ENDOVENOUS LASER ABLATION

MYTHS UNRAVELED

WENDY S.J. MALSKAT

Endovenous Laser Ablation - Myths unraveled

Wendy S.J. Malskat

Financial support for the printing of this thesis was generously provided by

And also by LEO Pharma, La Roche Posay, Medi, Mylan, Dos Medical,
Livit Orthopedie, Fagron, Chipsoft, Schmidt Medica

ISBN: 978-94-6361-158-9

Layout and printed by: Optima Grafische Communicatie (www.ogc.nl)
Design: Maarten Smits

Endovenous Laser Ablation - Myths unraveled

Endoveneuze laser ablatie - mythes ontrafeld

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus Prof.dr. R.C.M.E. Engels
en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
vrijdag 9 november 2018 om 11.30 uur

door

Wendy Sophia Jacoba Malskat
geboren te Heerlen

Erasmus University Rotterdam

Erasmus

Promotiecommissie

Promotor:	Prof.dr. T.E.C. Nijsten
Overige leden:	Prof.dr. H.J.M. Verhagen Prof.dr. E.P. Prens Prof.dr. C.W.M. van der Geld
Copromotor:	dr. R.R. van den Bos

In time and with water, everything changes
Leonardo Da Vinci

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Chapter 1

General introduction

BACKGROUND AND EPIDEMIOLOGY

Chronic venous disease (CVD) is defined as (any) morphological and functional abnormalities of the venous system of long duration either by symptoms and/or signs indicating the need for investigation and/or care (1). CVD is a common medical condition; the prevalence of varicose veins is about 20-25% of the general Western population (2). Chronic venous insufficiency (CVI) is a term used only for advanced CVD, with functional abnormalities of the venous system resulting in edema, skin changes or venous ulcers (1). Prevalence of CVI is increasing with age and is somewhat higher in females than in males (3). The incidence of venous leg ulcers, the end stage of CVI, is much lower than the incidence of varicose veins; about 1% of the patients with CVI will develop a venous leg ulcer (2). It is estimated that about 50% of the venous leg ulcers are the result of superficial varicose (4), but it is difficult to predict which of the patients with superficial venous incompetence will develop an ulcer. CVD has a substantial socio-economic impact, mainly because the care for patients with venous leg ulceration is very expensive (5). The costs of patients with CVD account for approximately 1.5% of the national healthcare budget in the Netherlands (6).

PATHOPHYSIOLOGY

Several mechanisms are associated with venous insufficiency, such as venous valve incompetence, inflammation of the vessel wall, hemodynamic factors and venous hypertension (7). Dysfunctional pump mechanisms (muscle, vascular) can further impair these mechanisms. In the leg, the most important muscle pump is the calf muscle, followed by the plantar plexus.
In upright position, the pressure in the veins is approximately 90 mmHg. After activation of the muscle pumps (by walking), the pressure decreases to 20 mmHg. When there is venous insufficiency this pressure will decrease less. This high venous pressure will result in wall stress and activation of venous endothelial and smooth muscle cells, inducing remodeling of the vein wall (8). In the microcirculation, the high pressure translates to dilated capillaries and an increased capillary filtration of plasma proteins, leukocytes and erythrocytes (9, 10). As a consequence, this results in edema, inflammation, microthrombosis and fibrosis, clinically visible as lipodermatosclerosis and white atrophy. These are serious skin changes that lead to vulnerable skin, predisposing the development of ulcerations (9, 11, 12). Primary varicose veins develop as a result of venous dilatations and/or valve damage in the superficial venous system. Superficial venous disease can originate at the level of a connection between the deep and superficial venous system (saphenofemoral or saphenopopliteal junction or perforating veins) or at the level of

tributaries (13, 14). There is increasing evidence that superficial venous incompetence can either be 'descending' from the most cranial part of a vein/junction distally to the saphenous trunk and tributaries (following the effect of gravity) (15), or 'ascending' with reflux starting from the tributaries upwards towards the saphenous trunk and further up to the junction (13, 15-19).

Secondary varicose veins are caused by reflux or obstruction in the deep venous system after deep vein thrombosis (DVT). Deep venous reflux is the result of dysfunction of the valves of the deep venous system, and may be transferred to the superficial venous system. Residual obstruction of the deep venous system may lead to collateral (superficial) veins, which may have the same appearance as varicose veins, but with absence of reflux. Also, secondary varicose veins may appear as a result of the venous hypertension, caused by venous obstruction.

CLINICAL CHARACTERISTICS AND CLASSIFICATION

Patients with CVD often report multiple and in general subjective symptoms, such as leg heaviness, tiredness, itching, tingling, aching, discomfort, evening edema or muscle cramps. Initial signs of CVD frequently include telangiectasia and reticular veins around the ankle (corona phlebectatica), followed by varicose veins. As CVD progresses, the clinical line of appearance is edema, hyperpigmentation, eczema, induration, lipodermatosclerosis, white atrophy and finally ulceration (Figure 1).

The CEAP classification (Table 1) is used to classify patients with CVD, based on clinical and duplex ultrasound (DUS) findings (20, 21). The CEAP classification describes the Clinical signs of CVD, Etiology (congenital, primary or secondary), Anatomy (superficial, deep and perforating veins) and Pathophysiology (reflux, obstruction or both). The 'C' of the CEAP classification differentiates seven clinical stages categorized from C0 to C6: C0, no visible or palpable signs of CVD; C1, telangiectasia or reticular veins; C2, varicose veins; C3, edema; C4a, pigmentation or eczema; C4b, lipodermatosclerosis or white atrophy; C5, healed venous ulcer; C6, active venous ulcer. The CEAP classification has been developed to allow uniform diagnosis and comparison of patient populations.
Since CEAP is a descriptive classification, a clinical scoring system was developed as a tool to measure disease severity; the Venous Clinical Severity Score (VCSS) (22). The VCSS evaluates different features of venous disease that may alter after treatment: it incorporates ten items concerning symptoms and clinical signs, which are each rated on a four-point scale from 0 to 3. The VCSS is often used in clinical trials, as it facilitates assessment during follow-up.

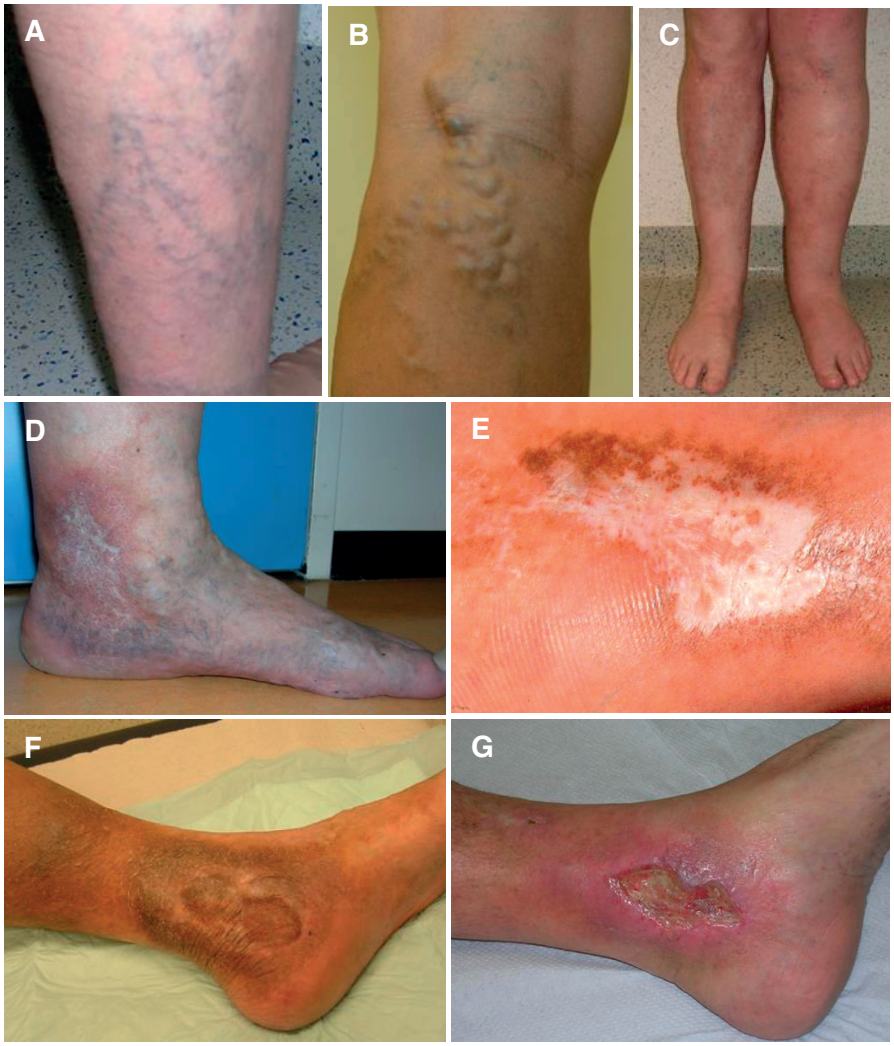

Figure 1. Clinical characteristics of chronic venous insufficiency. A. Reticular veins. B. Varicose veins. C. Edema. D. Lipodermatosclerosis. E. White atrophy and hyperpigmentation. F. Hyperpigmentation and healed leg ulcer. G. Active leg ulcer.

DIAGNOSIS

Duplex ultrasound (DUS) is the gold standard technique in diagnosing varicose veins (23). It is a safe, non-invasive, cost-effective and reliable investigation. With the patient in upright position venous anatomy and hemodynamic parameters of the superficial, deep and perforating veins can be evaluated (diameter, flow direction, reflux time, peak reflux velocity, etc.). Detailed information on the methodology for making a complete

assessment, before and after treatment, is described in consensus documents of the Union Internationale de Phlébologie (UIP) (23-25). Reflux in superficial veins is defined as reversed flow during more than 0.5 seconds, following Valsalva maneuver (for the saphenofemoral junction (SFJ)) or manual compression in the calf or foot. Intensive training is required in order to correctly perform DUS and interpreting the findings. In addition to DUS, other investigations may be indicated to assess venous function and anatomy, mostly in patients with more complex anatomy or when clinical signs are not corresponding with DUS findings. Phlebography, CT- or MR- venography can all be valuable for further assessment.

Table 1. Revision of CEAP classification of chronic venous disease: summary(20)

Clinical classification	
C0	No visible or palpable signs of venous disease
C1	Telangiectasies or reticular veins
C2	Varicose veins
C3	Edema
C4a	Pigmentation or eczema
C4b	Lipodermatosclerosis or white atrophy
C5	Healed venous ulcer
C6	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 (post-thrombotic)
En	No venous cause identified
Anatomic classification	
As	Superficial veins
Ap	Perforator veins
Ad	Deep veins
An	No venous location identified
Pathophysiologic classification	
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	

TREATMENT

There are several reasons to treat varicose veins: it relieves complaints caused by varicose veins, it prevents occurrence of complications such as leg ulcers and it improves cosmetic appearance. The most important treatment options are listed below.

Endovenous thermal ablation

In agreement with current guidelines, endovenous thermal ablation (EVTA) is nowadays the most commonly used technique to treat incompetent saphenous veins (26-28). Most frequently used treatments are endovenous laser ablation (EVLA), radiofrequency ablation (RFA) and to a lesser extent, endovenous steam ablation (EVSA). All procedures are technically quite similar; the vein is entered under ultrasound guidance. A catheter or fiber is inserted in the vein and its tip is positioned about 1-2 cm below the saphenofemoral of saphenopopliteal junction. Under ultrasound guidance, local tumescent anesthesia is administered around the vein, along the entire course that acquires treatment. When the device is switched on (and the fiber/catheter is pulled back), energy is emitted intraluminally, causing thermal damage of the vein wall. Success rates of most frequently used EVTA treatments (EVLA and RFA) seem to be comparable (29, 30).

Endovenous laser ablation

Nowadays EVLA is a generally accepted, easy to execute and patient friendly procedure (31). The precise mechanism of EVLA and the influence of wavelength, type of fiber and power settings are not completely understood. The first EVLA procedures were performed with 810 nm diode laser, at the beginning of the twenty-first century (32, 33). Since then, several EVLA devices with longer wavelengths (for instance 940, 980, 1064, 1320, 1470 and 1500 nm) have been developed. Also, modifications of laser tips are ongoing, with for instance radial, tulip or NeverTouch® tips, replacing the originally used bare fiber. The current tendency is to find the most patient friendly setting and/or device.

Radiofrequency ablation

The first EVTA procedures, nearly twenty years ago, were with RFA using the VNUS® Closure Plus System (34). Nowadays RFA devices such as VNUS® Closure Fast (segmental RFA) and to a lesser extent RFITT (radiofrequency induced thermotherapy) are commonly used. Over the years, RFA has proven its patient-friendliness and long-term efficacy (35).

Endovenous steam ablation

The newest EVTA technique is EVSA. With this technique, sterile water is heated up to a constant temperature of 120°C, and emitted into the vein in pulses. The EVSA catheter

is quite small (1.2 mm in diameter) and more flexible, in comparison to RFA or EVLA catheter/fibers. This flexibility can facilitate placement of the catheter into smaller veins, such as perforating veins or tributaries. EVSA seems to be effective, safe and well tolerated for treatment of incompetent saphenous trunks in two non-comparative studies (36, 37). In the Netherlands, EVSA is currently only used in few occasions, since the health care insurance currently does not cover the treatment costs.

Non-thermal non-tumescent techniques

Within the last few years, several new devices have been introduced, which can be used without tumescent anesthesia and without application of heat, referred to as non-thermal, non-tumescent techniques. One of those devices is Clarivein®, which is used to perform mechanicochemical ablation of saphenous trunks; a combination of mechanical injury of the vein wall and infusion of a liquid sclerosans. Another method is cyanoacrylate glue ablation, which aims to occlude the lumen of the saphenous vein with stepwise injection of small amounts of glue through an intravascular catheter, by means of the VenaSeal® or VariClose® technique (38).

Sclerotherapy

Nowadays sclerotherapy is commonly used with detergent sclerosant solutions such as polidocanol and sodium tetradecyl sulfate. Injections of sclerosant can be applied in liquid or in foam (liquid mixed with air), and can be used for treating telangectasies, reticular veins, incompetent tributaries, perforating veins, saphenous veins or neovascularization. Polidocanol is the only available sclerosant in the Netherlands and can be used in different concentrations varying from 0.5% to 3%. In ultrasound guided foam sclerotherapy (UGFS), foam is obtained by using 1 ml of sclerosant mixed with 3 or 4 ml of air (by means of the Tessari method) (39), and is immediately injected in the incompetent vein under ultrasound guidance. The sclerosant reacts with the endothelial cells of the vein wall, which induces spasm of the vein, thrombus formation and eventually fibrosis (40). Since foam has an increased contact time with the vein wall, increased surface area and induces contraction of the vein, it appears to be more effective than liquid sclerotherapy (41).

Surgery

Until about 20 years ago, surgical treatment of varicose veins was virtually always performed under general anesthesia and consisted of high ligation and stripping of the incompetent saphenous vein, combined with phlebectomies of incompetent tributaries if necessary. Nowadays, since there are way less invasive techniques available, surgery under general anesthesia has become superfluous in the treatment of (uncomplicated cases with) incompetent saphenous trunks. However, ambulatory phlebectomies (AP)

are still the golden standard of treating clinically visible and palpable incompetent tributaries. AP's are performed in technically the same manner for decades, but are currently executed under local or tumescent instead of general anesthesia.

Compression therapy

Compression therapy has been used for centuries and still plays an important role in treatment of CVI, especially after endovenous or surgical treatment, and as a key therapy for patients with venous ulcers (26, 27). In patients with CVD, elastic and non-elastic garments, bandaging or intermittent pneumatic compression devices decrease the venous pressure at level of the ankle/lower leg, improving microcirculation and therefore reducing edema and clinical symptoms (27, 42).

AIMS OF THIS THESIS

The aim of this thesis was to unravel some enduring myths of EVLA, regarding action mechanisms, in vitro effects, efficacy and patient reported outcomes.

In order to do so, we first summarized the technically known working mechanisms of EVLA in a review, along with additional explanatory optical-thermal mathematical models (chapter 2).

Secondly, we created temperature profiles of different EVLA devices and settings, EVSA and RFA, with in vitro experiments (chapter 3), to give more insight in what happens in the veins when the EVTA device is switched on during treatment.

Thirdly, we investigated the efficacy and patient reported outcomes of EVLA versus the newest form of EVTA, EVSA, in the first RCT with EVSA worldwide (chapter 4).

Fourthly, we examined the difference in patient reported outcomes between short (hemoglobin-target) and long (water-target) EVLA wavelengths in the first RCT on this topic, in order to investigate the deeply rooted, but never properly studied assumption that longer wavelengths are more patient-friendly (chapter 5).

Finally, a meta-analysis of EVLA efficacy was performed to summarize the overall efficacy, but also to differentiate between efficacy of different EVLA settings (energy), wavelengths, outcome definitions and follow-up duration (chapter 6).

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Chapter 2.1

Endovenous Laser Ablation (EVLA): a review of mechanisms, modeling outcomes and issues for debate

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Lasers Med Sci; 2014 Mar;29(2):393-403

ABSTRACT

Endovenous Laser Ablation (EVLA) is a commonly used and very effective minimal invasive therapy to manage leg varicosities. Yet, and despite a clinical history of almost 15 years, no international consensus on a best treatment protocol has been reached so far. Evidence presented in this paper supports the opinion that insufficient knowledge of the underlying physics amongst frequent users could explain this shortcoming. In this review we will examine the possible modes of action of EVLA, hoping that better understanding of EVLA-related physics stimulates critical appraisal of claims made concerning the efficacy of EVLA devices, and may advance identifying a best possible treatment protocol. Finally, physical arguments are presented to debate on long-standing, but often unfounded, clinical opinions and habits. This includes issues such as 1. the importance of laser power versus the lack of clinical relevance of laser energy (Joule) as used in Joule per cm vein length, i.e. in Linear Endovenous Energy Density (LEED), and Joule per cm^2 vein wall area, 2. the predicted effectiveness of a high power and fast pullback velocity, 3. the irrelevance of whether laser light is absorbed by hemoglobin or water, and 4. the effectiveness of reducing the vein diameter and the vein's blood content during EVLA therapy.

INTRODUCTION

Endovenous laser ablation (EVLA) has become a common minimal invasive therapy to manage leg varicosities. Clinically, scientifically and commercially it is a fascinating therapy. Clinically, because EVLA took over surgical stripping as a result of its very high success rate with minimal complications at all laser wavelengths, laser powers and pullback velocities used (1). Scientifically, because the consented mechanism of action, i.e. achieving irreversible thermal injury of the vein wall, may be reached by several mechanisms of which the individual contribution is still under debate (2, 3). Commercially, because gaps in knowledge of the mechanism of action created space for a wide variety of treatment protocols, frequently introduced by the industry as new and more effective laser wavelengths. Yet, and despite all efforts since 1999 (4), it is still unknown whether an optimal protocol can be defined.

There are two main modes of action in EVLA proposed so far, both related to the conversion of absorbed laser light energy into heat. The first is heating of blood, vein wall and perivenous tissue by direct absorption of the laser power emitted from the fiber and scattered by the blood towards the other tissues, where the generated heat in the blood also diffuses to the vein wall (5). When direct absorption of laser light by the blood close to the fiber tip generates temperatures in excess of 100°C, steam bubbles will be generated and spread within the lumen in the same way as mentioned below (under C). The second mode of action is heating of the vein wall by heat transfer from the hot black layer of carbonized blood sticking to the fiber tip. This transfer may be: (A) via direct contact between the hot tip and the vein wall (4, 8), (B) via diffusion through the blood (5-11), (C) by boiling steam bubbles which are formed in the hot carbonized layer, grow, detach and travel downstream from the tip to condense near or at the wall (12, 13), or (D) by Planck's black body radiation (7).

This review aims at increasing the knowledge of the physics surrounding EVLA amongst clinical users of the technique. We suppose that limited awareness of EVLA-related physics may have left too much room for inadequately substantiated claims from industrial parties concerning the efficacy and safety of specific laser settings. This may also have hampered the development of an internationally consented best treatment protocol. We will therefore review (some of) the physics involved in EVLA and will analyze the contribution of the main modes of action of EVLA in an optical-thermal computational simulation model. Finally, physical arguments are presented to debate on certain long-standing, but unfounded, clinical opinions and habits.

Presentation of this paper is in two parts plus two Appendices. Part I includes details surrounding the two mechanisms of action proposed so far, as well as a brief presentation of the two computational models of EVLA. Part II addresses important issues for debate within the EVLA community. Appendix 1 presents the underlying physics of the optical-

thermal interaction of laser-irradiated tissue and Appendix 2 presents an estimate of steam production by a laser irradiated hot carbonized blood layer of about 1000°C.

PART I. MECHANISMS

Optical-thermal response of laser-irradiated tissue

The optical-thermal response of laser-irradiated blood, vein wall and perivenous tissue aims to assess the temperature distribution of these tissues when irradiated by laser light. There are two separate mechanisms. First, the optical interaction, where the laser power is incident on an area of the tissue, i.e. the irradiance (Watt/area), propagates into the tissue and rearranges itself into a spatial fluence rate distribution (Figure 1), due to the tissue's absorption and reduced scattering coefficients, μ_a, μ_s' (see Table 1 for definitions). Second, the thermal interaction, where the absorbed part of the laser fluence rate in an infinitesimal small tissue volume (Figure 1), which equals the product of fluence rate and absorption coefficient (Eq. [8] in Appendix 1), is converted into heat and causes an increased temperature in that volume. Fluxes of heat (Watt/area) then develop which propagate from hotter to cooler tissue locations by heat conduction (see Appendix 1, part B1). These heat flows (or fluxes) affect the temperature distribution within the tissue. The temperature controls the energy stored in that small tissue volume. Finally, the rate of change of energy that is stored in the small tissue volume (Figure 1) follows from combining the absorbed power in that tissue volume (the product of fluence rate and absorption coefficient, Eq. [8] in Appendix 1 below) and heat conduction into or out of that volume. The bio-heat equation describes this mechanism of optical-thermal tissue response as a power conservation law in that infinitesimal volume (Watt/vol) as

$$\frac{\textit{Rate of Change of Stored Energy}}{\textit{Volume}} = \frac{\textit{Absorbed Power}}{\textit{Volume}} \pm \frac{\textit{Rate of Heat Conduction}}{\textit{Volume}} \qquad [1]$$

The plus sign denotes heat diffusion into the infinitesimal volume and the minus sign out of the volume. In Appendix 1, we give a brief survey of the underlying physics of optical-thermal laser-tissue interaction, including the derivation of the bio-heat equation in part B2 of Appendix 1, Eq. [9], which is the basis for the two existing computational models of EVLA (5-7), explained below in section 'computational models of EVLA therapy'.

Heating the vein wall by heat transfer from the hot layer of carbonized blood

When a fiber tip emits laser light in air or in clear water, the tip will not be heated up. However, when embedded in blood, the tip will be covered by a thin layer of carbonized blood, virtually immediately after switching on the laser power because the blood close to the tip absorbs the power, heats up, coagulates, denatures, and subsequently reduces

to carbon particles of high temperatures, typically over 200°C (14), which form a thin carbonized blood layer that sticks to the fiber tip. The layer absorbs a substantial part (measured to about 45%) of the emitted light (10), which causes very high temperatures, in the order of 1000°C (15-17).

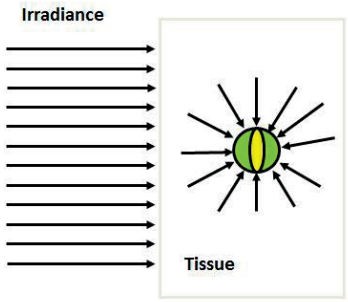

Figure 1. Definition of laser fluence rate. The tissue is irradiated by a collimated laser beam of power P incident on tissue area A, i.e. with irradiance P/A (Watt/area). The infinitesimally small volume inside the tissue, here the green sphere receives a continuous stream of collimated and diffused photons through its surface (represented by the "arrows"). The fluence rate is defined as all the incoming laser power divided by the (yellow) cross sectional area of the sphere (Watt/area).

Table 1. Definitions, symbols and physical units of important physical parameters in optical-thermal modeling

Physical term	Symbol (unit)	Description
Absorption coefficient	μ_a (m^{-1})	Fraction of absorbed light after travelling over an infinitesimally small distance through the medium
Scattering coefficient	μ_s (m^{-1})	Fraction of scattered light after travelling over an infinitesimally small distance through the medium
Reduced scattering coefficient	μ_s' (m^{-1})	A parameter incorporating the scattering coefficient and the scattering anisotropy factor g. It equals μ_s (1 - g)
Irradiance	E (*Watt/area*)	Incident laser power (P) on area (A) of the tissue, where $E=P/A$
Radiant exposure	H (*Joule/area*)	Incident laser energy on area (A) of the tissue. The radiant exposure is the irradiance times irradiation time, or $H=E\cdot t$
Fluence rate	Φ (r) (*Watt/area*)	The total amount of collimated and diffuse light *power* entering the surface of an infinitesimal small sphere *inside* the tissue, at tissue coordinate r, divided by the cross sectional area of that sphere
Fluence	Ψ (r) (*Joule/area*)	The total amount of collimated and diffuse light *energy* entering the surface of an infinitesimal small sphere *inside* the tissue, at tissue coordinate r, divided by the cross sectional area of that sphere. The fluence is the fluence rate times the irradiation time, or $\Psi(r) = \Phi(r) \cdot t$
Specific heat capacity	c ($J{\cdot}kg^{-1}{\cdot}°C^{-1}$)	Amount of heat (Joules) required to raise the temperature of one kg of a medium by one °C in the absence of any heat loss
Thermal conductivity	k ($W{\cdot}m^{-1}{\cdot}°C^{-1}$)	The thermal energy that is conducted in one second (J/s = W) over one meter driven by a difference in temperature of one °C
Temperature	T (°C)	A thermal measure of the average kinetic energy (or thermal vibrations) of particles or matter or radiation, independent of the amount of material
Laplace differential operator	Δ (m^{-2})	In Cartesian coordinates: $(d^2 / dx^2) + (d^2 / dy^2) + (d^2 / dz^2)$

There are at least four mechanisms by which the hot tip may transfer its heat to the vein wall: (A) by direct contact, (B) by heat conduction, (C) by steam bubbles and the heat-pipe principle, and (D) by Planck's black body radiation.

Direct contact between the hot fiber tip and the vein wall

Direct contact between hot tip and vein wall occurs when bare fibers are used. These contact points show as carbonization of the tissue, and because of the temperatures of over 200°C, prolonged contact may perforate the vein wall, an adverse effect of the use of bare fibers (12, 16, 17). Remarkably, this direct contact mechanism has been suggested as the primary mechanism of action. First, by Navarro et al. in their patent, filed in 1999 (4) and more recently by Fan and Anderson (8). The latter authors, however, discarded three important alternative mechanisms not yet identified as an EVLA mechanism in 1999. First, apparently unaware of the fact that steam bubbles are a consequence of the hot carbonized layer, they argued against steam bubbles as an EVLA contributor because these bubbles (indeed) cannot cause the very high tip temperatures (see also 'steam bubbles and the heat pipe principle' below). Second, optical-thermal interaction of laser light by blood and vein wall was ignored, in part due to penetration depth estimates of 0.2 to 0.3 mm, rather than 1.1 to 1.2 mm, based on blood absorption and scattering at 980 and 1320 nm (5, 18), see also Table 2 below. Third, heating the vein wall by conduction from the hot fiber tip was mentioned neither (11). In our opinion, it is unlikely that direct tip-wall contact is the main EVLA interaction mechanism: first, because EVLA procedures are effective without direct tip-wall contact (19) and second, because it seems unlikely that a line of denatured vessel wall of about 0.6 mm width can achieve permanent closure of the entire vein.

Table 2. Optical parameters

	μa [1/mm]			**μ's [1/mm]**		
λ (nm)	**Blood**	**Vein wall**	**Perivenous tissue**	**Blood**	**Vein wall**	**Perivenous tissue**
810	0.21	0.2	0.017	0.73	2.4	1.2
840	0.21	0.18	0.019	0.75	2.33	1.18
940	0.28	0.12	0.027	0.64	2.13	1.1
980	0.21	0.1	0.030	0.6	2.0	1.0
1064	0.12	0.12	0.034	0.58	1.95	0.98
1320	0.3	0.3	0.045	0.54	1.8	0.9
1470	3.0	2.4	0.35	0.52	1.7	0.84
1950	10.0	7.5	0.35	0.52	1.7	0.84

λ, wavelengths as used in our model computations (23); μ_a, absorption coefficient; μ'_s, reduced scattering coefficient

Heat conduction

Heat conduction is described by a flow (or flux) of heat (Watt/area) that propagates from a hotter to a colder tissue location. The temperature gradient is the driving force of this flow with the thermal conductivity (Watt·m^{-1}·°C^{-1}) as proportionality factor, accounting for the effectiveness of the medium (here tissue) to facilitate this thermal transport process. The heat conduction part of the bio-heat equation follows from the gradient of the heat flow over the infinitesimal volume (it is instructive to consider the x-direction only, the small volume then is a small area and an infinitesimal small length in the x-direction), which becomes a diffusion equation in the temperature of that volume (see Appendix 1, section B1, for more details).

Steam bubbles and the heat-pipe principle

The condition of a 1000°C carbonized layer on the fiber tip facilitates heterogeneous nucleation in the tiny pores of the layer, because the associated (thermal) energy content allows the formation of a considerable amount of small steam bubbles per second from residues of blood soluble gases, in Appendix 2 estimated to be at least several mm^3/s. These bubbles then grow, detach and travel downstream from the fiber tip. Travel distances of about 20 mm have been observed (13). During their travel, the bubbles cause additional motion and stirring in the fluid, which promotes the convective transfer of heat to the near surroundings. The bubbles may condense already during their travel, and by condensation they release their latent heat by vaporization. As a consequence, the volume of blood in which steam bubbles travel readily achieves a high temperature of about 100°C.

A fluid flow and heat transfer process, in which evaporation takes place in one part of the volume and condensation in another part, resembles a heat pipe. Heat pipes were developed in the forties of the last century for industrial applications, because of their remarkable efficiency of heat transport (20). When a bubble is formed, the liquid around it is superheated*, i.e. in* blood at a temperature exceeding the saturation (steam) temperature of 100°C. The energy content of the liquid is used for bubble growth and only when sufficient energy is available the bubble detaches and moves to colder spots in the vein lumen. In an industrial heat pipe, the condensed bubble content moves as a liquid film back to the hot part of the heat pipe, where superheating, bubble formation, propagation, condensation and moving back keeps occurring. This results in a much faster and more effective transfer of heat than is possible by diffusion. In a vein, the condensed bubble content is a small amount of water, which is transported away from the location of the fiber tip, where the EVLA treatment takes place, because of the pullback velocity.

When bubbles are non-condensing over 20 mm, the temperature of the volume in which they move must be at 100°C. Because tissue becomes irreversibly damaged if a

temperature of 75°C occurs during one second, or 70°C during 10 s, suggested by thermal rate process theory (Figure 13.19 of (14)), pullback velocities of a few mm/s warrant the conclusion that the vein wall will be in close contact with a volume of liquid close to 100°C consisting of steam bubbles and hot carrier liquid long enough to become irreversibly damaged. It should also be noted that heat loss mechanisms such as thermal conduction and convection create a temperature gradient around the steam bubbles, thus also at the vein wall. However, the temperature of the steam bubbles is not influenced by these heat loss mechanisms. Since this is a very effective mode of heat transfer, it has been postulated albeit not proven to be the most import mode of action of EVLA (9, 12).

In case the heat pipe mechanism of creation and moving of steam bubbles fails to occur, the hot carbonized layer at the fiber tip becomes deprived from this effective cooling mechanism. The immediate consequence is the generation of a stagnant steam bubble close to the fiber tip. By the absence of bubble transport the steam bubble stays and grows. The thermal conductivity of steam is low so that the temperature of the carbonized layer will increase even more than otherwise. Eventually, the fiber tip may start to glow and even melt. We have observed this process in vitro in the laboratory and are currently assessing the conditions under which it occurs. Melting of the fiber tip has been observed clinically (8, 9) and is obviously an undesirable event during EVLA treatment.

Planck's black body radiation

A medium at surface temperature T emits a spectrum of "black body" radiation with a heat flow proportional to T^4. The wavelength of maximum heat flow also depends on T. The sun's surface of about 6000°C, emitting visible light with a maximum in the yellow, is a good example. However, fiber tip temperatures of about 1100°C turn out to be too low to produce a significant thermal effect at the vein wall, due to the very low radiated power of 0.023 W over the whole black body spectrum; maximum emission at 2650 nm and wavelengths of half maximum at 1600 and 4800 nm. These wavelengths are however well absorbed by water (7).

Computational models of EVLA therapy

Mordon's model

The first computational model of EVLA was by Mordon et al. (5, 6). Mordon's model uses solutions of Eq. [1], or Eq. [9] of Appendix 1, incorporating for the fluence rate an approximate analytical solution of the transport equation of light propagation in an absorbing and scattering medium (21). The assumption is that the laser light emitted out of the fiber is from a point source at $r = 0$ with power P (W), implying that the fluence rate at radial distance r from the source is given by

$$\Phi(r) = P \frac{3(\mu_a + \mu_s')}{4\pi r} e^{-r\sqrt{3\mu a(\mu a + \mu s')}} \quad [2]$$

where μ_a, μ_s' are the absorption and reduced scattering coefficients (see Table 1 for definitions). Mordon's model additionally includes that a blood temperature in excess of 100℃ is approximated by keeping it to 100℃. The efficacy of EVLA was related to the computed maximum temperature of the inner vein wall.

Our model

The second computational model for EVLA was developed by our group (7). We used the same fluence rate distribution, Eq. [2], in Eqs. [1] and [9], as Mordon did, but we also included the thermal effects of the thin layer of carbonized blood. We used that the source term of absorbed laser power in this layer is given by 0.45*P* / (*layer volume*), incorporating that the black layer absorbs about 45% of the power, virtually independent of wavelength, measured between 450 and 1650 nm (10). Furthermore, the strong heat transfer from fiber tip to vein wall by the steam bubbles and the heat-pipe principle has been approximately incorporated by raising the thermal conductivity of blood 200 times when blood temperature exceeds 95°C. Although this tends to restrict calculated blood temperatures to about 100°C, temperatures in excess of that value do occur in the simulations. As in Mordon's model, EVLA efficacy was related to the maximum temperature of the inner vein wall. Some results of computations with our model are shown below.

We acknowledge that EVLA modeling still lacks a realistic mathematical account of the effects of steam bubbles. This computational fluid dynamics project, although in progress, is a very complex numerical problem which requires simultaneously solving of several coupled partial differential equations, including the Navier-Stokes equation, for describing the production, growth, propagation and condensation of steam bubbles, in combination with the bio-heat equation [9] and Eq. [2].

PART II. ISSUES FOR DEBATE

Clinical relevance of laser power, laser energy, and Joule per cm vein length in Linear Endovenous Energy Density (LEED)

A photon of light at a specific wavelength either behaves as an electro-magnetic wave or as a particle, see e.g. the book chapter by Walsh (22). Importantly, a photon has energy (Joule) whose value is proportional to the frequency of the associated wave, hence inversely proportional to the wavelength. Thus, a photon, once absorbed by a tissue molecule, elevates the energy of that molecule which may result in a very small temperature rise. Clinically, two phenomenons are important. The first is a continuous stream of photons interacting with a volume of tissue; the photon stream then is represented by the fluence rate of laser power (Watt/area), see Figure 1 and Table 1.

The second is a short pulse of photons interacting with the same tissue volume; the photon stream then is represented by the fluence of laser energy, the product of fluence rate and pulse duration (Joule/area). We stress that the term fluence denotes the total energy of all photons that enter the infinitesimal spherical volume inside the tissue divided by the sphere's cross sectional area (see Figure 1 and Table 1). Unfortunately, fluence often is misused to denote the radiant exposure (Joule/area), the total energy of laser light that is incident on a tissue surface, the product of irradiance and irradiation time (Table 1). So, in the first case of continuous wave laser irradiation (laser light given during at least 0.1 s), laser power, not laser energy, is the most suitable way to describe the thermal response of the irradiated tissue (see Eq. [8] of Appendix 1). Therefore, the frequently used Linear Endovenous Energy Density (LEED), in units of Joules per cm of vessel treated (Joule/cm), does not properly represent the setting of EVLA procedures. LEED originates from the ratio of laser power (Watt) and pullback velocity (cm/s)

$$\frac{Watt}{cm/s} = \frac{Watt \cdot s}{cm} = \frac{Joule}{cm} \qquad [3]$$

Obviously, crucial information disappears when two essential parameters are amalgamated into one, here by taking their ratio. Using LEED, without specifying power or pullback velocity, would imply that, e.g. for 25 Joule/cm at 1470 nm, one cannot distinguish between, for instance 10 Watt given with 0.4 cm/s, most likely resulting in permanent vein closure, and 1 Watt with 0.04 cm/ s, most likely without much clinical effect. Our model simulates for at 2 mm inner wall diameter a maximum increase in inner vein wall temperature of 79℃ and 62℃ respectively. The first temperature will certainly result in irreversible damage of the vein wall, but with the second temperature irreversible damage is not certain. Interestingly however, this result at 1 W, 0.04 cm/s gives a surprisingly high inner wall temperature of 62℃, which is close to coagulation temperatures. The parameters laser power and pullback velocity are both essential since the laser power (fluence rate) rather than laser energy, is the source for the thermal response of EVLA, and the pullback velocity determines the time period during which the laser power affects a location on the vein wall. In addition, we acknowledge that the diameter of the vein treated during EVLA should also be considered an essential parameter for EVLA efficacy.

In conclusion, we strongly recommend to always provide the two parameters laser power and pullback velocity in all future papers on EVLA and to avoid the use of laser energy (Joules), in LEED, and the incorrect usage of 'fluence'.

Laser power versus pullback velocity ratios

Comparing the efficacy of combination of various powers and pullback velocities requires EVLA outcomes at constant power/velocity ratios, i.e. at constant Joule/cm

values (Eq. [3]), because other ratios are bound to yield different efficacies. Our model predictions (23) suggest an interesting and perhaps clinically relevant outcome. The maximum temperature during EVLA with a 1470 nm laser, of a 2 mm inner vein wall diameter, simulated with a power/velocity ratio of 30 Joule/cm (24), at three different power settings (3, 6 and 12 W), necessitating appropriate pullback velocities (1, 2 and 4 mm/s), showed that the highest power setting and fastest pullback velocity resulted in the highest inner vein wall temperature (Figure 2). This simulation thus predicts a better EVLA efficacy at higher power and higher velocity combinations and underscores the value of reporting both parameters.

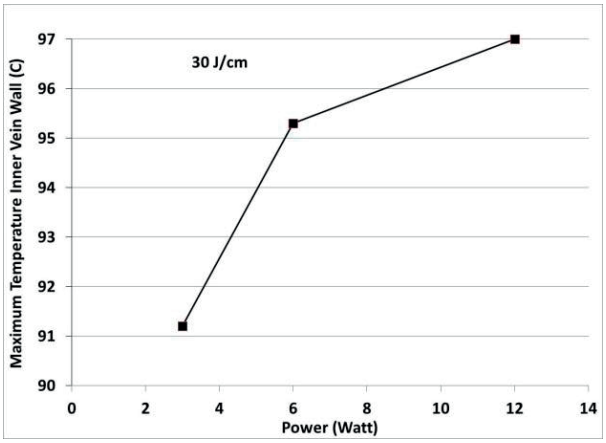

Figure 2. Maximum temperatures at the inner vein wall at 1470 nm at various laser powers (3, 6, 12 Watt) and pullback velocities (1, 2, 4 mm/s), at a power/velocity ratio of 30 Joule/cm, Eq. (3).

Influence of target chromophore and wavelength on efficacy of EVLA

Laser light causes a rise in temperature when it is absorbed by a tissue chromophore. Table 2 gives absorption and reduced scattering coefficients of the blood, vein wall and perivenous tissue that we used in our model (23). The absorption target of the shorter wavelengths (810 nm, 940 nm, 980 nm and 1064 nm) was assumed to be the hemoglobin in intravascular red blood cells. In contrast, wavelengths of over 1200 nm are absorbed by water, and more so with increasing wavelength (24-26). From this, the assumption was that the absorption target of the longer wavelength lasers (1320 nm, 1470 - 1500 nm and 1950 nm) had to be water in the endothelial cells (25). Physiologically, however, this is a questionable reasoning, since blood cells also contain over 60% water (27) that equally absorbs these longer wavelength waves. So, with sufficient laser power the irradiated blood volume will always heat up to coagulation temperatures, irrespective of whether (most of) the laser light was absorbed by hemoglobin or by water.

Consistent with this conclusion are the findings of comparative EVLA studies, which demonstrated that all wavelengths are equally effective in obliterating veins, although patients treated with longer wavelengths reported less postoperative pain, used fewer

painkillers and/or were less likely to have ecchymoses (26, 28-30). However, laser power, pullback velocity and/or type of fiber tip also varied, and longer wavelength treatments were favored by lower power settings. Thus, to contribute this favorable effect to wavelength only is illegitimate. A randomized controlled trial, comparing short and long wavelength EVLA with the same laser parameters (power, pullback speed and fiber) is needed to ascertain if long wavelengths are indeed superior to short wavelengths in terms of patient reported outcomes.

Model simulations at 1470 nm with commonly used settings for power and pullback velocity showed, quite interestingly, that a hot fiber tip doubles the temperature increase at the inner vein wall compared to the simulated situation of keeping the tip at room temperature (23) (Figure 3). This phenomenon explains, at least in part, why differences in wavelengths have little, if any, influence on the efficacy of the procedure, here expressed by the maximum temperature of the inner vein wall. Nevertheless, our model simulations (23) do predict a slightly increased EVLA efficacy at 1470 nm, compared to EVLA with the shorter wavelengths (about 10 ^{0}C greater rise in vein wall temperature), for all vein diameters larger than 1 mm considered in the model (Figure 4). However, the reliability of this interesting prediction has yet to await the full mathematical introduction of the effects of steam bubbles.

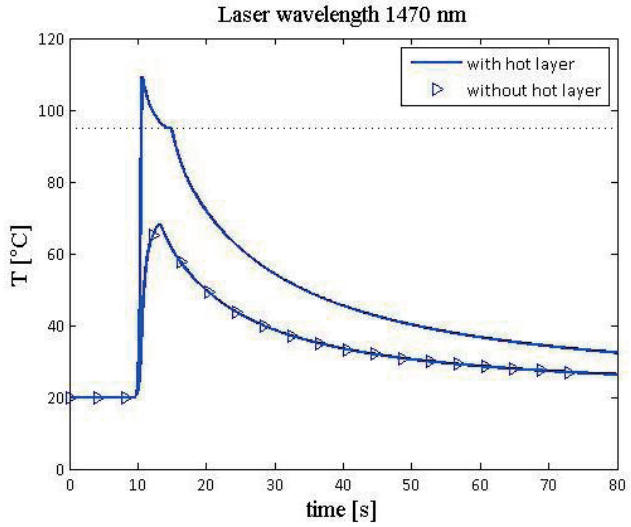

Figure 3. Computations of vein wall temperatures in a 3 mm diameter vein, using a 0.6 mm diameter laser fiber, 15 Watt of power and 0.2 cm/s pullback velocity, as a function of time. The computations give the temperature at a fixed inner vein wall position, 2 cm above the fiber tip's starting position at t = 0, so the tip is closest to that vein wall position at 10 s after laser switch-on and start of pullback. The computations are either with the hot tip layer included (normal line), or simulated with this layer kept at room temperature (line with symbols) (from (23)).

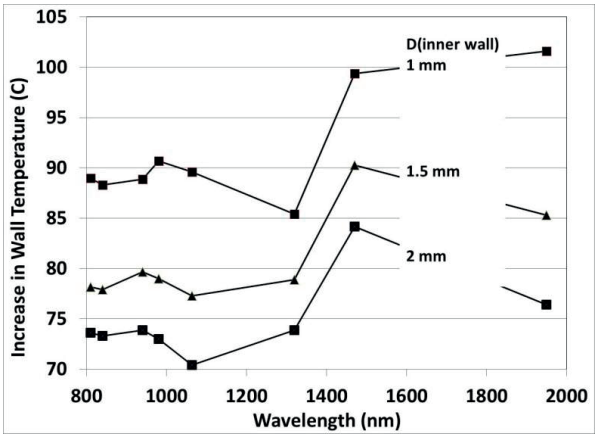

Figure 4. Inner vein wall temperature increase versus wavelength simulated for inner vein diameters of 1, 1.5, and 2 mm, at 15 Watt, 2 mm/s.

Vein diameter reduction

It is thought that the amount of intraluminal blood volume affects destruction of the vein wall. A higher blood volume is assumed to absorb a larger amount of light power, hence limiting the power that reaches the vein wall and, thus, reducing the vein wall's increase in temperature. In vitro and in vivo studies have been performed to demonstrate the importance of reducing the blood volume of the vein, expressed as emptying the vein of its blood (31, 32), by tumescent anesthesia and Trendelenburg positioning.

In a recent review, Vuylsteke et al. (2) stated that direct energy absorption by the vein wall is the most efficient mechanism of EVLA. However, an interesting prediction of our model (23) is that direct absorption of the laser light power by the vein wall had little effect on the increase in wall temperature (Figure 5). Nevertheless, our model does show a

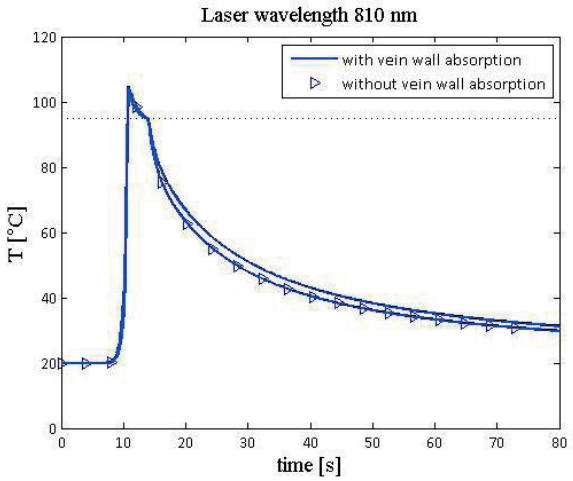

Figure 5. Temperature profiles at the inner vein wall, 3 mm diameter, as a function of time, with vein wall absorption included (lines) and with zero vein wall absorption (lines with symbols), at 810 nm, 15 Watt, 2 mm/s (from (23))

progressive increase in vein wall temperature during EVLA with progressive diminution of vein diameter (Figure 4), however, with a different explanation for this phenomenon than Vuylsteke's (2). According to our model it is caused by the combination of two separate heat flows to the vein wall, which originate from two independent heat sources at or near the fiber tip. The hot carbonized layer on the fiber tip is the first heat source, and the hot blood surrounding the fiber tip, heated by direct absorption of the emitted laser light, is the second heat source. This latter mechanism is obviously also included in Mordon's model (5, 6), although not explicitly mentioned as a source for the thermal effects.

In conclusion, our model predictions confirm the beneficial effects of diameter reduction of the vein lumen as proposed by Vuylsteke's group (2, 31, 32).

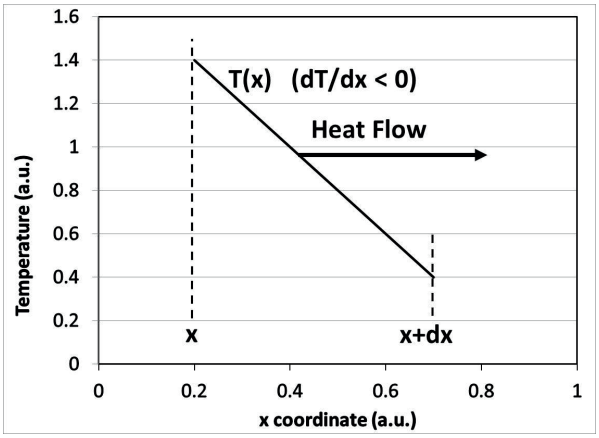

Figure 6. Cartoon of Fourier's law of thermal diffusion, relating the negative gradient of the temperature (T) to the heat flow (or heat flux, in Watt/area) by Eq. (4). The temperature versus x-coordinate curve is linearized between x and x+dx because dx is assumed to be infinitesimally small.

DISCUSSION

EVLA is a fascinating therapy in clinical phlebology and there are several ways to express this perception. One is to address the great efficacy of any EVLA protocol, seemingly irrespective of the chosen laser wavelength, power and pullback velocity, perhaps a consequence of over-treatment by the collective effects of all contributing mechanisms. However, another is the recognition expressed in this paper that despite its great efficacy, EVLA-related physics is still poorly disseminated.

In part, this may be due to the small number of medical physicists and biomedical engineers involved in phlebology, compared to other laser related clinical specialties. Nevertheless, the two computational models developed to simulate EVLA procedures under varying experimental conditions (power, pullback velocity, vein diameter), have significantly contributed to the identification of the various EVLA mechanisms and how

these affect EVLA efficacy, particularly the importance of the hot fiber tip and the unimportance of direct absorption of laser power by the vein wall. Furthermore, we hypothesize that predictions by the future model, in which the effects of steam bubbles are fully incorporated, may result in identifying the most efficient protocol for EVLA therapy.

Concomitantly, the function and effects of the different fiber tips have to be assessed too, and in more experimental detail than has been done so far. For example, it is essential to experimentally verify whether the hypothesis is true that a carbonized layer will not occur on a bare (centered) fiber when the treated vein is more or less 'emptied' of blood by Trendelenburg position and tumescence anesthesia (2). This requires comparing transmission spectra and microscopy of clinically used versus new fibers (10). This part of EVLA related research might confirm or refute the importance of having a very hot tip as well as its subsequent production of steam bubbles. Our model showed a hot tip to be a viable and clinically important EVLA mechanism (Figure 3), whereas the steam bubbles it produces have been previously touted to be the most important EVLA mechanism (9, 12).

In conclusion, we showed that laser power, not energy, pullback velocity and vein diameter during EVLA procedures determine the thermal response of EVLA. The total energy (Joule) given during EVLA contains insufficient information to identify the clinical setting of the procedure, so reporting LEED (Joule/cm) or Joule per cm^2 vein wall, is without much clinical value. However, in the spirit of the Joules/cm^2 equation, it could perhaps be an interesting thought to adjust the laser power to the vein wall diameter, attempting to reduce the incidence of perforation, extravasation of blood and postoperative pain. Whether hemoglobin or water is the EVLA target chromophore is irrelevant because blood consists of over 60% water and about 15% hemoglobin. Thus, the previously stated superiority of longer EVLA wavelengths is flawed, not only on this theoretical basis, but also because patient reported outcomes (26, 28-31) are based on unequal laser parameter settings (power, pullback velocity and/or fiber type), actually applying lower power levels at the longer wavelengths. A smaller vein diameter during EVLA, by Trendelenburg positioning and tumescent anesthesia, is confirmed to be beneficial, not because the vein wall may absorb more scattered laser light but because the vein wall is closer to the two heat sources, i.e. the hot tip with its constant production of steam bubbles, and the thin layer of hot blood immediately surrounding this tip.

APPENDIX 1: OPTICAL-THERMAL LASER-TISSUE INTERACTION

Table 1 summarizes some key terms used in optical-thermal modeling to facilitate understanding the following sections.

Optical laser-tissue interactions

Laser irradiation by a collimated laser beam of power P (Watt), covering a tissue area of A (m^2), implies an irradiance (or incident power per area) of $E = P / A$ (Watt/m^2). When the laser beam is coupled to an optical fiber and the fiber end is kept in air, the emitted light has a divergence which can be as large as 23° (with respect to the fiber axis, thus 46° full divergence), however, when kept in water, or blood, as in EVLA, the divergence angle is smaller, say around 17°, due to the small refractive index difference between fiber material and blood. The sinus of this angle is called the numerical aperture (NA) of the fiber (33). In EVLA therapy (bare) fibers usually have a 0.6 mm diameter.

It is commonly assumed that tissue, including blood, is an isotropic (equal properties in all directions) and homogeneous medium that has wavelength dependent absorbing and scattering properties. Molecules like hemoglobin, melanin, bilirubin and water display strong absorption in the UV region so tissue penetration between 200-400 nm is only up to tens of µm. Blue, green and yellow light (400-550 nm) is absorbed primarily by hemoglobin and melanin. Red and near infra-red light (600-1400 nm) penetrates several mm in tissues, where scattering additionally limits this penetration. Still, longer wavelengths become absorbed intensely by water, and therefore tissue penetration of longer wavelengths is progressively reduced.

Inside the tissue, the collimated beam attenuates exponentially with tissue depth, due to absorption and scattering of the photons. The scattered light is the source for the diffuse light distribution in the tissue. Scattering changes the angle of propagation of a photon. On average, the scattering angle of a photon is much more often in forward than in backward directions relative to its original direction of propagation, which is expressed by the dimensionless anisotropy factor g, having values between -1 and 1, and which are about 0.8 for tissues and over 0.99 for blood (18).

The theory of light propagation in an absorbing and scattering medium is complex and an exact formulation of this theory has not even been created so far. As a next best, the photons are assumed to be particles that interact with randomly distributed absorbing and scattering centers within the tissue, neglecting the possible effects of their electro-magnetic wave-like properties. Even then, photon propagation requires solving the transport integro-differential equation, with only very few known analytical solutions. Here, Monte-Carlo numerical techniques are commonly used to find solutions relevant for the clinical anatomy (34). However, a frequently used approximation, also employed to simulate EVLA therapy (5-7, 23), is the diffusion approximation, where the

transport equation has been reduced to a diffusion equation (including second order spatial derivatives, in Cartesian coordinates expressed in Table 1), assumed to be valid only when scattering dominates over absorption (21). Equation (2) is the example used in the two EVLA models. The most important parameter describing the laser light power distribution within the tissue is the laser light fluence rate, $\Phi(r)$ (Watt/m^2), see Figure 1 and Table 1. Coordinate *r* denotes the radial distance between the origin of a frame of reference (in EVLA the fiber tip in the center of the vein) and the infinitesimal small volume of tissue.

Since the fluence rate includes scattered photons from all directions, a thought-provoking example is wide beam irradiation of tissue, which may result in a fluence rate near the inside tissue surface that exceeds the incident irradiance significantly, even up to a factor of eight (Figure 6.8, page 175, of (21)).

Thermal laser-tissue interactions

Heat conduction

Part of the fluence rate, $\Phi(r)$ (Watt/m^2), will become absorbed in the infinitesimal volume at coordinate *r* (Figure 1) and converted into heat, this part is denoted with the product $\mu_a \varphi(r)$. A local increase in temperature results which causes the heat to flow to surrounding regions that are cooler, a mechanism called heat conduction (35). Different media may differ in their ability to facilitate this thermal transport process. This is expressed in the thermal conductivity (k), (Watt·m^{-1}·°C^{-1}). First, the flow of heat, the official physics term is a flux of heat (Watt/area), at position *x* follows from taking the flow proportional to the temperature gradient over a small distance (*dx*) in the *x* direction, i.e. the temperature at $x + dx$ minus the temperature at *x* divided by *dx*, with the thermal conductivity as proportionality coefficient. Because heat flows from higher to lower *T*, the flow of heat is proportional to *minus* the temperature gradient, thus to $-dT/dx$, or (Figure 6)

$$Heat\ Flow = -k \cdot \frac{T(x+dx) - T(x)}{dx} = -k \cdot \frac{dT}{dx} \qquad [4]$$

This equation is known as Fourier's law of thermal diffusion (Figure 6). Our aim is to derive the bio-heat equation, Eq. [1] and [9] below, whose solution, $T(r,t)$, is the space and time dependent temperature of the infinitesimal small tissue volume (Figure 1), where *t* denotes the irradiation time. This requires an expression for the conduction (diffusion) of heat into or out of that small volume.

In one direction, say the *x* direction, the stored energy will change because of the heat flow that enters at $x + dx$ minus the heat flow that enters at *x*, divided by distance dx, hence, the negative gradient of the heat flow. Thus, from Eq. [4], a second order derivative over coordinate *x* occurs, which is mathematically a diffusion equation, basically expressing the curvature of *T* in the *x* direction, as

$$- \text{Gradient of Heat Flow} = - \frac{\text{HeatFlow}(x + dx) - \text{HeatFlow}(x)}{dx} = k \frac{d^2T(x)}{dx^2} \quad [5]$$

In 3-dimensions, 2nd order differentials then also occur in the other two coordinate directions (see Table 1), which is generally abbreviated by the Laplace 2nd order differential diffusion operator Δ.

The bio-heat equation: conservation of power in an infinitesimal volume

First, from Eq. [1], we recall that the state of the tissue is characterized by its stored energy, which is directly related to its temperature (35), and which may vary with position and time. As before, Figure 1, we consider an infinitesimal volume of tissue at coordinate r. The stored energy in that volume (Joule/volume) then is given by

$$\frac{\text{Stored Energy}}{\text{Vol}} = \rho c T(r) \quad \text{(Joule/vol)} \quad [6]$$

Parameters ρ and c (Table 1) are respectively the tissue density (kg/m^3) and the specific heat capacity (Joule·kg^{-1}·°C^{-1}) at r. We now consider the change in the stored energy/vol in a short time period dt, which is expressed as

$$\frac{d}{dt}(\rho c T(r)) = \rho c \frac{dT(r)}{dt} = \rho c T(r) \quad \text{(Watt/vol)} \quad [7]$$

We assumed that ρc is independent of time. The source for this rate of change in stored energy is the absorbed part of the fluence rate in that infinitesimal volume, which can be derived to equal the product of absorption coefficient and fluence rate, called the source term (36)

$$\frac{\text{Absorbed Power}}{\text{Vol}} = \mu_a \Phi(r) \quad \text{(Watt/vol)} \quad [8]$$

Finally, the rate of change in stored energy in the infinitesimal volume during dt, Eq. [7], can be written as the sum of the absorbed power within that volume, Eq. [8], and the change in power in that volume due to heat diffusion, Eq. [5], which is called the bio-heat equation

$$\rho c \frac{dT(r,t)}{dt} = \mu_a \Phi(r) + k \Delta T(r,t) \quad \text{(Watt/vol)} \quad [9]$$

Operator Δ is positive when the infinitesimal sphere is colder than its surrounding (i.e. heat will be flowing in) and negative when it is hotter (i.e. heat will be flowing out). The result is a time and space varying temperature profile within the tissue volume, $T(r, t)$, where t denotes the time since the laser was switched on.

APPENDIX 2: STEAM PRODUCTION BY A 1000°C LAYER OF CARBONIZED BLOOD

There are two ways to estimate the vapor production by the carbonized layer. In the first, this layer is assumed to be at 1000°C when the laser has just been switched off. If all the energy contained in this layer is used to vaporize water, the following estimate shows that about 30 mm^3 of steam is formed.

The carbonized layer is about 30 μm thick (7), has 0.6 mm diameter, thus a volume of $30 \cdot 10^{-6} \cdot \pi \cdot (0.3 \cdot 10^{-3})^2 \sim 10^{-11}$ m^3. From thermodynamics (37) it is known that conversion of x kg of water into x kg of steam requires an energy of $x \cdot Dh$ (Joule), with specific enthalpy of vaporization $Dh \sim 2.2 \cdot 10^6$ Joule/kg. The available energy of a layer of volume V at a temperature of 900°C above 100°C, the temperature of steam, is denoted by $\rho \cdot c_p \cdot V \cdot 900 \approx 0.04$ Joule, using $\rho = 1000$ kg/m^3 and $c_p \sim 4.2 \cdot 10^3$ Joule/kg/°C. Thus, 0.04 Joule creates $0.04 / 2.2 \cdot 10^{+6} = 1.8 \cdot 10^{-8}$ kg of steam. With a ρ of steam of about 0.6 kg/m^3 this implies $\sim 3 \cdot 10^{-8}$ m^3 or 30 mm^3 of steam. This estimate shows that steam bubbles can be created by the "rest" energy residing in the layer of carbonized blood at 1000°C just after switching-off the laser.

The second estimate is obtained assuming the amount of energy given per second to the carbonized layer by the laser, 45 % of the emitted laser power (10) minus Planck's radiation, equals the energy per second given off by this layer to the blood. Per second this is about 4 Joule, if 10 W is the laser power and about 5% is assumed to represent Planck's black body radiation (which is one of the cooling mechanisms for the carbonized layer, the others are heat conduction and convection). With the same estimate as above for 0.04 Joule, 4 Joule produces 100 times more, thus 3000 mm^3, or 3 cm^3, steam vapor per second. However, the heat needed to heat up the blood to 100°C must be subtracted from this value. Again with the above estimate, a cylinder of fresh blood with a length of (say) 3 mm (assuming a 3 mm/s pullback velocity) and a 0.6 mm diameter has a volume close to 10^{-9} m^3 and requires $\rho \cdot c_p \cdot V_{blood} \cdot 100 \approx 0.4$ Joule per s to be heated up to 100°C. This is one tenth of the available energy per second, so vapor production by the laser-irradiated carbonized layer occurs without any doubt.

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Chapter 2.2

Some controversies in endovenous laser ablation of varicose veins addressed by optical-thermal mathematical modeling

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Lasers Med Sci; 2014 Mar;29(2):441-52

ABSTRACT

Minimally invasive treatment of varicose veins by endovenous laser ablation (EVLA) becomes more and more popular. However, despite significant research efforts performed during the last years, there is still a lack of agreement regarding EVLA mechanisms and therapeutic strategies. The aim of this article is to address some of these controversies by utilizing optical-thermal mathematical modeling.

Our model combines Mordon's light-absorption based optical-thermal model with the thermal consequences of the thin carbonized blood layer on the laser fiber tip that is heated up to temperatures of around 1000°C due to the absorption of about 45% of the laser light. Computations were made in MATLAB. Laser wavelengths included were 810, 840, 940, 980, 1064, 1320, 1470 and 1950 nm. We addressed: The effect of direct light absorption by the vein wall on temperature behavior, comparing computations using normal and zero wall absorption; Predicting the influence of wavelength on the temperature behavior; The effect of the hot carbonized blood layer surrounding the fiber tip on temperature behavior, comparing wall temperatures from using a hot fiber tip and one kept at room temperature; The effect of blood emptying the vein, simulated by reducing the inside vein diameter from 3 down to 0.8 mm; The contribution of absorbed light energy to the increase in total energy at the inner vein wall in the time period where the highest inner wall temperature was reached; The effect of laser power and pullback velocity on wall temperature of a 2 mm inner diameter vein, at a power/velocity ratio of 30 J/cm at 1470 nm; A comparison of model outcomes and clinical findings of EVLA procedures at 810 nm, 11 W and 1.25 mm/s, and 1470 nm, 6 W and 1 mm/s.

Interestingly, our model predicts that the dominating mechanism for heating up the vein wall is *not* direct absorption of the laser light by the vein wall but heat flow to the vein wall and its subsequent temperature increase from two independent heat sources. The first is the exceedingly hot carbonized layer covering the fiber tip; the second is the hot blood surrounding the fiber tip, heated up by direct absorption of the laser light. Both mechanisms are about equally effective for all laser wavelengths. Therefore, our model concurs Vuylsteke et al.'s finding of more circumferential vein wall injury in veins (nearly) devoid of blood, but it does not support their proposed explanation of direct light absorption by the vein wall. Furthermore, EVLA appears to be a more efficient therapy by the combination of higher laser power and faster pullback velocity than by the inverse combination. Our findings suggest that 1470 nm achieves the highest EVLA efficacy compared to the shorter wavelengths at all vein diameters considered. However, 1950 nm EVLA is more efficacious than 1470 nm albeit only at very small inner vein diameters (smaller than about 1 mm, i.e. veins quite devoid of blood). Our model confirms the efficacy of both clinical procedures at 810 and 1470 nm.

In conclusion, our model simulations suggest that direct light absorption by the vein wall is relatively unimportant, despite being the supposed mechanism of action of EVLA that drove the introduction of new lasers with different wavelengths. Consequently, the presumed advantage of wavelengths targeting water rather than hemoglobin is flawed. Finally, the model predicts that EVLA therapy may be optimized by using 1470 nm laser light, emptying of the vein before treatment, and combining a higher laser power with a greater fiber tip pullback velocity.

INTRODUCTION

Minimally invasive treatment of varicose veins by endovenous laser ablation (EVLA) has become a widely used clinical method because of its high efficacy and low complication rate. Guided by the general consensus that irreversible injury of the vein wall by sufficient temperature increase is the therapeutic goal to be achieved, performed research during the past years still has not provided agreement regarding the mechanisms by which this injury is reached and which laser power setting and pullback velocity is optimal in reaching this goal effectively and safe (1, 2). So far, four EVLA mechanisms of action that produce an increase in vein wall temperature have been proposed: 1. Direct contact between laser fiber tip and vein wall (3). 2. The optical-thermal interaction between the laser light emitted out of the fiber and the surrounding tissues. First, the laser light power is redistributed over the surrounding blood, vein wall and perivenous tissue by absorption and scattering. Subsequently these structures are being heated up by the combined effects of absorbed laser light power and heat flows that develop between locations of higher and lower temperatures (4, 5) 3. Heat flowing from the exceedingly hot layer of carbonized blood around the laser fiber tip, diffusing through the blood and reaching and heating up the vein wall (6, 7). 4. Heat transfer from boiling bubbles to the vein wall. These steam bubbles most likely originate in tiny pores of the hot carbonized layer but also in the blood when the blood temperature exceeds the threshold for boiling. They subsequently propagate a few cm distal from the tip before condensing and transferring their energy to blood and vein wall (8-10).

The exact contribution of these mechanisms in achieving EVLA efficacy is unknown (1, 2). Equally so, there is no consented best therapeutic strategy, clearly demonstrated by the large variety of laser wavelengths, laser power settings, pullback velocities and degree of blood emptying of treated veins that are currently in clinical use (1, 3). The available and clinically used wavelengths vary from 810 nm to 1470 nm. The hemoglobin molecules in red blood cells are the absorption target of the shorter wavelengths (810 nm, 940 nm, 980 nm and 1064 nm) and the water molecules in the endothelial cells the assumed target of the longer wavelengths (1320 nm and 1470 nm) (11, 12). We also included 1950 nm, this wavelength is absorbed about three times better in blood and vein wall than 1470 nm and has therefore been touted to be an interesting wavelength for EVLA therapy (12)

In this article, we address some of the existing controversies by utilizing our optical-thermal mathematical model (13). The first controversy concerns the question whether the increased amount of circumferential vein wall destruction at 1470 nm EVLA and at smaller inner vein diameters (1, 2), can be explained by direct light absorption of the vein wall (4), by heat conduction-related mechanisms from the hot fiber tip, or by both (4, 6). The second concerns the question whether EVLA efficacy increases at lower or

higher laser power and pullback velocity combinations. The third whether laser wavelength affects the EVLA modes of action (1, 2, 4, 6, 7, 10, 14) The latter addresses the controversy whether EVLA at wavelengths targeting water rather than hemoglobin are advantageous (11, 12).

METHODS

Our model (13) combines Mordon's optical-thermal model of light absorption (4) with the thermal consequences of the thin layer of carbonized blood (6), always covering the laser fiber tip and which absorbs about 45% of the laser light before it reaches the surrounding blood (7). The effects of steam bubbles, their propagation and condensation centimeters distal to the fiber tip has been approximately accounted for in the model by increasing the thermal conductivity of blood by a factor of 200 when the blood temperature exceeds 95°C (13). Although this mitigates the calculated blood temperatures to about 100°C, temperatures in excess of that value do occur. We assumed a vein temperature of 20°C following administration of tumescent anesthesia before switching on the laser power, accounting for the fact that the tumescent fluid is kept in the refrigerator before it is administrated by multiple injections around the vein at body temperature.

The geometry used in the simulations is presented in Figure 1. It consists of a cylindrical blood vessel with wall and perivenous tissue with a length of L = 200 mm. The total radius of the considered (mathematical) domain is R = 10 mm. The inner radius, *ri*, of the vein is varied between 0.4 and 1.5 mm. The outer radius, *r0*, is 1 mm larger than *ri*, accounting for a vein wall thickness of 1 mm. The laser fiber tip, with a radius of *rfiber* =

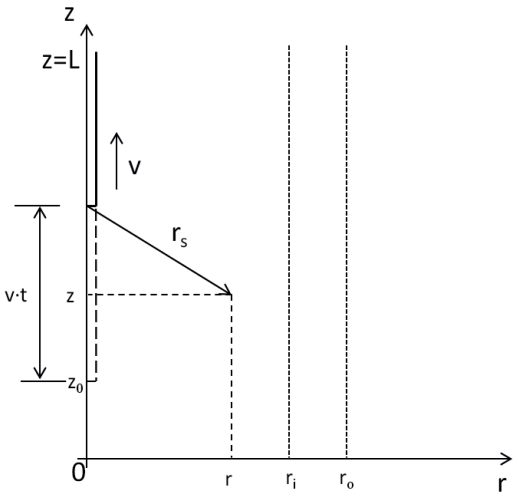

Figure 1. Geometry of vein and fiber with r_i and r_o the inner and outer radii of the vein, z_0 = 20 mm, temperature evaluation is at z = 40 mm. Not to scale.

0.3 mm, is centered within the vessel, at $r = 0$, and moves up in axial direction, z, with a constant velocity, v, varied between 1 and 4 mm/s. At time $t = 0$, the fiber tip is located at axial coordinate $z0 = 0.1L = 20$ mm. We have chosen $z0 = 20$ mm instead of 0 mm to allow heat to flow in the distal direction too when, at time $t = 0$, the laser is switched on and pulling back of the fiber begins at a constant velocity of v mm/s. At time t, the fiber tip is at axial position $z = z0 + v \cdot t$. The laser light is entering the fiber tip with power, P, varying between 3 and 25 W, and because 45% is absorbed by the carbonized layer of blood, the remaining 55% is emitted out of the fiber into the blood (i.e. between 1.65 and 13.75 W).

The observation point where we will evaluate the computed temperatures is at axial coordinate $z = 0.2L = 40$ mm just inside the vein wall. Thus, at e.g. $v = 2$ mm/s, the fiber tip reaches the observation point 10 s after switching on the laser and starting the withdrawal of the fiber (Figure 2).

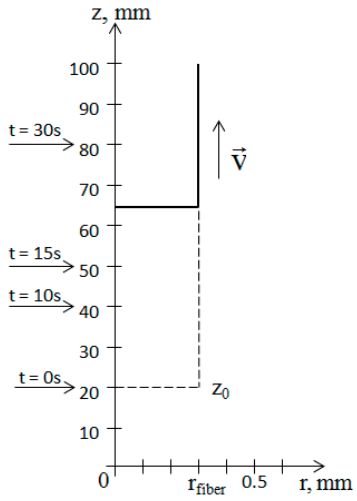

Figure 2. The axial location of the fiber tip over time for v = 2 mm/s.

The thermal properties of blood, vein wall and perivenous tissue, i.e. thermal conductivity, k, mass density, ρ, heat capacity at constant pressure, cp, and thermal diffusivity, a, are summarized in Table 1. Their optical properties, i.e. absorption coefficient, μa, and reduced scattering coefficient, $\mu's$, are presented in Table 2. The data for all wavelengths but 1950 nm come from the original model (13). For 1950 nm, the blood and vessel wall absorption are from the same source (13); the reduced scattering coefficient of vessel wall comes from an extrapolation of the $\mu's$ of skin, from Zonios and Demou (15), as displayed in Figure 4B of Lister et al. (16). For blood, the reduced scattering coefficient is an extrapolation from the value at 1470 nm assuming the same ratio at 1470 versus 1950 nm as for the vein wall. The other parameters are from Vuylsteke and Mordon (1).

Table 1. Thermal properties

Symbol	Unit	Fiber	Blood	Vein wall and perivenous tissue
k	[W/m°C]	1.3	0.6	0.56
ρ	[kg/m3]	2400	1000	1050
c_p	[J/kg°C]	703	4181	3780
$\alpha = k/(\rho \cdot c_p)$	[m2/s]	7.7·10-7	1.43·10-7	1.41·10-7

k, thermal conductitivity; ρ, density; c_p heat capacity at constant pressure; α, thermal diffusivity

The mathematical formulation of the problem is briefly explained in Appendix 1. Details can be found elsewhere (13). All calculations were made for laser wavelengths of 810 nm, 840 nm, 940 nm, 980 nm, 1064 nm, 1320 nm, 1470 nm and 1950 nm. However, to keep the number of Figures practicable we will present most of the results for 810 and 1470 nm only, because the temperature effects caused by 810 nm appeared to be representative for all shorter wavelengths, including 1320 nm, and the 1470 nm results are representative for 1950 nm as well.

The mathematical model evaluates the temperature behavior in the blood, vein wall, perivenous tissue and the carbonized blood layer. The model therefore allows studying the influence on calculated temperatures of relevant clinical settings, e.g. by varying the laser wavelength, laser power, degree of collapse of the treated vein, and pullback velocity. However, it also permits establishing the influence on the wall temperature of factors such as absorption of the vein wall and temperature of the hot fiber tip. We studied the following issues.

Table 2. Optical properties

	μa [1/mm]			μ's [1/mm]		
λ [nm]	Blood	Vein wall	Perivenous tissue	Blood	Vein wall	Perivenous tissue
810	0.21	0.2	0.017	0.73	2.4	1.2
840	0.21	0.18	0.019	0.75	2.33	1.18
940	0.28	0.12	0.027	0.64	2.13	1.1
980	0.21	0.1	0.030	0.6	2.0	1.0
1064	0.12	0.12	0.034	0.58	1.95	0.98
1320	0.3	0.3	0.045	0.54	1.8	0.9
1470	3.0	2.4	0.35	0.52	1.7	0.84
1950	10.0	7.5	0.35	0.30	1.0	0.15

λ, wavelengths; μ_a, absorption coefficient; μ'_s, reduced scattering coefficient

The effect of vein wall absorption of laser light on the inner vein wall temperature

The contribution of directly absorbed laser light by the vein wall to the inner vein wall temperature follows from comparing computations with normal vein wall absorption (see Table 2), and simulated zero absorption of the vein wall and surrounding perivenous tissue. The simulations were performed for an inner radius of the vein of ri = 1.5 mm, power P = 15 W, and velocity v = 2 mm/s.

The effect of wavelength on the inner vein wall temperature

The simulations were performed as before, only the inner vein diameter varied from 0.8 to 3 mm.

The effect of the hot carbonized blood layer on the inner vein wall temperature

The contribution of the hot fiber tip to the inner vein wall temperature follows from comparing computations with normal vein wall absorption and including that 45% of the emitted laser power is absorbed by the carbonized blood layer on the fiber tip (7), and normal vein wall absorption but keeping the fiber tip at body temperature despite also including the 45% power reduction of the emitted laser light. The simulations were performed with the same parameters as before.

The effect of blood emptying of the vein on the inner vein wall temperature

Grades of blood emptying of the vein by Trendelenburg positioning of the patient and introduction of tumescent anesthetic fluid into the great saphenous vein compartment was mimicked by varying the inside vein diameter from respectively 0.8, 1, 1.5, 2, 2.5 to 3 mm. Considering that fiber tips normally measure 0.6 mm, a diameter of 0.8 mm mimics a nearly totally collapsed vein, and a diameter of 3 mm a rather small vein.

Contribution of the absorbed light energy to the increase in total energy at the inner vein wall while reaching the highest temperature

Equation (A.2) of Appendix 1 describes the amount of light power absorbed in an infinitesimally small tissue volume located at radial coordinate r from the fiber tip and at time t. We choose this infinitesimal volume just inside the inner vein wall, at z = 40 mm and $r = r_i$. Then, integrating Eq. (A.2) over the time period between $t = 0$ and $t = t_{end}$, where t_{end} is the time at which the inner wall temperature reaches its maximum value, gives the total energy of the absorbed light in that small infinitesimal volume in this time period, denoted by $E_{light}(r_i, t_{end})$ (J/vol). We compare this to the total increase in energy in that infinitesimal volume in the same period of time, $E_{total}(r_i, t_{end})$. Appendix 2 gives the details.

The effect of emitted laser power and pullback velocity on the inner vein wall temperature

We varied the laser power at 3, 6 and 12 W, and proportionately the pullback velocity at 1, 2 and 4 mm/s respectively, at a power/velocity ratio of 30 J/cm, at 1470 nm and 2 mm inner vein diameter (12).

Comparison of model outcome and clinical findings of two EVLA procedures

We simulated two clinical procedures of EVLA, performed at the Helder Clinic (by CMAB). The first is at 810 nm, 11 W, 1.25 mm/s pullback velocity, the second at 1470 nm, 6 W and 1 mm/s. In these simulations, the axial coordinate of the initial fiber tip position was at $z0 = 0.1 \cdot L = 10$ mm and the observation point at $z = 0.2 \cdot L = 20$ mm. For better comparison with the clinical findings, the inner vein radius was set to 1 mm and the outer radius to 2 mm, based on the ultrasound findings. Comparison was with ultrasound pictures obtained during the procedures.

RESULTS

The effect of vein wall absorption of laser light on the inner vein wall temperature

Figure 3 shows the temperature profiles at the inner vein wall (at $ri = 1.5$ mm) as a function of time at axial position $z = 40$ mm. The lines show the results for the case with normal vein wall absorption, the lines with symbols correspond to the case with simulated zero vein wall absorption.

For both normal and zero wall absorption, the temperature at the vein wall reaches the same maximum value and virtually at the same time for each of the wavelengths. For 810 nm, the maximum vein wall temperature is 104°C reached at $t_{end} = 10.8$ s and for 1470 nm it is 109°C reached at 10.6 s. Over time, the curves for normal and zero vein wall absorption show only very small differences at 810 nm, implying that the scattered light that is directly absorbed by the vein wall does not play an important role in the mechanism of induced temperature compared to the heat flow from the hot fiber tip and heated blood toward the vein wall. The temperature profiles for 1470 nm are exactly the same for both cases (with and without vein wall absorption). It confirms that, at 1470 nm and 3 mm inner vein diameter, virtually no photons reach the vein wall for absorption.

The effect of wavelength on the inner vein wall temperature

Figure 4 shows computations of the inner vein wall temperature versus wavelength, at inner vein diameters varying between 0.8, 1, 1.5, 2, 2.5 and 3 mm. Interestingly, a higher

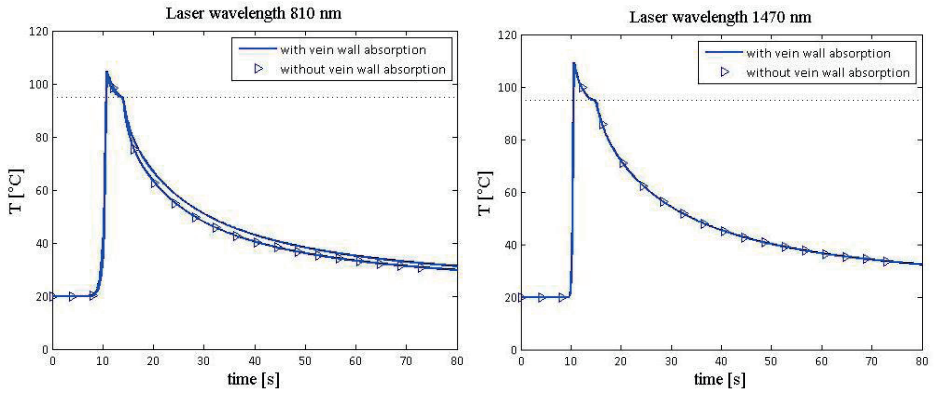

Figure 3. Temperature profiles at the inner vein wall, 3 mm diameter, as a function of time, with vein wall absorption (lines) and without vein wall absorption (lines with symbols), at 810 nm (left) and 1470 nm (right), at 15 W, 2 mm/s.

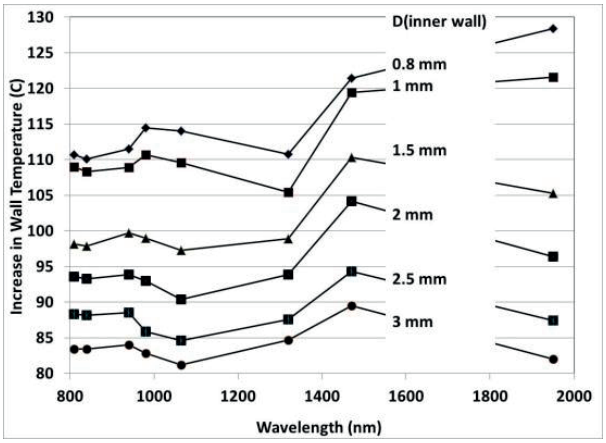

Figure 4. Increase in the inner vein wall temperature versus wavelength for inner vein diameters of 0.8, 1, 1.5, 2, 2.5 and 3 mm, at 15 W, 2 mm/s.

EVLA efficacy is predicted at 1470 nm compared to EVLA with the shorter wavelengths, for all vein diameters considered. For very small vein diameters (0.8 and 1 mm), our model predicts a slightly larger inner vein wall temperature at 1950 nm EVLA than at 1470 nm, a consequence of the higher temperature of the carbonized blood layer of about 111°C (1084°C at 1470 nm versus 1195°C at 1950 nm, see also Figure 6 below) and, less importantly, of the (very) small fraction of the light that reaches the vein wall.

The effect of the hot carbonized blood layer on the inner vein wall temperature

Figure 5 shows the contribution of the hot tip to the temperature at the inner vein wall at $z = 40$ mm as a function of time, at 810 nm and 1470 nm, using a 3 mm diameter, 15 W and 2 mm/s. Lines indicate the model with the hot tip included, and lines with symbols the model with the tip kept at room temperature.

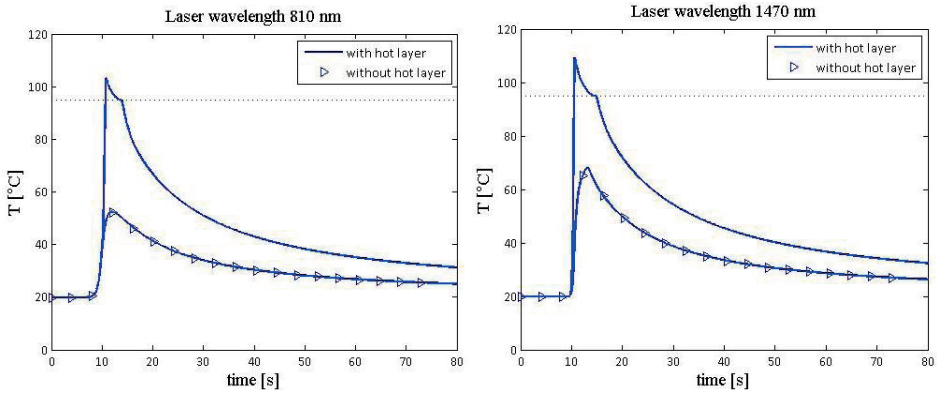

Figure 5. Temperature profiles at the inner vein wall with a diameter of 3 mm, as a function of time, with the hot tip (lines) and with the tip kept at room temperature (lines with symbols) at 810 nm (left) and 1470 nm (right). P = 15 W, v = 2 mm/s.

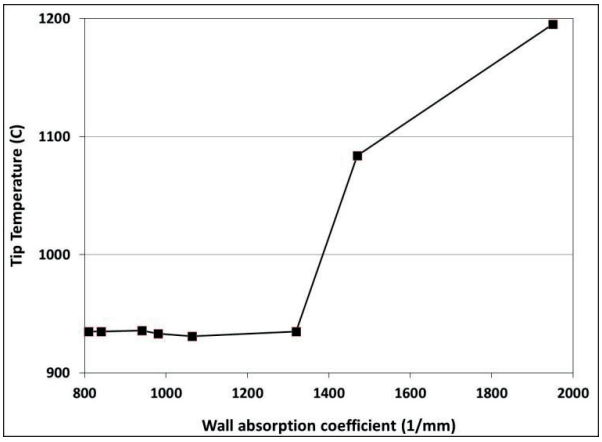

Figure 6 shows the computed temperatures at the fiber tip as a function of wavelength, at 15 W and 2 mm/s. The results were found to be independent of the

Figure 5 shows a quite interesting and we believe unexpected phenomenon. First, when the hot tip is included, the computed temperature rise at the inner vein wall is more than twice as large compared to when the tip is kept at room temperature. Remarkably, however, our model predicts that there is still a significant rise in temperature, despite keeping the fiber tip at room temperature and despite the results displayed in Figure 3, which show that this temperature rise cannot come from direct absorbed laser light by the vein wall. The mechanism responsible here is the thermal effect induced by direct absorption of the emitted laser light by the surrounding blood, causing heating up of the blood, first beginning close to the fiber tip and subsequently propagating to the vein wall as a heat flow, leading to the increase in wall temperature. This mechanism is also included in Mordon's model (4).

The effect of blood emptying of the vein on the inner vein wall temperature

The calculations for different vein wall inner diameters (0.8 mm, 1 mm, 1.5 mm, 2 mm, 2.5 mm, 3 mm), the smaller diameters mimicking blood emptying of the vein, were made for all wavelengths. We included computations with direct light absorption by a normal and by a zero absorbing vein wall, and presence and absence of a hot tip.

Figure 7 shows an example of temperature profiles at the vein wall, at 1470 nm, for two inner vein diameters (0.8 mm, left curve, and 2.5 mm, right curve), as a function of time. The solid lines indicate the temperatures in the normal situation, with 45% of power absorbed by the hot carbonized layer around the fiber tip, and the remaining power (55%) absorbed by the blood, vein wall and surrounding tissue. The dashed lines with symbols indicate the temperatures with *zero* vein wall absorption. The solid lines with symbols indicate the temperatures with the fiber tip kept at room temperature. For an inner vein diameter of 2.5 mm (right curves) there is no difference between the model computations with and without vein wall absorption, implying that the plain line and the dashed line with symbols overlap. Again, this is due to fact that virtually no photons reach the vein wall at a distance of ≥ 1 mm from the tip (Figure 3). For a distance of 0.4 mm or smaller (inner vein diameter ≤ 0.8 mm), a few photons reach the vein wall and become absorbed, giving rise to a very small and clinically insignificant increase in temperature. However, the other mechanisms of heating up the vein wall during EVLA, i.e. heat flow toward the vein wall from the hot fiber tip and from the hot blood around the fiber tip, identified above (Figure 5), occur much stronger at well emptied veins (diameter below 1.5 mm, see also Figure 8).

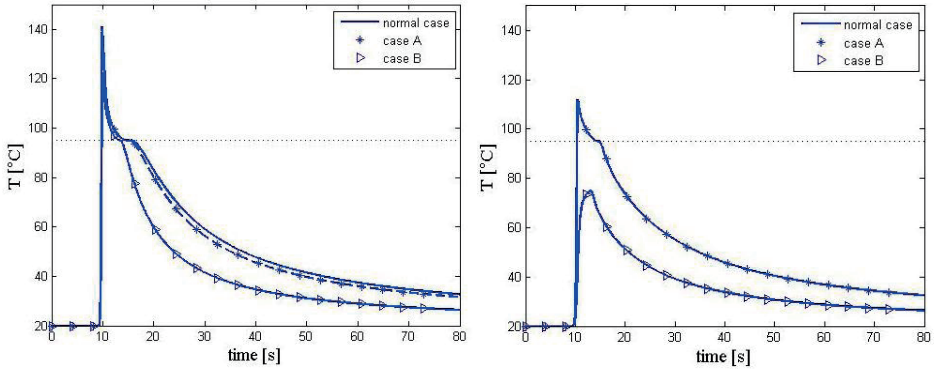

Figure 7. Temperature profiles at 1470 nm for two inner vein diameters, 0.8 mm (left) and 2.5 mm (right). Case A: results with zero vein wall absorption. Case B: results with the fiber tip kept at room temperature.

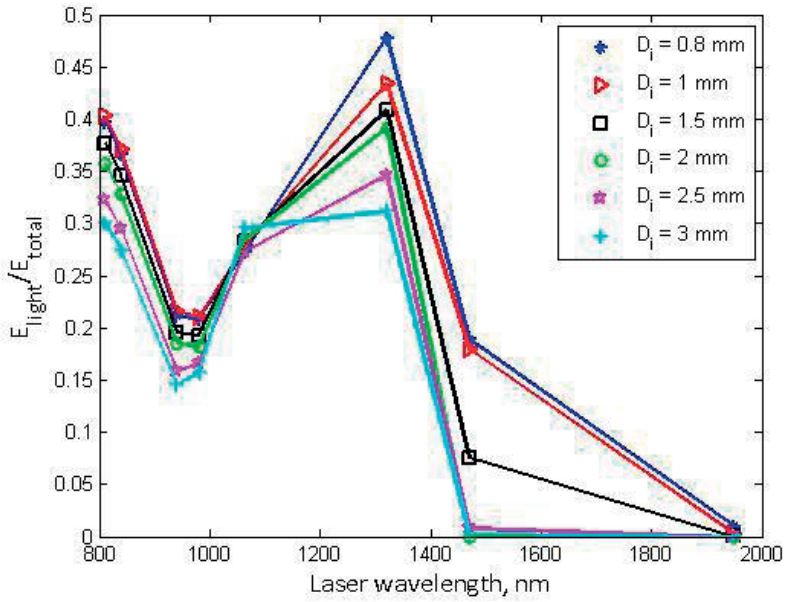

Figure 8. Laser wavelength dependence of E_{light}/E_{total}, calculated at the inner vein wall at z = 40 mm, for different inner vein wall diameters D_i.

Contribution of the absorbed light energy to the increase in total energy at the inner vein wall while reaching the highest temperature

Figure 8 shows the computed ratio E_{light}/E_{total} for all wavelengths and vein diameters used. It is a measure of the contribution of the absorbed laser light energy, relative to the increase in total energy, in an infinitesimally small volume element just inside the vein wall, during the time period between laser onset and reaching the maximum inner wall temperature. Figure 8 suggests that direct light absorption by the vein wall plays some role in the heating up of the wall for EVLA at 810, 940, 980, 1064 and 1320 nm, albeit only contributing between about 15% and 50%. Using 1470 nm EVLA, it contributes almost 20%, provided the vein is (nearly) totally collapsed. At 1950 nm EVLA, direct absorption of the laser light by the vein wall contributes virtually nothing to the increase in inner wall temperature.

The effect of emitted laser power and pullback velocity on wall temperature

Figure 9 shows computed inner vein wall temperatures versus laser power, at 1470 nm and 2 mm diameter, for a power/velocity ratio of 30 J/cm, previously used clinically (12). It is clearly shown that the highest inner vein wall temperature corresponds to a power of 12 W and a pullback velocity of 4 mm/s in the EVLA setting chosen for the simulations.

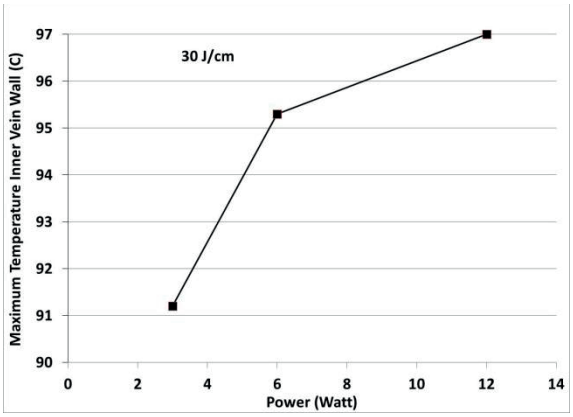

Figure 9. Maximum inner vein wall temperatures at 1470 nm and various laser powers (3, 6 and 12 W) and pull-back velocities (1, 2 and 4 mm/s), at a power/velocity ratio of 30 J/cm.

Comparison of model outcome and clinical findings of two EVLA procedures

Figure 10 shows the computed results for the two clinical EVLA cases of, first, 810 nm, 11 W, 1.25 mm/s pullback velocity (left curves), and, second, 1470 nm, 6 W and 1 mm/s (right curves). Figure 11 shows ultrasound pictures following these procedures. Although the calculated predictions at 810 and 1470 nm both suggest full coagulation of the entire vessel wall, the 810 nm model predictions suggest slightly better efficacy, because the calculated maximum temperature at the outer wall, although high enough for irreversible injury, is about 13°C higher at 810 nm than at 1470 nm. Nevertheless, ultrasonography suggests the inverse, a more intense injury at 1470 than at 810 nm. A possible explanation for this observation is that the two treatments were evaluated with two different ultrasound machines and that the displayed reflection pattern, the ultrasound picture, depends on the parameters set for ultrasound focusing and contrast, but also on the native reflectivity of individual tissue structures, e.g. fat separating membranes and air bubbles in the tumescent liquid.

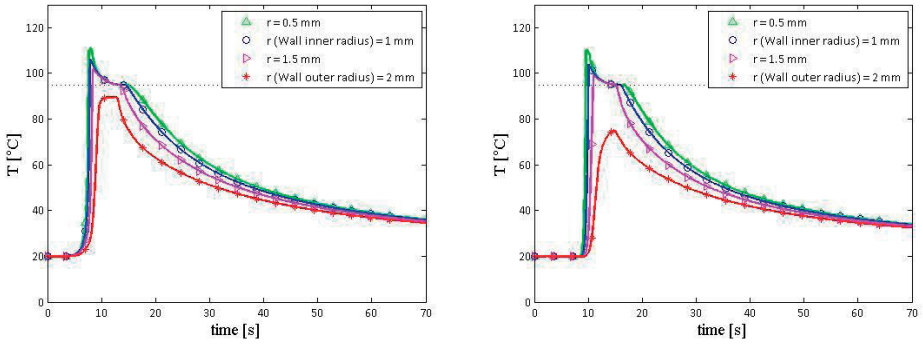

Figure 10. Temperature profiles as a function of time using a 2 mm inner vein wall diameter. Left curve: 810 nm, 11 W, 1.25 mm/s. Right curve: 1470 nm, 6 W, 1 mm/s.

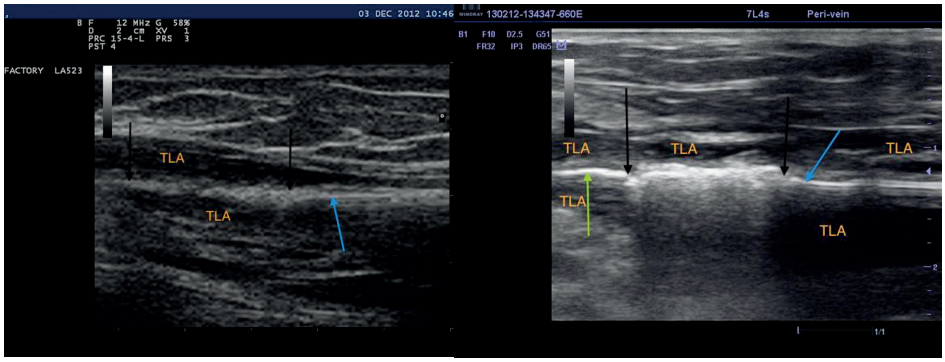

Figure 11. (Left) Ultrasound image of the central Great Saphenous Vein (GSV), about 8 s after starting EVLA at 810 nm. Blue arrow indicates the fiber tip. Part of the GSV between the black arrows just has been treated. TLA is the tumescent local anesthesia surrounding the GSV. Note that, compared to 1470 nm EVLA, lesser echogenicity of the GSV remnant. (Right) Ultrasound image of the central GSV, just 10 seconds after starting EVLA at 1470 nm. The segment of about 1 cm between the black arrows was treated; the fiber tip is at the point of the blue arrow. Left of the left black arrow, marked by a green arrow, a white line with a diameter of about 1 mm is visible, presumably caused by steam bubbles escaping into the common femoral vein. The untreated vein wall is visible around the fiber tip as grey lines, the treated vein wall as a linear and irregular but markedly echogenic structure.

DISCUSSION

Surprisingly, our model predicts that direct absorption of laser light by the vein wall is not the dominating contributor to the efficacy of simulated EVLA procedures. For example, at a very small, 0.8 mm, inner vein diameter, direct light absorption contributes a 47% maximum to the wall temperature at 1320 nm, but less than 20% at 1470 nm and about 1% at 1950 nm. At a more realistic diameter of about 1.5 - 2 mm (Figure 11), these numbers are about 37% at 1320 nm and virtually zero at 1470 and 1950 nm. Instead, the predicted leading mechanism is that two independent heat diffusion flows begin at the fiber tip, propagate through the blood to the vein wall and, after arrival, heat up the vein wall. The two heat sources that produce these heat flows and contribute about equally to the increase in vein wall temperature are the exceedingly hot fiber tip, as well as the hot blood surrounding the fiber tip, heated up by direct absorption of the emitted laser light out of the tip. This finding gives an interesting turn to the hypothesis of Vuylsteke and Mordon, that direct light absorption by the vein wall causes increased levels of circumferential vein wall destruction in blood emptied veins (1). Our model confirms their experimental finding in Figure 4 but, instead, the proposed mechanism by our model is that the heat flows from the hot tip and heated blood to the vein wall, as already explained in this paragraph. Additionally, it gives an equally interesting outlook on the past multiple introductions of new EVLA wavelengths, which were all based on increasing the direct absorption of laser light by the vein wall by "bypassing" absorption of the

light by hemoglobin. Our results thus firmly confirm the statement made by Vuylsteke and Mordon that classification into hemoglobin- and water-absorbed wavelengths is flawed (1). The results also suggest that 1950 nm, with very large absorption in water and blood, proposed to be an interesting future EVLA candidate, perhaps even requiring less tumescent anesthesia (12), will actually not be superior to 1470 nm.

Obviously, modeling such complex and coupled action mechanisms as in EVLA procedures performed in patients with individual variability in anatomy and pathophysiology cannot identify all possible events that may occur. However, the importance as well as limitation of this type of computational modeling has been expressed well by Brown et al. (17), in their paper on allometric scaling laws of mammalian circulatory systems, stating that (converted to EVLA) "like any model, it is a deliberate oversimplification that can serve as a point of departure for understanding a much more complicated (EVLA) reality. It should be useful if it captures the essence of the mechanisms that underlie EVLA". Particularly, our model relies on the accuracy of the optical and thermal parameters used. Although the absorption behavior of blood is well known below about 1000 nm and above 1400 nm, taking the latter equal to the absorption of water, it is not in the spectral in-between. The reduced scattering properties of blood in the spectral band beyond 1000 nm, needed for EVLA modeling, are not well known. For example, previous work showed that the large absorption peaks in the visible part of the spectrum causes related peaks in the scattering behavior (18). This mechanism likely occurs too at the strong water absorption peaks around 1500 and 1900 nm but it is not taken into account in the behavior of the reduced scattering coefficients yet. In addition, it is well known that the optical properties of blood also depend on the temperature (19), which was not taken into account in our model and neither in Mordon's model (4). We hypothesize that the thermal properties used for blood, vessel wall and perivenous tissue are more accurate than the optical properties, due to the large fraction of water included in soft tissues and blood, and the accurately known thermal properties of water.

A more fundamental issue is that the model does not fully capture the effects of steam bubbles by just increasing the thermal conductivity of blood by a factor of 200 at temperatures above 95°C. We are currently including the effects of steam bubbles more thoroughly using computational fluid dynamics methodology, which however requires solving several coupled partial differential equations, including the Navier-Stokes equation. Another approximation (in Mordon's as well as our model) is neglecting possible changes in the shape of the vein wall when tumescent anesthesia is administrated because this may cause thickening of the wall due to spasms but also an increased tissue pressure by pressing the wall to be fold around the catheter surface. However, we anticipate that the pressure is such that the vein wall volume remains homogeneous for absorption and scattering of the laser light. Besides, even if this is not exactly so, our

results will unlikely change significantly because of the relative unimportance of direct vein wall absorption of the laser light.

Our EVLA model, as well as Mordon's model, uses cylinder symmetry of the vein with the fiber centered in the middle. This geometry precludes studying the possible effects of EVLA with a bare fiber, the geometry often used in clinical practice, including the consequences of direct contact between fiber tip and vein wall. Although direct contact was the first proposed mechanism of action of EVLA efficacy, by Navarro et al. (3), we hypothesize that it is insufficient to achieve permanent closure of most varicose veins.

An important model finding of the new identified mechanism is the suggestion that 1470 nm achieves a higher inner vein wall temperature, hence a better EVLA efficacy, than all shorter wavelengths considered, at all inner vein diameters examined. This outcome at least confirms hitherto unproven opinions of many clinicians. It implies that the 1470 nm EVLA laser power can be lowered, predicted by about 10% compared to the power used at other wavelengths, at identical pullback velocity, and still obtaining the same EVLA efficacy. Our model also suggests that combining higher laser power with faster pullback velocity is more effective than the opposite at equal J/cm. The 1950 nm EVLA is only more efficient than 1470 nm for very small inner vein diameters, smaller than about 1 mm. However, the incomplete account of steam bubbles in the present model makes these predictions to remain slightly tentative.

In conclusion, our model simulations suggest that: 1. Direct absorption of laser light by the vein wall is relatively unimportant; previously, the presumed importance of this mechanism supported the unfounded introduction of so-called 'water targeting laser wavelengths' 2. EVLA classification between hemoglobin and water absorbed wavelengths is flawed (1) 3. EVLA procedures may be optimized by using 1470 nm laser light, (nearly) complete blood emptying of the vein, and combining a higher laser power with a higher pullback velocity of the fiber tip.

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APPENDIX 1

The mathematical formulation of the heat conduction governed by Fourier's law supplemented with appropriate boundary and initial conditions is given by

$$\rho c \frac{\partial T}{\partial t} = \nabla \cdot (k \nabla T) + q(r, z, t) \qquad at \quad (r, z) \in \Omega, t \geq 0, \tag{A.1}$$

$$q = \frac{0.55 \cdot P \mu_a}{4\pi D_{dif} \sqrt{(r^2 + (z - z_0 - v \cdot t)^2)}} \; exp\,(-\mu_{eff} \sqrt{(r^2 + (z - z_0 - v \cdot t)^2)}), \tag{A.2}$$

$$q(z, 0 \leq r \leq r_{fiber}) = q_{tip} = \frac{0.45 \cdot P}{V_{tip}}, \tag{A.3}$$

$$T(r_{int}^{-}, z, t) = T(r_{int}^{+}, z, t) \qquad if\, 0 \leq z \leq L, \quad t \geq 0, \tag{A.4}$$

$$(k \frac{\partial T}{\partial r}) \; (r_{int}^{-}, z, t) = (k \frac{\partial T}{\partial r}) \; (r_{int}^{+}, z, t) \qquad if\, 0 \leq z \leq L, \quad t \geq 0, \tag{A.5}$$

$$\frac{\partial T}{\partial t}(r, z, t) = 0 \qquad if\, r = 0 \veebar R, 0 \leq z \leq L, \quad t \geq 0, \tag{A.6}$$

$$\frac{\partial T}{\partial t}(r, z, t) = 0 \qquad if\, 0 \leq r \leq R, z = 0 \veebar L, \quad t \geq 0, \tag{A.7}$$

$$T(r, z, 0) = T_{initial} = 293[K] \qquad at \; (r, z) \in \Omega \tag{A.8}$$

with q the volumetric heat generation given by the product of absorption coefficient and fluence rate (W/m3) (5) μa the absorption coefficient (1/m), μs the scattering coefficient (1/m) and g the average cosine of the scattering angle (the anisotropy factor), *rfiber* the fiber radius (m), *Vtip* the volume of the carbonized layer (m3), which thickness is about 0.1 mm and does not change during the computation. We assumed that 45% of the light propagating towards the fiber tip is absorbed by the carbonized layer (6).

The rectangular computational domain is described by $\Omega = \{(r, z)\, R^2 \big|, 0 \leq r \leq R, \; 0 \leq z \leq L,$ where R is the radial size of the computational domain (m), and L the axial size of the computational domain (m). The optical parameters such as reduced scattering coefficient (μ_s'), the optical diffusion constant (D_{dif}) and the effective attenuation coefficient (μ_{eff}) are defined by

$$\mu_s' = \mu_s(1 - g) \tag{A.9}$$

$$D_{dif} = \frac{1}{3(\mu_s' + \mu_a)} \tag{A.10}$$

$$\mu_{eff} = \sqrt{3\mu_a(\mu_s' + \mu_a)} \tag{A.11}$$

This model is discussed in detail elsewhere (13).

APPENDIX 2

The amount of volumetric light energy absorbed at the inner vein wall at z = 40 mm and $r = r_i$, in the time period between $t = 0$ and $t = t_{end}$, where t_{end} is the time at which the inner wall temperature reaches its maximum value, $E_{light}(r_i, t_{end})$, is given by

$$E_{light}(r_i, t_{end}) = \int_0^{t_{end}} \mu_a(r_i)\varphi^*(r_i, t)dt \text{ where } \varphi^*(r, t) = \begin{cases} \varphi(r, t), & \frac{dT}{dt} \geq 0 \\ 0, & \frac{dT}{dt} < 0 \end{cases} \quad (B.1)$$

$\mu_a(r_i)$ is the light absorption coefficient and $\varphi(r_i, t)$ the fluence rate (W/m^2) of the vein wall at point r_i and time t and product $\mu_a(r_i)\varphi(r_i, t)dV$ is the absorbed power in an infinitesimally small volume dV centered at r_i, t; the reason not to consider times when the time rate of change of the temperature is negative is explained below. In the same period of time, from $t = 0$ to $t = t_{end}$, the total volumetric increase in energy, $E_{total}(r_i, t_{end})$, is given by

$$E_{total}(r_i, t_{end}) = \int_0^{t_{end}} \rho c_p \left.\frac{dT(r_i, t)}{dt}\right|^+ dt = \rho c_p[T(r_i, t_{end}) - T(r_i, t = 0)] \quad (B.2)$$

$\left.\frac{dT}{dt}\right|^+$ indicates the positive value of the derivative, which by definition is zero when the time rate of change of temperature is negative. At the latter times, no heat is accumulated at the point ri, which may imply that heat diffusion exceeds radiation power absorbation at these times. These times are simply not considered. As a consequence, the RHS of (B.2) is actually a summation of integrals over periods of time when the time rate of change of the temperature is positive. Ratio E_{light} / E_{total} has been computed for all wavelengths and vein diameters used.

Chapter 3

Temperature profiles of 980 nm and 1470 nm endovenous laser ablation, endovenous radiofrequency ablation and endovenous steam ablation

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Lasers Med Sci; 2014 Mar;29(2):423-9

ABSTRACT

Background: Endovenous thermal ablation (EVTA) techniques are very effective for the treatment of varicose veins, but their exact working mechanism is still not well documented. The lack of knowledge of mechanistic properties has led to a variety of EVTA protocols and a commercially driven dissemination of new or modified techniques without robust scientific evidence. The aim of this study is to compare temperature profiles of 980 and 1470 nm endovenous laser ablation (EVLA), segmental radiofrequency ablation (RFA) and endovenous steam ablation (EVSA).

Methods: In an experimental setting, temperature measurements were performed using thermocouples; raw potato was used to mimic a vein wall. Two laser wavelengths (980 and 1470 nm) were used with tulip tip fibers, and 1470 nm also with a radial emitting fiber. Different powers and pullback speeds were used to achieve fluences of 30, 60 and 90 J/cm. For segmental RFA, 1 cycle of 20 seconds was analyzed. EVSA was performed with 2 and 3 pulses of steam per cm. Maximal temperature increase, time span of relevant temperature increase, and area under the curve of the time of relevant temperature increase were measured.

Results: In all EVLA settings, temperature rise peaked and decreased rapidly. High fluence is associated with significantly higher temperatures and increased time span of temperature rise. Temperature profiles of 980 and 1470 nm EVLA with tulip tip fibers did not differ significantly. Radial EVLA showed significantly higher maximal temperatures than tulip tip EVLA. EVSA resulted in mild peak temperatures for longer duration than EVLA. Maximal temperatures with 3 pulses per cm were significantly higher than with 2 pulses. RFA temperature rises were relatively mild, resulting in a plateau shaped temperature profile, similar to EVSA.

Conclusion: Rise in temperature during EVLA is fast with a high peak temperature for a short time, where EVSA and RFA have longer plateau phases and lower maximal temperatures. Temperature profiles of 980 and 1470 nm EVLA are similar. Overall, differences in temperature levels of EVTA techniques are minimal.

INTRODUCTION

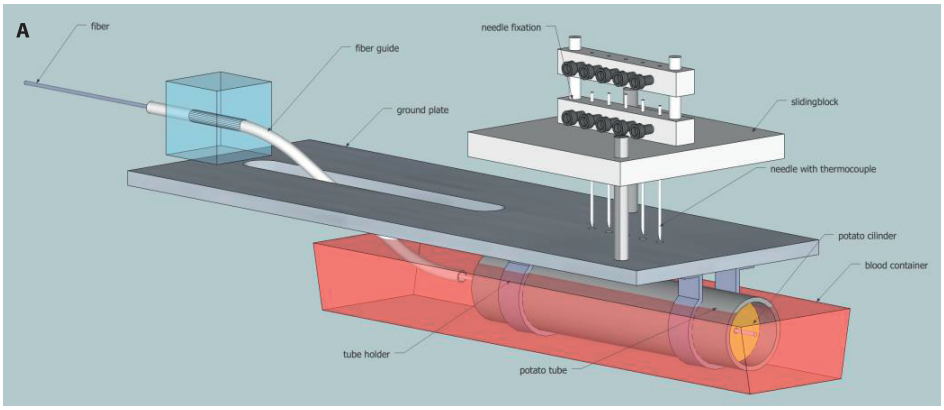
Endovenous thermal ablation (EVTA) techniques are nowadays commonly used as minimally invasive therapy for saphenous varicose veins. In comparison to surgical stripping or ultrasound guided foam sclerotherapy, endovenous laser ablation (EVLA) and radiofrequency ablation (RFA) are proven to have a higher success rate and lower complication rate (1). The efficacy and safety of endovenous steam ablation (EVSA) for varicose veins has been shown in sheep and humans in a pilot study (2).

Although EVTA (EVLA, RFA and EVSA) treatments are very effective, the exact working mechanism is not well documented, especially of EVLA of which temperature profiles and its determinants (e.g., power, wavelength, type of fiber tip and pull back speed) are not well studied. It is generally thought that thermal injury to the venous wall is responsible for vein occlusion in EVTA treatments (3-6). Recently, we performed endovenous simulated laser experiments showing no difference in the temperature profile between 940 and 1470 nm lasers suggesting wavelength independent temperature profiles (7). Also, experimental temperature measurements in EVSA demonstrated a dose-response relationship of heat induction of 1, 2 and 3 pulses of steam per cm (8). However, comparison of temperature profiles between the different EVTA treatments (i.e., EVLA, RFA and EVSA) in the same experimental setting, has never been performed.

The lack of knowledge of mechanistic properties in EVTA treatments has led to a variety of EVTA protocols and a commercially driven dissemination of new or modified techniques without robust scientific evidence. Therefore, we compared the temperature profiles (maximum temperature, seconds of heating > 50°C and area under the curve of the maximum temperature set against the time) of 980 and 1470 nm EVLA, segmental RFA and EVSA in an experimental setting simulating clinical conditions to asses differences in their main working mechanisms (i.e. heating of veins).

METHODS

The experimental set-up (Figure 1) consisted of a transparent plastic box, in which a poly vinyl chloride (PVC) tube was fixed. The tube was filled with 30 mm diameter cylinders of raw potato, to mimic a vein. Raw potato was chosen because it has a solid structure, consists of 80% water (which is similar to a vein wall), is relatively stable under high temperatures and can be cut. These cylinders had a 2.4 mm diameter hole in the centre, in which the laser fiber, radiofrequency or steam catheter was inserted. The box was filled with heparinized pig blood. The temperature measurements were performed with 5 0.5 mm K-type thermocouples (TC; Omega KMQSS-IM050G-150) connected to a data sampler (Omega, Pico TC08). Five TCs were positioned within the PVC tube (TC 1, 2, 3,



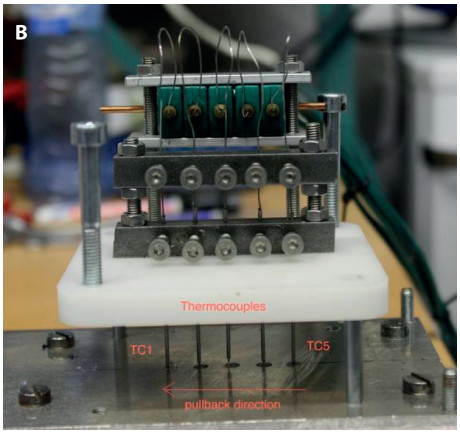
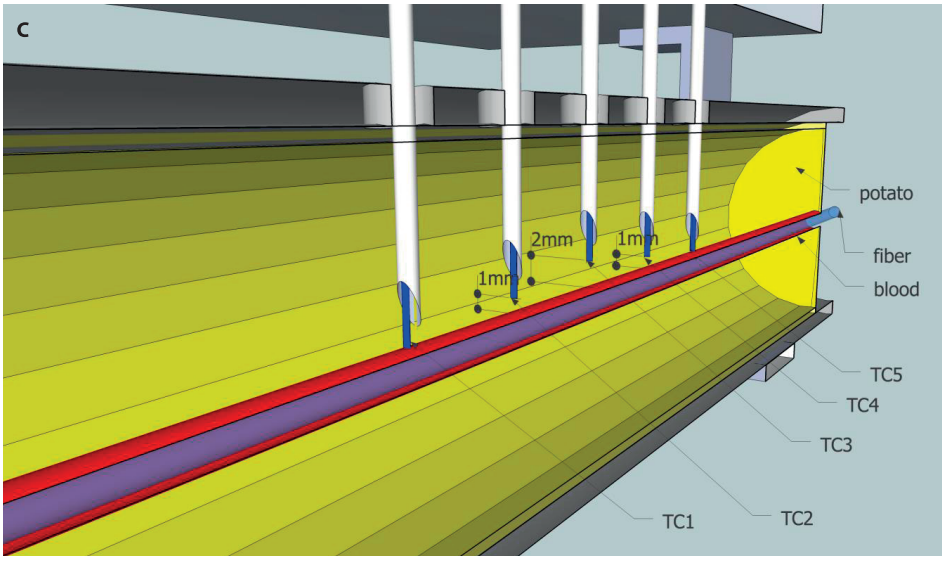


Figure 1. a. Schematic reproduction of the experimental setting. b. Detail of sliding block with thermocouples (TC1, thermocouple 1; TC5, thermocouple 5). c. Cross-section of potato with position of thermocouples (TC2, thermocouple 2; TC3, thermocouple 3; TC4, thermocouple 4) in relation to the fiber/catheter. TC 2, 3 and 4 are positioned inside the potato 'wall'.



4, 5) at three different distances from the fiber (TC 1 and 5 at 0 mm, TC 2 and 4 at 1 mm, TC 3 at 2 mm), because it was hypothesized that the temperature profiles would differ for various positions due to heat development by the moving fiber. The thermocouples were fixed on a sliding block, inserting and positioning the TCs for each experiment.

The EVTA, RFA and EVSA devices used and their settings were similar to clinical practice (2, 9). Two laser wavelengths were used: 980 nm Diode (Quanta System, Solbiate Olona, VA, Italy) and 1470 nm BioLitec, ElVeS (Quanta System ,Solbiate Olona, VA, Italy) with tulip tip fibers (10) (Tobrix, Waalre, The Netherlands) and 1470 nm also with a radial emitting fiber (11) (Tobrix, Waalre, TheNetherlands). A tulip tip is an umbrella-like cover that centers the laser fiber in the vein (diameter 600µm). A radial emitting fiber emits the laser light perpendicular to the fiber (diameter 2 mm). For steam ablation, the Steam Vein Sclerosis system (CERMA SA, Archamps, France) was used (fiber diameter 1.2 mm). For RFA, a segmental heating catheter of 7F (2.3 mm) diameter (ClosureFast catheter, VNUS Medical Technologies Inc, San Jose, Calif) with a 7-cm heating element was used.

For EVLA, 6 pullback speeds (0.5, 1, 1.5, 2, 3 and 4 mm/s), were combined with different laser settings (varying from 3 to 12 Watt (W) for both wavelengths), achieving linear endovenous energy densities (LEED) of 30 J/cm, 60 J/cm and 90 J/cm. In order to reach accurate and constant pullback speeds, a linear motor with frequency regulator was used. For segmental RFA, temperature experiments were done with 1 cycle of 20 seconds. EVSA was performed with 2 and 3 pulses of steam per cm separately. Every measurement was repeated 5 times, which resulted in 10 measuring points at 0 and 1 mm and 5 at 2 mm distance from the fiber.

To study the temperature profiles, dTmax, dt and dtdT were calculated from the graphical representation. Here, dTmax was defined as the maximum temperature increase above room temperature (20°C). Maximum temperatures above 50°C (thus an increase of 30°C above room temperature) were considered relevant, since it is the assumed threshold for collagen denaturation needed to irreversibly damage the vein wall (12-14). Parameter dt was defined as the time span that the temperature increase was relevant (duration of dTmax > 30°C). Parameter dtdT represents the area under the curve of the time that the temperature increase was more than 30°C.

STATISTICAL ANALYSES

The three continuous temperature measures (dTmax, dt and dtdT) are presented as means with a standard deviation (SD). We used SPSS 15.0 software (SPSS Inc, Chicago, Il) for the analyses. The comparison of these measures between the different settings of each EVLA device was done by ANOVA testing. Independent T-tests were performed to compare different EVLA wavelengths (980 nm and 1470 nm), different EVLA fiber tips

(tulip and radial), and 2 and 3 pulses of EVSA. Two-sided p-values were considered to be significant if <0.05.

RESULTS

EVLA

Table 1 shows the results of dTmax at 0 mm, dt and dtdT for 980 nm tulip, 1470 nm tulip and 1470 nm radial EVLA. Temperature profiles of EVLA tulip 980 and 1470 nm are depicted in Figure 2 and Figure 3.

Temperature profiles of 980 and 1470 nm EVLA were measured with tulip tip and radial fibers, with levels of energy varying from 30 to 90 J/cm. In all EVLA settings, the temperature rise peaked and decreased rapidly. In all settings, dTmax was at least 30°C (Tmax ≥ 50°C) at 0 mm distance from the fiber tip. At 1 mm distance, most values of dTmax were below 30°C. At 2 mm distance, none of the settings exceeded a dTmax of 30°C. In most settings, dt is more than 5 s. The results will be listed in detail below.

Table 1. EVLA measurements

	980 nm# Tulip fiber			**1470 nm# $ Tulip fiber**			**1470 nm#$ Radial fiber**		
	30 J/ cm*	**60 J/ cm***	**90 J/ cm***	**30 J/ cm***	**60 J/ cm***	**90 J/ cm***	**30 J/ cm***	**60 J/ cm***	**90 J/ cm***
dTmax 0 mm (mean ± SD)	49 ± 4	51 ± 7	65 ± 10	48 ± 8	59 ± 19	60 ± 12	68 ± 14	87 ± 16	94 ± 7
dt (mean ± SD)	4 ± 1	13 ± 3	22 ± 8	5 ± 2	15 ± 6	30 ± 5	5 ± 1	18 ± 4	26 ± 0
dtdT (mean ± SD)	193 ± 30	563 ± 136	1291 ± 281	220 ± 66	843 ± 316	1431 ± 306	236 ± 74	912 ± 203	1465 ± 37

dTmax, maximal temperature increase in degrees Celsius (°C) above room temperature (20°C); SD, standard deviation; dt, duration of dTmax >30°C in seconds (s); dtdT, area under the curve (°C x s) of the time that the temperature increase is >30°C;. *****Statistical comparisons of dTmax, dt and dtdT between the three fluence rates (30, 60 and 90 J/cm) of each device (980 nm tulip fiber, 1470 nm tulip fiber and 1470 nm radial fiber) were highly significant (ANOVA; p<0.001, except for dTmax of 1470 nm tulip fiber p=0.03); **#**Differences in the distribution of dTmax, dt and dtdT between 980 nm and 1470 nm tulip fiber lasers were not significant (Independent T-test; p=0.82. 0.10 and 0.18 respectively); **$**dTmax was significantly higher for 1470 nm radial fiber compared to 1470 nm tulip fiber (Independent T-test; p<0.001) whereas dt and dtdT were comparable (Independent T-test; p=0.11 and p=0.20 respectively).

LEED

A higher total level of delivered energy per cm vein length, resulting from a relatively high power and/or a lower pullback speed, generated a higher dTmax at 0 mm in all EVLA devices. A dt <5 s seemed to be associated with a relatively low total level of energy per cm vein length (30 J/cm).

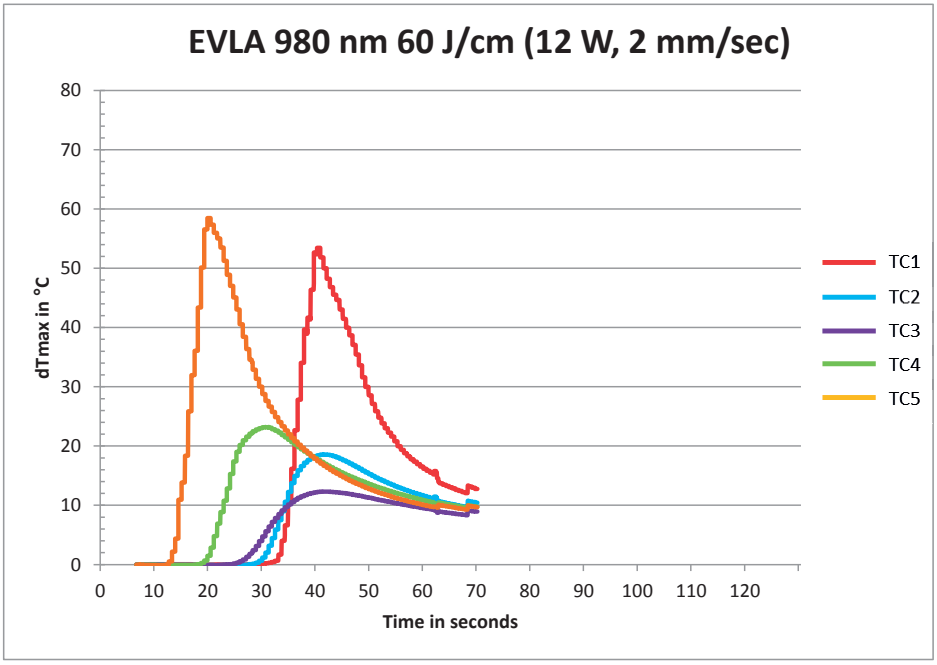


Figure 2. Temperature profile of 980 nm tulip EVLA. dTmax, maximal temperature increase above room temperature (20°C); TC1, thermocouple 1; TC2, thermocouple 2; TC3, thermocouple 3; TC4, thermocouple 4; TC5, thermocouple 5.

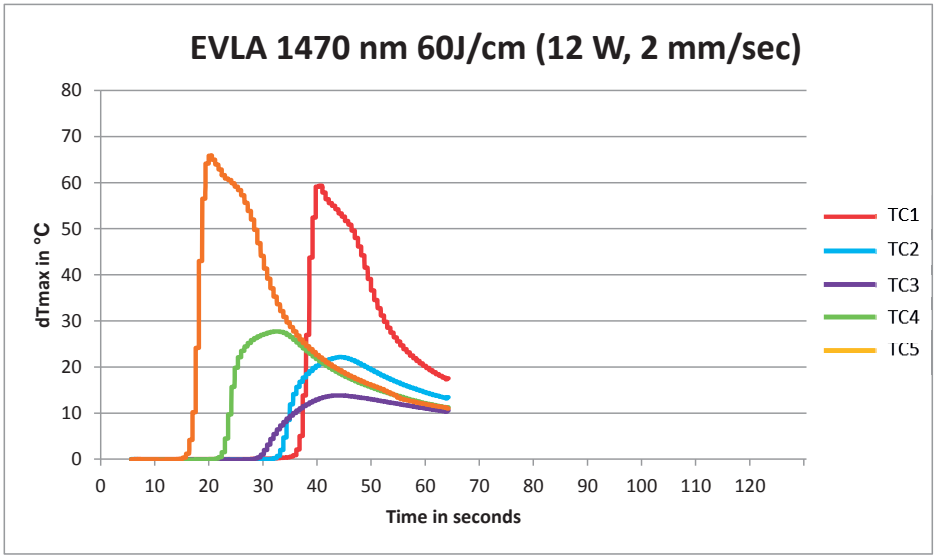


Figure 3. Temperature profile of 1470 nm tulip EVLA. dTmax, maximal temperature increase above room temperature (20°C); TC1, thermocouple 1; TC2, thermocouple 2; TC3, thermocouple 3; TC4, thermocouple 4; TC5, thermocouple 5.

Statistical comparison of dTmax, dt and dtdT between 30, 60 and 90 J/cm of each device (980 nm tulip fiber, 1470 nm tulip fiber and 1470 nm radial fiber), were highly significant (ANOVA; $p < 0.001$, except for dTmax of 1470 nm tulip fiber $p = 0.03$), indicating an increasing dTmax at 0 mm, dt and dtdT at higher LEED.

Wavelengths

The p-values of dTmax 0 mm, dt and dtdT were not significantly different between 980 and 1470 wavelengths (Independent T-test; $p = 0.82$, 0.10 and 0.18 respectively). Temperature profiles of 980 and 1470 nm EVLA were comparable.

Fiber tips

For 1470 nm EVLA, dTmax at 0 mm was significantly higher for the radial fiber than for the tulip tip fiber (Independent T-test; $p < 0.001$). However, dt and dtdT were comparable (independent T-test; $p = 0.11$ and 0.20 respectively).

EVSA

In Table 2, results are presented of dTmax at 0 mm, dt and dtdT for 2 and 3 pulses of steam. Temperature profile of EVSA is shown in Figure 4.

Temperature curves of EVSA showed a plateau phase, with a relatively constant temperature for a longer period of time. With 2 and 3 pulses of steam per cm, dTmax was over 30°C at 0 mm distance of the EVSA catheter. At 1 and 2 mm distance, dTmax was below this cut-off point. dTmax at 0 mm was significantly higher with 3 pulses of steam, than with 2 pulses (Independent T-test; $p = 0.024$). A significant difference was also found in dt; with 2 pulses/cm, dt was significantly lower than with 3 pulses (Independent T-test; $p < 0.001$), but both had a mean dt > 5 s.

Table 2. RFA and EVSA measurements

	RFA	EVSA	
	1 cycle	**2 pulses***	**3 pulses***
dTmax 0 mm (mean ± SD)	39 ± 11	43 ± 3	52 ± 7
dt (mean ± SD)	14 ± 9	17 ± 1	32 ± 2
dtdT (mean ± SD)	524 ± 318	583 ± 40	1308 ± 152

dTmax, maximal temperature increase in degrees Celsius (°C) above room temperature(20°C); SD, standard deviation; dt, duration of dTmax >30°C in seconds (s); dtdT, area under the curve (°C x s) of the time that the temperature increase is >30°C. *Statistical comparisons of dTmax 0 mm, dt and dtdT between 2 and 3 pulses of steam were significant (Independent T-test, p=0.02. <0.001 and <0.001 respectively).

RFA

Table 2 shows results of dTmax at 0 mm, dt and dtdT for RFA. Temperature profile of RFA is depicted in Figure 5.

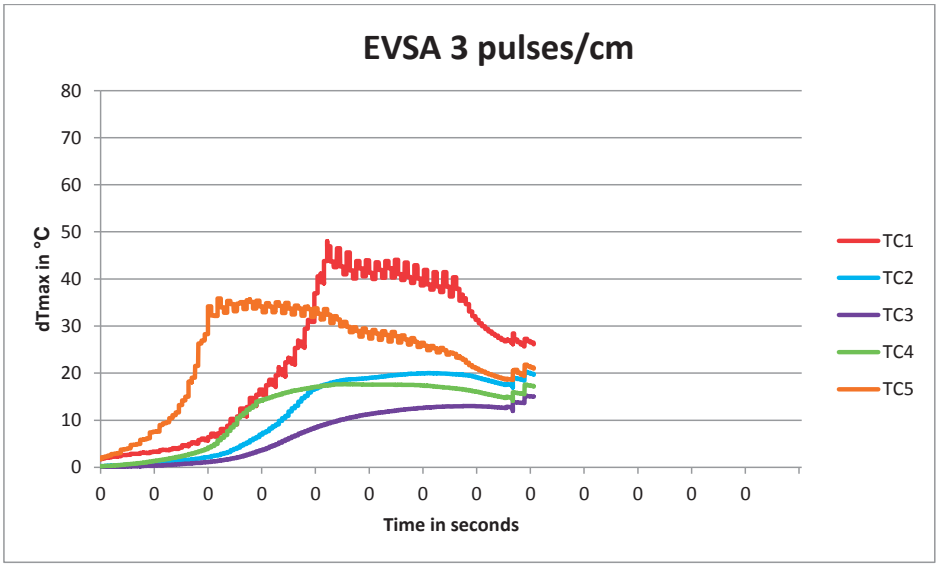


Figure 4. Temperature profile of EVSA. dTmax, maximal temperature increase above room temperature (20°C); TC1, thermocouple 1; TC2, thermocouple 2; TC3, thermocouple 3; TC4, thermocouple 4; TC5, thermocouple 5.

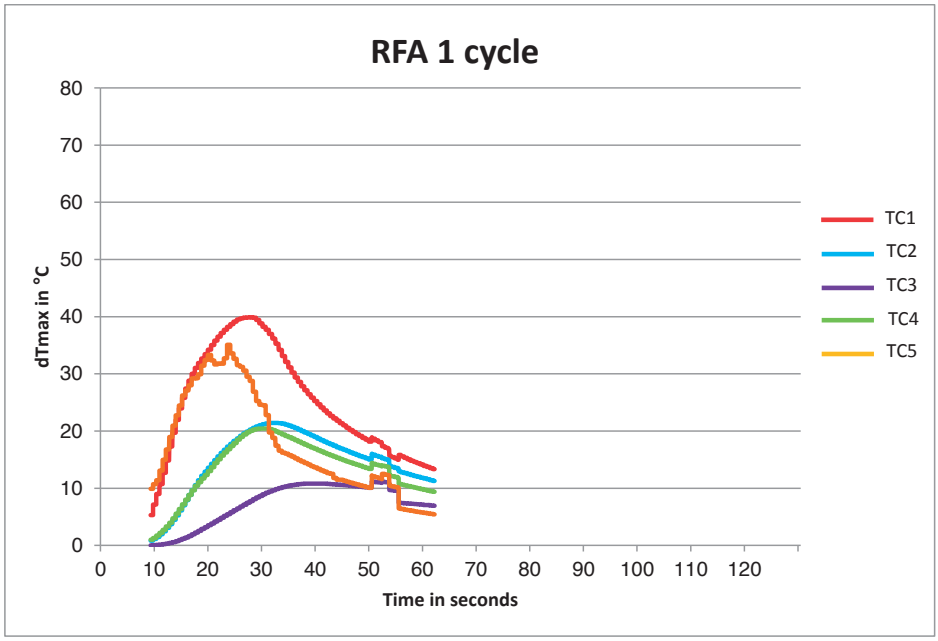


Figure 5. Temperature profile of segmental RFA. dTmax, maximal temperature increase above room temperature (20°C); TC1, thermocouple 1; TC2, thermocouple 2; TC3, thermocouple 3; TC4, thermocouple 4; TC5, thermocouple 5.

Temperature curves of segmental RFA showed a plateau phase, with a relatively constant temperature for a longer period of time. dTmax was over 30°C at 0 mm distance of the RFA catheter. At 1 and 2 mm distance, dTmax was below this cut-off point for both measurements. Also, dt was > 5 s.

Comparison of EVTA's

For both EVSA and segmental RFA, temperature curves showed a plateau phase, with a relatively constant temperature for a longer period of time, whereas for EVLA the temperature rise peaked and decreased more rapidly with less of a plateau phase. Also, the settings of EVLA in high LEED (90) J/cm, generated a higher dTmax, than RFA and EVSA. However, all devices were comparable in achieving a sufficient dTmax over 30°C at fiber or catheter level, and a dt >5 s. All EVTA devices could induce an adequate temperature rise at the fiber or catheter level and they all led to a long enough time span at the temperature needed for collagen denaturation.

DISCUSSION

This is the first experimental study that showed temperature profiles of EVLA for different wavelengths with tulip and radial fiber tips, in EVSA and segmental RFA. This study allowed us to compare temperature profiles of most of the available different endovenous thermal therapies, used in patients with varicose veins.
The results of these temperature measurements showed several interesting characteristics. We will discuss the results per device.

EVLA

The temperature rise of EVLA increased with higher LEED. Temperature behavior of EVLA was different compared to EVSA or segmental RFA; the peak temperature was higher for a shorter time. Possibly, high peak temperatures may result in vein wall perforation and/or more perivenous damage, causing (minor) side effects such as pain and ecchymoses, which seemed to occur more often in EVLA than in segmental RFA (15).

Temperature profiles of 980 and 1470 nm with tulip tip fibers did not differ significantly, which was in agreement with our previous findings (7). High LEED on the other hand, was again proven to be associated with significantly higher temperatures and increased time span of temperature rise, compared to lower LEED. It is likely that the alleged differences in side effect profiles between different wavelengths, as described in previous studies were the result of differences in administered J/cm (16), power (17) or laser tip design (18), rather than difference in wavelength.

Radial 1470 nm EVLA resulted in a significantly higher dTmax at 0 mm than tulip 1470 nm EVLA, but a comparable temperature profile with a peak shaped curve. The most likely explanation for the significant difference in dTmax is that radial fibers have a larger diameter than bare fibers and are therefore closer to the thermocouples. Also direct absorption of the laser light by the thermocouples could be an explanation for higher temperature measurements. In an additional experiment, we tested that direct irradiation of the thermocouple by the radial fiber resulted in barely any temperature rise, so direct emittance can be excluded as possible explanation for the difference.

EVSA

The dTmax of EVSA with 3 pulses per cm was significantly higher than with 2 pulses. Also, dt and dtdT were larger for EVSA with 3 pulses per cm. This outcome is in line with previously reported temperature measurements which led to the recommendation of administering 2 or more pulses per cm in human veins (8). EVSA resulted in mild peak temperatures for longer duration than EVLA, which was graphically shown as a long plateau phase. This implicated a longer homogeneous temperature rise of the vein wall, compared to EVLA, and could possibly result in a milder side effect profile, similar to segmental RFA. A clinical randomized trial should assess this possible difference.

Segmental RFA

Segmental RFA temperatures were measured for the standard setting (1 cycle). The catheter of segmental RFA was 2.2 mm in diameter and was therefore closer to the thermocouples than the other devices. However, this did not lead to significantly higher temperature measurements at catheter level. The temperature rise was relatively mild; comparable to EVSA and lower than EVLA. Parameter dt was > 5 s. This also resulted in a plateau shaped temperature profile, similar to EVSA. Segmental RFA values of dt and dtdT in our experiment were comparable to EVLA tulip tip 980 nm and 1470 nm at 60 J/cm. This is in line with the reported 68.2 J/cm as described by Proebstle et al. (19). The energy level of 1 cycle segmental RFA seemed to correlate with 60 J/cm EVLA, but the temperature profile was different because of the lack of peak temperature in segmental RFA. The absence of a peak temperature could be the explanation of the milder side effect profile of RFA, compared to EVLA (15).

In conclusion, temperature rise during EVLA is fast with a high peak temperature for a short time, whereas EVSA and RFA temperature increases have longer plateau phases and lower maximum temperatures. Temperature profiles of 940 / 980 nm and 1470 nm EVLA are again proven to be similar (7). Overall, differences in temperature levels of endovenous thermal ablation techniques are proven to be minimal. The studied temperature profiles suggest that in clinical practice all 3 EVTA methods will result in

sufficient heating to obliterate the targeted vein, with more minor side effects (pain, ecchymoses) in EVLA, due to higher maximum temperatures.

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Chapter 4

Randomized clinical trial of endovenous laser ablation versus steam ablation (LAST trial) for great saphenous varicose veins

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Br J Surg; 2014 Aug;101(9):1077-83

ABSTRACT

Background: The aim was to compare endovenous laser ablation (EVLA) and endovenous steam ablation (EVSA) for great saphenous varicose veins in a non-inferiority study.

Methods: Patients with primary great saphenous vein reflux were randomized to EVLA (940 nm) or EVSA (SVS™). Primary outcomes were treatment success at 52 weeks, and Venous Clinical Severity Score (VCSS) at 12 weeks. Secondary outcomes were pain, satisfaction with treatment, duration of analgesia use and days lost from daily activities, changes in Aberdeen Varicose Vein Questionnaire (AVVQ) and EQ-5D™ scores after 12 weeks, and complications at 2 and 12 weeks.

Results: A total of 227 legs were treated (EVSA, 117; EVLA, 110); 36 legs treated with EVSA received a low dose and the remaining 81 a higher dose. At 1 year, the treatment success after high-dose EVSA was not inferior to that of EVLA: 92 (95 per cent confidence interval (CI) 86 to 98) *versus* 96 (92 to 100) per cent respectively. Changes in VCSS after 12 weeks were similar: –2.69 (95 per cent CI –2.34 to –3.04) and –2.51 (–2.10 to –2.93). AVVQ, EQ-5D™ and EQ VAS scores improved equally 12 weeks after both treatments. Patients treated with EVSA reported less postprocedural pain, fewer days of analgesia use, were more satisfied with therapy, and had a shorter convalescence. Complication rates were comparable.

Conclusion: The 1-year treatment success of high-dose EVSA was not inferior to that of EVLA. Several secondary outcomes were in favour of EVSA.

INTRODUCTION

In many countries endovenous thermal ablation therapies have replaced high ligation and stripping as the treatment choice for primary incompetence of saphenous veins, as they are effective, have fewer complications, cause minimal postoperative pain and have faster recovery times (1–4). Because all endothermal treatments are effective, attention has shifted to finding the technique with the best side-effect profile, lowest pain scores and shortest convalescence. Only a few studies have compared the outcomes between different endothermal treatments. Two studies (5, 6) showed similar occlusion rates but faster recovery after segmental radiofrequency ablation (RFA) compared with laser ablation. Several studies (7-9) have tried to compare different endovenous laser ablation (EVLA) techniques to assess the possible advantages of higher wavelength or specific fiber tip design. However, these studies were not designed to compare a single variable, such as wavelength. Other parameters, such as power or fiber tip design also varied, making a valid comparison impossible.

The most recent innovation is endovenous steam ablation (EVSA). Its effectiveness and safety have been demonstrated in a small pilot study (10), in which microscopy of treated sheep veins showed thermally induced vein damage similar to that seen after RFA. A recent non-comparative case series (11) of EVSA reported a 96 per cent success rate after 12 months and favourable patient-reported outcomes. Possible advantages of this new steam procedure are: stable and relatively low temperature, easy procedure, potentially greater cost-effectiveness, low pain scores and greater patient satisfaction. EVSA uses sterile water, a natural fluid that does not have the possible disadvantage of inducing harm by generating exogenous substances (12). Another advantage of EVSA is strict temperature regulation; the steam produced has a constant temperature of 120°C. Because the induced temperature rise is limited (similar to the temperature applied in RFA), there may be fewer treatment-related symptoms (pain and bruising) and complications than with EVLA.

The aim of the present randomized non-inferiority study was to compare anatomical success rates and patient-reported outcomes following EVLA 940 nm and EVSA for treatment of incompetent great saphenous veins (GSVs).

METHODS

Three medical centres participated in this multicentre trial. Patients referred to the Erasmus MC Rotterdam, DermaPark Uden and Flebologisch Centrum Grave were screened for suitability for the LAST trial. Inclusion criteria were: age at least 18 years, informed consent, and symptomatic primary incompetence of the GSV with reflux time exceeding

0.5 s and diameter 5 mm or more (at mid-thigh level) according to duplex ultrasound (DUS) examination. Exclusion criteria were: acute deep or superficial vein thrombosis, agenesis of the deep venous system, vascular malformation or syndrome, post-thrombotic syndrome of the obstruction type, pregnancy, immobility, allergy to lidocaine and arterial insufficiency (ankle : brachial pressure index below 0.9). Consenting patients were randomized to either EVLA or EVSA, using a computerized randomization list. The legs of patients with bilateral GSV incompetence were included separately, provided that there was at least 3 months between the two treatments. The two treatments differed too much in technique (materials and typical noise of steam pulses) to achieve blinding of both the patient and the attending physician; assessors were not blinded for practical reasons. The study was approved by the Medical Ethics Committee of Erasmus MC Rotterdam (MEC-2009-269). The trial is registered at http://www.clinicaltrials.gov with registration number NCT02046967.

Treatment

All treatments were performed as an outpatient using local tumescent anaesthesia (0.5 mg adrenaline (epinephrine), 4.2 mg bicarbonate and 35 mg lidocaine diluted in 500 ml saline solution). When needed, tributaries were treated with phlebectomies at least 3 months after EVLA or EVSA.

Endovenous laser ablation

EVLA was done with a 940-nm diode laser (Dornier MedTech GmbH, Wessling, Germany) using a bare fiber. In brief, the vein was punctured under DUS guidance, preferably at the distal point of reflux or at knee level, for ease of access, with a 19-G needle (13). A guidewire was passed through the needle up to the level of the saphenofemoral junction (SFJ). The needle was removed and a 5-Fr catheter was inserted over the guidewire. After removing the guidewire, the laser fiber was inserted and the tip positioned 1–1.5 cm distal to the SFJ. Tumescent anaesthesia was administered under DUS guidance (250–500 ml, depending on the length of treated vein). The laser fiber was withdrawn continuously (at a speed of 2 mm/s) with a power setting of 12 W, delivering approximately 60 J/cm.

Endovenous steam ablation

EVSA was performed with the Steam Vein Sclerosis (SVS^{TM}) system (cermaVEIN, Archamps, France). Venous access was obtained by puncture with a 19-G cannula under DUS guidance. The steam ablation catheter (diameter 1.2 mm) was passed through the cannula into the vein and positioned 2-3 cm distal to the SFJ. Some 250-500 ml (depending on the length of treated vein) of tumescent anaesthesia was administered. First, 2 pulses of steam were delivered to dispel condensed water in the catheter. Three pulses were

then delivered at the catheter tip. The catheter was withdrawn by 1 cm and 1–4 pulses per cm of vein were emitted, depending on the diameter. For the first 36 procedures the treatment protocol was to apply 1 pulse/cm in veins smaller than 7 mm, 2 pulses/cm in veins of 7–10 mm, and 3 pulses/cm in veins larger than 10 mm. With insight and after temperature experiments (14), this was increased to 2, 3 and 4 pulses/cm respectively during the study.

After treatment

Following both treatments, patients were advised to wear medical elastic compression stockings for 1 week and to mobilize immediately. Prophylactic low molecular weight heparin was not administered routinely.

Outcomes assessed and follow-up protocol

Follow-up visits were scheduled at 2, 12 and 52 weeks after the initial procedure. Primary outcomes were treatment success, defined as obliteration of the GSV and/or absence of reflux (more than 0.5 s of retrograde flow) along the treated segment of the GSV, according to DUS examination at 12 and 52 weeks, and change in the VCSS recorded by a clinician at 12 weeks compared with the baseline score (15).

Secondary outcomes were divided into patient-reported outcomes and treatment safety. Pain was assessed by means of a visual analogue scale (VAS) and duration of painkiller use; satisfaction with treatment was measured on a VAS; and convalescence as number of days lost from work/daily activities. These were all assessed at 2 weeks after treatment. Health-related quality-of-life (HRQoL) was assessed with two questionnaires at 0 and 12 weeks: the Dutch translation of the Aberdeen Varicose Vein Questionnaire (AVVQ), which is a validated disease-specific quality-of-life questionnaire for varicose veins (16) and the EQ-5D™, a generic instrument measuring health status (http://www.euroqol.org). Changes in AVVQ, EQ-5D™ and EQ VAS scores were calculated as differences between scores at 12 weeks and baseline values. To evaluate treatment safety, major and minor complications were reported at 2 and 12 weeks. Major complications were: deep venous thrombosis (DVT), superficial thrombophlebitis in tributaries, nerve injury, skin burns and (sub)cutaneous infections. Minor complications were ecchymosis and hyperpigmentation, both measured as an area (cm^2) (17).

Statistical analysis

The success rate of EVLA was assumed to be about 92 per cent after 1 year (18) and was unknown for EVSA. The non-inferiority interval was set at 10 per cent with a β of 0.80 and one-sided α of 0.025. Based on these assumptions, the number of legs needed in this study was 116 per study group.

Success rates and other categorical variables for the two treatments were compared using proportions and 95 per cent confidence intervals (CI), which were estimated using the Wald method, with analysis by χ^2 test. Continuous variables (such as pain scores) were distributed normally and interpreted using means, 95 per cent CI, and independent or paired *t* test. A per-protocol analysis was carried out. The CONSORT statement for non-inferiority trials was used as a guideline for reporting the results (19,20).

RESULTS

Between November 2009 and November 2011, a total of 237 legs (in 217 patients) met the eligibility criteria and were randomized to receive treatment (Figure 1). Ten patients (ten legs) did not receive the allocated treatment owing to technical treatment failure (1 EVSA, 4 EVLA) or because the treatment was declined (5 EVLA). They were not included in the analysis because of the per-protocol design. A total of 227 legs were treated in 207 patients; 117 legs in 112 patients had EVSA and 110 legs in 106 patients had EVLA. Eleven patients had EVLA in one leg and EVSA in the contralateral leg, 4 patients had EVLA in both legs, and 5 patients had EVSA in both legs. For patients treated with EVLA, the mean(SD) energy delivered was 56.6(8.1) J/cm. Thirty-six patients treated with EVSA received the low dose, and the remaining 81 had the higher dose. Patients treated with EVSA received a mean(SD) of 2.1(0.6) pulses per cm of vein (higher dose 2.3(0.5) pulses/cm). Baseline characteristics were comparable between the treatment groups (Table 1).

Primary outcome primary outcomes: treatment success and Venous Clinical Severity Score

Table 2 summarizes the primary outcomes of the LAST trial. At 12 weeks, treatment success (obliteration of the treated GSV segment and/or absence of reflux) of all patients who had EVSA was not inferior to that of patients who had EVLA. After 1 year, EVSA was inferior to EVLA in achieving treatment success when all patients who had EVSA were considered (86.9 per cent *versus* 96 per cent who had EVLA; p = 0.032). Exclusion of patients who received low-dose EVSA resulted in similar success rates between EVSA and EVLA (92 *versus* 96 per cent; p = 0.331).

Of 107 legs treated with EVSA, 84 GSVs were obliterated, 9 were partially recanalized without reflux, and 14 treated GSVs were segmentally (more than 10 cm length of vein) or completely recanalized with reflux. Only 4 of 92 GSVs treated with EVLA were segmentally or completely recanalized, with reflux after 1 year. In both groups, the VCSS improved by 12 weeks after treatment: –2.51 (95 per cent CI –2.10 to –2.93) for EVLA and –2.90 (–2.42 to –3.58) for EVSA (all patients). Changes in VCSS scores between baseline

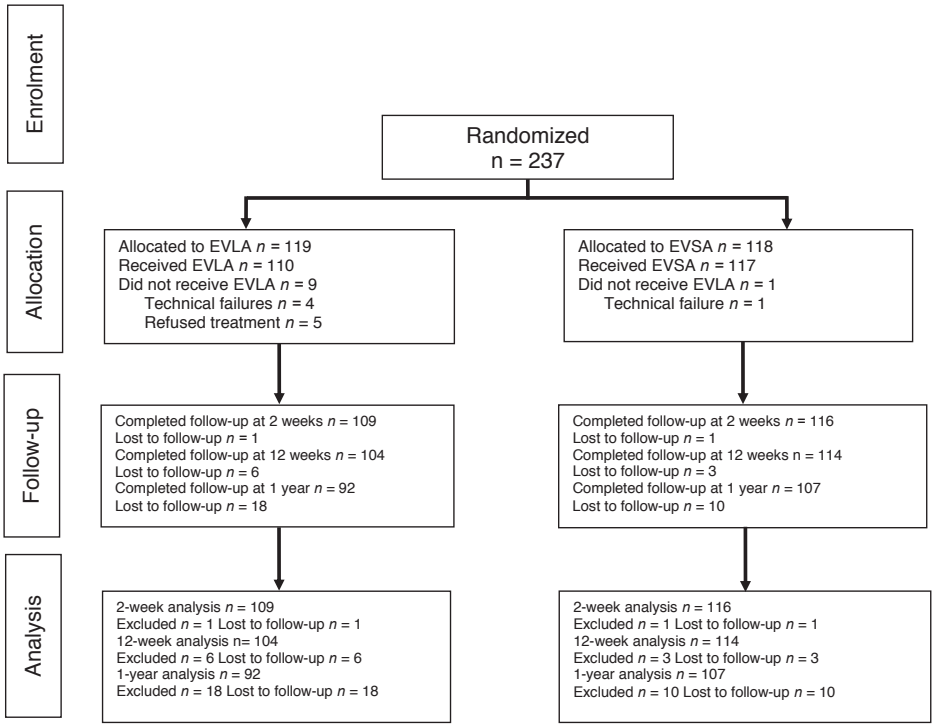

Figure 1. CONSORT diagram for the trial. EVLA, endovenous laser ablation; EVSA, endovenous steam ablation.

and 12 weeks were similar in the two groups, and there was no difference when patients who had low-dose EVSA were excluded.

Secondary outcomes

Postprocedural pain and analgesia use

Pain scores were available for 225 patients. EVSA-treated patients reported less post-procedural pain than those treated with EVLA (mean (95 per cent CI) VAS score 2.6 (2.1 to 3.1) *versus* 5.1 (4.7 to 5.6)) and a shorter duration of analgesia use (mean (95 per cent CI) 0.9 (0.5 to 1.4) *versus* 3.3 (2.6 to 4.1) days). There was no difference between the low-dose and high-dose EVSA groups (Table 3).

Satisfaction and convalescence

Patients who had EVSA were more satisfied with the therapy (mean (95 per cent CI) VAS score 8.6 (8.3 to 9.0) *versus* 7.7 (7.3 to 8.1)) and had a shorter convalescence (mean (95 per cent CI) 1.6 (1.0 to 2.1) *versus* 4.2 (3.4 to 5.0) days). The higher dose made no difference (Table 3).

Table 1. Demographic data and treatment characteristics

		EVLA	EVSA (all)	P†	EVSA (high-dose)	P‡
No. of legs		110	117		81	
No. of patients		106	112			
Age (years)*		55 (±12)	56 (±13)	0.801§	55 (±13)	0.824§
Sex				0.185¶		0.275¶
Male	patients	45 (42)	39 (35)			
	legs	48 (44)	41 (35)		29 (36)	
Female	patients	61 (58)	73(65)			
	legs	62 (56)	76 (65)		52 (64)	
C(EAP) class				0.186#		0.824#
C1		0 (0)	0 (0)		0 (0)	
C2		77 (70)	72 (62)		55 (68)	
C3		28 (25)	40 (34)		23 (28)	
C4		3(3)	3 (3)		1 (1)	
C5		1 (1)	1 (1)		1 (1)	
C6		1 (1)	1 (1)		1 (1)	
GSV diameter (mm)				0.342#		0.535#
<7 mm		84 (76)	91 (78)		66 (82)	
7-10 mm		26 (24)	24 (21)		14 (17)	
>10 mm		0 (0)	2 (2)		1 (1)	
Length treated GSV (cm)*		32.5 (±6.8)	31.2 (±6.7)	0.172§	31.0 (±6.8)	0.164§
Energy (Joules per cm/pulses)*		56 (±8.1)	2.1 (±0.6)		2.3 (±0.5)	

Values in parentheses are percentages unless indicated otherwise; *Values are mean (±standard deviation). EVLA, endovenous laser ablation; EVSA, endovenous steam ablation; CEAP, Clinical Etiologic Anatomic Pathophysiologic; GSV, great saphenous vein. †EVLA *versus* EVSA (all), ‡EVLA *versus* EVSA (high dose); §Independent T-test; ¶Chi-square test; #Chi-square test, linear by linear association.

Quality-of-life questionnaires

In both groups, all HRQoL outcomes improved 12 weeks after treatment, compared with scores at baseline ($p < 0.001$). The disease-specific questionnaire (AVVQ) improved substantially (by more than 30 per cent), but the generic questionnaires improved very little (less than 5 per cent). Changes in AVVQ, EQ-5D™ and EQ VAS scores between baseline and 12 weeks were comparable for EVSA and EVLA (Table 3).

Complications

Complications were mostly minor, and the side-effect profiles of EVSA and EVLA treatment appeared to be similar (Table 4). One patient who had EVLA developed a DVT in the common femoral vein of the treated leg 2 weeks after the intervention. Thrombophlebitis in tributaries was reported in ten legs (9.2 per cent) in the EVSA and ten (8.5

Table 2. Treatment success

	Anatomical success after 12 weeks*	Anatomical success after 1 year*	Change in VCSS after 12 weeks†
EVLA	101/104 (97; 94 to 100)	88/92 (96; 92 to 100)	-2.51 (-2.10 to -2.93)
EVSA (all)	107/114 (94; 90 to 98)	93/107 (87; 81 to 93)	-2.90 (-2.42 to -3.58)
P‡	0.251¶	0.032¶	0.242#
EVSA (high-dose)	76/78 (97; 94 to 100)	68/74 (92; 86 to 98)	-2.69 (-2.34 to -3.04)
P	0.896¶	0.311¶	0.279#

Values in parentheses are *percentages with 95 per cent confidence intervals (CI) and †mean with 95 per cent CI). VCSS, Venous Clinical Severity Score; EVLA, endovenous laseraAblation; EVSA, endovenous steam ablation. ‡EVLA *versus* EVSA (all), §EVLA *versus* EVSA (high dose); ¶Chi-square test; #independent T-test.

Table 3. Secondary outcome measures

	EVLA N=109	EVSA (all) N=116	P*	EVSA (high-dose) N=81	P†
2 weeks after intervention	*n* = 109	*n* = 116		*n* = 81	
Pain (VAS)	5.1 (4.7, 5.6)	2.6 (2.1, 3.1)	<0.001	2.7 (2.1, 3.3)	<0.001
Satisfaction (VAS)	7.7 (7.3, 8.1)	8.6 (8.3, 9.0)	0.001	8.5 (8.1, 8.9)	0.007
Duration of analgesia use (days)	3.3 (2.6, 4.1)	0.9 (0.5, 1.4)	<0.001	1.5 (0.5, 1.8)	<0.001
Limited in daily life (days)	4.2 (3.4, 5.0)	1.6 (1.0, 2.1)	<0.001	1.6 (0.9, 2.3)	<0.001
Changes in HRQoL (12 weeks after intervention *versus* baseline)					
AVVQ	-5.47 (-3.93, -7.01)	-5.17 (-3.63, -6.70)		-5.10 (-3.14, -7.06)	
EQ-5D™	0.039 (0.010, 0.067)	0.035 (0.011, 0.059)		0.033 (0.003, 0.062)	
EQ VAS	1.9 (0.4, 3.4)	0.8 (-0.9, 2.4)		0.0 (-2.1, 2.1)	

Values in parentheses are 95 per cent confidence intervals. EVLA, endovenous laser ablation; EVSA, endovenous steam ablation; VAS, visual analoge scale; HRQoL, Health Related Quality of Life; AVVQ, Aberdeen Varicose Vein Questionaire. *EVLA *versus* EVSA (all); †EVLA *versus* EVSA (high dose); all T-test.

Table 4. Complications

	EVLA	EVSA
2 weeks after intervention	*n* = 109	*n* = 117
Deep venous thrombosis	1 (0.9)	0 (0)
Superficial venous thrombosis	10 (9.2)	10 (8.5)
Nerve injury	0 (0)	1 (0.9)
Skin burn	0 (0)	0 (0)
Skin infection	0 (0)	1 (0.9)
Ecchymosis (cm^2)*	4.5 (13.1)	1.0 (3.1)
Hyperpigmentation (cm^2)*	0.9 (3.9)	0.9 (4.6)
12 weeks after intervention	*n* = 98	*n* = 107
Superficial venous thrombosis	0 (0)	3 (2.8)
Nerve injury	0 (0)	2 (1.9)
Ecchymosis (cm^2)*	0.0 (0.4)	0.0 (0.0)
Hyperpigmentation (cm^2)*	0.1 (0.5)	0.3 (1.8)

Values in parentheses are percentages unless indicates otherwise; *values are mean (SD). EVLA, endovenous laser ablation; EVSA, endovenous steam ablation

per cent) in the EVLA group 2 weeks after treatment. Three legs (2.8 per cent) in the EVSA group still had thrombophlebitis at 12 weeks. Two patients reported a sensory nerve injury 12 weeks after EVSA. Two weeks after EVLA the mean area of ecchymosis was 5 cm^2, which was larger than the mean of 1 cm^2 after EVSA.

DISCUSSION

This trial compared EVSA with EVLA, which is the most commonly used thermal treatment for varicose veins. With the appropriate (high) dose, EVSA was not inferior to EVLA (940 nm, bare fiber) regarding success rate of the treated GSV segment after 1 year. The patient-reported outcomes were all in favour of EVSA: pain scores, duration of painkiller use and satisfaction with treatment. Quality of life improved similarly in both groups.

EVLA occlusion rates are usually in the range 90–95 per cent (18), similar to the rate in the present study. In patients who had low-dose EVSA, the occlusion rate after 1 year was lower than that after EVLA. The initial dosing of EVSA was based on the short-term outcome of a pilot study (10), in which 1 or 2 pulses/cm resulted in seven of 20 treated veins being incompletely obliterated and two having a remaining segment with reflux after 6 months. The present randomized clinical trial was initiated after the pilot study, but before an experimental study (14) showing that 2 pulses/cm should be sufficient for a homogeneous temperature rise exceeding 50°C, explaining the rationale for violation of the protocol by increasing the number of pulses from at least 1 to at least 2 pulses per cm vein during the trial. The patients who received at least 2 pulses per cm vein had a success rate of 92 per cent, which is close to the 96 per cent in a recently published large case series (11) in which 2–4 pulses/cm were administered. Altogether, these findings suggest a clear dose–response relationship. Therefore, diameter of the veins and presence of tributaries should be taken into account when determining optimal EVSA methodology. To determine the optimal schedule for EVSA, further evaluation should be undertaken. The difficulty of designing dose-finding studies is a problem common to all endovenous thermal therapies, including EVLA for which there are numerous different laser parameters and little consensus on the optimal treatment.

In vivo measurements (temperature profile in the vein during treatment) are difficult to obtain. Ideally, these data should be investigated before setting up a randomized trial. Increasing the number of pulses/cm might influence the volume of tumescent anaesthesia needed for a painless procedure. However, it is unlikely to influence patient-reported outcomes at 2 weeks because the intravenous temperature rise is limited. Vein wall perforation and perivenous damage are usually responsible for side-effects of endothermal treatments; these are not found on histology of veins treated with EVSA (10).

Of the secondary outcomes, HRQoL scores improved equally after both treatments, but the remaining patient-reported outcomes were in favour of EVSA. Reduction in pain translated into quicker recovery after EVSA, which is an important advantage from a societal perspective. The minimal clinically important difference is unknown for the HRQoL questionnaires, making it difficult to evaluate their clinical relevance (21). The explanation for the favourable side-effect profile may be that the peak temperature in EVSA is far lower than that of EVLA (22). Peak temperatures of over 600°C at the fiber tip have been reported for EVLA, potentially leading to perforation and perivenous inflammation when the bare fiber tip is in direct contact with the vein wall (12,23–25). The relatively low temperature in EVSA does not seem to cause perforation of the vein wall, similar to previous findings for RFA in a bovine model (25). The lack of perforations after EVSA has been confirmed in experimental studies (10, 26). In another recent experimental study (22), temperature profiles of EVSA, EVLA and segmental RFA were compared. The LAST trial was performed with 940-nm bare-fiber EVLA, which was the most frequently used EVLA method when the study began. Developments in EVLA methodology aiming to improve the secondary outcomes are ongoing. Innovations in fiber tip design (such as tulip fiber) and power administered may result in better secondary outcomes, decreasing the difference between EVLA and EVSA (27).

The gap in knowledge concerning optimal EVSA dosing is an important limitation of this study. A second limitation is that patients and practitioners were not blinded. Owing to the different materials and the typical noise that EVSA makes, blinding was impossible.

Endovenous thermal ablation is very successful for the treatment of varicose veins. The 1-year success rate of high-dose EVSA is not inferior to that of EVLA (940 nm, bare fiber). The efficacy of EVSA might be improved by increasing the dose of the pulses, which will require formal assessment in future studies.

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Chapter 5

Randomized clinical trial of patient reported outcomes after endovenous 940 nm laser ablation versus 1470 nm laser ablation (COLA trial) for great saphenous vein incompetence

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Br J Surg; 2016 Feb 103(3):192-8

ABSTRACT

Background: The independent effect of wavelength used for endovenous laser ablation (EVLA) on patient reported outcomes, health-related quality of life (HRQoL), success and complications has not yet been established in a randomized controlled trial (RCT). Our aim was to compare two different wavelengths, with identical energy level and laser fibers, in patients undergoing EVLA.

Methods: Patients with great saphenous vein (GSV) reflux were randomized into 940 nm or 1470 nm EVLA. The primary outcome was pain at one week. Secondary outcomes were satisfaction, days of analgesia use and days without normal activities at one week, HRQoL after 12 weeks, treatment success after 12 and 52 weeks, change in Venous Clinical Severity Score (VCSS) after 12 weeks and adverse events at one and 12 weeks.

Results: A total of 139 legs were treated (940 nm EVLA, 68; 1470 nm EVLA, 71). Patients in the 1470 nm EVLA group reported significantly less pain on a visual analogue scale (VAS), compared to 940 nm EVLA; median(IQR) VAS of 3(5) and 6(5) ($p = .005$) respectively. Duration of analgesia use was significantly shorter after 1470 nm EVLA; median(IQR) of 1(3) and 2(5) days ($p = 0.037$). HRQoL and VCSS improved equally in both groups. There was no difference in treatment success rates. Complications were comparable in both groups, except for more superficial vein thrombosis 1 week after 1470 nm EVLA.

Conclusion: The only difference between 940 nm and 1470 nm EVLA is the short-term patient reported tolerability one week postoperatively, with reduction of pain scores and duration of analgesia use after 1470 nm EVLA.

INTRODUCTION

Chronic venous disease (CVD) (1, 2) of the lower extremities is a very common medical condition affecting about 15% to 35% of the general population in Western countries (3, 4). More than 75% of people with CVD have incompetence of the saphenous veins of the legs (5). CVD has a great impact on patients' health-related quality of life (HRQoL), comparable to other common diseases (6).

In many countries, endovenous laser ablation (EVLA) and other endovenous thermal ablation techniques, have replaced high ligation and stripping as the first choice of treatment for incompetent saphenous veins. The efficacy of EVLA is very high (>90% obliteration rate) and the available literature shows that this success rate is observed for different laser wavelengths, power settings and pullback speeds used (7, 8). However it is less clear if the EVLA induced adverse events and tolerability of the treatment are affected by the above-mentioned laser parameters. As all EVTA treatments are highly effective, the attention in research and clinical practice has now shifted towards minimizing adverse effects by modifying laser settings, procedures and medical devices (i.e, wavelength and type of fibers). Two comparative EVLA studies demonstrated that patients treated with EVLA with higher wavelengths (1320 and 1470 nm) reported less postoperative pain, used less painkillers and were less likely to have ecchymosis than those treated with lower wavelengths (9, 10). However, in addition to the wavelength, these studies also varied in laser power or laser fiber tip, so a conclusion based on the effect of wavelength only was not possible.

The objective of the present prospective randomized controlled trial (RCT) was to assess the independent effect of EVLA wavelength (applying identical energy levels and using identical laser fibers) on patient reported outcomes (PRO), quality of life, complications and success rate.

METHODS

Consecutive patients referred to the outpatient phlebology clinic at the Department of Dermatology, Erasmus MC Rotterdam, the Netherlands, were screened for eligibility for the comparative laser or 'COLA' trial between May 2012 and November 2013, by means of medical history, clinical examination and duplex ultrasound imaging. On estimation, about half of the referred patients were diagnosed with superficial venous incompetence. The inclusion criteria for our trial were age over 18 years, symptomatic primary incompetence of the GSV with a diameter of at least 5 mm at mid-thigh level and reflux (defined as reversed flow during ≥ 0.5 seconds) according to duplex ultrasound (DUS). Exclusion criteria were pregnancy, immobility, acute deep or superficial vein thrombosis,

agenesis of the deep venous system, vascular malformation, post-thrombotic syndrome of the obstructive type, peripheral arterial disease and allergy to lidocaine. Written informed consent was obtained in all selected patients. The eligible GSVs of patients were randomly assigned to either 940 nm or 1470 nm EVLA, using a computerized randomisation list, created by an independent research nurse. In case of bilateral GSV incompetence in one patient, both legs were randomized separately.

All patients were blinded for the treatment they received. The two laser devices differed too much in device materials to achieve blinding of the attending physician. Assessors were not blinded, since the principal assessor was the attending physician performing the EVLA treatment in a large number of cases. The Medical Ethics Committee of the Erasmus MC Rotterdam approved the COLA trial (MEC-2011-455). The study was registered at www.clinicaltrials.gov (registration number NCT01637181).

Treatment

All treatments were performed in an outpatient setting under local tumescent anesthesia (0.5 mg epinephrine, 4.2 mg bicarbonate and 35 mg lidocaine diluted in 500 mL saline solution) as described previously (11). EVLA was performed either using a 940 nm Diode laser (Dornier MedTech, Wessling, Germany) or a 1470 nm Diode laser (Quanta System, SolbiateOlona, VA, Italy); for all procedures a tulip tip fiber (Tobrix, Waalre, The Netherlands) was used.

Access to the GSV was obtained by puncture with a 19 G needle under ultrasound guidance, preferably at the most distal point of reflux. A guide wire was passed through the hollow needle into the vein up to the saphenofemoral junction (SFJ). The laser fiber was inserted through a 5-Fr introducer sheath and the fiber tip was positioned at 1-2 cm distally from the SFJ. Under ultrasound guidance, 250 to 500 ml of tumescent anesthesia (depending on the length of the treated GSV) was administered into the perivenous space. After activation, the 940 nm or 1470 nm laser fiber was pulled back continuously with 2.5 mm/s using 10 W, delivering approximately 40 J/cm vein. Proebstle et al. defined a threshold for the endovenous fluence equivalent which was 6.3 J/cm per diameter vein for durable occlusion (12). Another recent experimental study (13) showed that 30 J/cm and above has proven to generate a temperature high enough for a sufficient amount of time to cause collagen denaturation needed to inflict irreversible damage to the vein wall. Concomitant phlebectomies were performed in case of presence of incompetent GSV tributaries, suitable for treatment with phlebectomy. After the procedure, patients were advised to wear thigh-high medical elastic compression stockings with at least 25-30 mm Hg at the ankle for one week and mobilize immediately. In case of bilateral GSV incompetence in the same patient, both GSVs were treated separately with a treatment interval of more than three weeks.

Outcomes assessed and follow-up protocol

Patients were scheduled for follow-up visits at 1, 12, and 52 weeks after treatment. The primary outcome was pain score, measured by means of a visual analogue scale (VAS). One week after treatment, patients had to circle a number from zero to ten, defining the maximum number of experienced pain in the week after treatment. Other patient reported outcomes, being treatment satisfaction (also measured by a VAS), number of days of analgesia use and number of days lost at work or normal daily activities were also assessed at one week post treatment. Health related quality-of-life (HRQoL) was assessed with two questionnaires at baseline and 12 weeks after treatment; the Dutch Translated Aberdeen Varicose Vein Questionnaire (AVVQ), which is a validated disease-specific quality-of-life questionnaire for varicose veins (14) and the EQ-5D™, which is a generic utility instrument measuring health status (http://www.euroqol.org). Median changes in these parameters were calculated as AVVQ, EQ-5D™ and EQ VAS scores at 12 weeks minus the baseline scores.

Secondary outcomes were treatment success, defined as obliteration of the treated segment of the GSV and/or partial obliteration of the treated GSV segment with absence of reflux, measured by DUS at 12 and 52 weeks post treatment (15), change in Venous Clinical Severity Score (VCSS), scored at baseline and 12 weeks after treatment and the occurrence of complications (deep venous thrombosis (DVT), superficial venous thrombosis (SVT) of tributaries or the distal (untreated) part of the GSV, nerve injury, skin burn, skin infection, ecchymosis and hyperpigmentation), examined at one and 12 weeks post treatment. SVT was defined as thrombus formation in a tributary of the GSV or in the distal (untreated) part of the GSV, with or without clinical signs of inflammation.

Statistical analysis

To determine a difference of 1 between the mean/median pain (VAS) scores of the treatment groups, with a SD of 2, a number of 64 legs per study arm had 80% power (one-sided alfa 0.05). Assuming a dropout of approximately 10%, the number of legs needed in this study was 71 per treatment group.

Statistical analysis was done using SPSS v. 22.0 software (SPSS Inc, Chicago, Illinois, USA). A per-protocol analysis was carried out. The primary endpoint and other continuous data were not normally distributed and therefore analyzed with non-parametric Mann-Whitney U tests. The data were presented as median with interquartile range (IQR). For the length of the treated GSV, analysis with the Independent *t*-test was used and presented as means with SD. The analysis of improvements in HRQoL scores during the study was assessed using the Wilcoxon Signed Ranks test. Patients with bilateral GSV incompetence were randomized separately for each leg. For HRQoL analysis, these patients were excluded for analysis, since patients are unable to differentiate between the impact of varicose veins of each separate leg on HRQoL.

Treatment success, adverse events and other categorical data were expressed in terms of their frequencies and percentages. The data was analyzed using the Chi-square test or, in case of low frequencies (N≤5 per cell), the Fisher exact test. All statistical tests were two-sided and p-values of <.05 were considered to be significant.

General linear regression models were used to examine the association between pain scores and type of EVLA treatment, adjusted for (higher) energy level, vein diameter, additional phlebectomies performed at baseline, complications (for instance SVT), gender and side of the treated leg, and the association of treatment success and type of EVLA treatment, adjusted for GSV diameter, energy density, SFJ incompetence and additional phlebectomies at baseline.

RESULTS

Between June 2012 and November 2013, 142 legs in 129 eligible patients were randomized to the 940 or 1470 nm EVLA (Figure 1). Three legs were excluded from the per protocol analysis because they did not receive treatment; the GSV diameter appeared to be too small in 2 legs (1 patient) and 1 leg was excluded because the guidewire could not be advanced in the GSV. A total of 139 legs were treated in 127 patients; 68 legs in 65 patients had 940 nm EVLA and 71 legs in 68 patients had 1470 nm EVLA. Twelve patients were treated bilaterally; three patients had 940 nm EVLA in both legs, three patients had 1470 nm EVLA in both legs and six patients were treated with 940 nm EVLA in one leg and 1470 nm EVLA in the contralateral leg (Table 1). Demographic data and preoperative clinical findings were comparable in the two groups (Table 1), except for the side of the treated leg; there were more left legs treated in the 1470 nm group than in 940 nm group (p = 0.023). Concomitant phlebectomies were performed in 37 (54.4%) patients of the 940 nm EVLA group and 33 (46.5%) of the 1470 nm EVLA group (p = 0.350).

Patient reported outcomes (post procedural pain, satisfaction, analgesia use and convalescence)

One week after intervention, patients treated with 1470 nm EVLA reported significantly less postoperative pain than patients treated with 940 nm EVLA (median (IQR) VAS score of 3 (5) and 6 (5) p = 0.005), and a significantly shorter duration of analgesia use(median (IQR) days of 1 (3) and 2 (5) p = 0.037; Table 2).There appeared to be no association between pain scores and (higher) energy level, vein diameter, concomitant phlebectomies performed at baseline, complications (for instance SVT) and side of the treated leg (data not shown). Only gender showed to have an association with pain; women reported higher post procedural pain scores than men (p = 0.04). There were very few outliers in administered energy levels: 5 GSVs with equal distribution between the 2 EVLA groups.

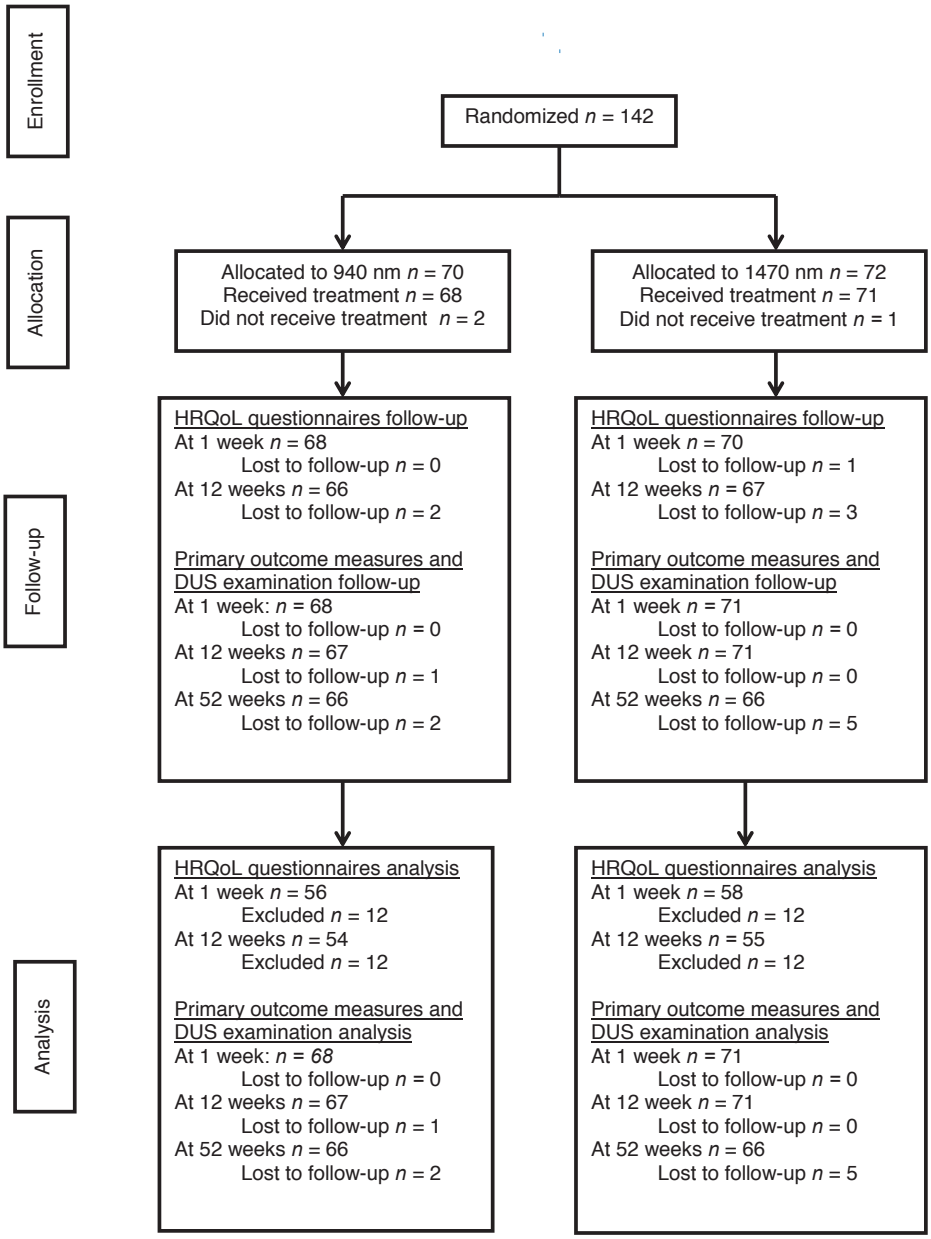

Figure 1. CONSORT diagram for the trial. HRQoL, health related quality of life; DUS, duplex ultrasound.

We performed a sensitivity analysis of the pain score including all 142 randomized limbs. For the missing values we implemented the median pain VAS of the group to which the untreated GSVs were randomized. The median pain VAS (IQR) did not change in this analysis, they remained 6.0 (5.0) and 3.0 (5.0) for 940 nm and 1470 nm EVLA respectively.

Table 1. Demographic data and preoperative clinical findings

		940-nm EVLA	1470-nm EVLA	P‡
No. of legs		70	72	
No. of patients		66	69	
Age (years)*		49.8	54.8	0.551§
Sex				
Male	patients	29 (44)	31 (45)	
	legs	29 (41)	32 (44)	
Female	patients	37 (56)	38 (55)	
	legs	41 (59)	40 (56)	
C(EAP) class				0.571¶
C1		0 (0)	0 (0)	
C2		14 (20)	15 (21)	
C3		38 (54)	41 (57)	
C4		15 (21)	14 (19)	
C5		2 (3)	2 (3)	
C6		1 (1)	0 (0)	
Side (legs)				0.019
Right		37 (53)	24 (33)	
Left		33 (47)	48 (67)	
Unilateral		56 (80)	60 (83)	0.821
Bilateral – same treatment		8 (11)	6 (8)	
Bilateral – different treatment		6 (9)	6 (8)	
GSV diameter (mm)*		33.4 (10.1)	33.1 (7.7)	.410§
Saphenofemoral junction				0.773
Competent		17 (24)	19 (26)	
Incompetent		53 (67)	53 (74)	
Length of treated GSV (cm)†		33.4 (10.1)	33.1 (7.7)	0.844#
Energy (J/cm)*		39.3 (37.8 – 41.6)	39.0 (36.7 – 40.7)	0.204§
Additional phlebectomy		39 (56)	34 (47)	0.311

Values in parentheses are percentages unless indicated otherwise; values are *median (IQR) and †mean (SD). EVLA, endovenous laser ablation; CEAP, Clinical Etiologic Anatomic Pathophysiologic; GSV, great saphenous vein. ‡Chi-square test, except §Mann-Whitney U-test, #Chi-square test, linear by linear association and #independent T-test.

Patients who had 1470 nm EVLA seemed somewhat more satisfied with the treatment, but this difference was not statistically significant (median (IQR) VAS score of 9 (2) and 8 (2) (p = 0.062)).The recovery time after treatment did not vary between both treatment groups (median (IQR) days limited in daily life 0 (2) and 0 (4) (p = 0.205)).

Quality of life

Significant improvement in AVVQ and EQ-5D™scores were seen in both groups, 12 weeks after treatment ($p < 0.001$). Changes in AVVQ, EQ-5DTM and EQ VAS between baseline and 12 weeks after treatment were comparable for 1470 nm and 940 nm EVLA (Table 2).

Table 2. Patient-reported outcomes and quality of life

	940-nm EVLA		1470 nm EVLA		
	No. of legs	**Score***	**No. of legs**	**Score***	**P‡**
1 week after intervention					
Pain (VAS)†	70	6 (3-8)	72	3 (2-7)	0.004
Satisfaction (VAS)	68	8 (7-9)	71	9 (8-10)	0.062
Duration of analgesia use (days)	68	2 (0-5)	71	1 (0-3)	0.037
Limited in daily life (days)	68	0 (0-4)	71	0 (0-2)	0.205
HRQoL at baseline					
AVVQ	56	13.38 (8.08-24.08)	58	9.37 (6.25-14.57)	0.008
EQ-5D™	56	0.843 (0.733-1.000)	58	0.843 (0.807-1.000)	0.018
EQ VAS	56	80 (61-90)	57	80 (75-90)	0.345
HRQoL 12 weeks after intervention					
AVVQ	54	7.13 (1.89-15.29)	55	4.58 (1.72-8.50)	0.047
EQ-5D™	54	1.000 (0.798-1.000)	55	1.000 (0.897-1.000)	0.017
EQ VAS	54	80 (70-85)	55	80 (80-90)	0.077
Changes in HRQoL (12 weeks *versus* baseline)					
AVVQ	54	-4.45 (-7.96 to -1.13)	55	-3.44 (-8.00 to -0.77)	0.773
EQ-5D™	54	0.034 (0-.193)	55	0.090 (0-0.157)	0.619
EQ VAS	54	0 (-5 to 10)	54	0 (-2 to 5)	0.624

*Values are median (IQR). Patients with bilateral treatment were excluded from health-related quality of life (HRQoL) analysis. †Three missing values were replaced by the median visual scale (VAS) score for each treatment group. EVLA, endovenous laser ablation; AVVQ, Aberdeen Varicose Vein Questionnaire; EQ, EuroQol. ‡Mann-Whitney U-test.

Treatment success

Treatment success was similar in 1470 nm and 940 nm EVLA groups, after 12 weeks (98.6% (95% CI 95.4 to 100) vs 98.5% (95% CI 94.7 to 100), $p = 1.00$) and after 52 weeks (93.9% (95% CI 87.7 to 98.6) vs. 90.9% (95% CI 83.3 to 97.1), $p = 0.511$; Table 3). After 52 weeks, of the 66 legs treated with 1470 nm EVLA, 61 GSV's (92.4%) were completely obliterated, 1 (1.5%) was partially recanalized without reflux and 4 (6.1%) were segmentally recanalized with reflux or completely recanalized; of the 66 legs treated with 940 nm EVLA, 55 GSV's (83.3%) were completely obliterated, 5 (7.6%) were partially recanalized without reflux and 6 (9.1%) were segmentally recanalized with reflux or completely recanalized ($p = 0.110$). There was no association between treatment success and GSV diameter or SFJ incompetence at baseline, energy density and concomitant phlebectomies.

VCSS

Twelve weeks after intervention the VCSS score had improved significantly in both the 1470 and 940 nm EVLA group, compared to baseline (p = 0.001), without difference between the two groups (Table 3).

Complications

No major adverse events occurred during this study, except for one DVT of a gastrocnemius vein in a patient of the 940 nm EVLA group 12 weeks after treatment (Table 4). One week after intervention, SVTs in tributaries or the distal (untreated) part of the GSV were more frequently seen in the 1470 nm EVLA patients(14.1% vs 4.4% (p = 0.05)). The overall side effect profile of both groups appeared to be comparable.

Table 3. Treatment success

	940-nm EVLA	1470-nm EVLA	P
Treatment success			
After 12 weeks	66 of 67 (99; 95, 100)	70 of 71 (99; 95, 100)	1.000†
After 52 weeks	60 of 66 (91; 83, 97)	62 of 66 (94; 88, 99)	0.511‡
Change in VCSS after 12 weeks*	-3 (-5 to -1) (67 legs)	-3 (-5 to -1) (69 legs)	0.883§

Values in parentheses are percentages with 95 percent CI unless indicates otherwist; values are median (IQR). EVLA, endovenous laser ablation; VCSS, Venous Clinical Severity Score. †Fisher's exact test; ‡Chi-square test; §Mann-Whitney U-test.

Table 4. Complications

	940-nm EVLA	1470-nm EVLA	P†
After 1 week	68 legs	71 legs	
Deep venous thrombosis	0 (0)	0 (0)	-
Superficial venous thrombosis	3 (4.4)	10 (14.1)	0.05‡
Nerve injury	0 (0)	0 (0)	-
Skin burn	0 (0)	0 (0)	-
Skin infection	0 (0)	1 (1.4)	0.326
Ecchymosis (cm2)*	3.82 (13.3)	7.86 (37.5)	0.668§
Hyperpigmentation (cm2)*	0.0 (0.0)	0.0 (0.0)	-
After 12 weeks	67 legs	71 legs	-
Deep venous thrombosis	1 (1.5)	0 (0)	0.486
Superficial venous thrombosis	0 (0)	2 (2.8)	0.497
Nerve injury	1 (1.5)	0 (0)	0.486
Skin burn	0 (0)	0 (0)	-
Skin infection	0 (0)	0 (0)	-
Ecchymosis (cm2)*	0.0 (0.0)	0.0 (0.0)	-
Hyperpigmentation (cm2)*	3.54 (24.6)	0.57 (3.0)	0.916§

Values in parentheses are percentages unless indicated otherwise; * values are median (IQR). EVLA, endovenous laser ablation. †Fisher's exact test, except ‡Chi-square test and §Mann-Whitney U-test.

DISCUSSION

This is the first randomized trial comparing 1470 nm and 940 nm EVLA, using identical power (10 W), energy level (40 J/cm) and laser fiber (tulip tip) and therefore solely investigating the effect of wavelength. Patients treated with 1470 nm EVLA reported significantly less pain and less duration of analgesia use one week after treatment, compared to patients with 940 nm EVLA. Improvement of HRQoL and VCSS, treatment success rates and adverse events were comparable between the two groups. Our RCT has proven that the only difference between low (940 nm) and high (1470 nm) wavelength EVLA treatment is the short-term patient reported tolerability (at one week postoperatively).

The sparse previous studies, comparing PRO's of higher EVLA wavelength to lower wavelength (9, 10), showed a benefit for the higher wavelengths by reducing postoperative pain. However these studies also varied laser parameters (laser fiber (10) and power (9)) between the groups, possibly creating confounding. Side effects after EVLA treatment, such as pain and ecchymoses, are assumed to be partly a result of vein wall perforations, due to high temperatures. In-vitro measurements have recently shown that temperature profiles of EVLA are wavelength-independent (13, 16). It is therefore unlikely that the identified difference in pain scores in the present study is due to varying temperature. Also, in both treatment groups tulip tip laser fibers were used, which are less likely to cause vein wall perforations, compared to bare fibers (17).

In experimental models, 1470 nm EVLA generate more steam bubbles than 940/980 nm EVLA, with a better temperature diffusion (12). The generated heat of 940 nm EVLA seems to diffuse less, and hence may cause more local tissue damage due to prolonged temperature elevation. Also, the absorption coefficient of 940 nm EVLA in blood is about 10 times less than 1470 nm, and about 20 times less in the vein wall (18). Theoretically, this could mean that 940 nm EVLA might be able to directly irradiate and heat up the perivenous tissue of the GSV. Anatomically, the anterior cutaneous branch of the femoral nerve lies within the saphenous compartment, close to the GSV. It is possible that patients report more pain when this sensory nerve is damaged by perivenous heat induced by the 940 nm EVLA fiber. More research on the technical elements of EVLA is needed, to better explain the results of our study.

Success rates of EVLA are usually 90-95% (7, 8) and in line with the outcomes of the COLA study. Additional phlebectomies during the EVLA treatment session did not alter these results. Complication rates were also comparable to the previous literature (19), except for may be higher SVT rates in the 1470 nm group. In the current literature, a higher frequency of SVTs has been reported after endovenous radiofrequency ablation (RFA) in one study (20), but not after 1470 nm EVLA (21), compared to 940/980 nm EVLA. In theory, it is possible that 1470 nm EVLA and RFA have a better temperature diffusion than 940 nm. The generated heat can therefore spread into the tributaries or the distal

(untreated) part of the GSV, potentially causing tissue reactions and superficial vein thrombosis.

A possible limitation of the study is the definition used for relevant difference in post-operative pain score. In the present study a difference of 1 in mean/median VAS score, was considered to be clinically relevant. The latter statement may be considered quite arbitrary, but there is no current literature available reporting on relevant differences in VAS scores. Also, in HRQoL the minimal clinically relevant difference may differ from statistically significant values. In our study though, no differences in HRQoL were detected between the two groups. Another limitation of the study is that the practitioners were not blinded. Patients, however, were blinded during the entire course of the study. Since this is the first RCT investigating the independent effect of 1470 versus 940 nm EVLA wavelength on postoperative pain scores, further research is needed with different wavelengths, fibers and technical settings to make our results generalizable to EVLA treatments with other parameters.

In conclusion, this first RCT investigating the independent effect of EVLA wavelength has shown that the only difference between 940 nm and 1470 nm EVLA is the short-term patient reported tolerability at one week postoperatively, with reduction of pain scores and duration of analgesia use in the 1470 nm EVLA group. Both EVLA treatments show similar improvements of HRQoL and VCSS, treatment success rate and post-procedural complications.

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Chapter 6

EVLA parameters do not influence efficacy – results of a systematic review and meta-analysis

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Submitted

ABSTRACT

Objectives: The objective of this systematic review and meta-analysis was to summarize available randomized controlled trials (RCTs) of EVLA efficacy, and define the differences in success rate of variation in wavelength, administered energy, outcome definition and follow-up period.

Methods: A systematic review was performed of RCTs with follow-up of more than three months. The studied outcome was the proportion of patients with EVLA treatment success, defined as absence of reflux or occlusion of the great saphenous vein (GSV). Pooled proportions of anatomical success were compared. Subgroup analysis and metaregression analysis included wavelengths (short (810, 940 and 980 nm), long (1470, 1500 and 1920 nm)) amount of energy (≤50 J/cm, >50 J/cm), follow-up (≤ 1 year, >1 year), outcome definition (occlusion, no reflux) and quality of the studies (low risk of bias, unclear/high risk of bias).

Results: Twenty-eight RCTs, with a total of 2,829 GSVs were included. Overall success rate of EVLA was 92% (95% CI 90-94%, I^2 68%). In subgroup analysis, no statistically significant differences were found for long or short wavelengths (95% (95% CI 91-97%) versus 92% (95% CI 89-94%), p = 0.15), high or low administered energy (93% (95% CI 89-95%) versus 92% (95% CI 90-94%), p = 0.99), long or short follow-up (89% (95% CI 84-93%) versus 93% (95% CI 91-95%), p = 0.13) and outcome definition (occlusion group 94% (95% CI 91-96%) versus absence of reflux group 91% (95% CI 87-94%), p = 0.26). Studies with low risk of bias had a significantly higher success rate than high or unclear risk of bias (93% (95% CI 90-95%) versus 89% (95% CI 83-93%), p = 0.04).

Conclusions: The overall success rate of EVLA is high (92%), also with increasing follow-up period. EVLA wavelength, administered energy and outcome definition have no influence on the treatment success rate of EVLA.

INTRODUCTION

Several treatment options are available for patients with great saphenous vein (GSV) incompetence. In accordance with current guidelines (1, 2), endovenous laser ablation (EVLA) and other endovenous thermal ablation (EVTA) techniques have replaced high ligation and stripping as the first choice of treatment for incompetent saphenous veins in many countries, as they have proven to be highly effective (3-5).

In contrast to radiofrequency ablation (RFA), EVLA is not a standardized procedure, and can be used in many different settings. As the years pass by, evidence of long-term follow-up from well-designed randomized controlled trials becomes more and more available and also the variation in EVLA devices and settings increases. The working mechanism of EVLA is not exactly known but is mainly based on heat transfer from the EVLA fiber tip to surrounding tissue. There are some known mechanisms by which the hot fiber tip may transfer heat to the vein wall; direct contact, heat conduction, and generation of steam bubbles (6). Although the focus in research and daily practice seems to be shifting from efficacy to patient reported outcomes, the differences in success rate for alterations in for instance wavelength, administered amount of energy and follow-up period have never been properly explored in a systematic review and pooled analyses. In the current maze of available options, it remains an important question if there are optimal effective EVLA devices or (power) settings, in terms of short and long-term efficacy. The objective of the present meta-analysis was to systematically review and summarize the available randomized controlled trials of EVLA efficacy and define the differences in success rate of variation in wavelength, administered energy, outcome definition and follow-up period.

METHODS

Literature search

The search was conducted in Embase, Medline (Ovid-SP), Cochrane Central Database and Web of Science from inception up to November 2017. A cross reference check was performed to identify additional relevant studies.

Inclusion criteria

In this meta-analysis, only randomized controlled trials (RCTs) regarding treatment of primary incompetent human GSVs by EVLA were included. The studied outcome was the proportion of patients with EVLA treatment success, defined as absence of reflux or occlusion of the treated GSV. Only trials that used duplex ultrasound (DUS) examination as outcome measure for EVLA efficacy were eligible. In comparative EVLA studies, all study

arms of interest were included separately. Follow-up of at least 12 weeks was required for inclusion. Only English articles were included.

Exclusion criteria

Studies that performed high ligation in combination with EVLA were excluded, since this approach may have influenced the outcome measures. Trials about EVLA treatment of perforating veins along the GSV were not included. If identical patient populations were described in different publications, the trial with the longest follow-up period was included. The definitions of treatment success by DUS examination varied considerably; studies that only reported 'clinical recurrence', 'inguinal recurrence at the saphenofemoral junction', 'inguinal reflux into the great saphenous vein' or 'patient satisfaction' were excluded. Also, studies without information (in the manuscript or provided by correspondence) about the number of patients examined with DUS at end of follow-up were excluded.

Data extraction

All titles and abstracts, followed by all retrieved full-text articles were independently screened for relevance by two researchers (W.M. and L.E.). Disagreements were discussed and resolved. Of all included RCTs, the number of patients and treated GSVs, the used EVLA wavelength(s), the administered energy, the duration of follow-up, the US outcome definition, the number of treated GSVs available at end of follow-up and success rate at end of follow-up were extracted. Extensive quality assessment of the studies was performed, according to the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (7).

Statistical analysis

The primary outcome was the proportion of successful treatment (occlusion or no reflux) at end of follow-up. Data were pooled with a random-effects model using the 'metaprop' function from the 'meta' package from R version 3.3.2 (www.r-project.org).

The I^2 was calculated and represents the amount of total variance explained by genuine differences between the studies (heterogeneity) rather than by chance due to sampling error (homogeneity). Metaregression was performed to identify the possible source of heterogeneity and the model included quality of the study (low or unclear/high risk of bias) (7), duration of follow-up (≤ 1 year, >1 year), wavelength (Hb-target (810, 940 and 980 nm), water-target (1470, 1500 and 1920 nm)), energy (≤50 J/cm, >50 J/cm (8)), and definition of successful outcome (occlusion or absence of reflux). The hypothesis was that differences in quality of the study, follow-up, wavelength, energy and outcome definition may lead to different proportions of success; we expected that low quality of the study, longer follow-up (9), lower amount of energy (8, 10) used and

defining occlusion as outcome (instead of absence of reflux) may result in lower success rate, differences between wavelengths were not expected (11). Subgroup analysis were performed to test these hypotheses and included wavelengths (short (810, 940 and 980 nm), long (1470, 1500 and 1920 nm)) amount of energy (≤50 J/cm, >50 J/cm), duration of follow-up (≤ 1 year, >1 year), definition of outcome (occlusion, no reflux) and quality of the studies (low risk of bias, unclear/high risk of bias). To compare the pooled proportions of the success rates between the subgroups, univariable and multivariable metaregression was used in which a two-sided p-value <0.05 indicated a statistical significance. Studies with missing values of subgroup variables were excluded from the univariable metaregression. The multivariable metaregression included all studies by using a 'missing' category for these variables.

Sensitivity analyses included subgroup analyses with different cut-off values for energy (≤40 J/cm, >40 J/cm) and follow-up (≤ 1 year, 1-3 years, ≥3 years), to examine if lower energy is still effective, and to differentiate between short, intermediate and long follow-up period.

In order to detect possible publication bias a funnel plot was constructed. For low and high proportional outcomes, traditional funnel plots (log odds vs 1/SE) can result in funnelplot asymmetry without publication bias (12). Therefore, an alternative funnelplot (sample size vs log odds) was constructed and visually inspected. Currently there are no suitable statistical test for funnel plot asymmetry for proportion meta-analysis (12).

This review was conducted and reported in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines (PRISMA)(13).

RESULTS

Study selection and characteristics

The search yielded a total of 4,567 articles (Figure 1). After reduplication 2,807 articles remained. We identified 91 eligible studies after screening title and abstract. After reading the full article texts, 28 studies met the eligibility criteria. The general characteristics of the selected studies are presented in Table 1. In the 28 studies, a total of 2,829 GSVs were included. The study size sample varied from 39 (14) to 212 (15) GSVs.

Quality of the studies/bias assessment

We assessed the risk of bias of the included 28 articles as having low, unclear or high risk of bias (Table 2). In most included RCTs, study treatments were technically too different, which made blinding of either physicians, patients or assessors impossible. Therefore, studies where no blinding was applied could still be categorized as low risk of bias in the present meta-analysis. The main reasons of assessing a study as high risk of bias were

reported missing outcome of more than 30% of the study population and/or unclear procedure of randomization.

Success rate

The pooled anatomical success rates are shown in Figure 2. The overall success rate of EVLA with random effects model analysis was 92% (95% CI 90-94%, I^2 68%). Success rates varied from 77% (16) to 100% (17, 18).

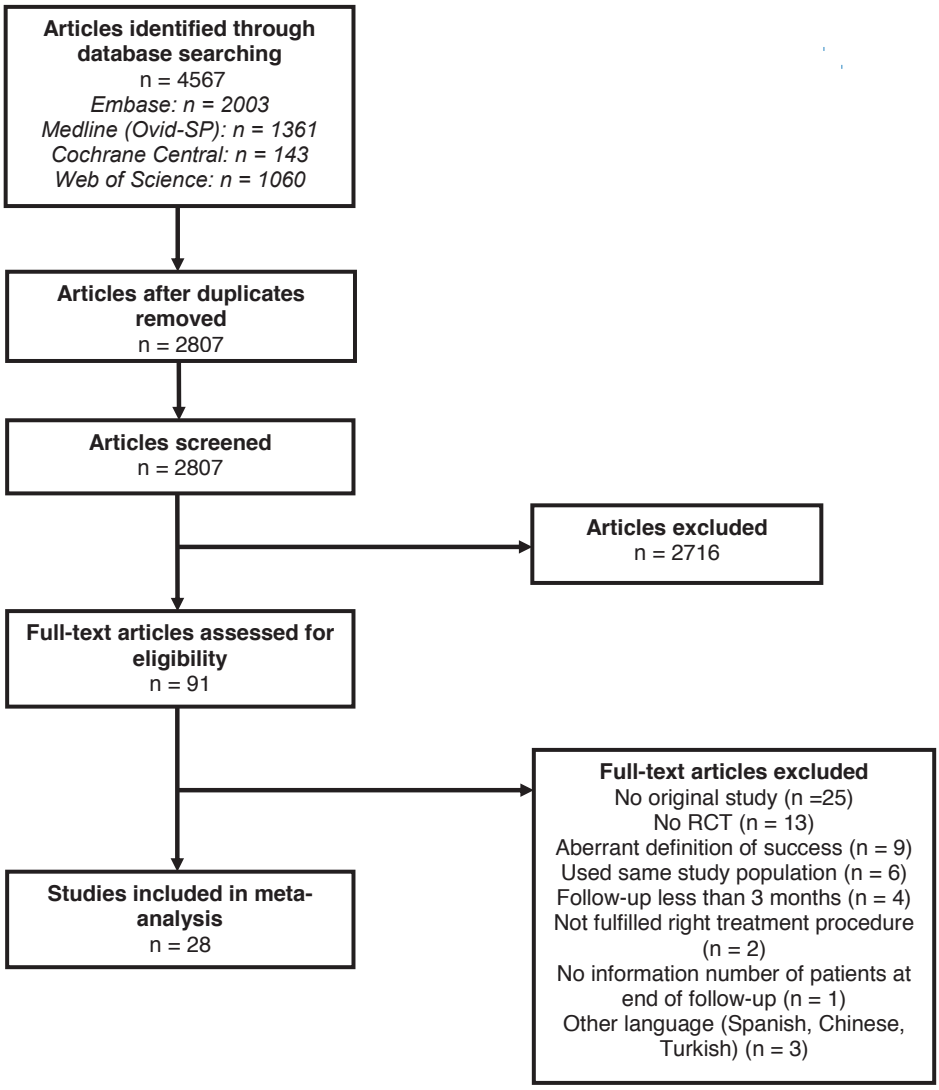

Figure 1. Flow chart of search strategy and study selection

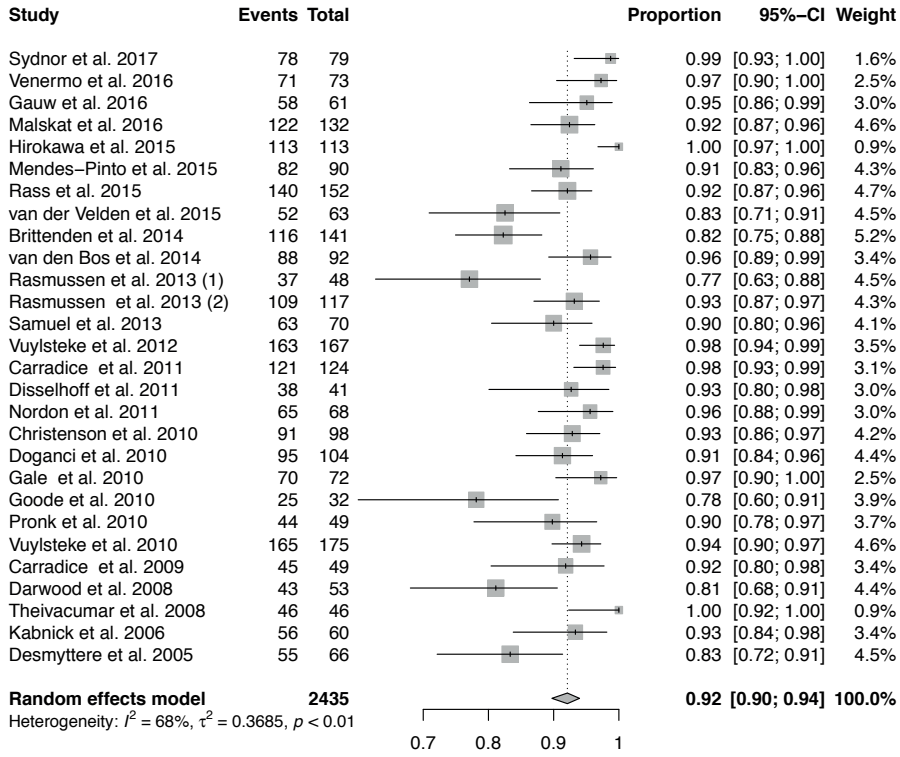

Figure 2. Overall EVLA treatment success

Metaregression and subgroup analysis

The results of uni- and multivariable metaregression analysis are summarized in Table 3. The outcomes of the univariable metaregression analysis are described below. There were no statistically significant differences in success rates in the multivariable model.

Wavelength

Three studies were excluded from this subgroup analysis, since they used multiple wavelengths in one study arm (15, 19, 20). EVLA devices with long wavelengths (1470, 1500 and 1920 nm) were used in one group in six studies (11, 17, 21-24), and with short wavelengths (810, 940 and 980 nm) in (at least) one group in 23 studies (5, 11, 14, 16-18, 21, 23, 25-38) (Figure 3). The success rates of long and short EVLA wavelengths were not significantly different; 95% (95% CI 91-97%) versus 92% (95% CI 89-94%), p = 0.15.

Administered amount of energy

Of two studies, the administered amount of energy during treatment was unknown (19, 29). In 20 studies, more than 50 J/cm was administered during EVLA (5, 14-18, 20, 21,

Table 1. Study characteristics

Study label	Authors	Year	Country	Study type	No included GSVs	Wavelength(s)	Administered energy (presented in study)	Follow-up (months)	No GSVs end of follow-up	Definition success	Success rate
Sydnor_2017 (39)	Sydnor et al.	2017	USA	RCT	100	980	50-80	6	79	occlusion	99%
Venermo_2016 (20)	Venermo et al.	2016	Finland	RCT	73	980, 1470	70	12	73	occlusion	97%
Gauw_2016 (32)	Gauw et al.	2016	Netherlands	RCT	62	980	65	62	61	occlusion	95%
Malskat_2016 (11)	Malskat et al.	2016	Netherlands	RCT	142	940; 1470	40	12	132	no reflux	91%; 94%
Hirokawa_2015 (17)	Hirokawa et al.	2015	Japan	RCT	113	980; 1470	70-85	3	113	occlusion	100%; 100%
Mendes-Pinto_2015 (22)	Mendes-Pinto et al.	2015	Brazil	RCT	90	1470; 1920	25; 18	12	90	occlusion	95%; 88%
Rass_2015 (36)	Rass et al.	2015	Germany	RCT	185	810	50	62	152	no reflux	92%
van der Velden_2015 (5)	van der Velden et al.	2015	Netherlands	RCT	80	940	60	62	63	occlusion	83%
Brittenden_2014 (15)	Brittenden et al.	2014	UK	RCT	212	unknown	83	6	141	both	82%
van den Bos_2014 (40)	van den Bos et al.	2014	Netherlands	RCT	110	940	60	12	92	no reflux	96%
Rasmussen_2013 (1) (16)	Rasmussen et al.	2013	Denmark	RCT	69	980	74	62	48	no reflux	77%
Rasmussen_2013 (2) (19)	Rasmussen et al.	2013	Denmark	RCT	144	980, 1470	unknown	36	117	no reflux	93%
Samuel_2013 (37)	Samuel et al.	2013	UK	RCT	76	810	60-70	12	70	no reflux	90%
Vuylsteke_2012 (24)	Vuylsteke et al.	2012	Belgium	RCT	174	1470	60	12	167	occlusion	98%
Carradice_2011 (26)	Carradice et al.	2011	UK	RCT	139	810	95	12	124	occlusion	98%
Disselhoff_2011 (30)	Disselhof et al.	2011	Netherlands	RCT	60	810	57	62	41	no reflux	93%
Nordon_2011 (34)	Nordon et al.	2011	UK	RCT	80	810	80	3	68	occlusion	96%

Table 1. Study characteristics (continued)

Study label	Authors	Year	Country	Study type	No included GSVs	Wavelength(s)	Administered energy (presented in study)	Follow-up (months)	No GSVs end of follow-up	Definition success	Success rate
Christenson_2010 (27)	Christenson et al.	2010	Switzerland	RCT	100	980	40	24	98	occlusion	93%
Doganci_2010 (21)	Doganci et al.	2010	Turkey	RCT	106	980; 1470	90	6	106	occlusion	100%; 100%
Gale_2010 (31)	Gale et al.	2010	USA	RCT	72	810	92	12	72	no reflux	97%
Goode_2010 (14)	Goode et al.	2010	UK	RCT	39	810	80	9	32	occlusion	78%
Pronk_2010 (35)	Pronk et al.	2010	Netherlands	RCT	62	980	65	12	49	no reflux	90%
Vuylsteke_2010 (23)	Vuylsteke et al.	2010	Belgium	RCT	180	980; 1500	72; 49	6	175	occlusion	96%; 93%
Carradice_2009 (25)	Carradice et al.	2009	UK	RCT	50	810	80-100	12	49	occlusion	92%
Darwood_2008 (28)	Darwood et al.	2008	UK	RCT	79	810	61	12	53	no reflux	81%
Theivacumar_2008 (18)	Theivacumar et al.	2008	UK	RCT	46	810	60-70	3	46	occlusion	100%
Kabnick_2006 (33)	Kabnick et al.	2006	USA	RCT	60	810, 980	50	12	60	occlusion	93%
Desmyttere_2005 (29)	Desmyttere et al.	2005	France	RCT	126	980	unknown	24	66	occlusion	83%

Table 2. Bias assessment

Study	Year	Random assignment	Foresee assignment	Group similarity	Blinding patients	Blinding doctors	Blind assessors	Missings	Reporting bias	Other bias	Overall assessment
Sydnor	2017	-	-	-	-	+	+	-	-	-	-
Venermo	2017	-	-	-	+	+	?	-	-	-	-
Gauw	2016	-	-	-	+	+	+	-	-	-	-
Malskat	2016	-	-	-	+	+	+	-	-	-	-
Hirakowa	2015	-	-	-	+	+	+	-	-	-	-
Mendes	2015	-	-	-	+	+	+	-	-	-	-
Rass	2016	-	-	-	+	+	+	-	-	-	-
vd Velden	2015	-	-	-	+	+	+	-	-	-	-
Brittenden	2014	-	-	-	+	+	+	+	-	-	+
van den Bos	2014	-	-	-	+	+	+	-	-	-	-
Rasmussen (1)	2013	-	-	-	+	+	+	+	-	-	+
Rasmussen (2)	2013	-	-	-	+	+	+	-	-	-	-
Samuel	2013	-	-	-	+	-	+	-	-	-	-
Vuylsteke	2012	-	-	-	+	+	+	-	-	-	-
Carradice	2011	-	-	-	+	+	+	-	-	-	-
Disselhoff	2011	-	-	-	+	+	+	+	-	-	+
Nordon	2011	-	-	-	-	+	-	-	-	-	-
Christenson	2010	-	-	-	+	+	+	-	-	-	-
Doganci	2010	-	-	-	+	+	+	-	-	-	-
Gale	2010	-	+	-	+	+	+	-	-	-	+
Goode	2010	-	-	-	-	+	+	-	-	-	-
Pronk	2010	-	?	-	+	+	+	-	-	-	?
Vuylsteke	2010	-	+	-	+	+	+	-	-	-	+
Carradice	2009	-	-	-	+	+	+	-	-	-	-
Darwood	2008	?	+	-	+	+	+	-	-	-	+
Theivacumar	2008	-	?	-	+	+	+	-	-	-	?
Kabnick	2006	-	-	-	-	-	+	-	-	-	-
Desmyttere	2005	-	-	-	+	+	+	+	-	-	+

High risk of bias	+
Low risk of bias	-
Unclear risk of bias	?

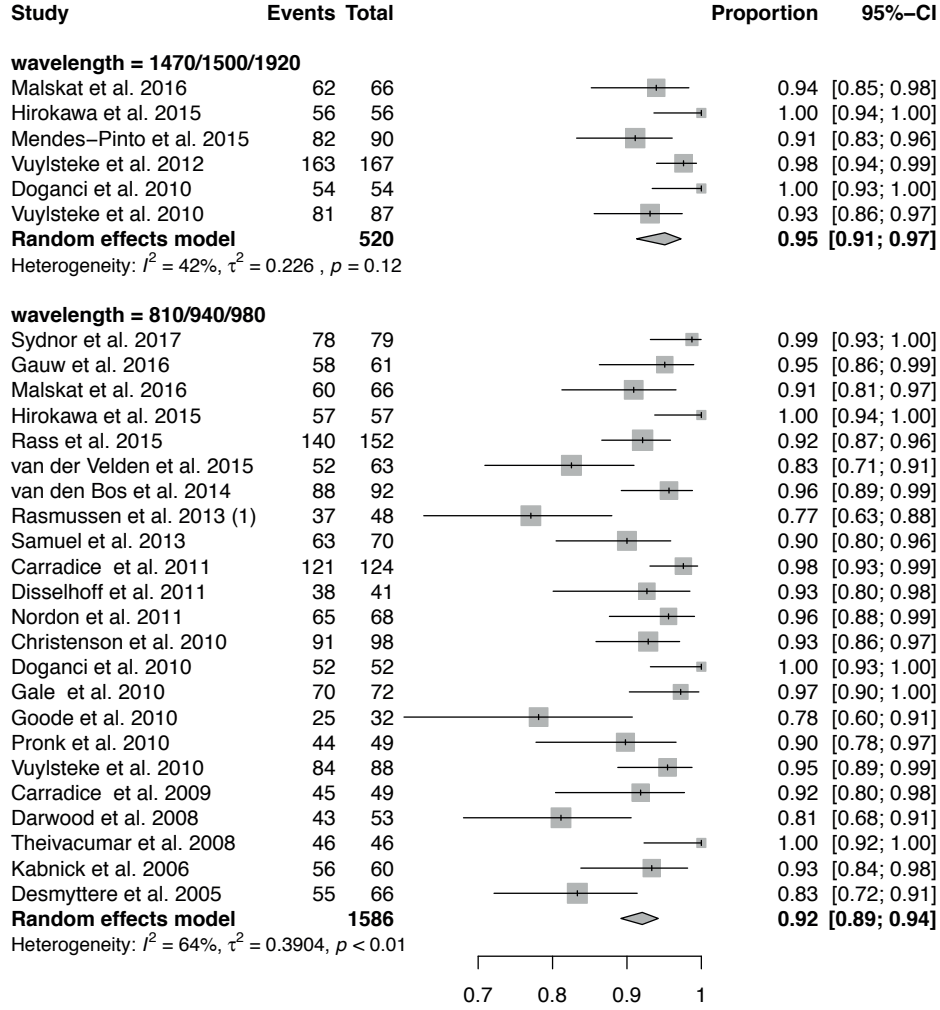

Figure 3. Wavelength subgroup analysis

24-26, 28, 30-32, 34, 35, 37, 39) in comparison to five studies with a administered energy of 50 J/cm or less (11, 22, 27, 33, 36) (Figure 4). There were no significant differences in success rates between these two groups; 93% (95% CI 89-95%) versus 92% (95% CI 90-94%), p = 0.99.

Follow-up

The mean follow-up period of all studies was 20,7 months. The maximum period of follow-up was 62 months. Eight studies had a follow-up of more than one year (5, 16, 19, 27, 29, 30, 32, 36), 20 studies of up to one year (11, 14, 15, 17, 18, 20-26, 28, 31, 33-35, 37-39) (Figure 5). Follow-up of >1 year did not correlate with a statistical significant

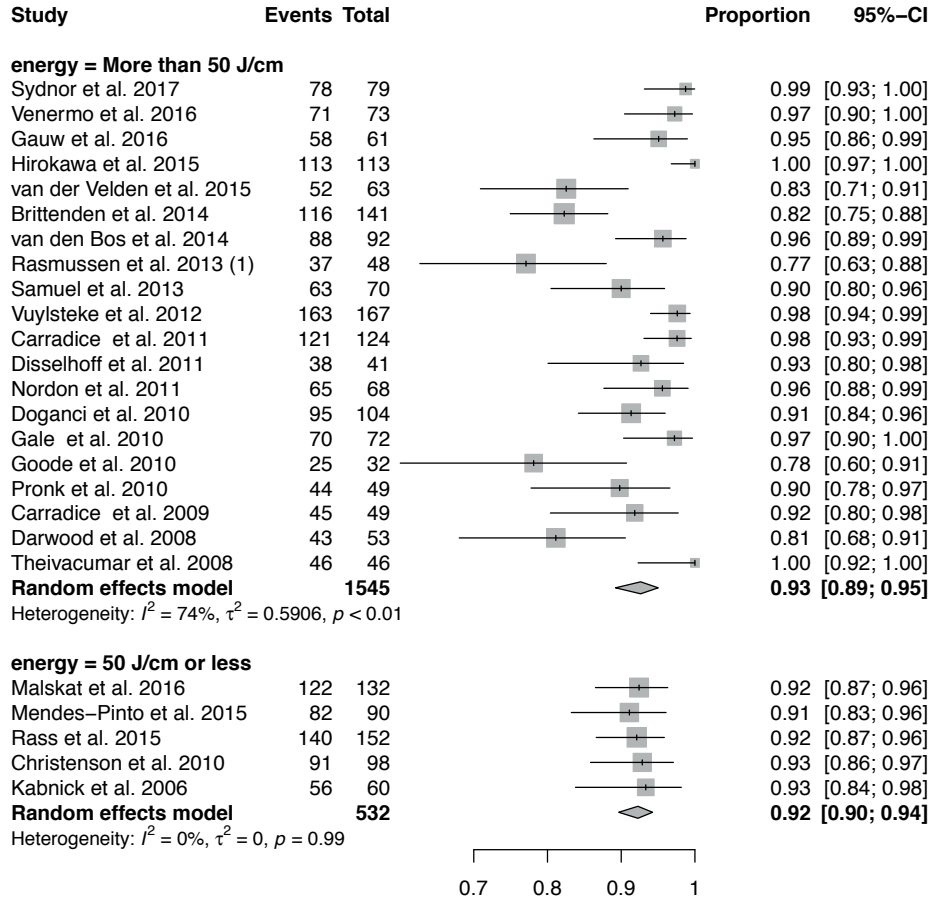

Figure 4. Energy subgroup analysis

lower success rate than ≤1 year; 89% (95% CI 84-93%) versus 93% (95% CI 91-95%), p = 0.13, respectively.

Definition of outcome

One study (15) was excluded from this subgroup analysis, since different definitions of anatomical success were used (both absence of reflux and occlusion used in the same study). In 18 studies occlusion was the stated outcome for anatomical success (5, 14, 17, 18, 20-27, 29, 32-34, 39), and absence of reflux in 10 studies (11, 16, 19, 28, 30, 31, 35-38) (Figure 6). There was no statistically significant difference between these two outcome definitions; 94% (95% CI 91-96%) in the occlusion group versus 91% (95% CI 87-94%) in the absence of reflux group, p = 0.26.

Table 3. Metaregression

Study characteristic	Number of studies	Reference numbers	Pooled proportion of anatomical success	I^2	p-value univariable metaregression*	p-value multivariable metaregression#
Wavelength					0.15	0.66
Long	6	11, 17, 21-24	0.9509 [0.9130; 0.9728]	42.3%		
Short	23	5, 11, 14, 16-18, 21, 23, 25-38	0.9205 [0.8919; 0.9421]	63.6%		
Energy					0.99	0.76
<= 50 J/cm	5	11, 22, 27, 33, 36	0.9227 [0.8967; 0.9426]	0.0%		
>50 J/cm	20	5, 14-18, 20, 21, 24-26, 28, 30-32, 34, 35, 37, 39	0.9264 [0.8923; 0.9503]	73.8%		
Follow up					0.13	0.27
<= 1 year	20	11, 14, 15, 17, 18, 20-26, 28, 31, 33-35, 37-39	0.9330 [0.9055; 0.9529]	69.4%		
> 1 year	8	5, 16, 19, 27, 29, 30, 32, 36	0.8927 [0.8430; 0.9281]	63.0%		
Outcome definition					0.25	0.37
Occlusion	18	5, 14, 17, 18, 20-27, 29, 32-34, 39	0.9353 [0.9055; 0.9561]	66.7%		
No reflux	10	11, 16, 19, 28, 30, 31, 35-38	0.9076 [0.8680; 0.9363]	59.9%		
Risk of bias					0.04	0.43
Low	19	5, 11, 14, 17, 19-22, 24-27, 32-34, 36-39	0.9324 [0.9098; 0.9496]	55.3%		
High or unclear	9	15, 16, 18, 23, 28-31, 35	0.8863 [0.8266; 0.9273]	70.2%		

*Only studies with non-missing variables were included in the analysis; #Also studies with unknown variables were included in the analysis

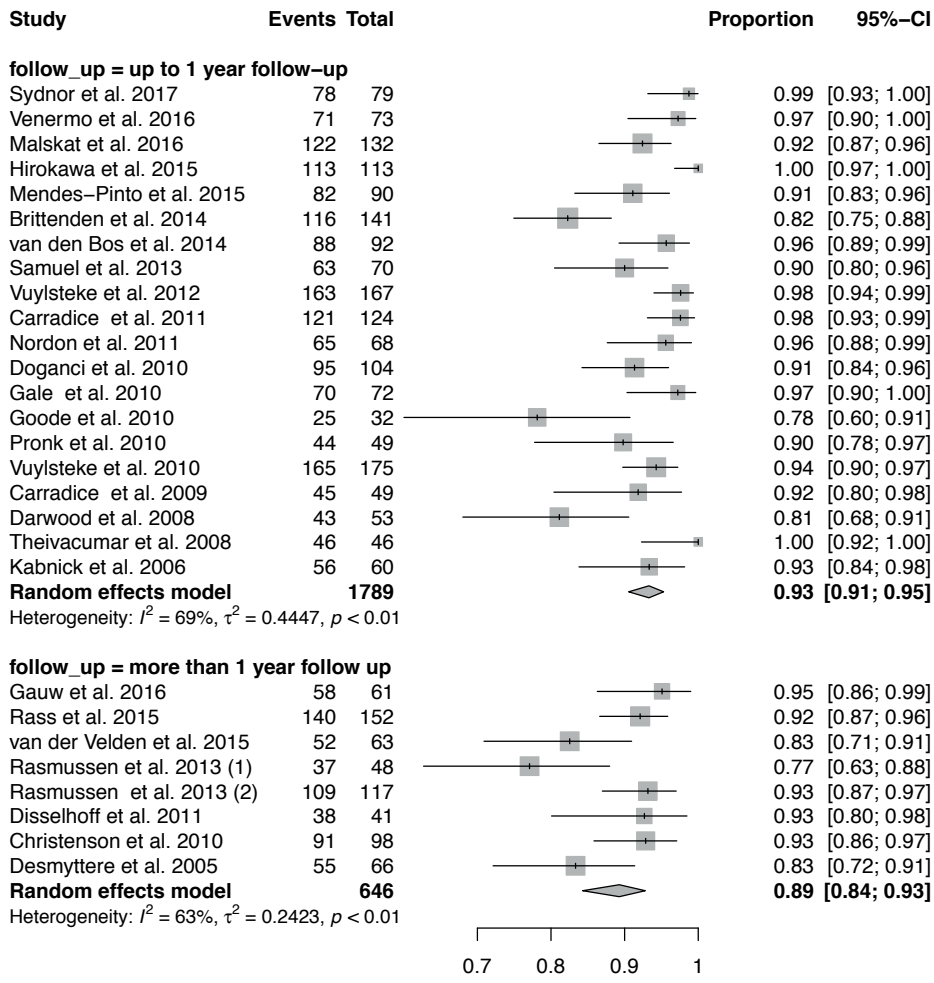

Figure 5. Follow-up subgroup analysis

Quality of the studies

Seven manuscripts were classified as studies with a high risk of bias (15, 16, 23, 28-31), two studies had an unclear risk of bias (18, 35) and 19 studies had a low risk of bias (5, 11, 14, 17, 19-22, 24-27, 32-34, 36-39) (Figure 7). Subgroup analysis showed that studies with a low risk of bias had a significantly higher success rate than the studies with a high or unclear risk of bias; 93% (95% CI 90-95%) versus 89% (95% CI 83-93%), p = 0.04. However, in the multivariable metaregression analysis, no significant difference was detected; p = 0.43.

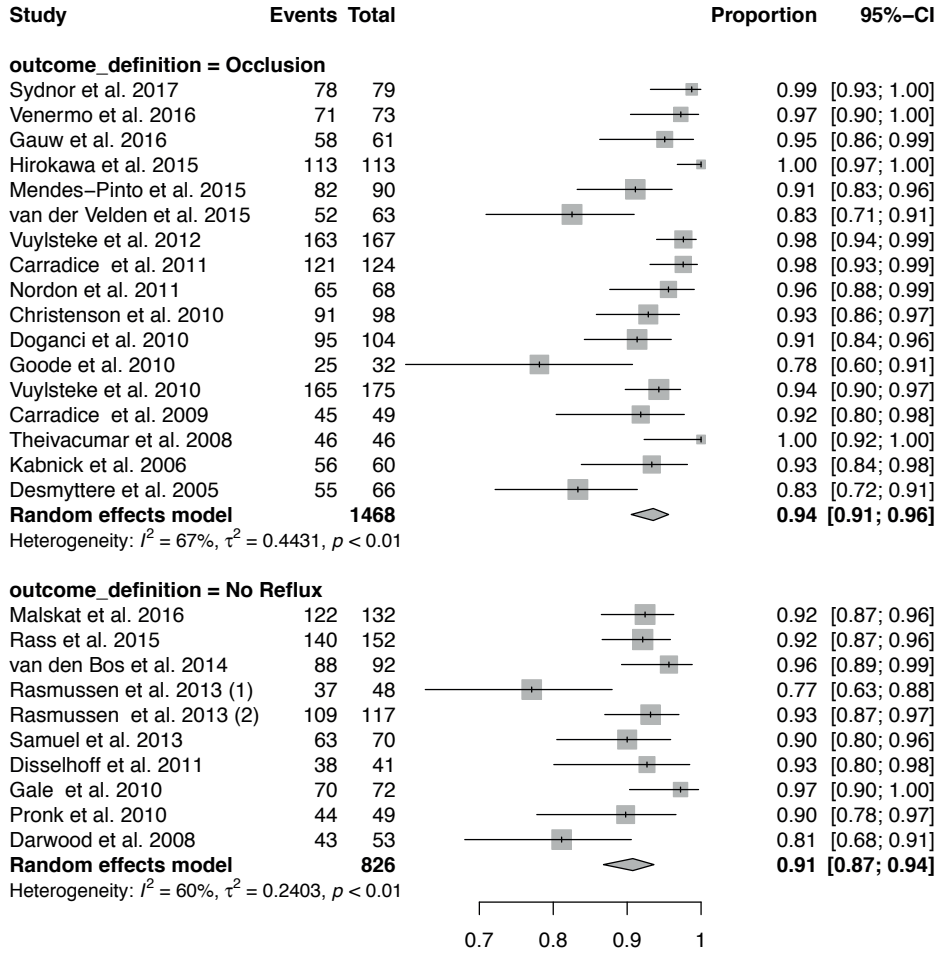

Figure 6. Outcome definition subgroup analysis

Sensitivity analysis

Administered amount of energy

Two studies were excluded from this analysis, since the administered energy was unknown (19, 29). In 23 studies, more than 40 J/cm were administered during EVLA (5, 14-18, 20, 21, 23-26, 28, 30-39) in comparison to three studies with an administered energy of 40 J/cm or less (11, 22, 27) (Figure 8). There were no significant differences in success rates between these two groups; 93% (95% CI 80-95%) versus 92% (95% CI 89-95%), p = 0.43.

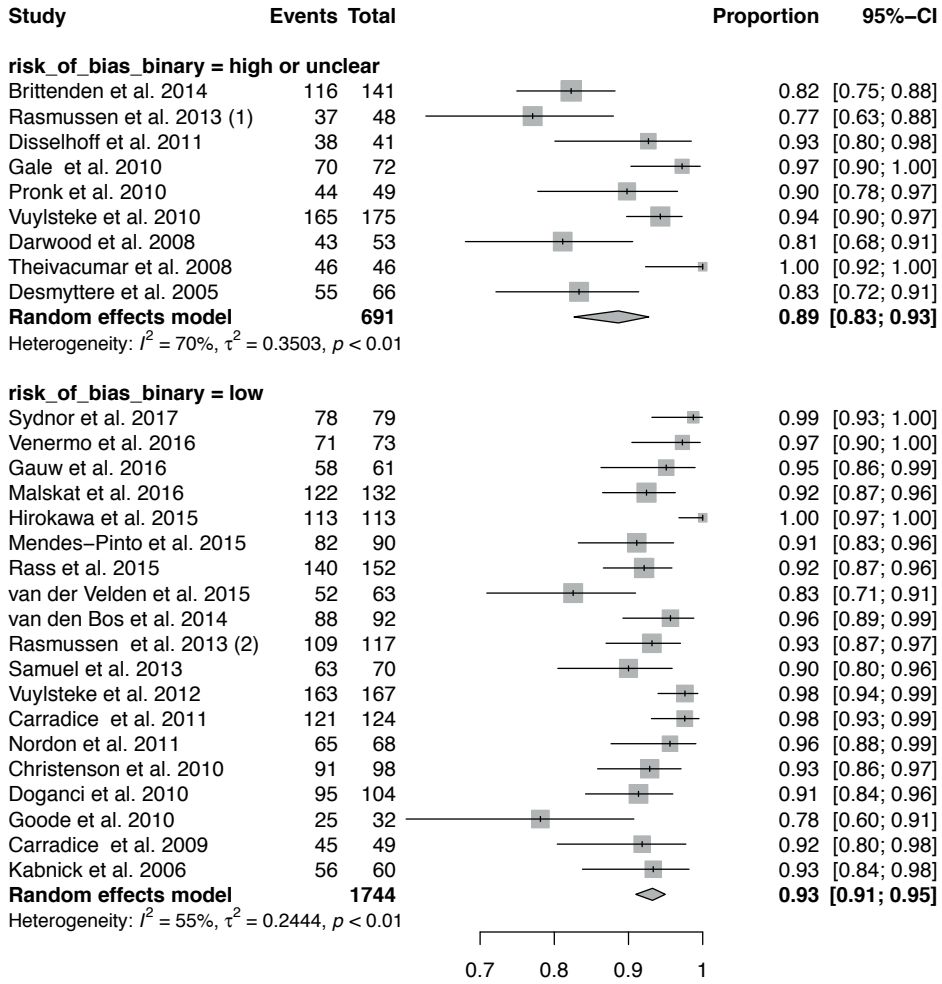

Figure 7. Bias subgroup analysis

Follow-up

Eight studies had a follow-up of less than one year (14, 15, 17, 18, 21, 23, 34, 39), 14 studies of one to three years (11, 20, 22, 24-29, 31, 33, 35, 37, 38) and six studies of three years or more (5, 16, 19, 30, 32, 36) (Figure 9). There were no significant differences in success rates between these three groups; 93% (95% CI 87-97%), 93% (95% CI 90-95%) and 90% (95% CI 83-94%) respectively, p = 0.82.

Publication bias

An alternative funnel plot was constructed and visually inspected (Figure 10). There appears to be a low chance of publication bias.

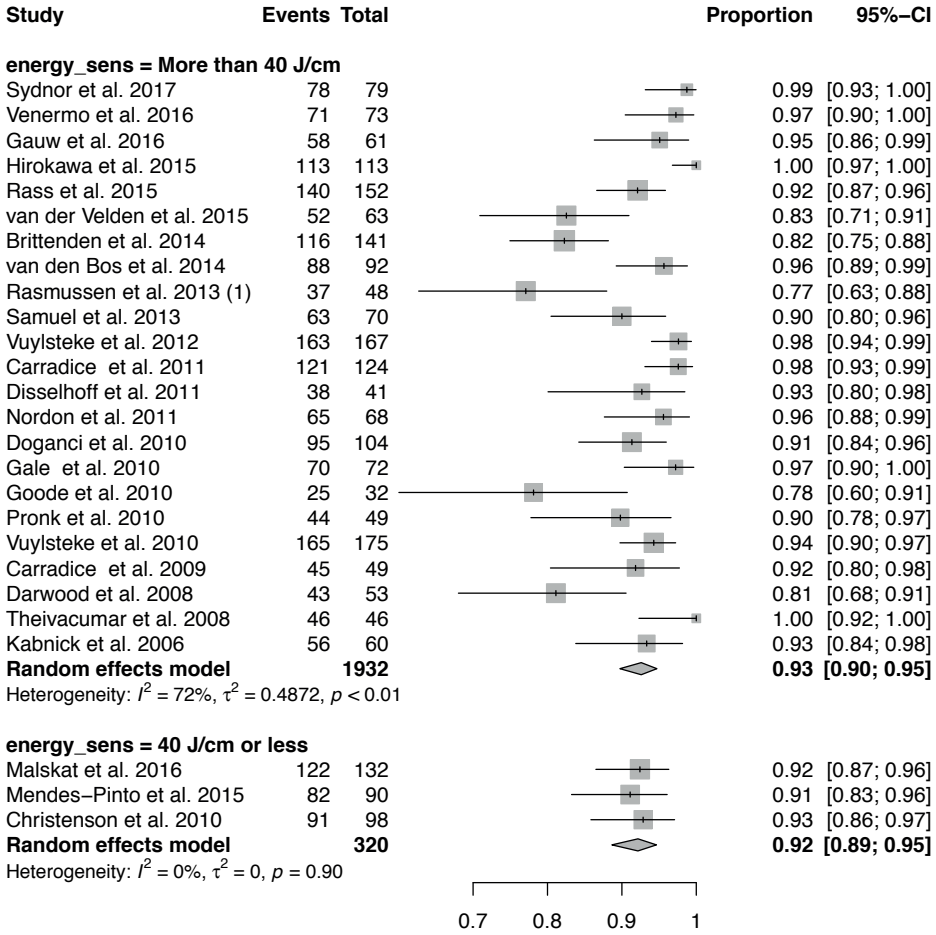

Figure 8. Energy sensitivity analysis

DISCUSSION

This pooled analysis showed an overall success rate of EVLA in GSVs is 92%, independent of wavelength, administered amount of energy, duration of follow-up and definition of outcome (occlusion/absence of reflux).

The reported overall success rate is in accordance with available systematic reviews reporting on EVLA (40-43). No difference in EVLA efficacy was expected between Hb-target (810, 940 and 980 nm) and water-target (1470, 1500 and 1920 nm) wavelengths, since Hb-target and water-target EVLA devices have shown to have similar temperature profiles in an experimental setting (44). Also, a RCT comparing short and long EVLA wavelengths, with equal amount of applied energy, showed comparable efficacy rates of

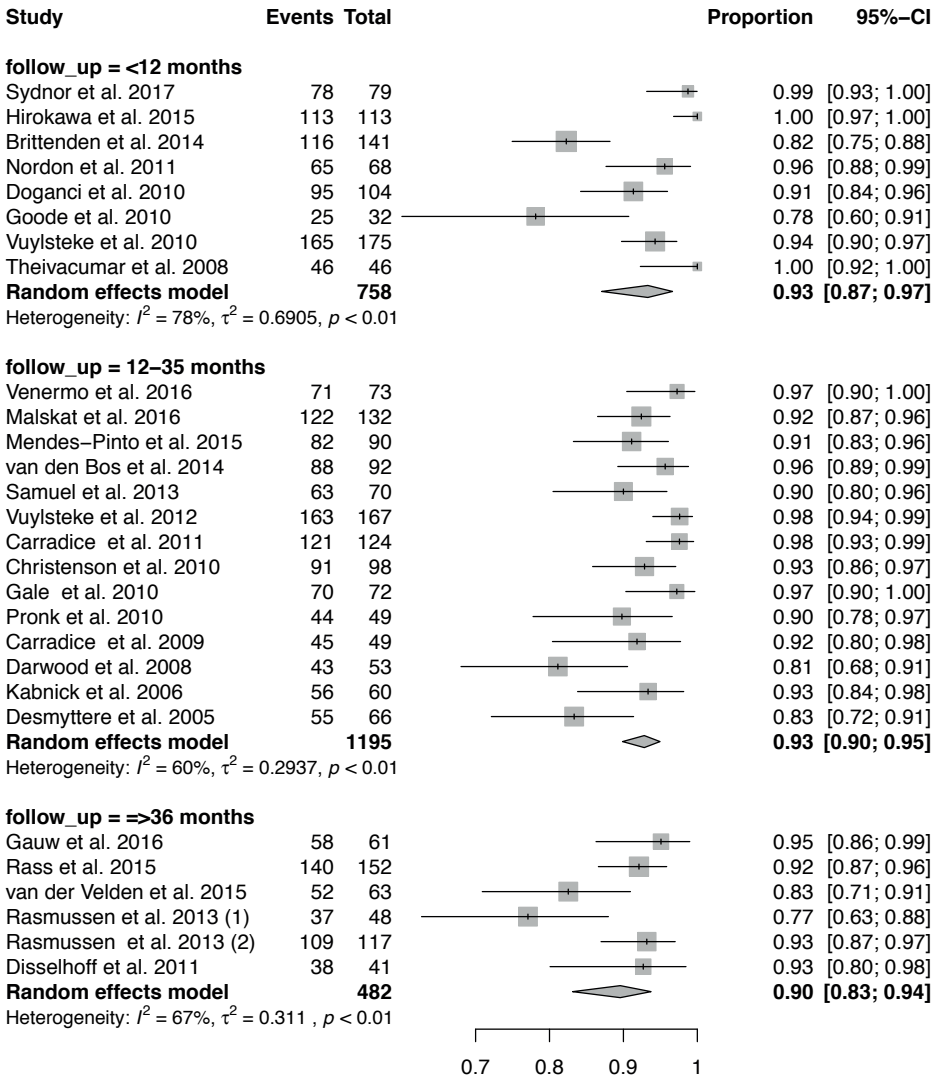

Figure 9. Follow-up sensitivity analysis

both devices (11). However, there seem to be differences in patient reported outcomes, favoring longer wavelengths (11).

According to our findings, it seems that higher administered amount of energy does not benefit the short- or long-term success rates of EVLA, in spite of what may have been suggested in previous clinical studies (8, 10, 45). In the current meta-analysis, studies with lower energy levels than 50 J/cm, often suggested as the threshold for successful EVLA, did not have lower success rates than the other studies, indicating that it may be too high. Obviously, a certain amount of energy is needed to generate a sufficient

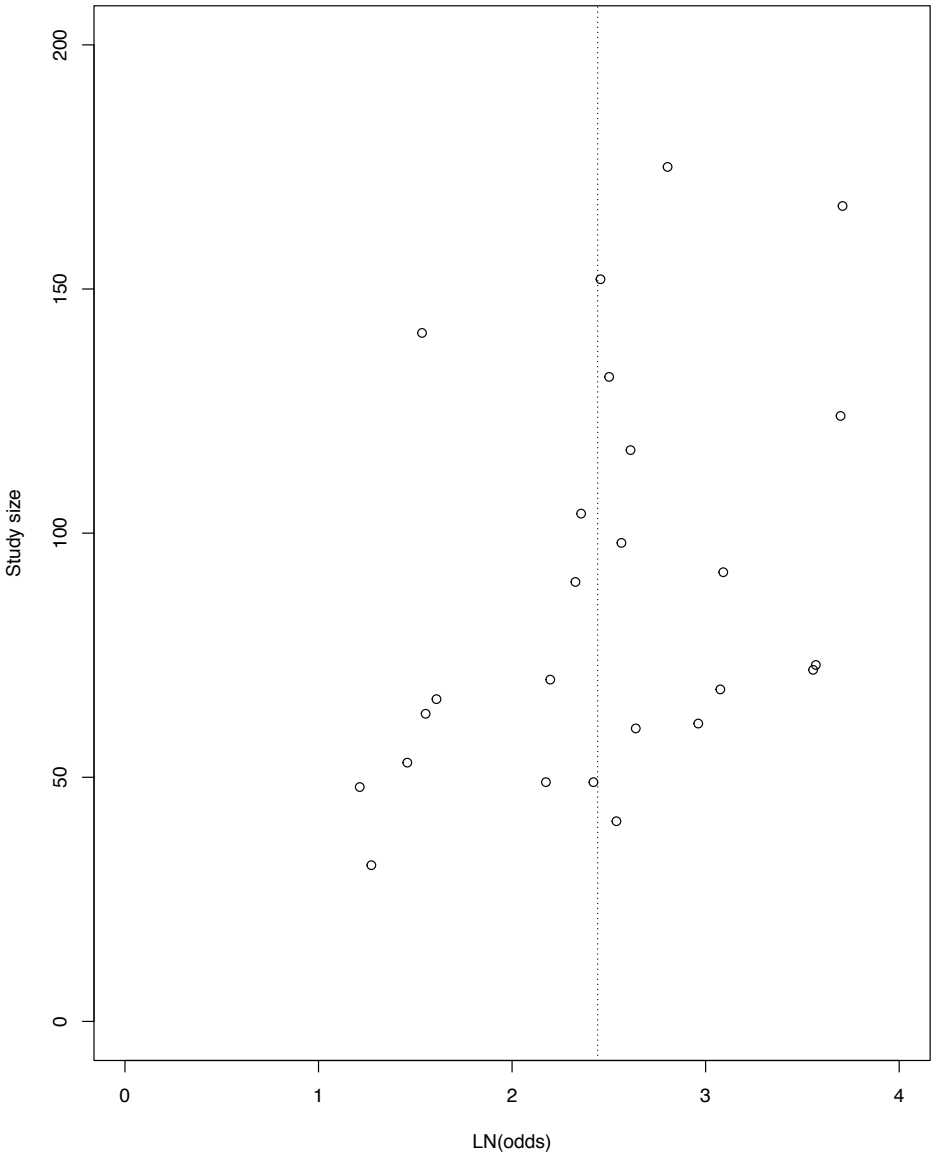

Figure 10. Alternative funnel plot

temperature for tissue damage resulting in vein closure, but it is unclear what the exact threshold is. In a study by Mendes-Pinto, application of 17.8 J/cm (mean) resulted in a significantly lower EVLA success rate than 24.7 J/cm (88% versus 95%), indicating that the threshold may be somewhere around these values.

In terms of follow-up, it may seem reasonable that longer follow-up period results in lower success rates. However, in this meta-analysis no significant decline in EVLA ef-

ficacy (GSV occlusion or absence of reflux) was demonstrated over the years. A possible hypothesis is that with increasing follow-up period, not the treated GSV will have recurrent reflux, but there will be neovascularization or reflux at the saphenofemoral junction or accessory anterior saphenous vein (5). To further investigate this hypothesis, further EVLA research is mandatory, with alteration of outcome definitions.

Harmonization of outcomes is pivotal in clinical research and facilitates pooled analyses. More stringent definitions of 'success' such as occlusion are likely to result in lower success rates. However, in this meta-analysis variations of outcome definitions did not influence EVLA success rates. A possible explanation is that the majority of patients treated with EVLA will have GSV occlusion after treatment, and only a small proportion will have absence of reflux. In our opinion, supported by this study, there is no clinically relevant difference between these two definitions.

EVLA fiber tips were not studied in this meta-analysis on ELVA efficacy, since no difference in ELVA efficacy between different types of fiber tips was ever detected in previous RCTs (17, 21, 24). The main difference between treatment with diverse EVLA fibers is the difference in postoperative patient reported outcomes, such as pain, satisfaction and minor complications such as ecchymoses, cutaneous hyperpigmentation and erythema, possibly related to direct contact with the vein wall (for instance bare fiber versus radial or tulip tip fiber) (17, 21, 24).

Limitations to consider when interpreting our results include the relatively high heterogeneity and inclusion of studies with a high or unclear risk of bias. Despite including only studies with at least 3 months of follow-up, where DUS was used for measuring the outcome, the heterogeneity in the main analysis was relatively high (I^2 = 68%). Differences in wavelength, energy, follow-up and outcome definition could not explain this diversity. The subgroup of studies with low risk of bias showed a higher success rate and less heterogeneity compared to high/unclear risk of bias studies. The difference in success rate was not statistically significant in the multivariable model, due to the distribution of other variables associated with success rate or a loss of power. Sensitivity analysis using other cut-off values for defining the subgroups confirmed the results from the main analyses.

A major strength of this systemic review is that only RCTs were included; they are the highest form of evidence for therapeutic studies. Consequently, the included studies were generally homogeneous, in contrast to other meta-analysis including different study types.

Attention in research and daily practice seems to be shifting from efficacy to clinically relevant outcomes. To our opinion, patient reported outcomes and symptoms should be the primary study outcome in future research on EVLA efficacy in order to find the most patient friendly EVLA setting, next to neovascularization or recurrent varicose veins as secondary outcome (5) instead of ST occlusion or absence of reflux. After all, this first

meta-analysis on only EVLA demonstrated that different kinds of EVLA settings and devices are proven to be effective in resolving GSV incompetence, and treated GSVs do not intend to re-open in time once they are successfully treated.

In conclusion, EVLA wavelength, administered energy and definition of outcome have no influence on the treatment success rate of EVLA. The overall success rate of EVLA is proven to be high (92%), confirming that EVLA is a highly effective treatment for incompetent GSVs, also with increasing follow-up period.

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Chapter 7

General discussion

ENDOVENOUS THERMAL ABLATION: WHICH TREATMENT SHOULD WE CHOOSE?

Since the beginning of this decennium, EVTA treatments have earned their way to the top, currently being the gold standard for treating incompetent saphenous veins. This thesis has verified this position for EVLA in particular. Choosing which type of EVTA to use, is not always easy and is dependent of many factors. Some considerations for instance can be efficacy, (minor) complications, costs, type of incompetent saphenous trunk (ST) (GSV or SSV), vein diameter, body mass index (BMI), signs of previous superficial vein thrombosis (SVT) in the ST lumen, patients' experience with previous treatments, etc.

In terms of efficacy, EVLA and RFA are proven to be highly effective, with EVLA having slightly higher success rates than RFA after 5 years of follow-up (1). EVSA was a promising but not well studied method up to this thesis. Our first worldwide RCT with EVSA (chapter 4) has taught us that EVSA is an effective EVTA technique with a very favorable side effect profile, and is not inferior to EVLA (2). EVSA is not frequently used, but can definitely be suitable for some patients; for instance patients with multiple perforating veins along the ST or with incompetent perforating veins alone, patients who experienced minor complications (such as post-procedural pain) in a previous treatment with a different EVTA method, or patients with ulcers of extensive lipodermatosclerosis which restrict local surgical options (3).

If minor complications are an issue for your patient, RFA can be a preferred option of treatment as well, instead of EVLA, as RFA seems to have less post-procedural pain and bruising than short wavelength (810, 940 or 980 nm) EVLA (4). It is less clear however, whether RFA is also superior to long-wavelength EVLA; a study from Mese et al. (5) showed beneficial results for 1470 nm EVLA in comparison to RFA at this topic. As this thesis presented in chapter 5, in the first RCT comparing different wavelengths while all other EVLA variables were set equally, patients treated with 1470 nm EVLA showed significantly less post-procedural pain than patients treated with 940 nm EVLA (6). With this knowledge and the lack of evidence of RCTs on tolerability comparing RFA to long wavelength EVLA, no conclusion can be made on which of these procedures has the most patient friendly side effect profile.

Signs of previous SVT (for instance intraluminal trabeculae) in the ST you are opting to treat, may influence your choice of EVTA method as well. The RFA catheter is more rigid and thicker than the EVLA guidewire and fiber, and may therefore sometimes be more effective to puncture through intraluminal post-SVT trabeculae.

When the incompetent ST has a large diameter of more than 8-10 mm at some point along its course, EVLA may be the preferred treatment option, since you can alter the amount of emitted energy per cm vein. It seems rational that it requires more energy to occlude a vein with a relatively large diameter, than a vein with a small diameter; GSV

diameter is found to be an independent predictor of recanalization after EVLA treatment (7). In RFA, you can alter the amount of RFA cycles, but you can never exactly administer a certain energy dose.

When it comes to costs, RFA is definitely the most expensive EVTA option, at least in the Netherlands. All EVLA devices have similar costs in the Netherlands, regardless wavelength and fiber type. A single EVSA is by far the least costly option, since it requires no guidewire or catheter. However, multiple EVSA sessions may be indicated and then the cost accumulate and may become comparable to the costs of EVLA.

In some cases, concomitant treatment of incompetent tributaries or perforating veins may be indicated. When there are large tributaries, post procedural SVT may be induced in these tributaries after EVTA treatment, causing pain and discomfort. Also, according to the 'ascending pathophysiologic theory', incompetent tributaries may render GSV incompetence and may therefore theoretically undo the treatment success of EVLA in time, with re-opening of the treated GSV or inducing incompetent neovascularization in the GSV compartment (8-10). Also, large incompetent perforating veins along the GSV course may theoretically induce GSV incompetence or neovascularization and may be opted to treat simultaneously with GSV treatment.

To our opinion, no EVTA treatment is superior; for each individual patient, it should be evaluated what the preferred method would be, keeping all above mentioned factors in mind. So personalized medicine also applies to phlebology.

ENDOVENOUS LASER ABLATION: INFLUENCE OF MANUFACTURERS

At the start of this millennium, several ideas and technical possibilities came together and created the EVLA procedure. Retrospectively, it is remarkable to observe the rapid development of this technique, especially since there was relatively little data of the ongoing processes during treatment. Compared to the year 2000 when the first case series of EVLA were published, our knowledge of the mechanisms of action of EVLA has now definitely increased, but several issues are still not well understood. Up until now, four possible mechanisms of action are proposed for EVLA (chapter 2): direct contact between fiber tip and vein wall (11), thermal interactions between the emitted laser light and the vein wall (12), the effects of steam bubbles including the 'industrial heat pipe mechanism and the effects of the carbonized blood layer on the fiber tip (13, 14).

Unlike pharmaceutical corporations, companies manufacturing endovenous devices do not spend a lot of financial resources on research, for the blunt reason that implementation of new endovenous devices does not need to meet strict requirements; the only requirement for implementation of a medical device in the Netherlands is a CE certification (15). Once this CE certificate is obtained, the device can be used in

patients. Several clinicians and physicists themselves have performed experimental and clinical research to explain the effectiveness of EVLA and its many different settings. Manufacturers obviously mainly benefit from new developments in EVLA treatments; introducing a new device/wavelength or fiber tip means an opportunity to increase sale and get more profit. Due to these constant and ongoing changes in EVLA possibilities, manufacturers made it almost impossible for clinicians to perform comparative registry based long-term research. It seems as if almost no device, setting or fiber tip (and definitely not a combination of these factors) lasts long enough to do a trial with a long follow up, let alone to perform a systematic review and meta-analysis; by the time the follow up has reached 2 years (or more), the device/setting/fiber has become old fashioned, and the outcomes of the trial clinically irrelevant. Similar issues are seen in other medical applications, such as breast implants, hip prostheses and lens implantations, where long-term safety is of even more importance than in EVLA. For us clinicians, it is therefore very important to keep the commercially origin of the alterations in EVLA procedures in mind while choosing an optimal EVLA treatment for our patients, and to stick to these settings, unless there is a valid - scientifically proven - reason to alter them.

ENDOVENOUS LASER ABLATION: THE EFFECT OF WAVELENGTH

The first EVLA devices had short wavelengths (810 nm), which was deliberately selected because it is targeting hemoglobin (Hb). Over the years, laser devices with longer wavelengths (1200 nm or more) were developed and shifted the theoretical chromophore from Hb to water. Devices with long wavelengths were thought to more specifically target the water in endothelial cells, and therefore to be more effective and have a more beneficial side effect profile. Temperature profiles of EVLA are independent of wavelength, as this thesis has shown in chapter 3 (16), which suggests that the working mechanism of EVLA is independent of wavelength and thus independent of the target (Hb or water) of laser light. Up until this thesis, all trials comparing short and long wavelengths also varied other parameters such as laser power or fiber tip making a true comparison impossible. To assess the impact of one variable (wavelength for instance), all other variables should be kept constant in the study, as we have done in our RCT included in this thesis (chapter 5) (6). In this trial, patients treated with long wavelength EVLA reported significantly less pain and had a shorter duration of analgesia use 1 week after treatment, than patients treated with short wavelength EVLA. As stated above, this difference cannot be explained by differences in temperature profiles, since they are similar. A possible explanation is that long wavelength EVLA has a better heat diffusion, as it generates more steam bubbles, compared to short wavelength EVLA, as we

observed in an experimental model (12). The heat generated in short wavelength EVLA seems to diffuse less, possibly causing more local tissue damage.

So in summary, all EVLA wavelengths are equally effective in getting optimal treatment results, but longer wavelengths (for instance 1470 nm) may have a more patient friendly side effect profile.

ENDOVENOUS LASER ABLATION: OPTIMAL SETTINGS

In EVLA, a lot of parameters can vary, such as wavelength, power, pullback speed and fiber tip. The EVLA procedure is far from standardized but has proven to be effective in many settings, as this thesis has confirmed (chapter 6). The administered amount of energy (J/cm), which is a result from power and pullback velocity, is currently a frequently used parameter to characterize the EVLA procedure in published EVLA studies. It is important to realize however that the thermal efficacy of EVLA is driven by laser power, not amount of energy; a 50 J/cm EVLA process produces an effective EVLA outcome when administered with 10 W laser power and a 2 mm/s pullback velocity, but it can equally be given as 0.1 W and 0.02 mm/s, with little possibility of an effective procedure (17). Therefore, it is essential to not only mention the administered energy when reporting on a procedure, but also the power and pullback velocity.

That being said, a certain energy threshold is probably needed to get effective EVLA treatment. In energy dosing studies by Proebstle et al. (18, 19), a threshold of around 50 J/cm was suggested. Chapter 6 in this thesis however revealed that there are no significant differences in success rates between EVLA RCT's with energy of more or less than 50 J/cm. A temperature of around 50°C is assumed to be the threshold for collagen denaturation, needed to cause irreversible damage to the vein wall. As shown in chapter 2 of this thesis (16), EVLA procedures with 30 J/cm energy (with a power of 12 W) still generate temperatures of around 70°C, implicating that a threshold of 30 J/cm is sufficient to occlude an incompetent vein. In addition to the energy related variables, there are physical characteristics of the laser fiber that may affect treatment outcome and occurrence of adverse events. During treatment, bare laser fibers have more direct contact with the vein wall, than alternative fibers such as a tulip tip, radial or NeverTouch fibers, which all have a sort of protective coating placed around the fiber tip. Some of the minor complications of EVLA can be explained by direct contact of the fiber tip with the vein wall, resulting in ulcerations and perforation of the vein wall. In RCTs, bare fibers have proven to have more post-procedural minor complications, such as pain and ecchymosis, than the other fibers (20, 21). Also, in an experimental setting described in this thesis (chapter 3), bare fibers had significantly higher peak temperatures than radial fibers. These findings indicate that bare fibers are less patient friendly than other laser fibers.

After carefully having studied the available evidence of the different parameters in EVLA we propose the following standard settings: use a long wavelength EVLA device (for instance 1470 nm) and do not use a bare fiber for the ideal side effect profile, use a functional power setting (for instance 10 W) and administer at least 30 J/cm energy (increase to 50 J/cm when the vein diameter is more than 8mm (7)) to get the intended anatomical effect.

OUTCOME MEASURES FOR ENDOVENOUS TREATMENTS

Since EVTA treatments have proven to be highly effective, attention in clinical practice is shifting from efficacy to patient reported outcome measures (PROMs, the experience of the patient with treatment results), and patient reported experience measures (PREMs, the experience of the patient with health care provision). Especially PROMs are now a main focus of health care providers in phlebology and can be measured with disease specific HRQOL tools such as AVVQ and CIVIC, or generic HRQOL questionnaires such as SF-36, EQ-5D or EQ-VAS, but also with NRS and VAS (pain, patient satisfaction). In addition, symptoms and signs of CVD can be well evaluated with the VCSS. However, in studies concerning EVTA treatments, DUS measured occlusion or reflux are unfortunately often still the primary study endpoints and PROMs are considered a secondary outcome.

In time, and with progression of venous disease, different kinds of recurrent varicose veins can be present after EVLA, either with or without clinical symptoms. There can be recurrence in the saphenofemoral junction (SFJ), along the GSV or AASV course, or as tributaries. To explain recurrence after EVLA, the focus has been on recanalization of a previously obliterated trunk; it is now well known that such recanalization occurs more frequently after ultrasound guided foam sclerotherapy (UGFS) than after EVLA (22). The incidence of neovascularization at the SFJ is much lower after EVLA than after surgical procedures (22). Progression of the disease cannot be avoided and is an important contributory factor in pathophysiology of recurrence in the long-term (23). Apart from genetic factors, other patient related factors (BMI > 30, pregnancy after intervention) have been claimed to be responsible for this progression.

In the end, the ultimate goal of EVLA should be to improve the patients' quality of life and to prevent complications, not to improve anatomic and hemodynamic outcomes (24). As is presented in previous studies, presence of reflux does not essentially relate to evolution of clinical disease (25, 26), or decrease in HRQOL (27). This seems counterintuitive and is quite difficult to comprehend for treating physicians. Therefore, we should evaluate the treatment outcome carefully and expand beyond the control US and include patients' perspectives.

FUTURE

As the position of EVTA/EVLA as the gold standard for incompetent STs is further established with this thesis, focus of future research on EVTA should be on patient reported complications. There is still a knowledge gap in post procedural patient reposted outcomes of long wavelength EVLA versus RFA. Also, the benefits of additional and/or combination treatments, such as complementary phlebectomies or UGFS treating incompetent tributaries simultaneously to EVTA treatment, have not been well studied, even though these simultaneous treatments are widely used clinically. In order to ensure that these treatments remain financially compensated for by health care providers in the Netherlands, more scientific evidence is needed to confirm the medical significance of these additional of combined treatments, especially for ambulatory phlebectomies. At the Erasmus MC in Rotterdam, the Netherlands, a large RCT is currently ongoing, studying the effects of solely ambulatory phlebectomy of tributaries on incompetence of the GSV (SAPTAP trial; NTR number NTR4821, www.trialregister.nl).

In the present time, with rapid health technology improvement and ongoing cost-effectiveness analyses, treatment related costs will remain an important issue in phlebologic management strategies. The past few years we have noticed the growing influence of health care providers in the Netherlands, indicating that in the years to come, treatment costs may even become a more pressing issue than physicians wish them to be. The remaining challenge is to choose the most appropriate therapy for each individual patient, and thereby reducing unnecessary therapies and costs and providing the best possible care for our patients.

It is important to define and record your opted treatment goal in advance, distinguishing globally between one of these four groups: 1. Cosmetic, 2. Symptom reduction, 3. Prevent disease progression to clinically relevant stages such as C4+, 4. Reverse clinically relevant C4+ disease or increase healing speed and rate of venous ulcers. Defining these groups and communicating them with our patients is important for interpreting treatment outcomes, in both clinical and research settings, and to be able to justify the treatments costs in the future.

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Chapter 8

Summary / Samenvatting

SUMMARY

Chapter 1 is a general introduction to this thesis. Chronic venous insufficiency is a common and socio-economic health problem with a complex pathophysiology and diverse clinical characteristics and symptoms. Varicose veins can be diagnosed with duplex ultrasound and treated in many different ways. Over the past two decades, minimally invasive treatments for varicose veins are more frequently used and have now become the gold standard for treating incompetent saphenous veins. All different treatment options are briefly described, followed by the motivation of this thesis: to unravel some enduring myths of EVLA, regarding mechanisms of action, in vitro effects, efficacy and patient reported outcomes.

Chapter 2 starts with a review summarizing the known mechanisms of action of EVLA: 1. Direct contact between fiber tip and vein wall; 2. Thermal interactions between the emitted laser light and the vein wall; 3. The effects of steam bubbles including the suggestion that veins resemble an industrial heat pipe; 4. The effects of the carbonized blood layer on the fiber tip. Despite a clinical history of EVLA of almost 2 decades, no international consensus on an optimal treatment protocol has been reached so far. We present physical arguments to debate on long-standing but often unfounded clinical opinions and habits, such as the importance of laser power versus energy, the predicted effectiveness of a higher power and faster pullback velocity, the irrelevance of whether laser light is absorbed by hemoglobin or water and the effectiveness of reducing the vein diameter during EVLA treatment. The second part of **chapter 2** addresses some of the controversies on EVLA by utilizing optical-thermal mathematical modeling are addressed: the effect of direct light absorption by the vein wall on temperature behavior, the predictions of influence of wavelength on temperature behavior, the effect of the hot carbonized blood layer surrounding the fiber tip on temperature behavior, the effect of blood emptying of the vein, the contribution of absorbed light energy to the increase in total energy at the inner vein wall, the effect of laser power and pullback velocity on vein wall temperature and a comparison of outcomes of laser models and clinical findings. Our model predicts that the dominating mechanism for heating up the vein wall is heat flow to the vein wall and its subsequent temperature increase, resulting from (1) the hot carbonized blood layer covering the laser tip and (2) the hot blood surrounding the fiber tip, instead of previously suggested direct absorption of laser light by the vein wall.

Chapter 3 compares temperature profiles of 980 and 1470 nm EVLA with radial and tulip tip fibers, RFA and EVSA are compared in an experimental setting. Temperature measurements were performed using thermocouples, fixed in raw potato to mimic a

vein wall. Temperature increase during EVLA was fast with high peak temperature for a short time, where temperatures in EVSA and RFA had long plateau phases and lower maximum temperatures. Temperature profiles of 980 and 1470 nm EVLA did not differ significantly. Radial fiber EVLA showed significantly higher maximum temperatures than tulip tip EVLA. This implicates there are no differences in intravenous temperatures between lasers with short or long wavelengths, but there are differences between different laser fibers and between EVLA and the other EVTA methods.

In **chapter 4** we present the world's first RCT on EVSA versus 1470 nm EVLA. A total of 227 legs were treated (EVSA, 117; EVLA, 110); 36 legs treated with EVSA received a low dose (2 pulses of steam) and the remaining 81 a higher dose (3 pulses of steam). After 1 year, the treatment success rate (occlusion or absence of reflux of the GSV) after high-dose EVSA was not inferior to that of EVLA: 92% (95% CI 86-98%) versus 96% (95% CI 92-100%) respectively. Changes in VCSS after 12 weeks were similar. AVVQ, EQ-5D™ and EQ VAS scores improved equally 12 weeks after both treatments. Patients treated with EVSA reported less post procedural pain, fewer days of analgesia use, were more satisfied with their therapy and had a shorter convalescence. Complication rates were comparable. In conclusion, EVSA is not interior to EVLA in treating an incompetent GSV and seems to be more patient friendly.

Chapter 5 compares patient reported outcomes of two different EVLA wavelengths in an RCT, with identical energy level and type of laser fiber. A total of 142 legs were randomized (940 nm EVLA, 70; 1470 nm EVLA, 72). Patients treated with 1470 nm laser reported significantly less pain, measured with a visual analogue scale from 0 to 10, one week after treatment, than patients in the 940 nm laser group: median (i.q.r.) score 3 (2–7) versus 6 (3–8) ($p = 0.00$). Duration of analgesia use was significantly shorter after 1470 nm EVLA: median (i.q.r.) 1 (0–3) versus 2 (0–5) days ($p = 0.04$). HRQoL and VCSS improved equally in both groups. There was no difference in treatment success rates. Complications were comparable in both groups, except for more superficial vein thrombosis 1 week after treatment with 1470 nm EVLA. We concluded that 1470 nm EVLA is more patient friendly than 940 nm EVLA.

Chapter 6 summarizes all available RCTs of EVLA efficacy in a systematic review and meta-analysis, and defines the differences in success rate of variation in wavelength, administered energy, outcome definition and follow-up period. We included 28 RCTs, with a total of 2,829 GSVs. Overall success rate of EVLA was 92% (95% CI 90-94%, I^2 68%). In subgroup analysis, no statistically significant differences were found for long or short wavelengths (95% (95% CI 91-97%) versus 92% (95% CI 89-94%), $p = 0.15$), high or low administered energy (93% (95% CI 89-95%) versus 92% (95% CI 90-94%), $p = 0.99$), long

or short follow-up (89% (95% CI 84-93%) versus 93% (95% CI 91-95%), p = 0.13) and outcome definition (occlusion group 94% (95% CI 91-96%) versus absence of reflux group 91% (95% CI 87-94%), p = 0.26). Studies with low risk of bias had a significantly higher success rate than high or unclear risk of bias (93% (95% CI 90-95%) versus 89% (95% CI 83-93%), p = 0.04). We concluded that EVLA is a highly effective treatment for incompetent GSVs, in many energy settings, regardless of outcome definition and also with increasing follow-up period.

In **chapter 7**, we discuss the current role and influence of EVLA manufacturers, and the relative lack of studies of new treatments in phlebology. Also, we try to guide clinicians through the current maze of treatment and setting options in EVLA, with providing factors to take into account while choosing a EVTA treatment method and to suggest a guideline for the ideal EVLA setting, to get an optimal anatomical and patient-friendly outcome. We explain and summarize the effect of wavelength and address different outcome measures for endovenous treatments. The discussion ends with reflecting on future perspective for further research.

SAMENVATTING

Hoofdstuk 1 is een algemene inleiding van dit proefschrift. Chronische veneuze insufficiëntie is een veel voorkomend en sociaal-economisch gezondheidsprobleem met een complexe pathofysiologie en diverse klinische kenmerken en symptomen. Spataderen kunnen worden gediagnosticeerd met duplex-echografie en kunnen op veel verschillende manieren worden behandeld. In de afgelopen twee decennia werden minimaal invasieve behandelingen voor spataderen geïntroduceerd, welke nu de gouden standaard zijn geworden voor de behandeling van insufficiënte saphene venen. Alle verschillende behandelingsopties voor spataderen worden kort beschreven, gevolgd door de motivatie en doelstellingen van dit proefschrift: het ontrafelen van enkele aanhoudende mythes over EVLA, betreffende werkingsmechanismen, in vitro effecten, effectiviteit en patiënt gerapporteerde uitkomsten.

Hoofdstuk 2 beschrijft eerst de technisch bekende werkingsmechanismen van EVLA samen in een review: 1. Rechtstreeks contact tussen de fiber en de venewand; 2. Thermische interacties tussen het uitgestraalde laserlicht en de venewand; 3. De effecten van stoombellen, inclusief de suggestie dat de vene vergelijkbaar werkt met een industriële warmtepijp; 4. De effecten van de gecarboniseerde laag van bloed op de fibertip. Ondanks een klinische geschiedenis van EVLA van bijna twee decennia, is tot nu toe geen internationale consensus over een optimaal behandelprotocol bereikt. Fysische argumenten worden gepresenteerd om te debatteren over oude maar vaak ongegronde klinische opvattingen en gewoonten, zoals het belang van laservermogen versus energie, de voorspelde effectiviteit van een hoger vermogen en snellere terugtreksnelheid, de irrelevantie of laserlicht door hemoglobine wordt geabsorbeerd of door water en de effectiviteit van het verminderen van de venediameter tijdens EVLA behandeling. In het tweede deel van **hoofdstuk 2** worden enkele controverses over EVLA besproken met behulp van optisch-thermische wiskundige modellen: het effect van directe lichtabsorptie door de venewand op de temperatuur, de voorspelling van invloed van golflengte op temperatuur, het effect van de hete gecarboniseerde laag van bloed rond de fibertip op temperatuur, het effect van bloedleegte van de vene, de bijdrage van geabsorbeerde laserlicht aan de toename van de totale energie aan de venewand, het effect van laservermogen en terugtreksnelheid op venewand-temperatuur en een vergelijking van modeluitkomsten en klinische bevindingen. Ons model voorspelt dat het overheersende mechanisme voor het opwarmen van de venewand warmtestroming naar de venewand is en de daaropvolgende temperatuurstijging, resulterend van (1) de hete gecarboniseerde laag van bloed die de lasertip bedekt en (2) het hete bloed rondom de fibertip, in plaats van eerder gesuggereerde directe absorptie van laserlicht door de venewand.

In **hoofdstuk 3** worden temperatuurprofielen van 980 en 1470 nm EVLA met radiale en tulip tip fibers, RFA en EVSA, vergeleken in een experimentele setting. Temperatuurmetingen werden uitgevoerd met behulp van thermokoppels, gefixeerd in rauwe aardappel om een venewand te simuleren. De temperatuurstijging tijdens EVLA was snel met een hoge piektemperatuur gedurende een korte tijd, terwijl de temperaturen in EVSA en RFA lange plateaufasen en lagere maximale temperaturen lieten zien. Temperatuurprofielen van 980 en 1470 nm EVLA waren niet significant verschillend. EVLA uitgevoerd met radiale fiber had significant hogere maximale temperaturen dan EVLA met tulip tip fiber. Dit impliceert dat er geen verschillen zijn in intraveneuze temperaturen tussen lasers met korte of lange golflengtes, maar wel tussen verschillende laser fibers en andere EVTA behandelingen.

In **hoofdstuk 4** beschrijven we de eerste gepubliceerde RCT met EVSA, versus 1470 nm EVLA. Een totaal van 227 vena saphena magna's (VSM's) werden behandeld (117 met EVSA; 110 met EVLA); 36 venen behandeld met EVSA kregen een lagere dosis (2 stoompulsen) en de resterende 81 een hogere dosis (3 stoompulsen). Na 1 jaar was het succespercentage van de behandeling (occlusie of afwezigheid van reflux van de VSM) na een hoge dosis EVSA niet slechter dan dat van EVLA: 92% (95% CI 86-98%) versus 96% (95% CI 92-100%). Veranderingen in VCSS na 12 weken waren vergelijkbaar. De scores van AVVQ, EQ-5D™ en EQ VAS waren tevens verbeterd na 12 weken bij beide behandelingen. Patiënten die behandeld waren met EVSA meldden minder post-procedurele pijn, minder dagen gebruik van analgetica, waren meer tevreden met hun therapie en hadden een kortere herstelperiode. Complicaties waren vergelijkbaar na beide behandelingen. In conclusie is EVSA niet inferieur aan EVLA qua effectiviteit, maar lijkt wel patiëntvriendelijker te zijn.

Het doel van **hoofdstuk 5** is om de patiënt-gerapporteerde uitkomstmaten van twee verschillende EVLA-golflengtes te vergelijken in een RCT, met identieke overige laserparameters zoals energieniveau en laser fiber. Een totaal van 142 VSMs werden geïncludeerd en gerandomiseerd (70 bij 940-nm EVLA, 70; 72 bij 1470 nm EVLA). Eén week post-procedureel rapporteerden patiënten in de 1470 nm EVLA groep significant minder pijn (gemeten met een visuele analoge schaal (VAS)) dan de patiënten in de 940 nm groep: mediaan (i.q.r.) score 3 (2-7) versus 6 (3-8) ($p = 0,00$). De duur van het gebruik van analgesie was significant korter na 1470 nm EVLA: mediaan (i.q.r.) 1 (0-3) versus 2 (0-5) dagen ($p = 0,04$). HRQoL en VCSS toonde gelijke verbetering in beide groepen. Er was geen significant verschil in effectiviteit tussen beide EVLA groepen. Post-procedurele complicaties waren vergelijkbaar in beide groepen, behalve vaker voorkomende oppervlakkige veneuze trombose één week na behandeling met 1470 nm laser. We concludeerden dat 1470 nm EVLA patiëntvriendelijker is dan 940 nm EVLA.

Hoofdstuk 6 vat alle beschikbare RCT's betreffende de effectiviteit van EVLA samen in een systematische review met meta-analyse. Tevens worden de verschillen in succespercentage ten gevolge van variatie in golflengte, toegediende hoeveelheid energie, uitkomstdefinitie en follow-up periode onderzocht. Achtentwintig RCT's, met een totaal van 2829 VSM's waren geïncludeerd. Het totale succespercentage van EVLA was 92% (95% CI 90-94%, I^2 68%). In subgroep analyses werden geen statistisch significante verschillen gevonden voor lange versus korte golflengtes (95% (95% CI 91-97%) versus 92% (95% CI 89-94%), p = 0,15), hoge versus lage toegediende hoeveelheid energie (93% (95% CI 89-95%) versus 92% (95% CI 90-94%), p = 0,99), lange versus korte follow-up periode (89% (95% CI 84-93%) versus 93 % (95% CI 91-95%), p = 0,13) en verschil in uitkomstdefinitie (occlusiegroep 94% (95% CI 91-96%) versus afwezigheid van refluxgroep 91% (95% CI 87-94%), p = 0,26). Studies met een laag risico op bias hadden een significant hoger succespercentage dan studies met een hoog of onduidelijk risico op bias (93% (95% CI 90-95%) versus 89% (95% CI 83-93%), p = 0,04). We concludeerden dat EVLA een zeer effectieve behandeling is voor incompetente VSM's, met verschillende energieinstellingen, ongeacht de uitkomstdefinitie van behandelsucces en ook met oplopende follow-up periode.

In **hoofdstuk 7** wordt commentaar gegeven op de huidige invloed van fabrikanten van EVLA apparatuur en het relatieve gebrek aan studies van nieuw geïntroduceerde behandelingen binnen de flebologie. Er is gepoogd om praktiserende clinici het huidige doolhof van behandeloptie en instellingen binnen EVTA en EVLA heen te leiden door uiteen te zetten met welke factoren rekening dient te worden gehouden als het gaat om het kiezen van een EVTA behandeling. Tevens hebben we getracht een richtlijn voor te stellen voor de zo ideaal mogelijke EVLA-behandeling, die streeft naar optimale anatomische en patiëntvriendelijke uitkomst. De veelbesproken invloed van de golflengte wordt uitgelegd en samengevat, en verschillende uitkomstmaten voor endoveneuze behandelingen passeren de revue. De discussie eindigt met een toekomstperspectief voor verder onderzoek.

Chapter 9

Dankwoord
Abbreviations
List of co-authors
List of publications
Curriculum Vitae
PhD Portfolio

DANKWOORD

Het voelt nog erg onwerkelijk, maar mijn promotietraject is nu dan echt ten einde. Ik vind het oprecht jammer dat het voorbij is, omdat ik altijd met veel plezier onderzoek heb gedaan en het spijtig vind dat ik deze periode nu achter me moet laten. Aan de andere kant is het natuurlijk heerlijk dat er na deze promotie geen druk meer is van dat er altijd nog een proefschrift afgerond moet worden en zal ik de hectiek van de afgelopen maanden absoluut niet missen. Graag wil ik een aantal mensen in het bijzonder bedanken, die mij hebben geholpen of gesteund bij de verwezenlijking van dit proefschrift.

Allereerst mijn promotor, prof. dr. Nijsten. Beste Tamar, toen ik begon als ANIOS heb je me leren duplexen en enthousiast gemaakt voor de flebologie. Vanaf het begin heb je in mij geloofd en mij het vertrouwen gegeven om samen met Renate ons onderzoek op te zetten en uit te werken. Zonder jou was ik waarschijnlijk niet gekomen waar ik nu ben en daar ben ik je dankbaar voor. Je hebt me de ruimte gegeven om het onderzoek in mijn eigen tempo te doen, maar je was in onze overleggen wel altijd de onmisbare persoon met het overzicht, de prikkelende opmerkingen en nieuwe ideeën. Ik heb respect voor je analytisch vermogen en zakelijk inzicht. Bedankt dat ik straks als staflid de (ingewikkelde) flebologie op onze afdeling kan blijven beoefenen.

Mijn copromotor, dr. Van den Bos. Lieve Renate, jij was mijn rots in de branding tijdens dit promotietraject. Zonder jou was me dit oprecht niet gelukt. Je hebt me op weg geholpen, je geloofde in mij, en daardoor geloofde ik ook in mezelf. Er was nooit een drempel om je iets te vragen en van begin tot eind stond je voor me klaar. Misschien ben ik soms inderdaad 'zo gesloten als een mossel', maar jij weet bij mij altijd snel de juiste snaar te raken, waardoor ik binnen no time alles bij je op tafel leg. Bedankt voor je heldere en gestructureerde blik op ons onderzoek, je betrokkenheid en je onvoorwaardelijke steun. Ik hoop dat we nog lang kunnen samenwerken in de toekomst.

Prof. dr. Verhagen en prof. dr. Van der Geld, bedankt voor de tijd en moeite die u genomen heeft voor het beoordelen van mijn proefschrift en het plaatsnemen in de kleine promotiecommissie.

Prof. dr. Prens, beste Errol, bedankt dat je mijn proefschrift wil beoordelen en plaats wil nemen in de kleine promotiecommissie. Ik heb tijdens mijn opleiding prettig met je samengewerkt en heb veel geleerd van de manier waarop jij altijd in mogelijkheden denkt en voor iedere individuele patiënt een (soms experimentele) oplossing bedenkt.

Prof. dr. De Maeseneer, beste Marianne, bedankt dat u plaats wilt nemen in de grote commissie. Tijdens mijn specialisatie heb ik van u de fijne kneepjes van het flebologie vak geleerd, en bent u een mentor voor me geweest in het diepe veneuze deel. U heeft mij altijd geprikkeld om beter te worden en ik heb ontelbaar veel van u geleerd. Bedankt dat u uw kennis aan mij heeft willen overdragen, ik heb er nog dagelijks profijt van.

Beste prof. dr. Neumann, bedankt dat u lid wilt zijn van mijn grote commissie. Ik voel me bevoorrecht dat ik u nog als opleider heb gekend en op het nippertje het van vliet spreekuur heb meegemaakt. Als het gaat om de flebologie en dermatologie bent u een wandelende encyclopedie, daar heb ik veel bewondering voor.

Dear prof. dr. Proebstle, thank you for reading my thesis. It is an honor having you, an important researcher in the field of phlebology, as a member of the doctoral examination board.

Beste dr. K.P. de Roos, bedankt voor het beoordelen van mijn proefschrift en het plaatsnemen in de grote commissie.

Beste Loes, wat ben jij toch intelligent. Bedankt dat je altijd voor me klaar stond als ik een statistische vraag had, en voor je analyses en interpretaties van onze meta-analyse.

De overige co-auteurs van mijn manuscripten bedankt voor jullie betrokkenheid en inbreng. In het bijzonder prof. dr. Van Gemert, beste Martin, het was een genoegen om met je samen te werken en van gedachten te wisselen over 'ons review', bedankt voor je begeleiding.

Graag wil ik alle patiënten bedanken voor hun deelname aan de studies.

Alle secretaresses en ondersteuning van de afdeling Dermatologie van het Erasmus MC, bedankt voor jullie hulp en interesse tijdens mijn promotietraject.

Beste stafleden van de afdeling Dermatologie van het Erasmus MC en het Amphia Ziekenhuis, bedankt voor jullie begeleiding en supervisie in mijn opleidingstraject en interesse in mijn promotie. Beste Bing, bedankt voor je flexibiliteit rondom onderzoekstijd binnen mijn opleiding. Colette, bedankt dat je al die jaren zo een betrokken mentor voor me was, ik vond onze gesprekken altijd erg prettig en verhelderend.

Lieve ex-AIOS, AIOS, ANIOS en onderzoekers van de afdeling Dermatologie van het Erasmus MC, wat hebben we een geweldige groep! Bedankt voor al jullie begrip, geduld

en overnames tijdens mijn promotietraject, voor jullie hulp bij inclusies en controles van de LAST en COLA trial, maar vooral voor alle gezelligheid tijdens lunches, borrels en uitstapjes. Lieve Claire, wat ben je een fijne collega en wat kunnen we samen lekker dansen! Bedankt dat ik af en toe even mijn hart bij je kon luchten, gedeelde smart over slaaptekort is halve smart! Lieve Simone, mijn flebo-maatje, bedankt voor al je gezelligheid tijdens congressen e.d., wat hebben we het leuk gehad! Hopelijk kunnen we nog lang samenwerken in de toekomst. Göran, zaalbuddy, wat botsten we in het begin op de zaal, maar daarna konden we lezen en schrijven met elkaar. Bas, Armanda, Annemarie, Sophie, Emmilia, Robert, Deepak, Leonie, Iris, Anne, Joris, Lotte, Niels, Yeelai, Barbara, Justine, Merel, Judith, Karin, Sylvia, Tristan, Vi, Marissa, Fabiënne, Martijn, Allard en Sterre, bedankt voor de samenwerking en de leuke tijd.

Lieve derma-vriendinnen, Hanneke en Lotte, samen met Hilke hebben we onvergetelijke shop-weekendjes in Maastricht en Antwerpen doorgebracht en veel gezellige borrelavonden en kookclub-dinertjes; jullie hebben mijn opleidingstijd kleur gegeven. Bedankt voor jullie vriendschap. Lisette, samen zijn we begonnen als ANIOS en zaten we in hetzelfde schuitje. Daardoor vonden we veel steun en gezelligheid bij elkaar, en dat is door de jaren heen altijd zo gebleven, bedankt daarvoor.

Lieve paranimfen, Jenneke en Hilke, wat een topvrouwen zijn jullie en wat ben ik trots dat jullie vandaag naast me staan! Lieve Hil, zonder jou was dit promotietraject niet hetzelfde geweest. Vanaf onze eerste ontmoeting in 2011 was het al snel dikke mik tussen ons en waren we onafscheidelijk. We werden gezien als 'jut en jul', en zo voelden we ons ook. Jij voelt me feilloos aan, we maken elkaars zinnen af en weten elkaars gedachten zonder iets zeggen. Werk is nu echt niet meer hetzelfde zonder jou! Alle lachbuien (tijdens overdrachten en besprekingen, DOO, COCOM, met een regenpet of zomaar), koffiemomentjes, diepzinnigheid en gedeelde interesses hebben voor een intense vriendschap gezorgd, waarvan ik zeker weet dat die voor altijd zal duren. Lieve Jen, mijn wederhelft, jij weet en begrijpt mij helemaal en ook al bevinden we ons altijd in tegenovergestelde levensfases, we vinden elkaar meteen weer als we samen zijn. Dankjewel dat je mij altijd probeert te doorgronden en dat je mij helemaal accepteert zoals ik ben. Veel van de beste herinneringen die ik heb, zijn met jou. Laten we nog vaak samen zelfgebakken chocoladetaart eten als avondeten, onze levensjaren reflecteren en dansen alsof niemand ons ziet! I carry your heart with me, I carry it in my heart.

Lieve Luckxies, bedankt voor de nodige ontspanning en gezelligheid tijdens mijn promotietraject. Lieve Liesbeth, bedankt voor je trouwe vriendschap en voor de talloze goede gesprekken die we gevoerd hebben, je hield me dikwijls een spiegel voor waardoor ik weer nieuwe inzichten kreeg.

Mijn lieve Limburgvriendinnen, Aniek, Bo, Merijn, Nadine en Kay, op de middelbare school waren jullie al 'mijn groepje' en nu zijn jullie dat nog steeds. Ik vind het heel bijzonder dat we elkaar al zo lang kennen en dat we nog steeds zo een hechte en oprechte vriendschap hebben. Jullie zijn stuk voor stuk prachtmeiden en ik ben trots op ieder van jullie! Onze tripjes (Ibiza!), weekendjes en etentjes waren heerlijke afleiding en er volgen er ongetwijfeld nog veel meer.

Mijn lieve schoonfamilie, Henk, Miriam, Maarten, Marlieke, Laurent, Marijke, Cathelijne en Paul, bedankt voor jullie interesse en betrokkenheid bij mij en mijn proefschrift. Familie Smits is een warm nest waar ik me helemaal thuis voel. Henk en Miriam, bedankt voor jullie hulp met de kindjes, jullie zijn echt onmisbaar voor ons. Maarten, bedankt voor je hulp met de cover van het boekje, ik ben er heel blij mee!

Lieve papa en mama, woorden schieten te kort om uit te drukken hoe dankbaar ik ben en hoeveel ik van jullie hou. Iedere stap die ik maak ik het leven volgen jullie op de voet, en welke stap ik ook neem, jullie zijn altijd onverminderd trots op mij. Mijn hele leven hebben jullie mij gesteund in mijn keuzes en voor mij klaar gestaan. Ik hoop dat ik mijn kinderen in de opvoeding net zoveel liefde kan meegeven als jullie bij mij hebben gedaan.

Lieve Roeland, mijn knappe en fijne man, mijn rots in de branding, mijn thuis. Als ik weer eens loop te ratelen, ben jij degene die rustig blijft en helpt om mijn gedachten te ordenen en een oplossing te bedenken. Je kent me als geen ander en bij jou voel ik me helemaal mezelf. Dankjewel dat je altijd voor me klaarstaat en voor je onvoorwaardelijke liefde. Ik hou heel veel van jou!

Lieve Florian en Hannah, elke ochtend ontploft mijn hart weer van liefde als ik jullie slaperige snoetjes zie en word begroet met een nat kusje. Jullie maken al het andere onbelangrijk.

ABBREVIATIONS

AVVQ	Aberdeen Varicose Vein Questionnaire
CEAP	Clinical Etiologic Anatomic Pathophysiologic
CI	Confidence Interval
CVD	Chronic Venous Disease
CVI	Chronic Venous Insufficiency
DUS	Duplex UltraSound
DVT	Deep Vein Thrombosis
EVLA	EndoVenous Laser Ablation
EVSA	EndoVenous Steam Ablation
EVTA	EndoVenous Thermal Ablation
EQ-5D	EuroQol – 5D
EQ-VAS	EuroQol – Visual Analogue Scale
GSV	Great Saphenous Vein
Hb	Hemoglobin
HRQOL	Health-Related Quality Of Life
IQR	InterQuartile Range
NRS	Numeric Rating Scale
RCT	Randomized Controlled Trial
RFA	RadioFrequency Ablation
SD	Standard Deviation
SFJ	SaphenoFemoral Junction
SSV	Small Saphenous Vein
ST	Saphenous Trunk
SVT	Superficial Vein Thrombosis
UGFS	Ultrasound Guided Foam Sclerotherapy
VAS	Visual Analogue Scale
VCSS	Venous Clinical Severity Score

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LIST OF PUBLICATIONS

W.S.J. Malskat, L.K. Engels, L.M. Hollestein, T.E.C. Nijsten, R.R. van den Bos; EVLA parameters do not influence efficacy – results of a systematic review and meta-analysis. Submitted

W.S.J. Malskat, J. Giang, M.G.R. de Maeseneer, T.E.C. Nijsten, R.R. van den Bos; Randomized clinical trial of patient reported outcomes after endovenous 940 nm laser ablation versus 1470 nm laser ablation ('COLA trial') for great saphenous vein incompetence. Br J Surg; 2016 Feb 103(3):192-8

W.S.J. Malskat, E. Racz, S. ten Raa, P.J. Lugtenburg, V. Noordhoek Hegt, M.G.R. de Maeseneer; Multiple venous aneurysms in a patient with hypereosinophilic syndrome. Phlebology; 2016 Feb;31(1):66-8

R.R. van den Bos, **W.S.J. Malskat**, M.G.M. de Maeseneer, D.A.G. Groeneweg, M.A. Kockaert, H.A.M. Neumann, K.P. de Roos, T.E.C. Nijsten; Randomized clinical trial of endovenous steam ablation versus laser ablation for great saphenous varicose veins. Br J Surg; 2014 Aug;101(9):1077-83

W.S.J. Malskat, A.A. Poluektova, C.W.M. van der Geld, H.A.M. Neumann, R.A. Weiss, C.M.A. Bruijninckx, M.J.C. van Gemert; Endovenous Laser Ablation (EVLA): a review of mechanisms, modeling outcomes and issues for debate. Lasers Med Sci; 2014 Mar;29(2):393-403

W.S.J. Malskat, M. Stokbroekx, C.W.M. van der Geld, T.E.C. Nijsten, R.R. van den Bos; Temperature profiles of 980 nm and 1470 nm endovenous laser ablation, endovenous radiofrequency ablation and endovenous steam ablation. Lasers Med Sci; 2014 Mar;29(2):423-9

A.A. Poluektova, **W.S.J. Malskat**, M.J.C. van Gemert, M.E. Vuylsteke, H.A.M. Neumann, C.W.M. van der Geld; Some controversies in Endovenous Laser Ablation of varicose veins addressed by optical-thermal mathematical modelling. Laser Med Sci; 2014 Mar;29(2):441-52

W.S.J. Malskat, A.C. Knulst, C.A.F.M. Bruijnzeel-Koomen, H. Rockmann; Tolerance to alternative cyclooxygenase-2 inhibitors in nonsteroidal anti-inflammatory drug hypersensitive patients. Clin Transl Allergy; 2013;3:20

R.R. van den Bos, **W.S.J. Malskat**, H.A.M. Neumann; Stoomablatie van varices. Ned Tijdschr Geneesk;2013;157:A5636

W.S.J. Malskat, M.G.R. de Maeseneer; Acute superficial posterior compartment syndrome after ambulatory phlebectomy. Dermatol Surg; 2012 Dec, 38(12):2035-7

W.S.J. Malskat, R.I.F. van der Waal; Lentekriebels op de oorschelpranden. Ned. Tijdschr. Dermatol. Venereol; 2010, 20 (11), p. 727

W.S.J. Malskat, C. van der Tas, A.C. Knulst, C.A.F.M. Bruijnzeel-Koomen, H. Rockmann; Aspirin tolerance in patients with NSAID-hypersensitivity. Allergy; 2010 Feb 4

CURRICULUM VITAE

Wendy Malskat werd op 22 mei 1984 geboren in Heerlen en groeide op in het Limburgse dorpje Dieteren. In 2002 behaalde zij haar Gymnasium diploma aan de Trevianum Scholengroep te Sittard. Hetzelfde jaar begon zij met de studie Biologie aan de Universiteit van Utrecht, met de ambitie om marine bioloog te worden. Na een jaar besloot zij echter om de opleiding Geneeskunde te gaan volgen, ook in Utrecht. Al spoedig werd hierbij haar interesse voor de Dermatologie gewekt. Nadat zij in september 2009 haar artsexamen behaalde, werkte zij eerst als arts niet in opleiding tot specialist (ANIOS) bij de afdeling Heelkunde in het Antonius Ziekenhuis te Nieuwegein. In 2011 werd ze tot haar genoegen aangenomen als ANIOS Flebologie bij de afdeling Dermatologie van het Erasmus MC Rotterdam, waarnaast zij in 2012 met haar promotieonderzoek begon onder begeleiding van prof. Nijsten en dr. van den Bos. Sinds 2013 is zij in opleiding tot dermatoloog in het Erasmus MC. Naar verwachting zal zij op 1 januari 2019 haar specialisatie afronden en o.a. bij het Erasmus MC werkzaam blijven voor de flebologie. In augustus 2016 trouwde Wendy met Roeland Smits. Ze hebben samen twee kinderen, Florian (18 september 2015) en Hannah (2 januari 2017).

PHD PORTFOLIO

Name PhD student: Wendy Malskat
Erasmus MC department: Dermatology
PhD-period: 2012 – 2018
Promotor: Prof. dr. T.E.C. Nijsten
Copromotor: Dr. R.R. van den Bos

	Year	Workload (Hours/ECTS)
1. PhD training		
General academic skills		
- DOO Samenwerken	2013	1.0 ECTS
- DOO Communicatie	2014	1.0 ECTS
- Teach the teacher	2014	1.0 ECTS
- DOO Ethiek	2015	1.0 ECTS
- DOO EBM	2016	1.0 ECTS
- DOO Medisch management	2017	1.0 ECTS
Courses		
- BROK (Basis Registratie Onderzoek Klinische Trials)	2012	1.0 ECTS
- Systematisch literatuuronderzoek in Pubmed	2012	5 hours
- Systematisch literatuuronderzoek andere databases	2012	3.5 hours
- Endnote	2012	3.5 hours
- Molmed: basic introduction course on SPSS	2012	1.0 ECTS
- NIHES: Methods of clinical research	2012	0.7 ECTS
- Research integrity	2013	0.3 ECTS
- NIHES: Topics in meta-analysis	2014	0.7 ECTS
Oral presentations		
- Multicenter Flebologie Overleg (MFO), Erasmus MC, Rotterdam. *Veneuze hart – de kuitspierpomp*	2012	1.0 ECTS
- Benelux Society of Phlebology meeting, Brugge, Belgium. *Complication after ambulant phlebectomy*	2012	1.0 ECTS
- MFO, Erasmus MC, Rotterdam. *Dreigend compartimentsyndroom na Muller*	2012	1.0 ECTS
- Cabourg V Flebologie congres, Cabourg, Frankrijk. *Temperatuurprofielen van EVLA, RFA en EVSA*	2013	1.0 ECTS
- XVII UIP World Phlebology Meeting, Boston, USA. *Temperature profiles of EVLA, RFA and* EVSA	2013	1.0 ECTS
- Skintermezzo, Erasmus MC, Rotterdam. *Bijzondere flebologie door een roze bril*	2013	1.0 ECTS
- Benelux Society of Phlebology meeting, Dinant, Belgium. *A collection of curiosities in a flebologic patient*	2014	1.0 ECTS

	Year	Workload (Hours/ECTS)
- DCOP meeting, Utrecht. *LAST trial*	2014	1.0 ECTS
- MFO, Erasmus MC, Rotterdam. *COLA trial*	2015	1.0 ECTS
- Cabourg VI Flebologie congres, Cabourg, France. *COLA trial*	2015	1.0 ECTS
- European Vascular Course, Maastricht. *Endovenous steam ablation*	2015	1.0 ECTS
- CACVS, Paris, France. *COLA trial*	2016	1.0 ECTS
Conferences (attending)		
- 1st PhD weekend, Maastricht, The Netherlands	2013	1.0 ECTS
- XVII UIP World Phlebology Meeting, Boston, USA	2013	1.0 ECTS
- SNNDV, Amsterdam, The Netherlands	2013	1.0 ECTS
- Cabourg V Flebologie congres, Cabourg, France	2013	1.0 ECTS
- 2nd PhD weekend, Maastricht, The Netherlands	2014	1.0 ECTS
- EADV, Amsterdam, The Netherlands	2014	1.0 ECTS
- SNNDV, Brussel, Belgium	2014	1.0 ECTS
- Benelux Society of Phlebology meeting, Kijkduin, The Netherlands	2015	1.0 ECTS
- Cabourg VI Flebologie congres, Cabourg, France	2015	1.0 ECTS
- CACVS, Paris, France	2016	1.0 ECTS
- Benelux Society of Phlebology meeting, Gent, Belgium	2016	1.0 ECTS
- Benelux Society of Phlebology meeting, St Michielsgestel, The Netherlands	2017	1.0 ECTS
- Dermatologendagen, Papendal, The Netherlands	2017	1.0 ECTS
- SNNDV, Utrecht, The Netherlands	2017	1.0 ECTS
- Benelux Sciety of Phlebology meeting, Charleroi, Brussels, Belgium	2018	1.0 ECTS
Other		
- Research meetings and Journal Clubs, Department of Dermatology, Erasmus MC, Rotterdam, The Netherlands	2012-2015	1.0 ECTS
- Skintermezzo meetings, Department of Dermatology, Erasmus MC, Rotterdam, The Netherlands	2012-2018	1.0 ECTS
- Multicenter Flebologie Onderwijs (MFO), Department of Dermatology, Erasmus MC, Rotterdam, The Netherlands	2012-2018	1.0 ECTS
- Graduation Committee Amit de Boer, TuE Eindhoven. *Differences between boiling of water and blood in EVLA applications*	2013	1.0 ECTS
Occasional reviewer for		
- European Journal of Vascular and Endovascular Surgery (EJVES)	2016-2018	14 hours

	Year	Workload (Hours/ECTS)
Scientific awards		
- Benelux grant, oral presentation at Benelux Society of Phlebology meeting, Dinant, Belgium	2014	
- Andre Davy award, oral presentation at Cabourg VI Flebologie congres, Cabourg, France	2015	
2. Teaching		
- ICK education Phlebology medical students, Erasmus MC, Rotterdam	2012	6 hours
- MINOR education Phlebology medical students, Erasmus MC, Rotterdam	2012, 2013 and 2017	8 hours
- Surgical skills education medical students, Erasmus MC, Rotterdam	2012	4 hours
- Course Thermal Ablation, European Venous Training Center, Maastricht	2014	6 hours
- ICK education infectious diseases medical students	2014	15 hours
- Supervising research project medial student Jenny Giang	2015	0.5 ECTS