributaries in direct connection with the saphenous vein in a first stage.[27] This strategy may reduce the incidence of thrombophlebitis after EVTA. Additional phlebectomies, EVSA or foam sclerotherapy of remaining varicosities may complete the treatment in a second stage. The above described strategies should be further evaluated in prospective clinical studies.

Table 1. Advantages and disadvantages of the different treatment options for varicose veins.

Characteristics	Stripping[‡]	EVLA	RFA	EVSA	UGFS
Effective	+	+++	++	¶	+
Major complications	+	+/-	+/-	+/-	+/-
Device-related complications	+	+	+/-	+/-	+/-
High patient' satisfaction / preference	+	++	+++	+++	+
Standardized procedure	++	+	++	++	+
Costs	+++	+	++	+	+/-
Treatment of perforator veins	N.A.	+/-	+/-	++	+
Treatment of tributaries	N.A.	-	-	+	+

N.A., Not applicable.
[‡] Conventional stripping using spinal or general anesthesia.
¶ No evidence yet.

Future studies should also try to answer the remaining questions about the exact working mechanism of the different EVTA treatments. Such studies will probably be performed ex vivo, because for example temperature measurements and the use of video or camera systems are very difficult in vivo. RCTs using well defined criteria for clinical assessment, quality of life and duplex ultrasound evaluation should show the difference between the different treatment options, and dose-finding studies should be performed to assess the optimal treatment parameters. A high level of evidence to select the optimal EVTA that is suitable for treating all types of varicose veins is currently lacking. Based on literature study and personal experience, we formulated several advantages and disadvantages of the different treatment options (Table I). In an era of health technology assessment and cost-effectiveness analysis, treatment related costs will become increasingly important and this will certainly remain an important issue in the future.

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CHAPTER 14

Summary / Samenvatting

Summary

Chapter 1 is a general introduction of this thesis. Chronic venous insufficiency (CVI) is a great socio-economic problem that causes complaints and clinical symptoms, and it can lead to serious complications. Varicose veins are part of venous insufficiency and are very common. For more than a century, the treatment of saphenous varicose veins consisted of surgery (stripping). Since ten years, minimally invasive treatments for varicose veins are very frequently used. The endovenous thermal ablation treatments are the most effective. The different treatment options are described briefly and then the motivation and aims of this thesis are articulated.

Chapter 2 gives an overview of the different minimally invasive treatment options. The potential advantages of these treatments compared to surgery, which is considered the 'gold standard', are explored. The procedure, the indications, the efficacy and the safety of ultrasound-guided foam sclerotherapy (UGFS), endovenous laser ablation (EVLA) and radiofrequency ablation (RFA) are described. The differences and similarities between these treatment options and to the position of these treatments within all other treatments are discussed by an international panel of experts in phlebology.

Chapter 3 describes a systematic review of the effectiveness of four different treatment options for primary insufficiency of the great saphenous vein (GSV) and the small saphenous vein (SSV). We included 64 studies (72 study arms) with a total of 12.320 treated legs, of which 2804 (23%) were stripped, 2126 (17%) were treated with UGFS, 4876 (40%) were treated with EVLA, and 2514 (20%) with RFA. An important inclusion criterion was that the outcome or efficacy had to be assessed by ultrasound examination.

After adjustment for follow-up, the comparative meta-analysis shows that EVLA has a significantly higher success rate than stripping (AOR, 1.13; 95% CI, 0.40-1.87), UGFS (AOR, 1.02; 95% CI, 0.28-1.75), and RFA (AOR, 0.71; 95% CI, 0.15-1.27). This result was also observed in subgroup analysis, such as randomized controlled trials. Because all the individual data of the different studies are pooled, the biases of the individual studies are minimized, which is one of the strengths of meta-analysis. A disadvantage of meta-analysis is the heterogeneity of the different studies. We tried to minimize this heterogeneity by applying selection criteria such as the use of ultrasound examination when assessing treatment outcome.

Chapter 4 discusses the role that endovenous thermal ablation has between the treatment options of varicose veins. Surgery of varicose veins should be refined, i.e. with using tumes-

cent anesthesia and without leaving substantial scars, to remain a good treatment option next to minimal invasive treatments of primary GSV and SSV insufficiency. The future will show which type of endovenous thermal ablation will become the first choice. Randomized comparative trials should be performed to show which treatment option is superior. Especially the cost-benefit ratio, safety and patients' satisfaction will influence the outcome.

Chapter 5 is meant to inform practitioners on EVLA and the influence of different laser parameters on the treatment. Several parameters, such as energy setting, the way of administering energy (continuous or pulsed), the pullback speed and the wavelength may play a role in the effectiveness and side effect profile of EVLA. We found that many studies on EVLA using many different laser parameters are published. There are, however, very few studies that truly compare different parameters. This lack of comparison sometimes leads to unjustified conclusions. An example is when effectiveness and side effects of different laser wavelengths are compared whilst using also different energy dosing.

Chapter 6 describes a systematic literature research to complications associated with EVLA. The complications are classified as minor or major according to the Society of Interventional Radiology Standards of Practice Committee guidelines on reporting complications. Ecchymoses and pain are frequently reported side effects of EVLA. Nerve injury, skin burns, deep vein thrombosis and pulmonary embolism seldom occur. An exceptional complication is a material or device that by accident remains inside the body after the procedure. Ecchymosis, pain, induration, skin burns, dysesthesia, superficial thrombophlebitis, and hematoma were classified as minor complications. Deep vein thrombosis and nerve injury were classified as major complications. EVLA is a safe treatment and the incidence of frequently occurring side effects may be lowered by using the optimal laser parameters, leading to a higher patients' satisfaction. The following three chapters discuss why EVLA may be so effective and why it is often associated with minor complications such as pain.

In chapter 7 we propose a new element in the working mechanism of EVLA. Direct absorption of the laser light, collapsing steam bubbles and direct fiber-wall contact have all been mentioned as contributing mechanisms in the literature. Because fiber tips have reported temperatures of 800–1,300°C during EVLA, we sought to assess whether heat conduction from the hot tip could cause irreversible thermal injury to the venous wall. We approximated the hot fiber tip as a sphere with diameter equal to the fiber diameter, having a steady state temperature of 800°C or 1,000°C. We computed venous wall temperatures due to heat conduction from this hot sphere, varying the pullback velocity of the fiber and the diameter of the vein. Venous wall temperatures corresponding to irreversible injury resulted for a 3 mm diameter vein and pullback velocities <3 mm/s but not for 5 mm and ≥1 mm/s. We concluded that heat conduction from the hot fiber tip is a contributing mechanism in EVLA.

Chapter 8 describes that a layer of carbonised blood is deposited at the fibre tip during EVLA. We analyzed fibres that were used in EVLA by optical coherence tomography (OCT) and microscopy. OCT scans showed a thin layer deposited on all fibers investigated, which were used in EVLA at 810 nm, 940 nm and at 1,470 nm. Microscopy showed inhomogeneities over the tip surface area, caused by the high temperature during EVLA. In conclusion, we found strong evidence that all EVLA procedures in blood filled veins deposit a heavily absorbing hot layer of carbonized blood on the fiber tip, with concomitant tip damage. This major EVLA mechanism is dependent on the total amount of administered energy, but is unlikely to have much wavelength dependence.

Chapter 9 describes the experiments that we performed to study the influence that several laser parameters, such as wavelength, pullback speed and energy dosing have on the temperature profile generated during EVLA. In an experimental setting, temperature measurements were performed using thermocouples. The experiments showed that decreasing the pullback speed and increasing the power both cause higher maximal temperatures. The use of different laser wavelengths (940 or 1470 nm) did not influence the temperature profile. The results of our experiments suggest that the heat induction, which is a mechanism for vein occlusion in EVLA, is independent of laser wavelength.

Chapter 10 describes the procedure of RFA of incompetent perforator veins (IPV) and evaluates its short-term effectiveness and safety. In a clinical pilot study, 14 IPV in 12 patients were treated with a radiofrequency stylet. After three months, ultrasound (US) examination was used to assess anatomical success rate and exclude deep venous thrombosis. Also, self-reported side-effects were investigated. Of the 14 treated IPV, nine (64%) were obliterated on US examination and the others showed remaining reflux. Two patients reported localized paresthesia, but no DVT was recorded. In conclusion, RFA of IPV may be a promising procedure, but patient and incompetent perforator vein selection is important and further standardization of the procedure is required. Comparative clinical trials between RFA and other therapies are warranted.

In chapter 11 a proof-of- principle study on endovenous steam ablation (EVSA), which is a novel thermal therapy, in animal and human subjects is described. In sheep, the safety of the procedure was assessed by cardiovascular monitoring during treatment. We used ultrasound to examine occlusion of the veins, and changes in treated veins were examined microscopically. In a pilot study, 19 human patients with insufficiency of the GSV or SSV were treated with EVSA. All veins in the sheep were occluded; there were no cardiovascular changes during treatment. Histological examination of treated veins showed typical changes of the vein wall, such as disappearance of the endothelial layer, fibrotic thrombosis, and major alterations in collagen fibers in the media. In the 19 patients the steam ablation was effective; 13 of 20

veins were completely closed and 7 showed a very small segment of recanalization after 6 months of follow-up which did not seem to be of clinical relevance. Nine of 20 patients had some ecchymoses at the puncture site, 1 patient had a transient superficial phlebitis, and a median maximal pain score of 1 (0-10) was reported. No serious side-effects such as deep vein thrombosis, nerve injury, skin burns, or infections were reported. Patients were very satisfied about the treatment with a median satisfaction score of 9.25 (0-10). In this proof-of-principle study, EVSA was an effective and safe treatment for saphenous varicose veins.

Chapter 12 describes an experiment that we performed to better understand the heat profile induced by steam and to investigate the heat induction of 1, 2 and 3 puffs/cm using EVSA. We performed these experiments because we found in the pilot study that not all veins of the patients were occluded. In an experimental set-up, we measured the temperature profiles induced by steam ablation using thermocouples located in and outside the wall of the tube. The maximum temperature rise (ΔT_{max}) at the wall of the plastic tube was modest for 1 pulse and increased considerably with increasing number of pulses/cm. One steam pulse/cm showed inhomogeneous ΔT_{max} compared to 2 or 3 pulses/cm. At 2 mm distance from the catheter, the duration that the temperature was above 50°C (inducing denaturation of collagen; t_{den}) was zero for one pulse/cm. For 2 pulses/cm the Δt_{den} was >10 s and for 3 pulses/cm it was higher (>20 s) and more homogenous compared to 2 pulses. The experiments suggest that the temperature induced by 1 steam pulse/cm is insufficient whereas at least 2 pulses/cm seems adequate to ablate varicose veins.

In chapter 13 the relative lack of randomized, mechanistic and dose-finding studies of new treatments in phlebology is discussed and compared to the launch of other new treatments such as pharmaceuticals. We demonstrate that the results of comparable studies are sometimes difficult to interpret. Then, some commentary is given to the results of our study on complications of EVLA, especially the controversy that exists in diagnosing and treating DVT. Furthermore, we discuss the different theories on the working mechanism of EVLA that have been proposed and we discuss the theory that we based on our studies on the mechanism of EVLA. The discussion ends with reflecting on the potential position of EVSA and with future perspectives for further research.

Samenvatting

Hoofdstuk 1 geeft een algemene inleiding tot dit proefschrift. Chronisch veneuze insufficiëntie geeft veel klachten en kan leiden tot serieuze complicaties. Om die reden kan het gezien worden als een groot socio-economisch probleem. Varices zijn onderdeel van veneuze insufficiëntie en komen veelvuldig voor. De behandeling van grote varices bestond lange tijd uit het chirurgisch verwijderen ervan (strippen). Sinds circa 10 jaar worden nieuwe, minimaal invasieve, behandelingen steeds vaker toegepast. De endoveneuze thermische ablatie methoden zijn inmiddels het meest effectief gebleken. Na een beknopte bespreking van de verschillende behandelmethoden formuleren we de motivatie en de doelen van dit proefschrift.

Hoofdstuk 2 biedt een overzicht van de beschikbare minimaal invasieve behandelmethoden. De mogelijke voordelen ten opzichte van de 'gouden standaard', het chirurgisch strippen, worden verkend. Achtereenvolgens beschrijven we de procedure, de indicaties, de effectiviteit en de veiligheid van echogeleide sclerocompressie therapie met schuim (ESCT), endoveneuze laser ablatie (EVLA) en radiofrequente ablatie (RFA). De verschillen en de overeenkomsten tussen de behandelingen en de plaats die deze drie technieken innemen in het volledige behandel arsenaal worden besproken door een internationaal panel van experts in de flebologie.

Hoofdstuk 3 beschrijft een systematische review naar de effectiviteit van vier verschillende behandelmethoden voor primaire insufficiëntie van de vena saphena magna (VSM) en de vena saphena parva (VSP). We includeerden 64 studies (72 studie armen) met een totaal van 12.320 behandelde benen, waarvan 2804 (23%) gestript waren, 2126 (17%) met ESCT waren behandeld, 4876 (40%) met EVLA, en 2514 (20%) met RFA. Een van de belangrijkste inclusiecriteria is dat de uitkomst (effectiviteit) van de behandeling gemeten werd door middel van echo duplex onderzoek.

De vergelijkende meta-analyse wijst uit dat EVLA een significant hogere effectiviteit heeft dan strippen (AOR, 1.13; 95% CI, 0.40-1.87), ESCT (AOR, 1.02; 95% CI, 0.28-1.75), en RFA oude stijl (AOR, 0.71; 95% CI, 0.15-1.27). Deze uitkomst geldt na correctie van follow-up duur en blijft ook overeind wanneer bijvoorbeeld alleen gerandomiseerde vergelijkende studies in de berekening zijn meegenomen. Een van de sterke punten van een meta-analyse is dat door het samennemen van veel verschillende studies, de bias van de individuele studies wordt geminimaliseerd. Een nadeel van meta-analyse is de heterogeniteit van de verschillende geincludeerde studies. Dit nadeel hebben we geprobeerd te minimaliseren door het toepassen van selectiecriteria zoals het gebruik van echo duplex bij bepaling van de uitkomst.

In hoofdstuk 4 wordt op basis van de tot nu toe beschikbare literatuur besproken welke plaats endoveneuze thermische ablatie inneemt temidden van de diverse behandelmogelijkheden voor varices. Het strippen zal verfijnder moeten plaatsvinden (o.a. onder tumescent anesthesie en met minimale littekens) om zijn plaats te behouden naast de minimaal invasieve methoden voor de behandeling van primaire VSM en VSP insufficiëntie. De vraag rijst welke vorm van thermische ablatie de eerste keus behandeling zal worden. Om de verschillende behandelingen tegen elkaar af te kunnen wegen zal meer gerandomiseerd vergelijkend onderzoek moeten plaatsvinden en zullen kosteneffectiviteit, veiligheid en patiënt tevredenheid een zeer belangrijke factor zijn in deze afweging.

Hoofdstuk 5 geeft behandelaars informatie over EVLA en geeft inzicht in de invloed die de verschillende laser parameters hebben op de behandeling. Dit hoofdstuk is gebaseerd op de eerder uitgevoerde systematische literatuur studie in hoofdstuk 2. De energie instelling, de energie verdeling, de manier van energie toediening (continu of gepulseerd), de terugtreksnelheid en de golflengte kunnen in meer of mindere mate invloed hebben op de effectiviteit en het bijwerkingenprofiel van EVLA. Het blijkt dat er veel studies zijn verschenen met evenzoveel diversiteit aan gebruikte laser parameters; het aantal studies dat verschillende laser parameters met elkaar vergelijkt is echter nihil. Dit leidt soms tot conclusies die niet gerechtvaardigd zijn, zoals gebeurd bij het vergelijken van de effectiviteit en bijwerkingen tussen verschillende golflengtes met gelijktijdig variëren van andere laser parameters zoals energie.

In hoofdstuk 6 beschrijven wij een systematische literatuurstudie naar de complicaties die geassocieerd zijn met EVLA. De complicaties zijn ingedeeld volgens de richtlijn van de "Interventional Radiology Standards of Practice Committee" in mineure en majeure complicaties. Ecchymosen en pijn blijken frequent voor te komen na EVLA. Zenuwletsel, huidverbranding, diep veneuze trombose (DVT) en longembolie komen zelden voor. Een zeer uitzonderlijke complicatie ontstaat als er materiaal (zoals een stuk voerdraad) achterblijft in het lichaam na afloop van de procedure. Ecchymosen, pijn, induratie, huidverbrandingen, dysesthesieën, oppervlakkige tromboflebitis en hematomen zijn mineure complicaties. DVT en zenuwschade zijn majeure complicaties. Geconcludeerd wordt dat EVLA een veilige behandeling is en dat de incidentie van veel voorkomende neveneffecten mogelijk kan verminderen (waardoor de behandeling nog patiëntvriendelijker kan worden) door optimale laser instellingen. De volgende drie hoofdstukken proberen te verklaren waarom EVLA zo effectief is en hoe het komt dat EVLA pijn en ongemak geeft tot twee weken na de behandeling.

In hoofdstuk 7 poneren wij een nieuw onderdeel van het werkingmechanisme van EVLA. In de literatuur is beschreven dat directe absorptie van het laser licht, condenserende stoombellen ter plaatse van de vaatwand en direct contact van de lasertip met de vaatwand de werking van EVLA (deels) kunnen verklaren. Aangezien de lasertip tijdens EVLA zeer heet kan

worden (800–1300°C) veronderstellen we dat ook hitte conductie irreversibele thermische schade aan de vaatwand kan veroorzaken. We veronderstellen de hete lasertip als een bol met een diameter gelijk aan de fiber diameter met een temperatuur van 800°C of 1000°C. We berekenen de vaatwand temperatuur veroorzaakt door hitte conductie van deze hete bol terwijl we de terugtreksnelheid van de fiber en de diameter van de vene variëren. De instellingen waarmee de temperatuur van de vaatwand hoog genoeg wordt om irreversibel te beschadigen is bij een terugtreksnelheid van <3 mm/s in een vene van 3 mm doorsnede. Dit is niet het geval bij een doorsnede van de vene van 5 mm en een terugtreksnelheid ≥1 mm/s. We concluderen dat hitte conductie van de hete lasertip onderdeel is van het werkingsmechanisme van EVLA.

In hoofdstuk 8 wordt het ontstaan van een gecarboniseerd laagje bloed op de lasertip tijdens EVLA beschreven. Gebruikte laserfibers zijn met microscopie en door middel van Optical Coherence Tomograpy (OCT) bekeken en geanalyseerd. De OCT scans laten zien dat er een dun laagje gecarboniseerd bloed op de lasertip komt, tijdens EVLA procedures uitgevoerd met 810 nm, 940 nm en 1470 nm golflengte. Microscopisch onderzoek laat zien dat de fibertip kleine beschadigingen oploopt door de hoge temperatuur die ontstaat tijdens EVLA. Met deze experimenten tonen we aan dat er tijdens alle EVLA procedures uitgevoerd in een met bloed gevulde vene een sterk absorberend gecarboniseerd laagje bloed op de fibertip ontstaat en dat door de hoge temperatuur die hierdoor optreedt het glasfiber wordt beschadigd. Dit mechanisme is golflengte onafhankelijk, maar is wel afhankelijk van de totaal toegediende hoeveelheid energie.

In hoofdstuk 9 doen we verslag van de experimenten die tot doel hadden de invloed te onderzoeken die verschillende laser parameters, zoals golflengte, terugtreksnelheid en energie dosis hebben op het temperatuurprofiel dat ontstaat tijdens EVLA. Met thermokoppels onderzoeken we de temperatuur veranderingen tijdens EVLA in een experimentele situatie. Het blijkt dat een lagere terugtreksnelheid en een hogere energie instelling beide zorgen voor hogere maximum temperaturen. De verschillende laser golflengtes zijn niet van invloed op de hoogte van de maximale temperatuur. De uitkomsten van deze experimenten laten zien dat de hitte conductie, die kan zorgen voor occlusie van de vene in EVLA, onafhankelijk is van de gebruikte golflengte.

Hoofdstuk 10 beschrijft de behandeling met RFA van incompetente perforerende venen (IPV) en evalueert de effectiviteit en veiligheid op korte termijn. In een klinische pilot studie werden 14 IPV in 12 patiënten met de radiofrequente stylet behandeld. Na 3 maanden werd aan de hand van echo duplex onderzoek de effectiviteit van de behandeling onderzocht en werd gekeken naar complicaties (zoals DVT). Bij duplex onderzoek bleek dat 9 van de 14 IPV (64%) dicht waren en dat de overige perforerende venen nog reflux hadden. Twee

patiënten rapporteerden gelokaliseerde paresthesieën, er was geen sprake van een DVT. We concluderen dat RFA van IPV een veelbelovende behandeling zou kunnen zijn, maar voor het succes van deze behandeling is het noodzakelijk de juiste patiënt met een geschikte IPV te selecteren. Verdere standaardisatie van de procedure is nodig en vergelijkende onderzoeken tussen RFA en andere behandelingen van IPV zijn gewenst.

In hoofdstuk 11 wordt een pilot studie beschreven met een nieuwe thermische ablatie methode, namelijk endoveneuze stoom ablatie (EVSA). De veiligheid van EVSA is in schapen onderzocht door middel van cardiovasculaire metingen tijdens EVSA. Met echo duplex onderzoek is de occlusie van de behandelde vaten te beoordeeld en de behandelde vaten zijn microscopisch bekeken. Twintig vaten in 19 patiënten met een VSM of VSP insufficiëntie zijn met EVSA behandeld. Alle behandelde vaten van schapen waren geoccludeerd Er waren geen cardiovasculaire veranderingen gezien tijdens de behandeling. Microscopisch onderzoek van de behandelde vaten toonde typische veranderingen van de vaatwand, zoals het verdwijnen van de endotheellaag, fibrotische trombosering en grote veranderingen in collageen vezels ter plaatse van de tunica media. EVSA was effectief in de 19 behandelde patiënten, 13 van de 20 behandelde venen waren volledig geoccludeerd en in 7 venen was een klein segment gerecanaliseerd na 6 maanden, dit leek klinisch echter niet relevant. Negen van de 19 patiënten hadden enkele ecchymosen ter plaatse van de aanprikplaats, 1 patiënt had een oppervlakkige tromboflebitis, en de mediane maximale pijnscore was 1 (0-10). Er waren geen ernstige complicaties zoals DVT, zenuwschade of infecties. De patiënten waren tevreden met de behandeling met een score van 9.25 als mediaan (0-10). EVSA bleek effectief en veilig in deze pilot studie.

Ook hoofdstuk 12 geeft het verslag van een experiment. Met dat experiment wilden we inzicht krijgen in het temperatuurprofiel dat ontstaat bij EVSA en het verschil onderzoeken in hitte inductie van 1, 2 of 3 toegediende pulsen stoom per cm. We hebben dit experiment gedaan omdat niet alle venen van de 19 patiënten in de pilot studie dicht bleken na behandeling. In een experimentele situatie maten we de temperatuur die door toediening van stoom ontstaat met thermokoppels binnenin en aan de buitenkant van een buisje. De maximale temperatuurstijging (ΔT_{max}) aan de wand van het plastic buisje was vrij laag voor 1 puls stoom/cm, maar werd steeds hoger naarmate het aantal toegediende pulsen/cm steeg. Eén puls/cm veroorzaakte een inhomogene ΔT_{max} vergeleken met 2 of 3 pulsen/cm. Bij toediening van 1 puls/cm kwam de temperatuur niet boven 50°C (Δt_{den}, de temperatuur waarbij collageen denatureert) gemeten op 2 mm afstand van de catheter. Bij toediening van 2 pulsen/cm was de Δt_{den} >10 sec; bij 3 pulsen/cm was Δt_{den} >20 sec en meer homogeen dan bij 2 pulsen/cm. Deze experimenten suggereren dat de temperatuurstijging die veroorzaakt wordt door toediening van 1 stoom puls/cm niet voldoende is, terwijl het toedienen van 2 of meer pulsen/cm wel voldoende is om een vene te occluderen.

In hoofdstuk 13 wordt de relatieve schaarste aan gerandomiseerde, mechanistische en dosering studies van nieuwe behandelingen in de flebologie besproken en vergeleken met de lancering van andere nieuwe behandelingen zoals farmaceutica, waarbij vele studies worden gedaan. We laten zien dat de resultaten van bestaande vergelijkende studies soms moeilijk te interpreteren zijn. Daarna worden de resultaten van onze studie naar bijwerkingen van EVLA besproken en wordt speciaal aandacht besteed aan de controverse die bestaat over het diagnosticeren en het behandelen van DVT. Daarna bediscussiëren we de verschillende theorieën over het werkingsmechanisme van EVLA die zijn voorgedragen en we bespreken de theorie die we hebben gebaseerd op onze eigen studies naar het werkingsmechanisme van EVLA. De discussie eindigt met het nadenken over de toekomstige positie van EVSA en met het doen van aanbevelingen voor nader onderzoek.

CHAPTER 15

Dankwoord
List of co-authors
List of publications
Curriculum Vitae
Phd Portfolio

Dankwoord

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Book chapters

Van den Bos, RR, Nijsten T, Klem T. Endoveneuze technieken. In Handboek Flebologie. Neumann (Ed.), in print.

Van den Bos RR, Neumann HAM. Is steam the answer to all problems? In Best practice in venous procedures. Wittens C, (Ed.). 2011.

Van den Bos RR, Kockaert MA, Neumann HAM. Varicose veins. In The PCR-EAPCI textbook. Eeckhout E, et al (Eds). 2011, in print.

Curriculum Vitae

Renate Ruth van den Bos werd 20 augustus 1980 geboren te Gouda en in 1988 verhuisde zij naar Wateringen. In 1998 behaalde zij het VWO diploma aan het Christelijk Lyceum Delft. Het zelfde jaar startte zij haar studie geneeskunde aan de Erasmus Universiteit Rotterdam en ging in Rotterdam wonen. Na het behalen van het doctoraal examen in 2002 studeerde zij een jaar aan de Faculty of Social Sciences and Law van de University of Manchester (Verenigd Koninkrijk). Dat studiejaar sloot zij in 2003 af met een MA in "Health care ethics and law". In 2005 deed zij haar artsexamen en zij kon aansluitend aan het werk als agnio dermatologie op de soa-poli in het Erasmus MC Rotterdam. In februari 2007 werd zij toegelaten tot de opleiding tot dermatoloog bij professor H.A.M. Neumann in het Erasmus MC Rotterdam. Onder supervisie van dr T. Nijsten en professor Neumann begon zij naast de opleiding aan haar wetenschappelijk onderzoek in de flebologie. In de periode juli 2007 tot januari 2009 deed zij een perifere stage in het Catharina Ziekenhuis te Eindhoven. In augustus 2012 hoopt zij de opleiding tot dermatoloog af te ronden.

PhD Portfolio

Summary of PhD training and teaching activities

Name PhD student: Renate van den Bos

PhD period: February 2007 – January 2011

Erasmus MC Department: Dermatology

Promotor: Prof.dr. H.A.M. Neumann

Supervisor: Dr. T. Nijsten

	Year	Workload (Hours/ECTS)
1. PhD training		
General academic skills		
- Biomedical English Writing and communication	2009	4 ECTS
- Workshop Endnote	2009	4 hours
Research skills		
- NIHES course: Introduction to Clinical Research	2009	0.9 ECTS
- Evidence based Medicine Course, Erasmus MC Rotterdam	2009	8 hours
Presentations		
- Congres Cabourg II, Frankrijk. "Complicaties bij EVLT" and "PTS de oplossing van morgen".	2007	2 ECTS
- Course on endovascular techniques, Barcelona. "Treating saphenous varicose veins - the evidence".	2008	1 ECTS
- European Venous Forum, Barcelona. The treatment of saphenous varicose veins: Meta-analysis".	2008	1 ECTS
- European Society for Vascular Surgery, Nice. "Endovenous Laser Ablation, Literature overview".	2008	1 ECTS
- Benelux Vereniging voor Flebologie, Maastricht. "Complicaties na EVLT".	2008	1 ECTS
- Nascholing internisten, EMC Rotterdam. "Varices".	2009	1 ECTS
- Bijeenkomst Huidfonds, Rotterdam. "Nieuw in Flebologie".	2009	1 ECTS
- Congres Cabourg III, Frankrijk. "EVLA: Mechanisms of action".	2009	1 ECTS
- World meeting of the International Union of Phlebology, Monaco. "Complications of endovenous laser ablation: review of the literature and special cases".	2009	1 ECTS
- Duplex cursus, EMC Rotterdam. "Steam ablation" and "Side effects and complications following EVLA".	2010	2 ECTS
- Landelijke Nascholing Bandagisten, Wageningen. "Nieuwe behandelingen van spataderen –stoom- ".	2010	1 ECTS
- European Vascular Course, Maastricht. "The treatment of saphenous varicose veins: a meta-analysis".	2010	1 ECTS
- Landelijke dag voor vaatpatiënten, Oegstgeest. "Nieuw in Spataderen".	2010	1 ECTS
- European Venous Forum, Antwerp. "Steam ablation".	2010	1 ECTS
- American College of Phlebology, Orlando. "Steam ablation".	2010	1 ECTS
- Onderwijs afdeling Heelkunde, EMC Rotterdam. "Endoveneuze technieken voor varices".	2010	1 ECTS

International conferences

-	European Venous Forum, Istanbul, Turkey (29 June-1 July).	2007	1 ECTS
-	International Congress of Phlebology, Bologna, Italy (4-5 April).	2008	1 ECTS
-	European Venous Forum, Barcelona, Spain (26-28 June).	2008	1 ECTS
-	European Society for Vascular Surgery, Nice, France (5-7 September).	2008	1 ECTS
-	World meeting of the International Union of Phlebology, Monte Carlo, Monaco (31 August-4 September).	2009	1 ECTS
-	European Vascular Course, Maastricht, the Netherlands (25-27 February).	2010	1 ECTS
-	European Venous Forum, Antwerp, Belgium (24-26 June).	2010	1 ECTS
-	American College of Phlebology, Orlando, USA (3-6 November).	2010	1 ECTS

Seminars and workshops

-	Stichting Nederlandstalige Nascholing voor Dermatologie en Venereologie Workshop Flebologie.	2007	1 ECTS
-	Workshop en cursus Flebologie, "De varix: van richtlijn tot DBC".	2008	1 ECTS
-	Star Academy 2009 "Presenteer jezelf succesvol".	2009	1 ECTS

Other

-	Stichting Nederlandstalige Nascholing voor Dermatologie en Venereologie – Therapeutical innovations.	2008	1 ECTS
-	Wetenschappelijke vergadering van de Nederlandse Vereniging voor Experimentele Dermatologie.	2008	1 ECTS
-	Nederlandse Vereniging voor Dermatologie en Venereologie – Nascholing Basaalcelcarcinoom en Varices.	2008	1 ECTS

Occasional reviewer for:

-	Journal of Endovascular Therapy	2009	4 hours