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.

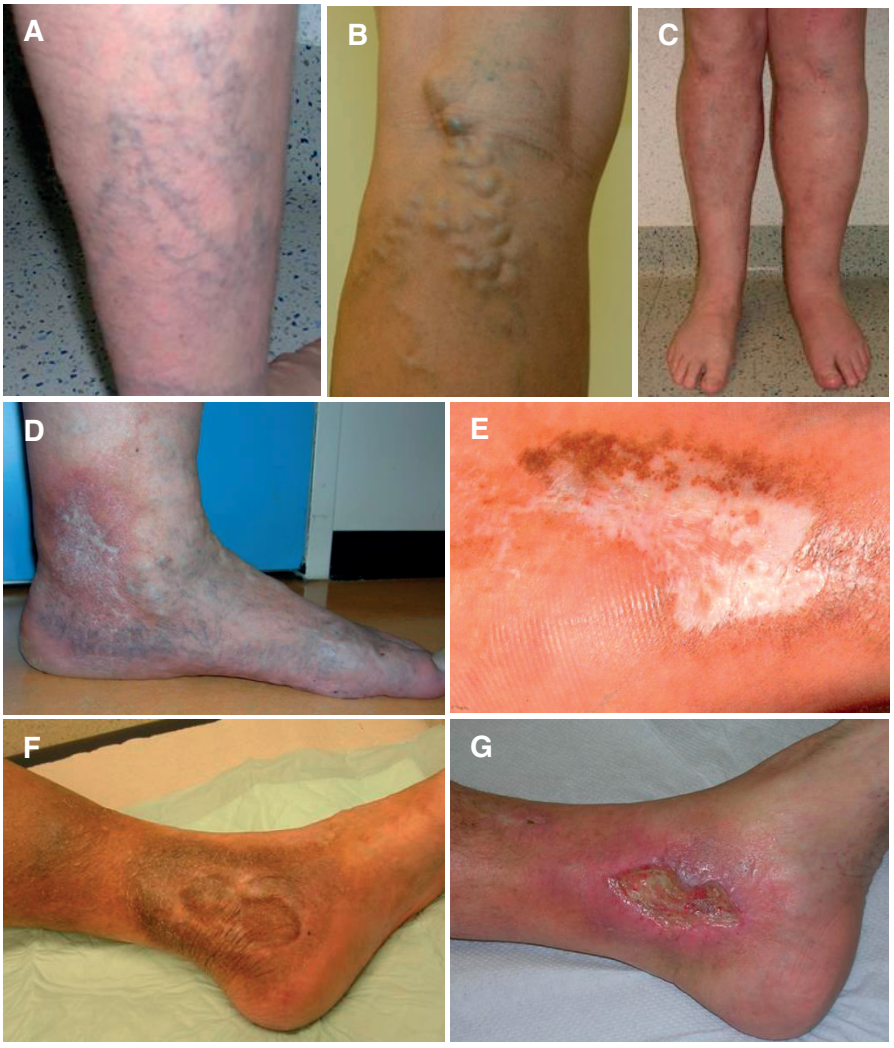

Figure 1. Clinical characteristics of chronic venous insufficiency. A. Reticular veins. B. Varicose veins. C. Edema. D. Lipodermatosclerosis. E. White atrophy and hyperpigmentation. F. Hyperpigmentation and healed leg ulcer. G. Active leg ulcer.

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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