Chronic Venous Disease under pressure

Suzan Reeder

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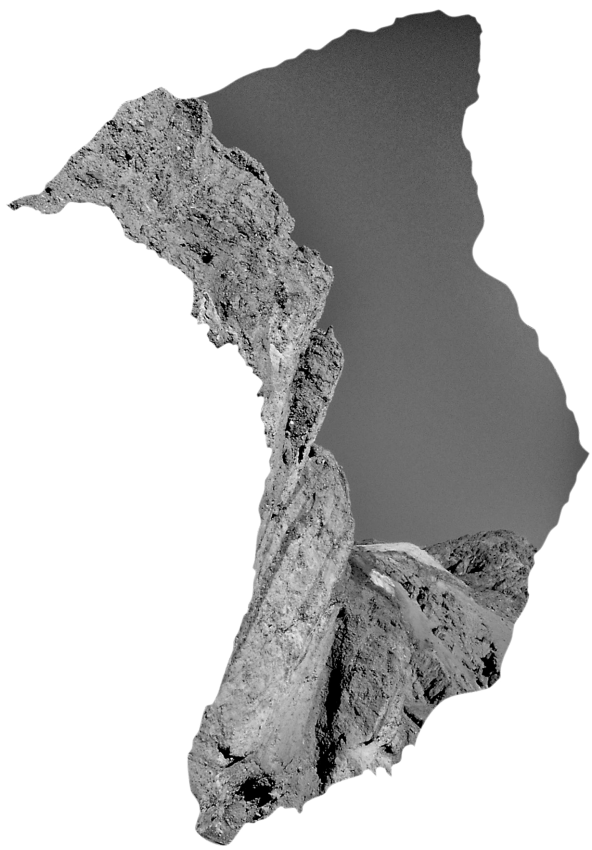
Introduction



Chapter 1

Introduction

S.W.I. Reeder
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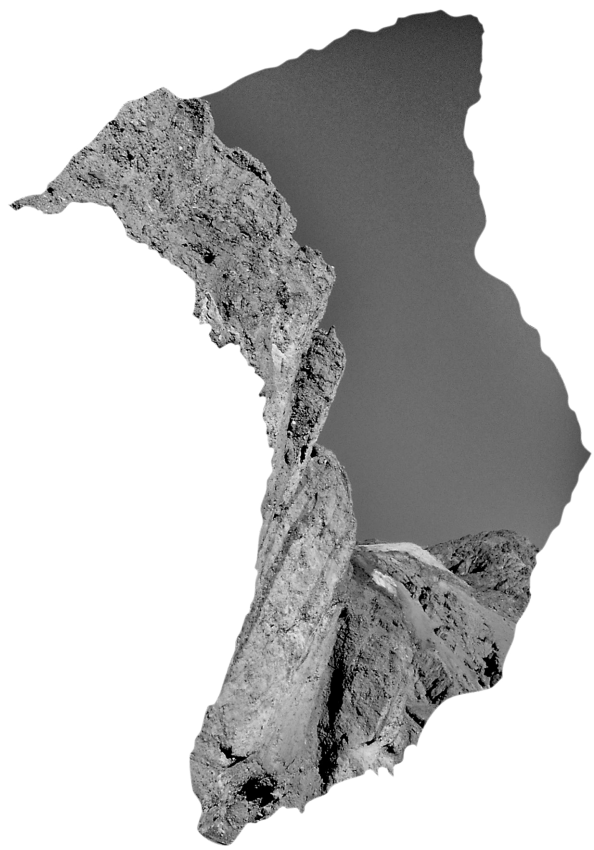
Based on: 'Chronic venous disease, a review'

Submitted



INTRODUCTION

Phlebology is a non-UEMS[a] approved medical specialty that comprises the pathophysiology of the veins. Since gravity plays a major role in the disturbed venous haemodynamic, most phlebological diseases such as varicose veins manifest at the level of the lower leg. Phlebology is much more than simple varicose veins and includes not only acute diseases, mainly thrombosis and bleeding, but also a wide range of syndromes and congenital diseases such as Klippel-Trenaunay syndrome, Bockenheimer syndrome, Servelle-Martorell syndrome and a wide spectrum of venous, veno-lymphatic and arterio-venous malformations. Moreover, varicose veins are not unique for the legs. Oesophageal varicose veins are a well- known complication of portal venous hypertension. Less known, although very common, are varicose veins in the fingers of the elderly. Except for congenital malformations the incidence of all phlebological diseases increases with the age.

Chronic venous insufficiency (CVI) is a combination of the complex of typical complaints and a disturbed venous return with the characteristic clinical signs in the lower leg. The term CVI illustrates the problem very well: it is a chronic disease, progressive in time and is based on the failure of return of the blood to the heart. However, in literature of the last decade most authors refer to chronic venous disease (CVD), which is a much broader description than CVI. In this article we use CVD as much as possible, although one should realize that both terms are not interchangeable since CVI is a part of CVD. Post-thrombotic syndrome (PTS) is another common term. It is a subset of CVI and comprises the consequences to the veins after a (deep) venous thrombosis (DVT).

CVD is extremely common and poses a serious social and economic burden on the society. It is interesting to note that in 1979 Feuerstein already reported that 50% of all venous leg ulcers were based on isolated superficial venous incompetence, thus varicose veins.[1] The most recent study in this field was reported by Magnusson et al.[2] and in spite of a 22-year gap between these two publications, the conclusions remain the same. Since primary varicose veins are easy to treat in a very effective and patient-friendly manner by using modern endovascular techniques such as laser, radiofrequency and steam ablation,[3,4] it is surprising to conclude that no progress has been made in this field.

CVD begins with few minor complaints, later some skin changes and after years the full spectrum may develop: oedema, iron- hyperpigmentation, venectasias, lipodermatosclerosis, white atrophy, secondary high-output lymphedema and finally leg ulceration. In severe cases, canyon varicose veins, a canal of Verneuilh, subcutaneous ossification, nail changes, cruralgia orthostatica and extreme dyskeratosis may be observed.[5-8] Therefore, it is logical that the quality

[a] Union Européenne des Médecins Spécialistes

of life is seriously diminished in CVD patients.[9] Leg ulcers are difficult to heal and prevention is essential. Early treatment of severe varicose veins (diameter ≥5 mm) and adequate compression therapy after DVT is imperative.[10,11]

Since there is no UEMS register for phlebology many differently educated physicians throughout Europe are involved in the diagnosis and the treatment of CVD. Among these are dermatologists, general surgeons, vascular surgeons, angiologists, cardiologists, general practitioners and the so-called "phlebologists". The subject CVD does not seem to have a high priority, which is highly in contrast to its impact on health and economy. Worldwide, there are a very limited number of dedicated academic medical centres that are fully involved in phlebology and where research of high standard is pursued. It is rather disappointing that (medical) society does not pay more attention to a common and serious problem that has a high impact on the patient's quality of life.

Nonetheless, new techniques such as duplex ultrasound and endovenous treatment modalities that were introduced in the last decades have pushed phlebology into the modern era. Phlebology has remained experience-based instead of evidence-based for a long period because of the indifference among so many physicians and an underestimated problem by university medical centres. Recently, many randomized controlled trials have been published and the assessment of quality of life is now incorporated into research programmes. The next step is to see how these new techniques are incorporated into the insurance packages offered by the healthcare insurance companies because the spectrum of the diseases varies from tiny spider veins, which is purely a cosmetic problem to leg ulcers, which are a serious worldwide medical problem.

The estimated total costs of leg ulcer treatment vary from € 800 to € 2,600 per ulcer.[12] However, the prevalence of varicose veins is high but the prevalence of venous leg ulceration is much lower.

Varicose veins are common in 77% of the women aged 70 years and leg ulceration occurs in 4-5% of the patients older than 80 years.[13,14] A predictive factor is unfortunately lacking. Nevertheless, most experts agree that an incompetent great saphenous vein with a diameter of ≥5 mm should be treated.[10]

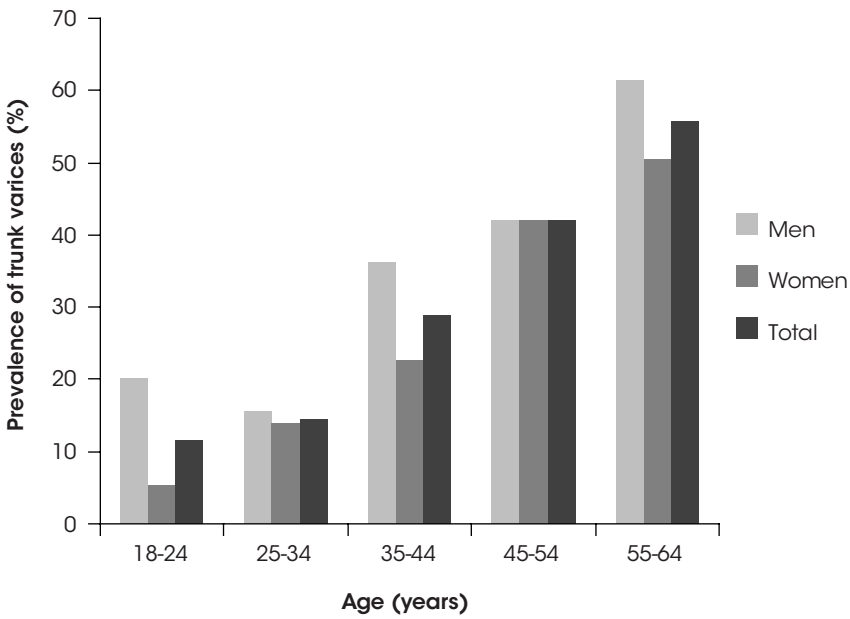
Besides early treatment of serious varicosities, awareness among physicians, especially general practitioners, is essential to reduce complications of CVD and to maintain the quality of these patients at the highest possible level.

EPIDEMIOLOGY

CVD of the legs is a common medical condition with an estimated worldwide prevalence that ranges from 2-64%.[13,15-20] Prevalence of clinical varicose veins ranges from 10-40% in men and 26-32% in women.[15,19,21,22] The reported variation in these estimates can partially be explained by the differences in the disease definition, the study population and the methods of estimation.

The prevalence of CVD increases linearly with age, but may even occur in children and adolescents.[13] Reticular veins were demonstrated in 10.2% of the secondary school children in the Bochum vein study.[23] The overall prevalence of saphenous varicose veins increased from 12% in the subjects 18-24 years of age to 56% in those 55-64 years of age in the Edinburgh vein study (Figure 1).[15] The results in the Framingham study correspond to those reported in the previous study with a prevalence of less than 10% for varicose veins in women younger than 30 years to 77% in women aged 70 years and older.[13]

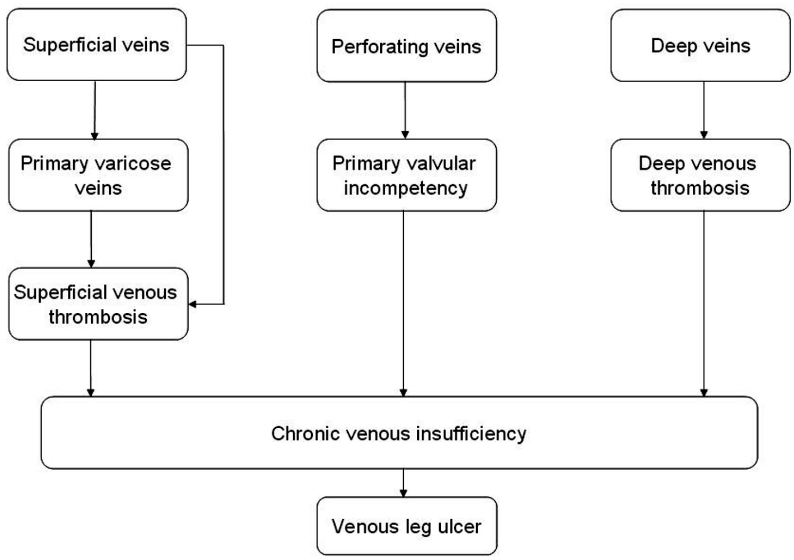
Figure 1. Prevalence of saphenous varicose veins by age and sex.[15]



Several of the previous mentioned studies reported that varicose veins were more common in women than in men. This difference may be explained by selection bias, since women consider varicose veins as a cosmetic problem more often

than men and consult a physician more often and consequently are more likely to participate in studies. Most general population studies failed to demonstrate a sex difference. Moreover, more advanced CVD occurred equally in both sexes.[24]
CVD may lead to leg ulceration as the end stage (Figure 2). Venous leg ulceration has a lifetime prevalence of 1% and a prevalence of active ulceration of 0.3% in the adult Western population.[25,26] The prevalence of venous leg ulceration increases with age.[14] Chronic ulceration in those younger than 60 years is unusual and often related to severe deep venous insufficiency.[27]

Figure 2. Flowchart of the development of CVI and venous leg ulceration.



The prognosis of venous leg ulceration is unfavourable. On the average 50% of the ulcers heal within 12 weeks, but about 8% of the treated ulcers were not healed after 5 years.[26,28,29] Risk factors for poor wound healing include sex, age, ulcer duration, previous surgery, history of DVT and a high body mass index.[30] A majority of the leg ulcers recur more than once. Venous ulcers have an annual recurrence rate of 6-15% and a lifetime recurrence rate of 3-15%. There is a high recurrence rate of 24 to 52% at three years.[31] These recurrence rates decrease to 23-32% after two years and 32-39% after five years if the gold standard compression therapy is continued after ulcer healing,[32] indicating that this chronic disease needs lifelong treatment.

In 1997, the costs of venous disorders were investigated in a Dutch study.[33] The social costs of venous disorders were estimated on the basis of the prevalence. The direct medical costs (medical consumption) were separated from the indirect medical costs caused by loss of productivity through absence because of illness, inability to work and premature death. By this, the total societal costs of venous disorders were estimated at € 274 million, of which € 225.5 million was spent on medical care. In other words, 6% of the total health care costs was annually spent on the treatment of venous diseases.[34] Wearing medical elastic compression stockings (MECS) to prevent PTS after a DVT cuts the costs by € 10.4 million a year. Moreover, wearing MECS after a first DVT reduces the risk of developing PTS by 50%.

Recent data on the costs of treating venous leg ulcers is lacking. A lot of the costs are incurred in the hospital outpatient care and in the primary care. Much money is spent on bandages and wound dressings. The annual costs of treating venous leg ulcers in Sweden and the United Kingdom were compared in one study.[12] Median cost per leg ulcer treatment amounted to € 1,300 to € 2,600 in Sweden and € 800 to € 2,000 in the United Kingdom. The treatment of large (>10 cm^2) and longstanding (>6 months) leg ulcers was the most expensive. The frequency and the duration of each change of bandage formed the major expense.

PATHOPHYSIOLOGY

CVD results from ambulatory venous hypertension and is the consequence of valvular incompetence, venous outflow obstruction, or a combination of both.[35,36] In standing position ambulatory venous pressure equals hydrostatic pressure and is approximately 80-100 mmHg in the dorsal foot vein of an average Western European. Venous pressure is only 5-10 mmHg in supine position. Venous pressure decreases to <25 mmHg during walking due to the closure of the venous valves. This pressure is called ambulatory venous pressure (AVP). In venous hypertension, there is a complicated relationship regarding the microcirculatory consequences that lead to the inability to decrease pressure during walking.

CVD may be divided into primary chronic venous disorders, mainly consisting of primary varicose veins and secondary chronic venous disorders, generally caused by PTS and congenital malformations. Varicose veins may develop primary or secondary to an underlying disease. Primary varicose veins may either be caused by a primary anomaly in the matrix of the vein wall that alters the elasticity or by a primary anomaly in the cusps of the valves that leads to white cell trapping, inflammation and destruction of the cusps.[37-39] Finally, both primary- and secondary varicose veins cause destruction of the valves. The bloodstream

is highly decreased in the cusps of the valves, which results in the deposition of fibrin and thrombocytes that leads to a thickening of the vein wall and induces thrombogenesis.[40] Monocytes may attach in the niches formed by the cusps and cause leucocyte adhesion and subsequent microthrombosis around the valves resulting in valve dysfunction and subsequent venous hypertension.[41]

Post-thrombotic syndrome may develop after a venous thrombosis because of the damage to the valve and re-canalisation (reflux type) or residual obstruction (obstructive type). The thrombotic process causes damage to the valves of the deep veins, which results in valvular incompetence. The perforating veins and the superficial varicose veins will consequently dilate, which induces valvular incompetence in the superficial veins. Dysfunction of the venous macrocirculation leads to changes in the venous microcirculation if the calf muscle pump does not fully compensate.[42] Besides calf muscle pump function, other factors that provoke CVD include reduced ankle joint mobility and obesity.[43,44]

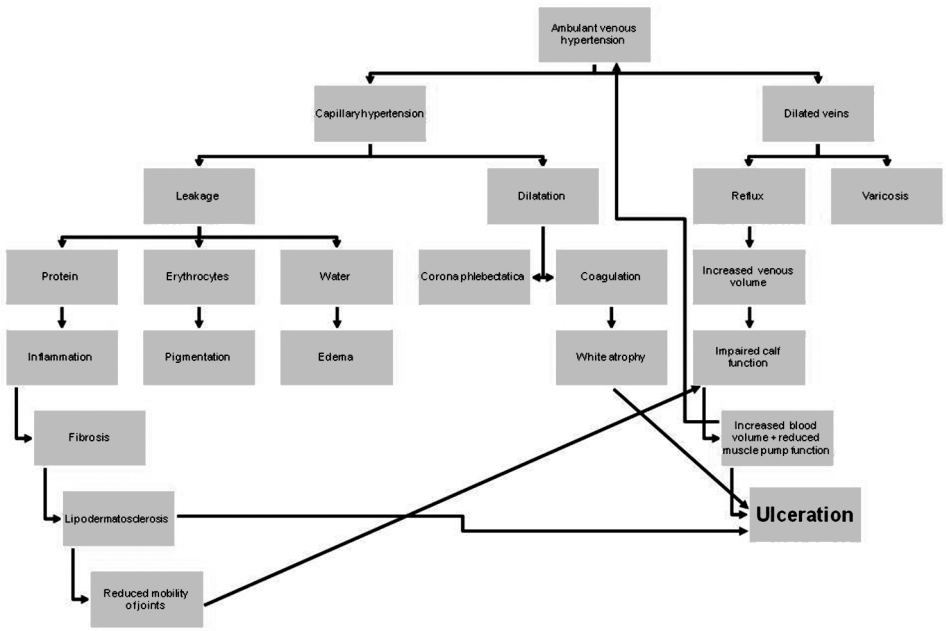
The pathophysiology of the venous microcirculation is very complex (Figure 3). Since CVD is a process that usually takes years to develop, it should be assumed that a combination of several mechanisms lead to the skin changes that are typical for this disease. Ambulatory venous hypertension leads to capillary hypertension and all the subsequent skin changes are caused by the disturbed microcirculation.[45] Capillary hypertension finally leads to the two most important phenomenons leading to venous leg ulceration as the severest complication of CVD, that are lipodermatosclerosis and 'atrophie blanche' (white atrophy).[46,47] The capillary hypertension leads to capillary leakage of water and later also erythrocytes and plasma proteins that results in a protein-rich oedema, which gives rise to oedema and fibrosis of the skin and subcutaneous tissue, the so-called lipodermatosclerosis.[48] Besides lipodermatosclerosis, capillary hypertension leads to dilated capillaries that cause decreased blood flow velocity with the formation of rouleaux and sludge leading to microthrombosis, the so-called atrophie blanche.[49]

CLINICAL CHARACTERISTICS

CVD is associated with multiple and generally subjective symptoms consisting of discomfort, aching, tingling, heaviness, burning, itching, muscle cramps and restless legs. The clinical characteristics of CVD appear when the mechanisms that compensate for the insufficient venous return fails. The clinical features increase almost linearly in time and consist of telangiectasias, varicose veins, oedema, hyperpigmentation, eczema, white atrophy, lipodermatosclerosis, nail changes and ulceration (Figure 4a-i).[17]

The progression of CVD is classically divided into three stages: the adaptation stage, the compensation stage and finally the de-compensation stage.[50] Venous ulceration is considered to be the final complication of CVD. It has a lifetime prevalence of 1-2%.[30,51]

Figure 3. The Rotterdam model.



DIAGNOSIS

Duplex ultrasound examination has replaced many functional tests for investigating and confirming the anatomy.[52] However, duplex ultrasound itself is not a true functional test since it does not display pressure, but only reflux. No venous hypertension will develop as long as the return mechanisms can compensate for the amount of reflux. A functional test is a test in which pressure is measured because ambulatory venous pressure measurement is the gold standard.[53] However, measuring ambulatory venous pressure is both invasive and time-consuming. Duplex ultrasound is a safe, cost-effective and non-invasive investigation and should be performed in all patients suspected of CVD and has become the gold diagnostic tool for most therapeutic decisions in phlebology.

Duplex ultrasound investigation is ideally performed with the patient in the upright position in order to investigate the diameter and the patency of the superficial, deep and perforating venous system. Reflux in the superficial, the deep and the perforating veins can be measured accurately. How complete duplex ultrasound assessment should be performed was described in details in two recently published consensus documents on the methodology of duplex ultrasound investigation by the Union Internationale de Phlébologie (UIP).[52,54] Additional investigations may be performed to visualize the anatomy in special cases, e.g. unusual presentation, vascular malformations or recurrent varicose veins. Phlebography, CT-angiography or MR-angiography may be very valuable in these challenging situations. Although largely replaced by duplex ultrasound, ambulatory venous pressure measurement is still the gold standard functional test in quantifying venous hypertension and may be added as a diagnostic and prognostic tool in selected cases, i.e. patients with clinical signs not corresponding with duplex ultrasound and patients with PTS.[55,56]

CLASSIFICATION

Since its introduction in 1994 the CEAP-classification has become the classification of choice to systematically describe the Clinical signs of CVD, Aetiology (congenital, primary, secondary), Anatomy (superficial, deep and perforating veins) and Pathophysiology (reflux, obstruction or both) (Table 1).[57,58] The CEAP-classification serves as a systematic guide to orderly document the phlebological status of each patient. It has made diagnosing CVD more accurate. Moreover, the CEAP-classification has made scientific studies comparable because of its international and worldwide use. However, the CEAP-classification was introduced at a time when duplex ultrasound was not yet routinely established in daily practice. Therefore, it does not mention duplex ultrasound investigation, which may bridge the gap between the physician's eyes and the – not always visible – varicose veins. Hence the CEAP-classification should be extended by mentioning the diameter of the saphenous veins.

TREATMENT

Today compression therapy is still the cornerstone in the treatment of CVD. In ancient times, the Greek and Romans used bandages around their calves as support to relieve symptoms during long marches.[59] In the 19th century the so-called Unna boot was introduced by a German dermatologist, Paul Gerson Unna (1850-1921) and was used in the treatment of leg ulcers. With the introduction of the Unna boot a new era of compression therapy started.[60]

Table 1. Revision of CEAP-classification of CVD: summary.[57]

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 atrophie blanche
C5	Healed venous ulcer
C6	Active venous ulcer
S	Symptomatic, including ache, pain, tightness, skin irritation, heaviness, and muscle
A	cramps, and other complaints attributable to venous dysfunction
	Asymptomatic
Etiological classification	
Ec	Congenital
Ep	Primary
eS	Secondary
eN	No venous cause identified
Anatomic classification	
As	Superficial veins
Ap	Perforator veins
Ad	Deep veins
An	No venous location identified
Pathophysiologic classification	
	Basic CEAP
Pr	Reflux
Po	Obstruction
Pr,o	Reflux and obstruction
Pn	No venous pathophysiology identifiable
	Advanced CEAP
	Same as basic CEAP, with addition that any of 18 named venous segments can be used as locators for venous pathology

The three main forms of compression therapy are:

1. Ambulatory compression bandages;
2. Medical elastic compression stockings (MECS);
3. Intermittent pneumatic compression.

Technically, it is very important to distinguish between elastic (i.e. MECS, short stretch bandages and long stretch bandages) and non-elastic compression (i.e. zinc oxide bandages, plaster cast and flannel bandages). Most elastic bandages

should be removed at night to prevent potential arterial inflow problems in supine position.[61]

The demonstrated beneficial effects of compression therapy in patients with CVD are improvement of the function of the calf muscle pump, reduction of venous volume, reduction of venous diameter, increase of venous flow velocity, reduction of reflux, reduction of venous hypertension, increase of arterial perfusion, increase of interstitial pressure, prevention and reduction of oedema and enhancement of the microcirculation.[62] Consequently, there are multiple indications for compression therapy in CVD. These indications are primary varicose veins, after varicose vein treatment (i.e. sclerotherapy, endovenous laser therapy), oedema, lipodermatosclerosis, eczema, atrophie blanche, deep venous insufficiency, superficial venous thrombosis, deep vein thrombosis, leg ulceration and venous malformations. It has been demonstrated that healthy individuals for instance athletes and people on long-haul flights also benefit from compression therapy.[63-66]

Several compression methods may be used in the treatment of venous leg ulceration. Most patients are initially treated with adhesive or non-adhesive short stretch bandages, unless these are contra-indicated as in patients with diabetes mellitus or peripheral arterial insufficiency. The main goal of these bandages, besides ulcer healing, is oedema reduction. Once all oedema has gone, bandages may either be continued or a MECS may be prescribed. Nowadays, MECS and specially the so-called ulcer kits are also a fair treatment modality in venous leg ulceration.[67,68] In addition to compression therapy, underlying pathology should also be treated if possible in patients with leg ulcers. Although a large variety of (compression) therapy with many different types of dressings and even hospitalization are available, the leg ulcer becomes a chronic medical disease in a small group of patients that sometimes persists for lifetime.

Figure 4a. C1: Telangiectasias.

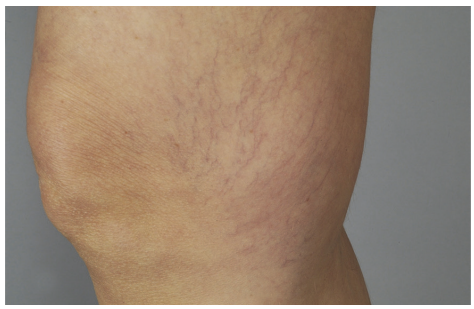


Figure 4b. C2: Varicose veins.

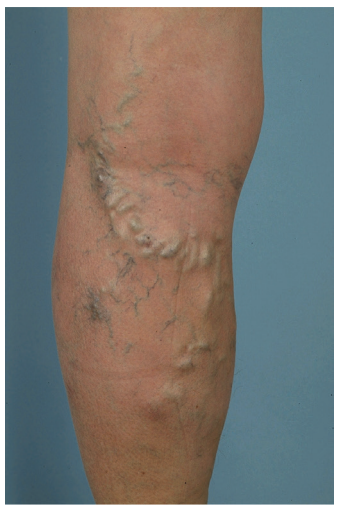


Figure 4c. C3: Oedema.

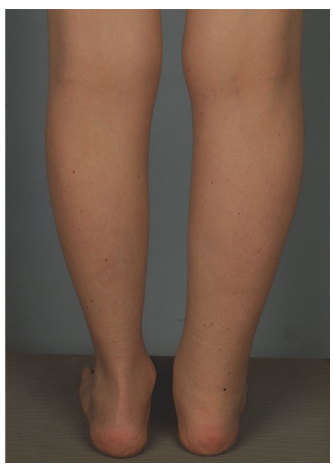


Figure 4d. C4a: Eczema.

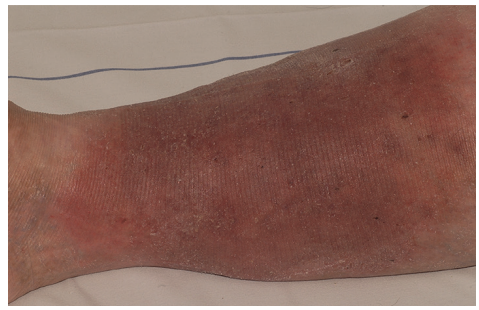


Figure 4e. C4a: Pigmentation.

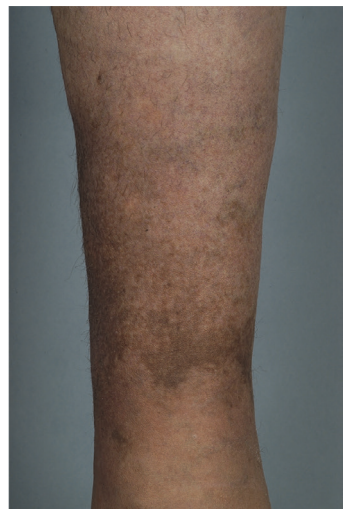


Figure 4f. C4b: Lipodermatosclerosis.

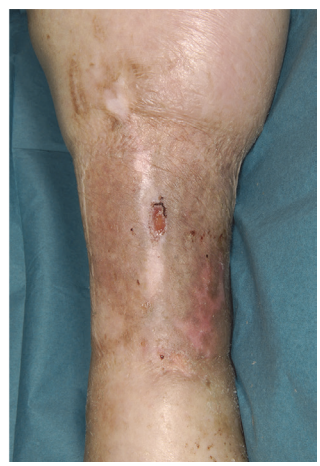


Figure 4g. C4b: Atrophie blanche.

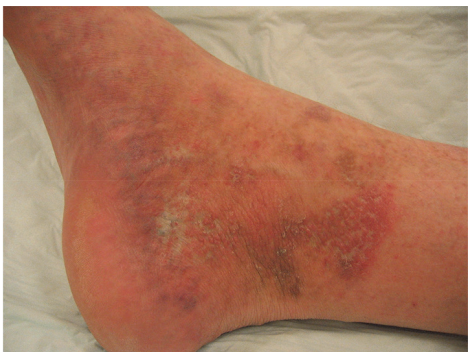


Figure 4h. C5: Healed venous ulcer.

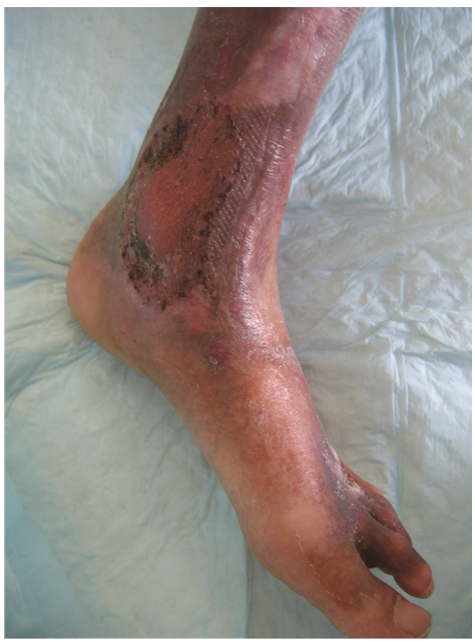
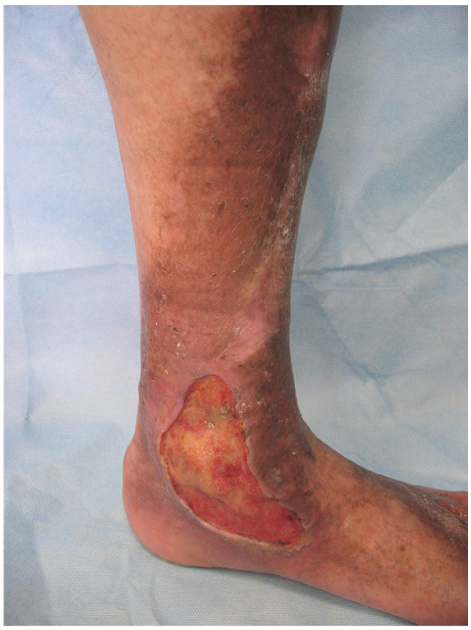


Figure 4i. C6: active venous ulcer, same patient as Figure 4h.



AIMS OF THIS THESIS

1. Does the supposed effectiveness of light-weight medical elastic compression stockings exist and if so is this based on lowering the capillary filtration rate?
2. Is the C in the CEAP-classification a predictive factor to make a correct statement on ambulatory venous pressure?
3. Is venous leg ulcer treated properly in the Netherlands?
4. Does hospitalisation reduce venous leg ulcer recurrences of venous leg ulcers with lack of healing tendency?
5. Which treatment modalities do exist for recalcitrant venous leg ulcers besides ambulatory compression therapy?

REFERENCES

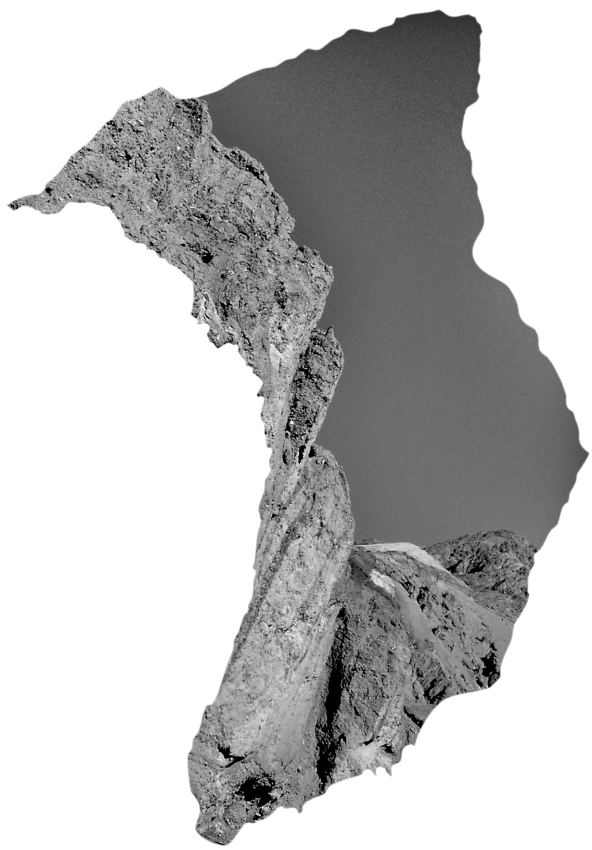
1. Feuerstein W. Die Etagenlokalisation postthrombotischer Venenveranderungen. Wien Med Wochenschr 1979;129(11):293-6.
2. Magnusson MB, Nelzen O, Risberg B, Sivertsson R. A colour Doppler ultrasound study of venous reflux in patients with chronic leg ulcers. Eur J Vasc Endovasc Surg 2001;21(4):353-60.
3. van den Bos R, Arends L, Kockaert M, Neumann M, Nijsten T. Endovenous therapies of lower extremity varicosities: a meta-analysis. J Vasc Surg 2009;49(1):230-9.
4. van den Bos RR, Milleret R, Neumann M, Nijsten T. Proof-of-principle study of steam ablation as novel thermal therapy for saphenous varicose veins. J Vasc Surg 2011;53(1):181-6.
5. Arnoldi CC. Idiopatisk dysfunktion af venepumpen i underbenet–cruralgia orthostatica. Ugeskr Laeger 1975;137(7):369-74.
6. Tessari L. Les canyon-varices. Consequence et cause d'hypodermite sclereuse et leur traitement. Phlebologie 1990;43(3):501-6.
7. Kumar R, Roper PR, Guinto FC, Jr. Subcutaneous ossification of the legs in chronic venous stasis. J Comput Assist Tomogr 1983;7(2):377-8.
8. Binaghi F, Cannas F, Fronteddu PF, Pitzus F. Le alterazioni del microcircolo nutritizio della plica ungueale dei piedi sono correlate al grado dell'insufficienza venosa cronica. Minerva Cardioangiol 1994;42(4):163-8.
9. Carradice D, Mazari FA, Samuel N, Allgar V, Hatfield J, Chetter IC. Modelling the effect of venous disease on quality of life. Br J Surg 2011;98(8):1089-98.
10. Neumann HAM. Haut, Venen und Beine. Phlebologie 2011;40:344-355.
11. Kolbach DN, Sandbrink MW, Hamulyak K, Neumann HA, Prins MH. Non-pharmaceutical measures for prevention of post-thrombotic syndrome. Cochrane Database Syst Rev 2004(1):CD004174.
12. Ragnarson Tennvall G, Hjelmgren J. Annual costs of treatment for venous leg ulcers in Sweden and the United Kingdom. Wound Repair Regen 2005;13(1):13-8.
13. Brand FN, Dannenberg AL, Abbott RD, Kannel WB. The epidemiology of varicose veins: the Framingham Study. Am J Prev Med 1988;4(2):96-101.
14. Margolis DJ, Bilker W, Santanna J, Baumgarten M. Venous leg ulcer: incidence and prevalence in the elderly. J Am Acad Dermatol 2002;46(3):381-6.
15. Evans CJ, Fowkes FG, Ruckley CV, Lee AJ. Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population: Edinburgh Vein Study. J Epidemiol Community Health 1999;53(3):149-53.
16. Heit JA, Rooke TW, Silverstein MD, Mohr DN, Lohse CM, Petterson TM, et al. Trends in the incidence of venous stasis syndrome and venous ulcer: a 25-year population-based study. J Vasc Surg 2001;33(5):1022-7.
17. Pannier-Fischer F, Rabe E. Epidemiologie der chronischen Venenerkrankungen. Hautarzt 2003;54(11):1037-44.
18. Rabe E, Guex JJ, Puskas A, Scuderi A, Fernandez Quesada F. Epidemiology of chronic venous disorders in geographically diverse populations: results from the Vein Consult Program. Int Angiol 2012;31(2):105-15.
19. Criqui MH, Jamosmos M, Fronek A, Denenberg JO, Langer RD, Bergan J, et al. Chronic venous disease in an ethnically diverse population: the San Diego Population Study. Am J Epidemiol 2003;158(5):448-56.

20. Maurins U, Hoffmann BH, Losch C, Jockel KH, Rabe E, Pannier F. Distribution and prevalence of reflux in the superficial and deep venous system in the general population–results from the Bonn Vein Study, Germany. J Vasc Surg 2008;48(3):680-7.
21. Abramson JH, Hopp C, Epstein LM. The epidemiology of varicose veins. A survey in western Jerusalem. J Epidemiol Community Health 1981;35(3):213-7.
22. Coon WW, Willis PW, 3rd, Keller JB. Venous thromboembolism and other venous disease in the Tecumseh community health study. Circulation 1973;48(4):839-46.
23. Weindorf N, Schultz-Ehrenburg U. Le developpement de la varicose chez les enfants et les adolescents. Phlebologie 1990;43(4):573-7.
24. Rabe E, Pannier-Fischer, F, Bromen, K, et al. Bonner Venenstudie der Deutschen Gesellschaft für Phlebologie. Epidemiologische Untersuchung zur Frage der Häufigkeit und Ausspägung von chronischen Venenkrankheiten in der städtischen und ländlichen Wohnbevölkerung. Phlebologie 2003;32:1-14.
25. Callam M. Prevalence of chronic leg ulceration and severe chronic venous disease in Western countries. Phlebology 1992;7(suppl):6-12.
26. Nicolaides AN, Cardiovascular Disease E, Research T, European Society of Vascular S, Organization TIASAC, International Union of A, et al. Investigation of chronic venous insufficiency: A consensus statement (France, March 5-9, 1997). Circulation 2000;102(20):E126-63.
27. The Venous Forum of the Royal Society of Medicine and Societas Phlebologica Scandinavia. The management of chronic venous disorders of the leg: an evidence-based report of an international task force. Phlebology 1999;14 Suppl 1:23-5.
28. Moffatt CJ, Doherty DC, Smithdale R, Franks PJ. Clinical predictors of leg ulcer healing. Br J Dermatol 2010;162(1):51-8.
29. Callam MJ, Harper DR, Dale JJ, Ruckley CV. Chronic ulcer of the leg: clinical history. Br Med J (Clin Res Ed) 1987;294(6584):1389-91.
30. Milic DJ, Zivic SS, Bogdanovic DC, Karanovic ND, Golubovic ZV. Risk factors related to the failure of venous leg ulcers to heal with compression treatment. J Vasc Surg 2009;49(5):1242-7.
31. Gohel MS, Barwell JR, Taylor M, Chant T, Foy C, Earnshaw JJ, et al. Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial. BMJ 2007;335(7610):83.
32. Nelson EA, Bell-Syer SE, Cullum NA. Compression for preventing recurrence of venous ulcers. Cochrane Database Syst Rev 2000(4):CD002303.
33. Van de Woude T, Rutten-van Mölken, MPMH. De kosten van veneuze aandoeningen in Nederland en de kosteneffectiviteit van therapeutische elastische kousen. Institute for Medical Technology Assessment, Erasmus Universiteit Rotterdam: Rapport 97.46. In.
34. Oostenbrink J, Rutten, FFH. Handleiding voor kostenonderzoek; methoden en richtprijzen voor economische evaluatie in de gezondheidszorg. iMTA/CvZ Amstelveen. 2000.
35. Hosoi Y, Zukowski A, Kakkos SK, Nicolaides AN. Ambulatory venous pressure measurements: new parameters derived from a mathematic hemodynamic model. J Vasc Surg 2002;36(1):137-42.
36. Recek C. Conception of the venous hemodynamics in the lower extremity. Angiology 2006;57(5):556-63.
37. Sansilvestri-Morel P, Nonotte I, Fournet-Bourguignon MP, Rupin A, Fabiani JN, Verbeuren TJ, et al. Abnormal deposition of extracellular matrix proteins by cultured smooth muscle cells from human varicose veins. J Vasc Res 1998;35(2):115-23.

38. Michiels C, Arnould T, Janssens D, Bajou K, Geron I, Remacle J. Interactions between endothelial cells and smooth muscle cells after their activation by hypoxia. A possible etiology for venous disease. Int Angiol 1996;15(2):124-30.
39. Yamada T, Tomita S, Mori M, Sasatomi E, Suenaga E, Itoh T. Increased mast cell infiltration in varicose veins of the lower limbs: a possible role in the development of varices. Surgery 1996;119(5):494-7.
40. Michiels C, Arnould T, Thibaut-Vercruyssen R, Bouaziz N, Janssens D, Remacle J. Perfused human saphenous veins for the study of the origin of varicose veins: role of the endothelium and of hypoxia. Int Angiol 1997;16(2):134-41.
41. Boisseau MR. Valvules veineuses des membres inferieurs: problemes hemodynamiques, biologiques et relations physiopathologiques. J Mal Vasc 1997;22(2):122-7.
42. Wentel TD, Neumann HA. Management of the postthrombotic syndrome: the Rotterdam approach. Semin Thromb Hemost 2006;32(8):814-21.
43. Uhl JF, Chahim M, Allaert FA. Static foot disorders: a major risk factor for chronic venous disease? Phlebology 2012;27(1):13-8.
44. Pannier F, Rabe E. The relevance of the natural history of varicose veins and refunded care. Phlebology 2012;27 Suppl 1:23-6.
45. Junger M, Steins A, Hahn M, Hafner HM. Microcirculatory dysfunction in chronic venous insufficiency (CVI). Microcirculation 2000;7(6 Pt 2):S3-12.
46. Belcaro G, Laurora G, Cesarone MR, De Sanctis MT, Incandela L. Microcirculation in high perfusion microangiopathy. J Cardiovasc Surg (Torino) 1995;36(4):393-8.
47. Neumann HAM. Measurement of microcirculation. In: Altmeyer, editor. Wound healing and skin physiology. Heidelberg: Springer Verlag Berlin; 1995. p. 115-26.
48. Grattenthaler C, Thoms KM, Kretschmer L. Paratibiale Fasziotomie beim Ulcus cruris postthromboticum mit dem Fasziotom nach Vollmar. J Dtsch Dermatol Ges 2007;5(12):1144-5.
49. Maessen-Visch MB, Koedam MI, Hamulyak K, Neumann HA. Atrophie blanche. Int J Dermatol 1999;38(3):161-72.
50. Eklof B. Classifying Venous Disease. In: Bergan JJ, editor. The Vein Book. San Diego: Elsevier Academic Press; 2007. p. 111-112.
51. Callam MJ, Ruckley CV, Harper DR, Dale JJ. Chronic ulceration of the leg: extent of the problem and provision of care. Br Med J (Clin Res Ed) 1985;290(6485):1855-6.
52. Coleridge-Smith P, Labropoulos N, Partsch H, Myers K, Nicolaides A, Cavezzi A. Duplex ultrasound investigation of the veins in chronic venous disease of the lower limbs–UIP consensus document. Part I. Basic principles. Vasa 2007;36(1):53-61.
53. Partsch H. Venendruckmessung in der phlebologie. Hautarzt 1981;32(2):53-8.
54. Cavezzi A, Labropoulos N, Partsch H, Ricci S, Caggiati A, Myers K, et al. Duplex ultrasound investigation of the veins in chronic venous disease of the lower limbs–UIP consensus document. Part II. Anatomy. Vasa 2007;36(1):62-71.
55. Nicolaides AN, Zukowski AJ. The value of dynamic venous pressure measurements. World J Surg 1986;10(6):919-24.
56. Nicolaides AN. Investigation of chronic venous insufficiency: A consensus statement (France, March 5-9, 1997). Circulation 2000;102(20):E126-63.
57. Porter JM, Moneta GL. Reporting standards in venous disease: an update. International Consensus Committee on Chronic Venous Disease. J Vasc Surg 1995;21(4):635-45.
58. Eklof B, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, Kistner RL, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg 2004;40(6):1248-52.

59. Reeder SWI, de Roos, K-P. Compressietherapie nog steeds de hoeksteen in de flebologie. Themabijlage Compressietherapie Elsevier November 2008:6-8.
60. Sulzberger M, Jack, W, Alfred, WK. Unna-Zinc gelatin boot. In: Dermatology Diagnosis and Treatment. Philadelphia: Saunders, W.B.; 1961. p. 185-7.
61. Callam MJ, Harper, DR , Dale, JJ, Ruckley, CV. Arterial disease in chronic leg ulceration: an underestimated hazard? Lothian and Forth Valley leg ulcer study. Br Med J (Clin Res Ed) 1987;294(6577):929-31.
62. Langendoen S, Veraart, JCJM, van Geest, AJ, Neumann, HAM. Compressietherapie. In: Neumann HAM, editor. Handboek flebologie; Diagnostiek en behandeling van veneuze ziekten. Houten: Prelum; 2011. p. 304-306.
63. Weiss RA, Duffy D. Clinical benefits of lightweight compression: reduction of venous-related symptoms by ready-to-wear lightweight gradient compression hosiery. Dermatol Surg 1999;25(9):701-4.
64. Scurr JH, Machin SJ, Bailey-King S, Mackie IJ, McDonald S, Smith PD. Frequency and prevention of symptomless deep-vein thrombosis in long-haul flights: a randomised trial. Lancet 2001;357(9267):1485-9.
65. Ali A, Caine MP, Snow BG. Graduated compression stockings: physiological and perceptual responses during and after exercise. J Sports Sci 2007;25(4):413-9.
66. Ibegbuna V, Delis K, Nicolaides AN. Effect of lightweight compression stockings on venous haemodynamics. Int Angiol 1997;16(3):185-8.
67. Amsler F, Willenberg T, Blattler W. In search of optimal compression therapy for venous leg ulcers: a meta-analysis of studies comparing diverse [corrected] bandages with specifically designed stockings. J Vasc Surg 2009;50(3):668-74.
68. Mosti G. Elastic stockings versus inelastic bandages for ulcer healing: a fair comparison? Phlebology 2012;27(1):1-4.

Symptoms and signs



Chapter 2

Effets des bas médicaux compressifs 10 à 20 mmHg (bas Proleg®) sur un groupe de choristes

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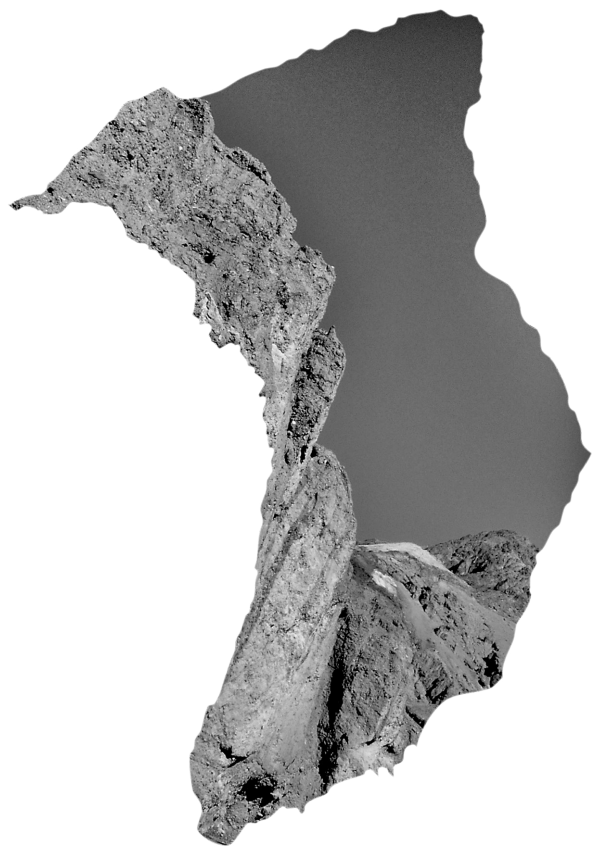
Phlébologie 2011; 64: 59-64



RÉSUMÉ

Introduction: Les bas médicaux compressifs 10 à 20 mmHg (BMC 20) diminuent la symptomatologie et certains signes physiques chez les patients soumis à une station debout prolongée. Ils affaiblissent l'intensité des myalgies après compétition sportive et ils réduisant le risque de thrombose lié aux vols sur longues distances.

Objectif: Evaluation de l'effet des bas Proleg® qui sont des BMC 20, sur les symptômes jambiers d'un groupe de choristes à l'issue d'une répétition en position debout prolongée.

Méthode: A l'occasion d'une répétition, un groupe de 58 choristes volontaires a été divisé en deux sous groupes : l'un ne portait pas de bas, l'autre portait des bas BMC Proleg. Avant la répétition, tous avaient rempli un questionnaire. Après répétition, l'effet était évalué par les réponses à un second questionnaire. Les participants répondaient aux questions en recourant à des scores visuels analogiques.

Résultats: Le port des BMC Proleg a généré une amélioration significative de la symptomatologie, surtout sur la lourdeur de jambe (P<0,01). Dans le même temps, on pouvait observer une diminution des crampes et de la sensation d'œdème, ainsi qu'une amélioration d'un syndrome de jambes sans repos. Cette dernière amélioration n'était cependant pas significative.

Conclusions: Les BMC 20 sont très efficaces sur la lourdeur jambière après station debout prolongée. Ils diminuent la symptomatologie du syndrome des jambes sans repos, de l'œdème et des crampes. Des recherches plus approfondies devraient permettre de déterminer si les heureux effets des BMC 20 se confirment sur de plus grandes séries de participants porteurs de tels bas et cela pendant des périodes plus prolongées.

SUMMARY

Introduction: Light medical compression stockings (pressure 10-20 mmHg – MCS 20) improve some objective and subjective symptoms in subjects with a standing profession, decrease the risk for thrombosis during long-haul flights, and improve muscular pain in sportsmen.

Objective: To evaluate the effect of Proleg® stockings (MCS 20) on leg symptoms in a choir after a standing rehearsal.

Materials and methods: We performed a case-control study, in which the cases wore MCS 20 during rehearsal, and the controls did not wear any stocking. Preceding rehearsal all the subjects filled in a questionnaire. After rehearsal the effect of the stockings was evaluated by a second questionnaire. A part of the questions was answered by visual analogue scores.

Results: Wearing MCS 20 leads to significant improvement of symptoms of leg fatigue ($P<0.01$). Improvement of symptoms of leg swelling, leg cramp, and restless legs was demonstrated, but this improvement was not significant.

Conclusions: MCS 20 are very effective in preventing symptoms of leg fatigue during sustained standing. Besides they reduce symptoms of restless legs, leg swelling, and leg cramp. Further research should show if standing for a longer period (>1 hour) improves the last mentioned symptoms significantly.

INTRODUCTION

Les bas médicaux compressifs (BMC) de 10 à 20 mmHg (classe I et II Française, BMC 20) améliorent les symptômes et certains signes physiques propres à l'insuffisance veineuse superficielle.[1-3] De longue date les BMC 20 ont prouvé leur efficacité sur la diminution de la sensation, de lourdeur, du mal-être des jambes et d'œdème jambier, et sur la douleur chez les patients soumis à une activité professionnelle en station debout prolongée.[4] On sait pas ailleurs que de tels bas "anti-thrombose" sont couramment prescrits à l'occasion de vols aériens à longues distance pour prévenir toute thrombose veineuse profonde.[5] Il est démontré également que les myalgies s'estompent chez les coureurs qui les portent.[6]

En réduisant partiellement les reflux, les BMC 20 agissent significativement sur l'hémodynamique veineuse: ils diminuent la fraction du volume résiduel et augmentent la fraction d'éjection.[7] Depuis quelques années ces bas sont disponibles de façon courante.

Les bas Proleg® (BMC 20) sont des bas élastiques Néerlandais vendus sans ordonnance et prescrits chez les personnes vouées à une activité professionnelle en position debout ou assise prolongé. Les recherches actuelles démontrent que les BMC 20 mmHg bloquent la filtration capillaire et surtout démontrent que chez le sujet en position assise, au repos, le rythme cardiaque est inférieur à celui que l'on observe chez le sujet ne portant pas de bas (données non publiées, Erasmus MC, www.proleg.nl).

OBJECTIF

L'objectif de l'étude est d'évaluer l'effet des BMC 20 sur la symptomatologie et sur certains signes physiques de sujets-membres d'une chorale lors des répétitions de longue durée. Chez de tels patients toute insuffisance veineuse risque de se décompenser en générant une sensation de fatigue, de lourdeur, ainsi que les crampes, la sensation d'œdème voire même un syndrome de jambes sans repos.[8]

Notre étude se propose de comparer l'effet des BMC 20 Proleg sur deux groupes: l'un portant des BMC 1, l'autre n'en portant pas.

MATÉRIELS ET MÉTHODES

Population d'étude

Le critère d'inclusion nécessaire et suffisant était la présence des sujets aux répétitions d'une chorale. Nous avons inclus 58 volontaires: 17 hommes et 41 femmes avec randomisation en un groupe porteurs de bas et un groupe sans BMC.

Concept de l'étude

Les 2 groupes: Le groupe porteur de bas était équipé de Proleg®, Medi Nederland, lors des répétitions debout. Le groupe témoin ne portait aucune compression. Les BMC Proleg ont une pression de 18-21 mmHg et comportent 57% d'élasthanne et 43% de polyamide.[9,10]

Le protocole de randomisation a été le suivant: à chaque participant il a été remis une enveloppe numéroté et scellée contenant soit une feuille vierge soit une feuille avec le dessin de deux chaussettes. Parmi les sujets qui ont participé deux fois à l'examen, ceux qui la première fois portaient des BMC n'en portaient pas la seconde fois et vice-versa.

Il a été rédigé deux questionnaires: le premier a été remis aux choristes avant la répétition, le second n'a été remis qu'après. Le premier questionnaire comportait les données relatives au sexe, à l'âge et à l'état général et il était complété par des questions relatives aux antécédents phlébologiques en particulier une éventuelle symptomatologie ayant pu survenir après une station debout prolongée (sensation de lourdeur, sensation d'œdème). Le second questionnaire contenait des questions sur le confort apporté pas les bas, sur la survenue éventuelle d'une sensation de lourdeur, sur un épisode de jambes sans repos après la répétition de la soirée.

Les BMC 20 Proleg ont été fournis gratuitement à tous les participants.

Tous devaient répondre aux questions concernant leurs antécédents médicaux, une symptomatologie phlébologique, les effets des BMC à l'aide d'une échelle visuelle analogique où la cote la plus basse était "aucune plainte", la cote la plus haute "nombreuses plaintes". Après examen des résultats le chercheur (S.W.I. Reeder) a déterminé le résultat des scores à une décimale près.

RÉSULTATS

Sur le plan général

28 choristes, dont 9 hommes, portaient les bas et 30 choristes, dont 5 hommes, n'en portaient pas. L'âge moyen des porteurs de bas était de 58,5 ans (fourchette: 27-70) et celui des témoins, sans bas, était de 54,0 ans (fourchette: 27-70).

Les porteurs de bas ont évalué leur état de santé comme étant d'un moyen de 7,0 (fourchette: 2,9-10,0), les témoins l'ont évalué à un niveau de 7,5 (fourchette: 2,7-10,0). Le Tableau 1 fait état des antécédents pathologiques connus des participants.

Tableau 1: Antécédents généraux des cas et des témoins.

	BMC 20 (n)	Témoins (n)	Signification
Hypertension	6	5	NS
Diabète sucré	0	0	NS
Hypercholestérolémie	3	2	NS
Maladies cardiovasculaires	5	2	NS
Troubles de la coagulation	1	0	NS
Autres (e.a. cancers, maladies de la peau)	5	7	NS
Total	20	14	NS

NS = non significatif.

Sur le plan d'antécédents phlébologiques

6 cas du groupe porteurs de bas avaient subi une intervention sur une jambe, contre 5 cas dans le groupe témoins. Parmi les 28 porteurs de bas: 22 n'en n'avaient jamais porté, 2 en portaient quotidiennement, 3 en portaient plus d'une fois pas semaine et 1 portait moins d'une fois pas semaine. En revanche parmi les 30 sujets témoins: 25 n'avaient jamais porté de BMC, 3 en portaient quotidiennement, 2 plus d'une fois pas semaine et 1 moins 1 fois par semaine (1 participant a répondu à la fois plus d'une fois par semaine et moins d'une fois par semaine).

Notons que les participants qui ne portaient pas quotidiennement de BMC, ne les portaient que dans des occasions où ils prévoyaient d'être en situation debout prolongée: 1 participant les portait lors de son activité professionnelle (Assistant de bloc opératoire) et 1 participant ne les portait qu'au cours de longues promenades. Les autres caractéristiques de groupe sont reprises dans le Tableau 2.

Tableau 2: Antécédents phlébologiques des cas et des témoins.

	BMC 20 (n)	Témoins (n)	Signification
Opération au niveau de la jambe	6	5	NS
Varices	9	5	NS
Traitement de varices	5	5	NS
Thrombose veineuse superficielle	1	0	NS
Thrombose veineuse profonde	1	1	NS
Erysipèle	0	0	NS
Ulcus crural	0	0	NS

NS = non significatif.

Résultats statistiques

Des tests t appariés ont analysé les données concernant la sensation d'œdème malléolaire ou jambier, de lourdeur des jambes, des crampes de jambe et de jambes sans repos avant et après la répétition. Seule la notion ressentie de lourdeur des jambes s'était améliorée de manière significative grâce au port de BMC 20 (P<0,01). Les autres manifestations pathologiques avaient certes diminué mais de manière non significative (Tableau 3).

Tableau 3: Moyenne des scores visuels analogiques de symptomatologie avant et après la position debout et les résultats des tests t.

	Moyenne avant la position debout	Moyenne après la position debout	Seuil de signification (P-valeur)
Oedème des jambes	1,588	1,424	0,784
Lourdeur des jambes	3,132	1,704	< 0,010*
Crampes des jambes	1,622	1,304	0,321
Jambes sans repos	1,969	1,500	0,274

*statistiquement significatif.

DISCUSSION

Eléments positifs de l'étude

- Le port de BMC 20 Proleg génère une amélioration significative au niveau de la sensation de lourdeur des jambes;
- Malgré la courte durée de l'expérimentation, les participants ont observé un effet significatif après le port de ces BMC;
- Certains participants nous ont avoué que, soulagé après la première répétition, ils avaient mis les BMC dans l'après-midi précédant la répétition et que la fin de soirée avait ainsi été rendue plus confortable. Nous pressentons qu'une station debout plus prolongée verrait se produire une amélioration significative des autres symptômes d'IVC.

Eléments négatifs de l'étude

Le nombre global de participants est relativement réduit, mais ils pratiquaient tous la même activité de piétinement.

Il n'a été procédé à aucun examen clinique des membres inférieures, ni même écho-Doppler, chez les participants ni avant ni après la répétition. En fait c'était impossible à mettre en œuvre, il eut fallu être nombreux à faire l'étude.

Le temps où les choristes ont constaté une amélioration, est trop court pour que l'on puisse affirmer que le port de BMC 20, reste sans effet positif sur les autres symptômes d'insuffisance veineuse superficielle.

De plus, 42% des participants se proposent de porter de nouveau des BMC lors d'une prochaine répétition (fourchette: 0-98%). Et si les participants devaient faire l'achat de BMC 20 dans les magasins au prix de 34,51 Euros par an en moyenne, 28% seulement en achèteraient (fourchette: 0-97%).

Notre recherche démontre que le port de BMC 20 Proleg génère une amélioration significative de la sensation de lourdeur des jambes. La symptomatologie de crampes, de jambes sans repos ou la sensation d'œdème n'est pas améliorée. Cette constatation va dans le sens des recherches antérieurement publiées selon lesquelles le port de BMC ayant un gradient de pression de 20-30 mmHg provoque une amélioration significative de l'œdème, de la lourdeur et de la douleur.[4] Par contre nous pensions qu'une pression de 10-20 mmHg est suffisante pour traiter une insuffisance veineuse chronique (IVC).[11] La différence de résultats semble pouvoir être expliquée du seul fait que la durée pendant laquelle le sujet a été en position debout prolongée a été courte: pas plus d'une heure.

Influence du sexe

Nous avons constaté que la plupart des participants étaient de sexe féminin alors que le chœur comporte un nombre sensiblement égal d'hommes et de femmes. Lors de l'inclusion, les femmes avaient été plus faciles à convaincre que les hommes. On a posé à certains hommes la question de savoir le pourquoi de leur refus. La plupart nous ont répondu qu'ils n'avaient aucune plainte à formuler et qu'ils refusaient de porter des BMC assimilables dans leur esprit à des sous-vêtements féminins. Il semble donc que l'idée règne dans la population moyenne, et le chœur en est un échantillon, qu'il est malséant pour un homme, en dehors de toute indication médicale, de porter des bas, objets d'usage essentiellement féminin. Nous n'avons aucune explication claire à donner à propos de ce comportement sinon que les femmes sollicitent plus volontiers un avis médicale pour raison cosmétique surtout s'il s'agit de varices, et l'on sait que les varices sont plus fréquentes chez la femme ce qui les encourage à porter préventivement des BMC ce qui n'est pas le cas des hommes.[8,12] Il est d'ailleurs étonnant de constater que les recherches antérieurs n'ont jamais étudié la notion de la différence de niveau d'observance thérapeutique entre hommes et femmes face au port de BMC.[13,14]

Nous en concluons avec toutes les réserves d'usage qu'il est plus difficile de convaincre un homme de porter des BMC qu'une femme mais que l'observance

thérapeutique devient identique chez les uns et les autres une fois qu'ils ont compris l'intérêt d'en porter.

Nombre faible de participants

Un point faible de notre étude est que le nombre de participants – 58 choristes – reste assez limité. De fait, nous avons vu moins de monde que prévu aux répétitions. Nous avions compté au départ sur le chiffre de 50 participants par répétition ce qui nous aurait fourni 100 cas au total pour deux répétions. Qui plus est peu d'hommes, comme nous l'avons déjà mentionné, ont accepté de se livrer à notre examen. Nous envisageons donc répéter notre étude en nous adressant à un chœur plus fourni ou en la réitérant à l'occasion d'une exécution publique. En effet lors d'une simple répétition de chœur n'est jamais au complet alors que le jour de l'exécution tous les choristes sont présents.

Coût du matériel

Notons qu'il y a discordance de probabilité entre les participants qui porteront de nouveau des BMC 20 (en moyenne 0,42) et les participants qui les achèteront (en moyenne 0,28). Une participante a jugé l'achat de tel bas trop coûteux alors qu'elle trouvait leur port plutôt agréable (sur échelle visuelle analogique elle a fait état d'une probabilité de 0,86 qu'elle les portera de nouveau). Un autre participant les portait préventivement dans la journée et avait beaucoup moins de plaintes à formuler en fin de journée. Il ne prévoyait donc pas l'achat de BMC (0,22). Ce fait nous a surpris car on s'attendrait à ce que les usagers achètent de tels bas dont il est amplement prouvé qu'ils sont efficaces. Si le port de BMC 20 était remboursé par l'assurance maladie Néerlandaise (ce qui n'est pas actuellement le cas) les ventes seraient probablement plus importantes.

Etude des questionnaires

Quelques remarques méritent d'être notées à la lumière du résultat de nos questionnaires.

– La petite taille: Trois participants se sont plaints d'une sensation de striction au niveau du genou. Pour les individus de petite taille – moins de 1,65 m – il existe des BMC plus courts. Or les bas utilisés pour notre expérimentation étaient destinés à des personnes de plus d'1,65 m. Il se peut qu'ils aient alors été mal tolérés. De plus, le porteur de bas croit devoir rabattre le bord supérieur du bas, ce qui induit une pression locale accrue et peut générer une sensation de striction;

- Une choriste a signalé une sensation de refroidissement des extrémités lorsqu'elle portait les BMC, mais nous n'avons pas d'explication claire à donner de ce fait. Un choriste nous a indiqué que ses bas retombaient spontanément après deux lessives;
- La symptomatologie typique des patients souffrant d'IVC est la sensation de lourdeur. Nous avons donc choisi délibérément un modèle issu de la vie réelle, à savoir un chœur qui reste debout pendant une heure, afin de voir si des BMC 20 mmHg arrivent à prévenir ce type de plainte.[2] Que ce symptôme caractéristique puisse être prévenu lors d'un piétinement d'une heure mérite toute notre attention. Malheureusement la sensation d'œdème n'a pu être évitée. La symptomatologie moins spécifique d'IVC comme les crampes de jambes, comme les jambes sans repos, n'a pas non plus été prévenue;
- Sur la base de notre étude le conseil de porter des BMC 20 pendant les périodes de station debout prolongée est justifié. On sait que l'ortho-stase accroît la filtration capillaire et qu'une telle filtration diminue significativement grâce au port de BMC 20.[15]

Conclusion

Les bas médicaux compressifs 10 à 20 mmHg (BMC 20) génèrent une amélioration significative de symptomatologie au niveau des jambes fatiguées par une station prolongée en orthostatisme. Dans le même temps, ils diminuent les effets des syndromes de jambes sans repos et limitent la sensation d'œdème jambier.

En dépit de la courte durée des épisodes de notre recherche expérimentale, les participants ont constaté un effet significatif dû au port de ces BMC 20. La question reste de savoir si cet heureux effet se confirmerait à la suite d'un protocole identique réalisé avec un nombre plus important de participants en position debout prolongée et sur un laps de temps plus grand.

D'autres recherches devraient aussi nous montrer si le port de BMC 20 préviennent et/ou retarderait le processus d'insuffisance veineuse.[15]

Remerciements

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RÉFÉRENCES

1. Shouler PJ, Runchman PC. Varicose veins: optimum compression after surgery and sclerotherapy. Ann R Coll Surg Engl 1989;71(6):402-4.
2. (CEN) ECfS. Non-active Medical Devices. Working Group 2 ENV 12718: European Prestandard 'Medical Compression Hosiery.' Brussels: CEN; 2001.
3. Partsch H, Flour M, Smith PC. Indications for compression therapy in venous and lymphatic disease consensus based on experimental data and scientific evidence. Under the auspices of the IUP. Int Angiol 2008;27(3):193-219.
4. Weiss RA, Duffy D. Clinical benefits of lightweight compression: reduction of venous-related symptoms by ready-to-wear lightweight gradient compression hosiery. Dermatol Surg 1999;25(9):701-4.
5. Scurr JH, Machin SJ, Bailey-King S, Mackie IJ, McDonald S, Smith PD. Frequency and prevention of symptomless deep-vein thrombosis in long-haul flights: a randomised trial. Lancet 2001;357(9267):1485-9.
6. Ali A, Caine MP, Snow BG. Graduated compression stockings: physiological and perceptual responses during and after exercise. J Sports Sci 2007;25(4):413-9.
7. Ibegbuna V, Delis K, Nicolaides AN. Effect of lightweight compression stockings on venous haemodynamics. Int Angiol 1997;16(3):185-8.
8. Nicolaides AN. Investigation of chronic venous insufficiency: A consensus statement (France, March 5-9, 1997). Circulation 2000;102(20):E126-63.
9. Rabe E, Partsch H, Junger M, Abel M, Achhammer I, Becker F, et al. Guidelines for clinical studies with compression devices in patients with venous disorders of the lower limb. Eur J Vasc Endovasc Surg 2008;35(4):494-500.
10. Partsch H, Clark M, Bassez S, Benigni JP, Becker F, Blazek V, et al. Measurement of lower leg compression in vivo: recommendations for the performance of measurements of interface pressure and stiffness: consensus statement. Dermatol Surg 2006;32(2):224-32; discussion 233.
11. Amsler F, Blattler W. Compression therapy for occupational leg symptoms and chronic venous disorders - a meta-analysis of randomised controlled trials. Eur J Vasc Endovasc Surg 2008;35(3):366-72.
12. O'Leary DP, Chester JF, Jones SM. Management of varicose veins according to reason for presentation. Ann R Coll Surg Engl 1996;78(3 (Pt 1)):214-6.
13. Palfreyman S, Michaels J. A systematic review of compression hosiery for uncomplicated varicose veins. Phlebology 2009;24:13-33.
14. Raju S, Hollis K, Neglen P. Use of compression stockings in chronic venous disease: patient compliance and efficacy. Ann Vasc Surg 2007;21(6):790-5.
15. van Geest AJ, Veraart JC, Nelemans P, Neumann HA. The effect of medical elastic compression stockings with different slope values on edema. Measurements underneath three different types of stockings. Dermatol Surg 2000;26(3):244-7.

Chapter 3

The effect of compression ulcer stockings on the capillary filtration rate and the formation of edema

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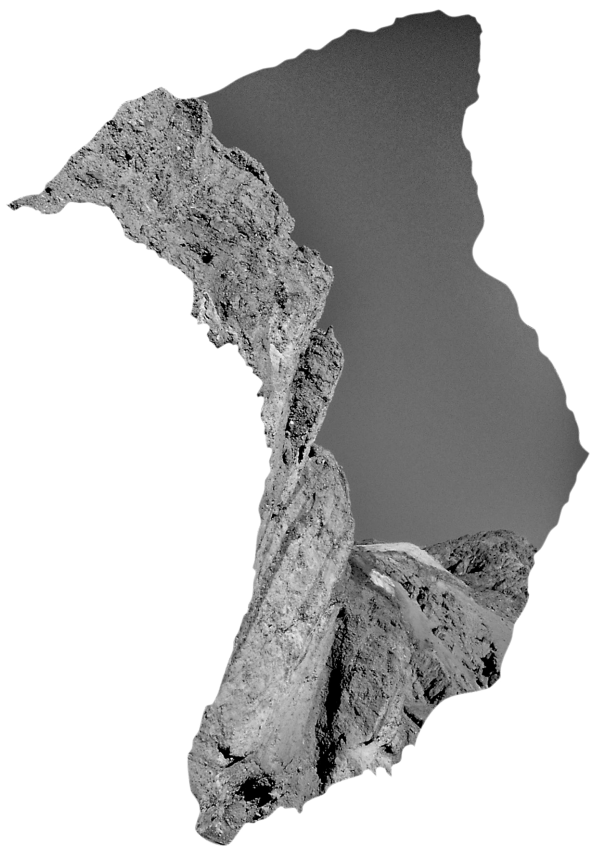
Phlebologie 2011; 40: 245–50



SUMMARY

Increased ambulatory venous pressure is the key feature of chronic venous insufficiency, and causes capillary leakage and venous edema. This capillary leakage can be measured with plethysmography and is called the capillary filtration rate (CFR).

Reduction of the CFR leads to less edema formation and improves the healing of venous ulcers.

Aim: To show that the use of compression ulcer stockings reduces the CFR.

Methods: The CFR of both legs of 17 patients, 6 with chronic venous insufficiency and 11 healthy subjects was measured with both (day and night) stockings, only the night stocking and without stockings.

Results: The reduction of the CFR was significant ($p < 0.0001$) for the total population in the group wearing 2 stockings versus 1 stocking (CFR = 0.019 vs. 0.084 ml/100ml/min), 1 stocking versus no stocking (CFR = 0.149 vs. 0.084 ml/100ml/min) and 2 stockings versus no stockings (CFR = 0.019 vs. 0.149 ml/100ml/min).

Conclusion: Compression ulcer stockings are highly effective in reducing CFR and thus reducing edema formation, which leads to improved healing of venous ulcers.

ZUSAMMENFASSUNG

Das zentrale Merkmal der chronischen venösen Insuffizienz ist ein erhöhter ambulanter Venendruck, welcher kapillare Leckagen und venöse Ödeme verursacht. Diese kapillare Leckage kann mit der Plethysmographie gemessen werden: die kapillare Filtrationsrate (CFR).

Reduktion der CFR führt zu weniger Ödembildung und verbessert die Heilung von venösen Ulzera.

Ziel: Ers sollte gezeigt werden, dass der Einsatz von Kompressionsstrümpfen die CFR reduziert.

Methode: Die CFR beider Beine von 17 Patienten, 6 mit chronisch venöser Insuffizienz und 11 gesunden Probanden wurde gemessen. Die Patienten unterschieden sich in drei Kategorien: Patienten mit zwei Kompressionsstrümpfen (Tag und Nacht), solche mit nur einem Nacht-Kompressionsstrumpf und Patienten ohne Kompressionsstrümpfe.

Ergebnis: Die Reduktion der CFR war signifikant (p<0,0001) für die Zweistrumpfkategorie im Vergleich zur Einstrumpfkategorie (CFR=0,019 zu 0,084 ml/100ml/min), die Einstrumpfkategorie im Vergelich zur Kategorie ohne Kompressionsstrümpfe (CFR=0,149 zu 0,084 ml/100ml/min) und in der 2-Kompressionsstrumpfkategorie im Vergleich zur Kategorie ohne Kompressionsstrümpfe (CFR=0,019 zu 0,149 ml/100ml/min).

Fazit: Kompressionsstrümpfe sind sehr wirksam zur Reduktion der CFR, wodurch die Ödembildung vermindert wird. Das führt zu einer besseren Heilung von venösen Ulzera.

INTRODUCTION

Increased ambulatory venous pressure is the key feature of chronic venous insufficiency. This leads to an increased pressure on the venular side of the capillary bed, which is followed by enlargement of the inter-endothelial space and leakage of fluid and proteins.

The increase of fluid in the intercellular space and the fibrin cuff, that is formed around capillaries due to inflammation causes imbalance of the filtration-diffusion equilibrium (the Starling equation).[1]

Clinical signs such as edema, lipodermatosclerosis, white atrophy and finally venous ulceration are the consequences of ambulatory venous hypertension and subsequent capillary dysfunction.[2,3] These clinical signs are described as the C in the CEAP-classification (Table 1).[4]

Table 1: CEAP-classification.

C0A/S	No visible or palpable signs of venous disease.
C1A/S	Telangiectasies or reticular veins.
C2A/S	Varicose veins; distinguished from reticular veins by a diameter of 3 mm or more.
C3A/S	Edema.
C4A/S	Changes in skin and subcutaneous tissue secondary to chronic venous disease (pigmentation, eczema, lipodermatosclerosis and white atrophy).
C5A/S	Healed venous ulcer
C6A/S	Active venous ulcer

A = asymptomatic
S = symptomatic

The rate at which fluid leakage occurs from the capillary bed is measured as the capillary filtration rate (CFR), which can be investigated by strain gauge plethysmography.[5-8]

Edema (C3) is the earliest outspoken clinical sign of a decompensated venous system. Reduction of edema improves the healing of venous leg ulcers.[9,10] Compression therapy improves healing rate in non-complicated venous leg ulcers and prevents recurrences.[11,12] All treatments for chronic venous ulcers are focused on edema reduction, which can be achieved by different forms of compression therapy.[11,13] The two most widely used compression methods are bandages (e.g. four layer system) and medical elastic compression stockings (MECS). For long-term compression therapy MECS will have the preference.

CEN (Commité Européen de Normalisation) divides the MECS into five classes with rising interface pressures (Table 2). Because class III MECS are more effective than CEN class II MECS in the reduction of edema and the use of MECS for the treatment of venous leg ulcers is at least as good as the treatment with compression bandages, the most efficient way to reduce edema and maintain this reduction, thus achieving a constant high interface pressure, is by the use of continuous elastic compression.[14-18]

Table 2: CEN classification of compression classes.

Compression class		Compression at the ankle[1]	
		hPa	mmHg[2]
Ccl A	light	13 to 19	10 to 14
Ccl I	mild	20 to 28	15 to 21
Ccl II	moderate	31 to 43	23 to 32
Ccl III	strong	45 to 61	34 to 46
Ccl IV	very strong	65 and higher	49 and higher

[1] The values indicate the compression exerted by the hosiery at a hypothetical cylindrical ankle.
[2] 1 mmHg=1,333 hPa.

Elastic compression at night is generally not recommended as impaired arterial influx can lead to severe complications such as ischemia and gangrene.[19] Low compression MECS, CEN class I, could offer the solution for continuous elastic compression in supine position, without impeding the arterial flow.[20]

Horakova and Partsch have already demonstrated the effectiveness of the treatment of venous leg ulcers with MECS.[15] However this has not yet led to the widespread use of MECS in the standard treatment of venous ulcers. Combination kits of different kinds of MECS have been introduced on the market. All these kits seem to be effective and safe in the treatment of venous leg ulcers.[21] Many systems combine a CEN class I MECS, which is applied day and night, with a CEN class II MECS, which is applied during the day. These systems warrant continuous compression. Because CEN class I and CEN class II MECS are applied over each other during the day, CEN class III pressures are achieved.[17] The combination of two MECS raises the hysteresis, which leads to even more edema reduction.[22]

The aim of this study was to prove the hypothesis that ulcer kit stockings reduce the CFR and thus edema formation. This reduction should be more obvious for the combination of the two MECS than for the single CEN class I MECS. The expected

reduction of the CFR and edema is expected to be even more in subjects wearing the class I and/or class I plus II MECS compared to subjects not wearing MECS.

MATERIAL AND METHODS

Study design

Open label study.

Patients

We included six patients diagnosed with CVI (median age 47 years, range 25-80, 2 males, 4 females) and 11 healthy controls (median age 27 years, range 21-55, all females). All patients were recruited from the department of dermatology at the Erasmus MC, Rotterdam, the Netherlands. The healthy controls, without clinical signs of CVI and abnormalities on duplex ultrasound, classified as C0a, were volunteers from our department.

The patients with CVI were classified as C3s in 2 patients, C4s in 3 patients and C6s in 1 patient, according to the CEAP classification.[4]

Equipment

The CFR was measured by the Filtrass Angio® plethysmograph (Domed GmbH, Uster, Switzerland) using a circular cuff that was applied to the upper leg. This type of nylon-cord plethysmograph uses electronic transducers with built-in calibration system. The plethysmograph measures the change in leg circumference and extrapolates these values to the change of volume.

The medical elastic compression stockings used, were the Mediven Ulcerkit® (supplied by Medi GmbH & Co. KG, Bayreuth, Germany), which consist of a class I stocking combined with a class II stocking.

Measurements

Patients and equipment were acclimatized at room temperature. A pressure of 70 mmHg was applied to the cuff on the upper leg, with the patient in supine position. This pressure was maintained during the entire measurement. Each patient was first measured wearing class I plus class II MECS then wearing only the CEN class I MECS and at last without MECS for a period of 10.5 minutes per measurement.

Both legs of each patient were measured simultaneously.

Data processing

The obtained graphs (Figure 1) were manually divided into a rapid filling phase from 0-4 minutes, and a CFR-phase from 4-10 minutes. The increase in volume of the leg in the CFR phase, measured in ml/100ml divided by 6 minutes, gives the

CFR for that leg, measured in ml/100ml/min, which equals the tangent of angle α (Figure 2).

All data were imported in Excel and were compared by the Wilcoxon signed rank test.

Figure 1: Screen result of plethysmographic examination, with on the x-axis time (min) and on the y-axis increase in volume of the leg (ml/100ml).

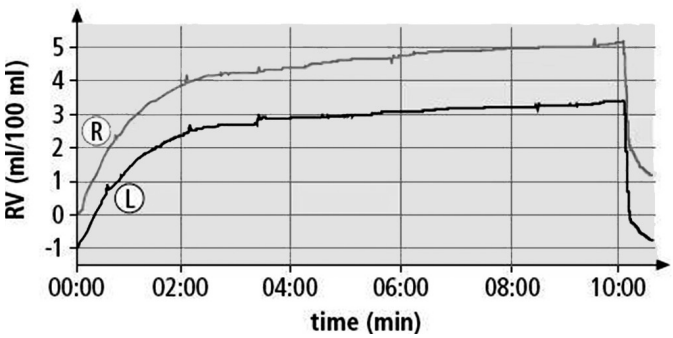
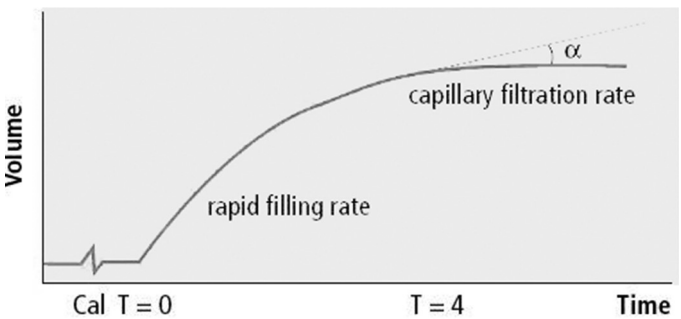


Figure 2: Plot of plethysmography; the calculation of the capillary filtration rate (CFR).



RESULTS

In total 101 CFR measurements of 34 legs were obtained.

1 measurement was lost because it was not saved (Table 3).

In the patient group wearing the class I and class II MECS the average CFR was 0.035 ml/100ml/min (range 0-0.09; SD 0.024). With one class I MECS the CFR was 0.098 ml/100ml/min (range 0.02-0.17; SD 0.036). Without MECS the CFR was 0.167 ml/100ml/min (range 0.06-0.27; SD 0.046).

Table 3: Datasheet of all the subjects.

Sex (male/female)	Age (years)	C (CEAP)	Investigated leg (right/left)	CFR class I + class II MECS (ml/100ml/min)	CFR class I MECS (ml/100ml/min)	CFR no MECS (ml/100ml/min)
Female	21	0a	L	0	0.07	0.13
Female	21	0a	R	0.01	0.08	0.13
Female	27	0a	L	0.01	0.07	0.15
Female	27	0a	R	0	0.11	0.15
Female	23	0a	L	0.01	0.09	0.15
Female	23	0a	R	0.03	0.13	0.17
Female	22	0a	L	0	0.06	-
Female	22	0a	R	0	0.09	0.13
Female	23	0a	L	0.02	0.04	0.13
Female	23	0a	R	0	0.07	0.14
Female	55	0a	L	0.01	0.05	0.12
Female	55	0a	R	0.03	0.02	0.1
Female	24	0a	L	0.03	0.11	0.18
Female	24	0a	R	0.04	0.13	0.21
Female	30	0a	L	0	0.1	0.13
Female	30	0a	R	0	0.07	0.17
Female	46	0a	L	0	0.07	0.11
Female	46	0a	R	0	0.04	0.17
Female	42	0a	L	0	0.1	0.11
Female	42	0a	R	0	0.05	0.15
Female	32	0a	L	0	0.09	0.11
Female	32	0a	R	0.02	0.06	0.1

Sex (male/female)	Age (years)	C (CEAP)	Investigated leg (right/left)	CFR class I + class II MECS (ml/100ml/min)	CFR class I MECS (ml/100ml/min)	CFR no MECS (ml/100ml/min)
Female	78	4s	L	0.02	0.15	0.22
Female	78	4s	R	0.07	0.17	0.25
Female	80	6s	L	0.04	0.08	0.23
Female	80	6s	R	0	0.14	0.27
Female	46	3s	L	0	0.04	0.06
Female	46	3s	R	0	0.05	0.12
Female	48	4s	L	0.05	0.1	0.18
Female	48	4s	R	0.02	0.1	0.18
Male	33	4	L	0.02	0.1	0.12
Male	33	4	R	0.09	0.07	0.14
Male	25	3	L	0.03	0.04	0.12
Male	25	3	R	0.08	0.13	0.11

In the control group the average CFR with both MECS was 0.010 ml/100ml/min (range 0-0.04; SD 0.013). With one class I MECS the CFR was 0.077 ml/100ml/min (range 0.02-0,13; SD 0.031). Without MECS the CFR was 0.140 ml/100ml/min (range 0.1-0.21; SD 0.028).

In all individuals the average CFR with both MECS was 0.019 ml/100ml/min (range 0-0.08; SD 0.031). With one class I MECS the CFR was 0.084 ml/100ml/min (range 0.04-0.17; SD 0.044). Without MECS the CFR was 0.149 ml/100ml/min (range 0.06-0.27; SD 0.065).

Comparing the patient group and the control group, the same difference between both, one and no MECS were found. The CFR values found in patients are consistently higher than in controls (Table 4).

A statistically relevant difference ($p<0.0001$) between the CFR in all three groups was found for the whole study population (Table 4 and 5):

1. CFR class I plus class II MECS vs. class I MECS: 0.020 vs. 0.085 ml/100ml/min;
2. CFR class I MECS vs. no MECS: 0.084 vs 0.149 ml/100ml/min;
3. CFR class I plus class II MECS vs. no MECS 0.020 vs. 0.149 ml/100ml/min.

Table 4: Mean CFR (ml/100ml/min).

	Class I + class II MECS	**Class I MECS**	**No MECS**	**p-value**
Patients	0.035	0.098	0.167	< 0.0001
Controls	0.010	0.077	0.140	< 0.0001
All subjects	0.019	0.084	0.149	< 0.0001

Table 5: Wilcoxon signed rank test.

MECS	**Mean CFR (ml/100ml/min)**	**Z-score**	**P-value**
No vs. class I	0.149 vs. 0.084	-5.074	< 0.0001
Class I vs. class I + class II	0.085 vs. 0.019	-4.759	< 0.0001
No vs. class I + class II	0.150 vs. 0.019	-4.941	< 0.0001

DISCUSSION

This study has shown a significant reduction of the CFR by using the Mediven Ulcerkit® compression system. Although the hypothetic treatment of venous leg ulcers is elimination of venous reflux or stasis and thus normalization of the ambulatory venous pressure, this ideal situation often can not be achieved.

The primary principle of treating venous leg ulcers consists of the reduction of edema, which can be achieved by rest in bed or by compression therapy.

Compression therapy has two major effects on the leg. The reduction of the venous volume leads to the increase in effectiveness of the calf-muscle pump and amelioration of venous drainage. The interface pressure, which influences the Starling equilibrium, results in edema reduction and healing of the venous leg ulcer.

We have shown that the CFR is reduced significantly (0.098 vs. 0.167 ml/100ml/min, $p<0.0001$) when a CEN class I MECS is worn day and night. Thus less edema is formed and ulcer healing can progress. The low physiological pressure gradient between the leg and the right atrium in supine position of only a couple of mmHg will rise by wearing the CEN class I under-stocking with a pressure at the ankle of around 18 mmHg. This will increase venous return in supine position.

The danger of impeding the arterial influx to the leg in supine position is almost negligible because the ankle-arm index for a person with systolic blood pressure of 120 mmHg should be lower than (20/120 =) 0.17 to cause arterial blockage.

By using a system consisting of two MECS, that is a class I combined with a class II MECS, class III pressure values are achieved and a higher stiffness is formed, which allows a higher working pressure. Besides it is much easier to put on these two MECS separately in stead of one CEN class III MECS with the same stiffness. This should improve the patients' compliance.

The difference in the CFR observed in patients and controls is most probably caused by the increased age and ambulatory venous pressure and thus increased pressure in the capillary bed of the ankle and foot in CVI patients. This difference tends to be significant, but the uneven distribution and the number of patients do not allow a definite statement. In the future a larger and more equal distribution of the study groups is desired to compare the CFR.

In our study we have not solely used patients with C5 or C6 CEAP-classification because our primary goal was to show the reduction of the CFR primarily by using MECS specially designed for treating venous leg ulcers.

Conclusion

CFR is a measurement for the capillary fluid leakage and thus for edema formation in the human leg.

In this study we have found a significant reduction of the CFR for the CEN class I and class II MECS and the CEN class I MECS compared to each other and compared to no MECS.

We have proved the effectiveness of an ulcer-kit system (in this study the Mediven Ulcerkit®) in reducing edema. The 24 hours-reduction of the CFR will lead to less edema formation.

We have also shown that the reduction of the CFR is equal for the patients and for the controls, although the CFR remains higher in patients.

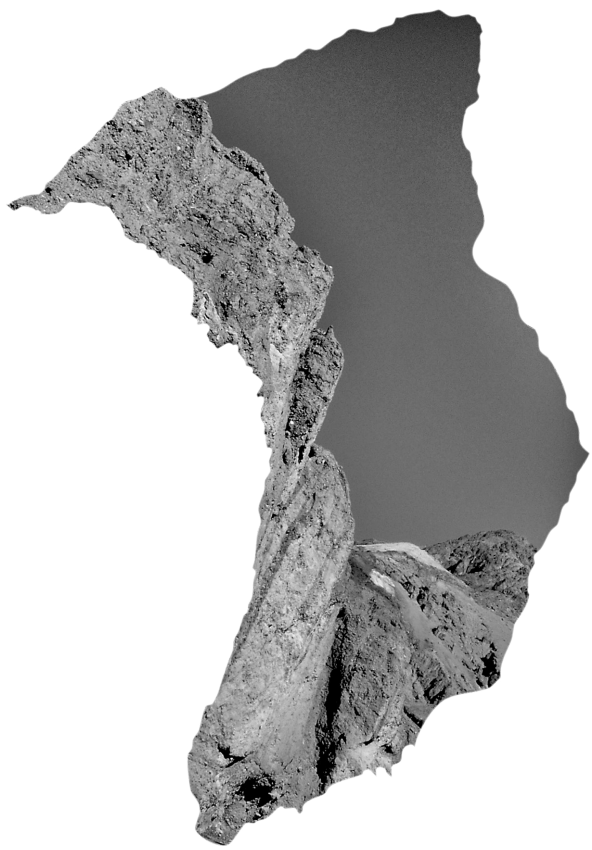
As a consequence of our positive results we want to propagate the use of MECS/ ulcerkit systems in the treatment of venous leg ulcers.

REFERENCES

1. Browse NL, Burnand KG. The cause of venous ulceration. Lancet 1982;2(8292):243-5.
2. Junger M, Hahn U, Bort S, Klyscz T, Hahn M, Rassner G. [Significance of cutaneous microangiopathy for the pathogenesis of dermatitis in venous congestion due to chronic venous insufficiency]. Wien Med Wochenschr 1994;144(10-11):206-10.
3. Leu HJ. [The current concept of the pathogenesis of trophic skin lesions in chronic venous insufficiency from the morphologic viewpoint]. Wien Med Wochenschr 1994;144(10-11):199-200.
4. Eklof B, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, Kistner RL, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg 2004;40(6):1248-52.
5. Nicolaides AN. Investigation of chronic venous insufficiency: A consensus statement (France, March 5-9, 1997). Circulation 2000;102(20):E126-63.
6. Gamble J, Gartside IB, Christ F. A reassessment of mercury in silastic strain gauge plethysmography for microvascular permeability assessment in man. J Physiol 1993;464:407-22.
7. van Geest AJ, Veraart JCJM, Kitslaar PJEHM, Neumann HAM. Capillary filtration rate, before and after stripping of the greater saphenous vein, measured with air-plethysmography. Phlebology 1998;13:50-52.
8. Mostbeck A. [Methodological aspects of the determination of the capillary filtrate in the extremities. Simultaneous measurement of leg and regional blood volume by plethysmography and Tc-99m-labeled erythrocytes]. Vasa 1986;15(3):233-40.
9. van Geest AJ, Veraart JC, Nelemans P, Neumann HA. The effect of medical elastic compression stockings with different slope values on edema. Measurements underneath three different types of stockings. Dermatol Surg 2000;26(3):244-7.
10. Stacey MC, Vandongen Y, Trengove N, Hoskin S, Thompson P, Pearce C. The effectiveness of compression in healing of chronic venous leg ulcers. Phlebology 1995;suppl. I:929-931.
11. Mayberry JC, Moneta GL, Taylor LM, Jr., Porter JM. Fifteen-year results of ambulatory compression therapy for chronic venous ulcers. Surgery 1991;109(5):575-81.
12. Nelson EA, Bell-Syer SEM, Cullum NA. Compression for preventing recurrence of venous ulcers. Cochrane Database Syst Rev 2000(4):CD002303.
13. Erickson CA, Lanza DJ, Karp DL, Edwards JW, Seabrook GR, Cambria RA, et al. Healing of venous ulcers in an ambulatory care program: the roles of chronic venous insufficiency and patient compliance. J Vasc Surg 1995;22(5):629-36.
14. van Geest AJ, Veraart JCJM, Nelemans P, Neumann HAM. The effect of medical elastic compression stockings with different slope values on edema. Measurements underneath three different types of stockings. Dermatol Surg 2000;26(3):244-7.
15. Partsch H, Horakova MA. [Compression stockings in treatment of lower leg venous ulcer]. Wien Med Wochenschr 1994;144(10-11):242-9.
16. Blair SD, Wright DD, Backhouse CM, Riddle E, McCollum CN. Sustained compression and healing of chronic venous ulcers. Bmj 1988;297(6657):1159-61.
17. Veraart JCJM, Neumann HAM. Interface pressure underneath elastic and non-elastic bandages. Phlebology 1996;suppl. I:2-5.
18. Veraart JCJM, Neumann HAM. Effects of medical elastic compression stockings on interface pressure and edema prevention. Dermatol Surg 1996;22(10):867-71.

19. Callam MJ, Ruckley CV, Dale JJ, Harper DR. Hazards of compression treatment of the leg: an estimate from Scottish surgeons. Br Med J (Clin Res Ed) 1987;295(6610):1382.
20. Ibegbuna V, Delis K, Nicolaides AN. Effect of lightweight compression stockings on venous haemodynamics. Int Angiol 1997;16(3):185-8.
21. Amsler F, Willenberg T, Blattler W. In search of optimal compression therapy for venous leg ulcers: a meta-analysis of studies comparing diverse [corrected] bandages with specifically designed stockings. J Vasc Surg 2009;50(3):668-74.
22. Junger M, Wollina U, Kohnen R, Rabe E. Efficacy and tolerability of an ulcer compression stocking for therapy of chronic venous ulcer compared with a below-knee compression bandage: results from a prospective, randomized, multicentre trial. Curr Med Res Opin 2004;20(10):1613-23.

Diagnostics



Chapter 4

Expert consensus document on direct ambulatory venous pressure measurement

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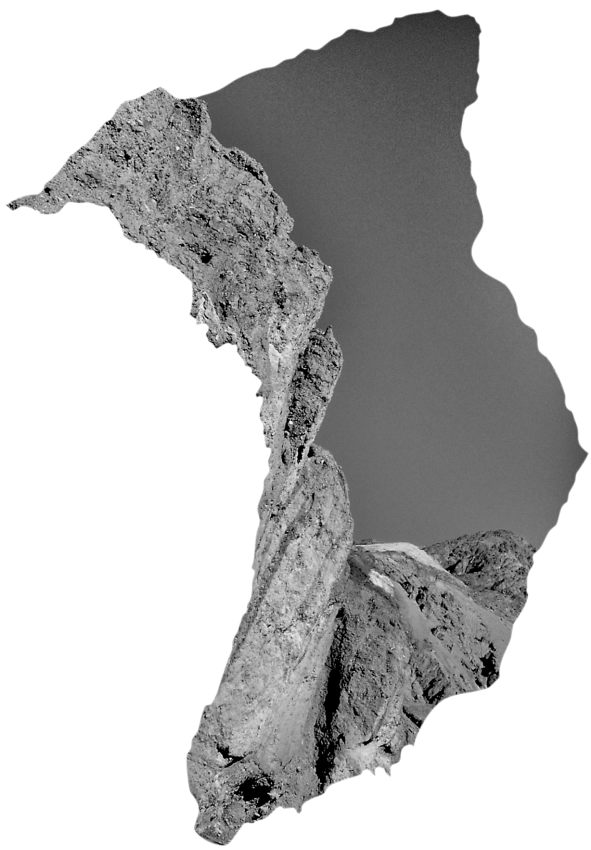


ABSTRACT

Introduction: Raised ambulatory venous pressure (AVP) is the hallmark of chronic venous disease (CVD). (Direct) AVP measurement is the "gold standard" for objectifying venous hypertension. However AVP measurement has never been fully standardised.

Methodology: Three of the authors (S.W.I.R., O.W. and H.A.M.N.) invited experts on AVP measurement to discuss this investigation and reach consensus on AVP measurement. After committing to participate to the consensus meeting during the IUP World Congress in Monaco 2009, each expert received statements and questions concerning the pitfalls in standardising AVP measurement by email. They also received the protocol of AVP measurement of the Department of Dermatology in Rotterdam, the Netherlands. From here, this protocol was revised.

Statements and questions: A list of questions was sent out beforehand based on which several proposals for future evaluations of venous pressure curves were formulated at the meeting.

Technique of AVP measurement revised: The most important change on the previous non-standardised protocol on AVP measurement is that AVP measurement should be performed on a treadmill at speed of 2 km/h and with an elevation of 8°. If no treadmill is available tiptoe or knee bending exercises may be used.

Interpretation of AVP measurement revised: It is proposed to define AVP as mean ambulatory venous pressure (systolic venous pressure + 2 x diastolic venous pressure)/ 3. Refill time (RT) should not be routinely used as outcome measure. The conclusion of AVP measurement may be: normal (no venous hypertension), intermediate ambulatory venous hypertension or severe venous hypertension. The related pressure ranges obtained by the proposed mode of evaluation should be validated in future studies.

Conclusions: AVP measurement is the "gold standard" to quantify the severity of hemodynamic abnormality of CVD in the lower extremity. Several proposals concerning a standardized evaluation of venous pressure measurements have been formulated.

INTRODUCTION

Venous hypertension during walking, that is increased ambulatory venous pressure (AVP), is the major characteristic of disturbed venous hemodynamics. Determining the exact AVP is therefore very valuable in expressing the severity of chronic venous disease (CVD).[1] For this purpose, direct AVP measurement is the "gold standard" up till now.[2-6]

At the beginning of the twentieth century, Von Recklinghausen (1906) was already able to measure venous pressure.[7] He was followed by Roulson (1911) and Beecher (1936).[8] The latter two introduced compression of the superficial venous system to distinguish superficial from deep venous insufficiency.

The technique of AVP measurement that is still used was developed in 1925 by Barber and Shatara.[9] McPheeters and Rice as well as Pollack and Wood demonstrated that venous pressure drops during walking.[10,11] Seiro showed that the venous pressure drop in patients with varicose veins is lower compared to healthy individuals.[12] Höjensgard and Stürup as well as Arnoldi proved the existence of a similarity between superficial and deep venous pressure.[13,14] A correlation between the calf muscle pump function and venous pressure exists.[5]

Although AVP measurement is considered to be the "gold standard" functional test for quantifying venous hypertension, it has largely been replaced by duplex ultrasound (DUS). However, DUS is not a real functional test that is able to give information on the quality of the venous pump expressed as pressure decrease in ambulatory condition. In daily practice DUS has become the gold diagnostic tool for all routine therapy decisions in phlebology, but AVP measurement still has its diagnostic importance and supplementary value in complex cases of CVD.

Despite the use of AVP measurement for almost a century it has never been fully standardised.[15] The following document results from a consensus meeting of experts on AVP measurement during the UIP World Congress in Monaco, August-September 2009. The aims were to agree about the technique, interpretation of the results and indications, which may lead to standardisation of AVP measurement.

METHODOLOGY

A few months before the UIP World Congress in Monaco, August-September 2009, S.W.I.R., O.W. and H.A.M.N. invited six experts on AVP measurement to discuss the pitfalls, whereby standardisation on AVP measurement was not fully reached so far. All invited experts agreed on participating in this project. Next, S.W.I.R. sent all the experts the protocol that describes the way in which AVP measurement is performed in Rotterdam, the Netherlands. Together with the protocol five statements and questions on AVP measurement were sent. These statements and questions

were formulated by S.W.I.R., O.W. and H.A.M.N. and included the main bottlenecks in standardising AVP measurement.

During the meeting in Monaco the experts discussed the protocol statements and the answers to the questions. After the meeting the minutes were sent to all experts and their comments were processed in order to come to this final consensus document.

First, the statements and questions will be outlined. Subsequently, the standardised protocol on AVP measurement is reported.

QUESTIONS AND STATEMENTS

1. AVP measurement is an important functional parameter to characterize the severity of insufficiency of the venous pump, i.e. CVD.
   - Revised statement: AVP measurement is the "gold standard" for assessing the severity of hemodynamic abnormality of CVD in the lower extremities.
2. Technique of AVP measurement: We use tiptoe and knee bend exercises, but these exercises do not mimic walking. During tiptoe movements the gastrocnemius veins do not empty.[16] Should a treadmill be used to copy a normal walking pattern? If we decide to do so, what should be the walking speed and for how long should the patient do this exercise?
   - Revised statements: The only way to get correct information is to mimic the normal walking pattern. This can be reached by performing the investigation on a treadmill;
   - The ideal speed to perform AVP measurement on a treadmill is 1 Hz (= 1 step/second) but the speed using the treadmill is expressed in km/h. 4 km/h would correspond to normal walking, but not all patients will be able to reach this speed. Therefore we recommend 2 km/h with an elevation of 8˚;
   - Walking should be continued at the same speed until a stable phase of the pressure curve is reached;
   - Only if a treadmill is not available, alternatively tiptoe or knee-bending exercises may be used.
3. Interpretation of AVP measurement: Until now, we determined AVP as the deepest point of pressure after 10 tiptoe/knee bend exercises.
   - A significant relation between the deepest point of pressure after 10 exercises and the clinical score of CEAP has been shown;[17]
   - Revised statement: It has to be questioned if this deepest pressure alone is the best representative value;

- Systolic pressure peaks during walking exceeding the standing pressure are an important parameter characterising severe reflux and/ or obstruction. Both, maximal systolic pressure and minimal diastolic pressure are taken into account if the mean venous pressure during walking is given.(3) In analogy to the mean arterial pressure (MAP) as used in cardiovascular physiology mean venous pressure is defined by the formula: (systolic pressure + 2x diastolic pressure)/ 3 (Formula 1).[18]

Formula 1: Formula of mean arterial pressure calculation.
Mean arterial pressure = (systolic blood pressure + 2 x diastolic blood pressure)/ 3

4. Interpretation of AVP measurement: AVP is normal if less than one half of standing venous pressure (SVP) is reached during exercise.
   - Revised statement: Instead of giving exact values of AVP it might be better to draw one of the following conclusions for the individual patient: normal, intermediate venous hypertension or severe venous hypertension (Table 1);
   - It has been shown that there is a correlation between the clinical severity and the range of ambulatory venous hypertension for the CEAP classes C3-C6 whereas patients with uncomplicated varicose veins usually present with no or mild ambulatory venous hypertension;[19]
   - Interpretation of AVP measurement: If venous refill time (RT) is used, 90% of venous refill time (RT90) should be used;[19]
   - Revised statement: Although the relation between RT90 and the clinical score of CEAP is significant, RT is dependent on several factors, i.e. temperature, arterial flow and vein diameter, and should therefore not be used as a primary outcome for AVP measurement,[17] even though no significant influence of ambient temperature within normal limits has been demonstrated.[20]

Table 1: Tentative interpretation of mean AVP values in percentages. AVP is expressed as a percentage of SVP to adjust for patient's height.

	AVP (%)
Normal	10 – 30
Intermediate venous hypertension	31 – 45
Severe venous hypertension	> 45

(These values for the proposed mean venous pressure have not yet been validated in clinical series).

TECHNIQUE OF AVP MEASUREMENT REVISED

The present report concentrates entirely on measuring venous pressure in a dorsal foot vein. One of the patients' feet is placed in a bucket filled with warm water. This is done for about 5 minutes to warm the foot and consequently cause vasodilatation of the foot veins. A (22 Gauge) syringe is inserted in a dorsal vein of the foot with the patient in sitting position with both legs depending. When the syringe is placed in the right position, it can be fixed like an infusion needle. Subsequently, a three-way tap (single (electronic pressure) transducer in combination with the connecting tube) is placed and the system is connected to a 0.9% saline infusion. Small amounts of heparin may be used to prevent clotting in the needle. The pressure transducer should be kept at the same height as the tip of the needle (zero calibration). The electronic pressure transducer is connected to the recorder, which is connected to a computer. After flushing possible air bubbles out of the system, the system should be calibrated for pressure increase with the patient in lying position, with the legs horizontal and the upper body at an angle of about 30° to the legs. In this position the puncture site is at the same height as the right atrium. When the three-way tap is switched, the pressure transducer is in direct communication with the superficial veins and the system can be calibrated for the zero level. The three-way tap is switched again to prevent blood to flow into the connection tube and the transducer. The patient is then asked to move the foot, by means of moving the toes towards the nose and back. This procedure is done to demonstrate that the system is in working order. After this measurement, the patient is helped in standing position on the treadmill (which has an 8° elevation) and standing venous pressure (SVP) can be recorded. The patient will walk at a pace of 2 km/h until the venous pressure has reached a plateau phase (= AVP). The treadmill is then stopped and the patient will stand still until SVP has been reached (= RT). Then again, the patient is disconnected from the recorder and is asked to lie down on the bed. After reconnecting the patient, zero calibration takes place and the patient is asked to move the foot a few times to check that the system is still in working order.

INTERPRETATION OF AVP MEASUREMENT REVISED

In supine position venous pressure should be between 5 and 10 mmHg, which is mainly determined by the exact position of the needle in relation to the pressure in the right atrium. In upright position venous pressure in a foot vein is defined by the hydrostatic pressure. SVP is therefore dependent on the person's height. This value will be between 80 and 100 mmHg in an adult of average height.

Determination of AVP has always been a point of discussion, since the introduction of AVP measurement.[15] Usually the deepest point of the pressure curve (= plateau phase) was taken as the deciding parameter (Figure 1).[17] In order to respect also the systolic pressure peaks the group suggests to define AVP as (systolic pressure + 2 x diastolic pressure)/ 3. In case a treadmill is used, the subject will walk with a speed of 1 Hz during a maximum period of 30 seconds.

We suggest not using RT or RT90 for routine practice. AVP remains the primary outcome. If RT90 is, for some reason, taken into account as secondary outcome it should be longer than 25 seconds to be normal.

The conclusion of AVP measurement may be: normal (no venous hypertension), intermediate venous hypertension or severe venous hypertension. Possible cut-off values are shown in Table 1. It needs to be considered that the proposed way to define AVP will shift up the pressure values in comparison to taking the minimal diastolic values (Figures 1-3, Table 2). Therefore, the values given in Table I need to be validated by future studies including clinical and duplex outcome (CEAP).

It needs to be stressed that it is problematic to reduce the information contained in a pressure curve to one single numeric value (AVP). An interobserver variation study has shown the large systematic and random errors in estimating AVP from AVP measurement graphs, especially in extraordinary cases (Figures 3A and 3B).[15] Experienced investigators may also look for the speed of pressure fall and on a possible pressure increase after exercise, pointing to a proximal venous obstruction. In general reflux, obstruction or both can not be differentiated by measuring peripheral venous pressure. The same is also true for a differentiation between superficial or deep venous pathology.

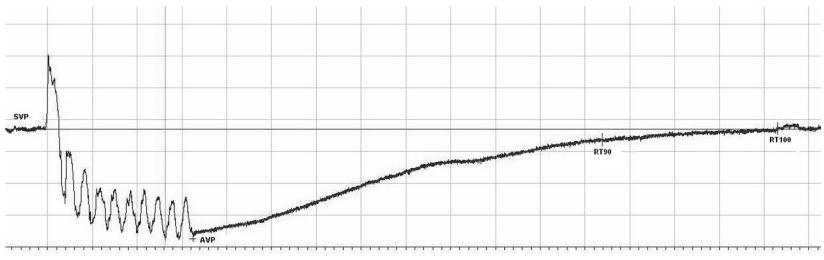
Table 2: Legends of Figures 1 to 3. This Table shows the outcome differences between the various ways of interpretation. The diastolic venous pressure is a misleading parameter to characterize AVP.

	Figure 1	**Figure 2**	**Figure 3A**	**Figure 3B**
SVP (mmHg)	80	106	100	100
Diastolic venous pressure (mmHg)	11	51	15	20
Systolic venous pressure (mmHg)	40	145	75	130
AVP (mmHg)*	21	82	35	57
Interpretation**	normal	severe	intermediate	severe

* AVP = (systolic blood pressure + 2 x diastolic blood pressure)/ 3.
** Interpretation according to Table 1.

A limitation of AVP measurement is that the patient should be capable of walking. In case a patient is not able to walk but is able to stand upright, it is possible to use an external foot pump or tiptoe exercise. However, this alternative of measuring AVP has never been validated with regard to the treadmill.

Figure 1: AVP measurement and definitions (normal individual).



X-axis: time (seconds).
Y-axis: venous pressure (mmHg).
SVP = standing venous pressure.
AVP = ambulatory venous pressure, as used up till now (deepest point of pressure drop).
RT90 = venous refill time to 90% of SVP.
RT = venous refill time to SVP.

Figure 2: AVP curve in a patient with a severe post-thrombotic syndrome. AVP defined as (systolic pressure + 2 x diastolic pressure)/ 3 = 98.

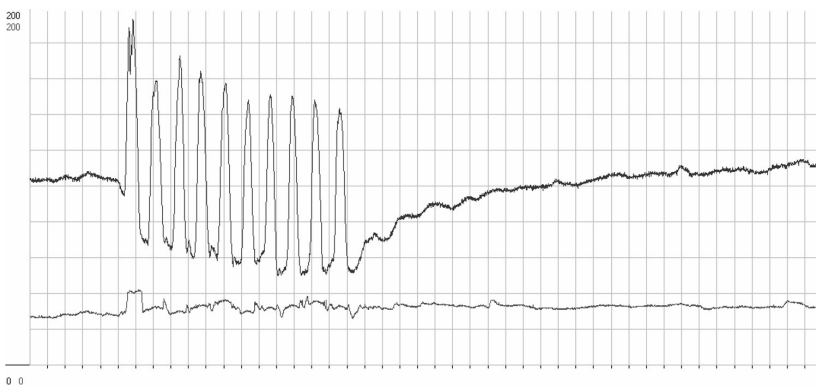
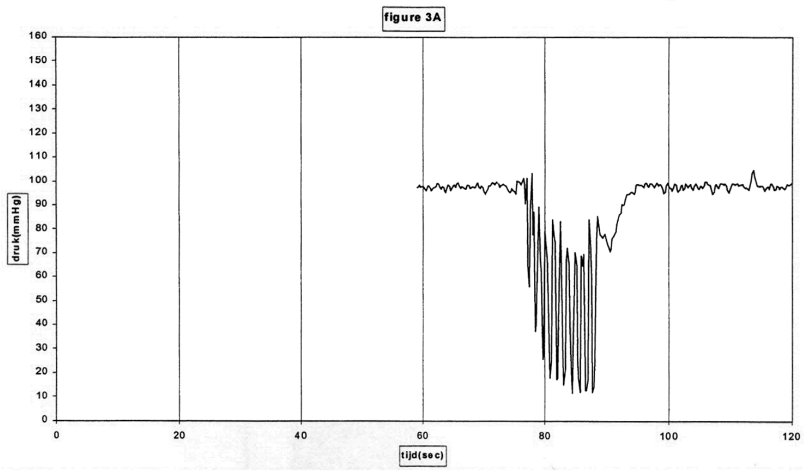
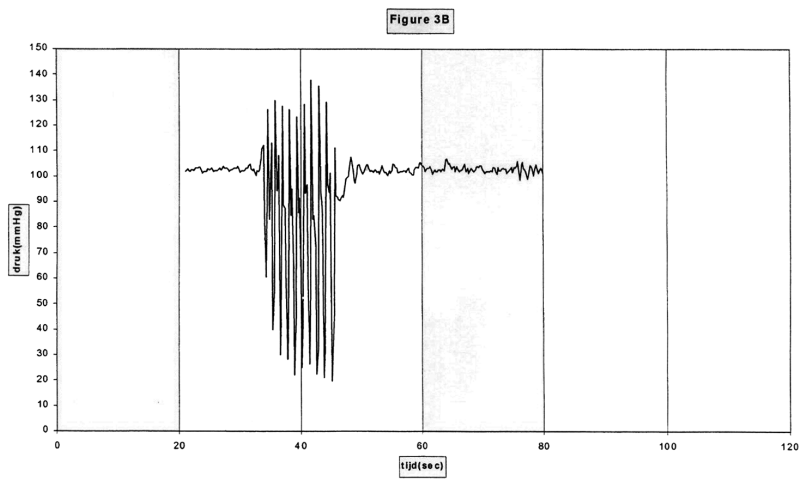


Figure 3A and **3B:** These graphs from patients with severe CVD showed a high interobserver variability in a previous study.[15] The deepest pressure readings (diastolic pressures) are 15 mmHg (Figure 3A) and 20 mmHg (Figure 3B), simulating "normal venous function". By calculating the mean venous pressure also the high systolic pressure peaks (caused by venous reflux) are taken into consideration (values see Table 2) putting both cases into the category of an intermediate (3A) or severe (3B) category of venous hypertension (Table 1).





INDICATIONS FOR AVP MEASUREMENT

Although AVP measurement is the "gold standard" functional test in patients with CVD, in daily practice it has largely been replaced by DUS. However AVP measurement is still very useful for the following indications:

- To support diagnosis. For example, a patient with clinical signs (and symptoms) of CVD without abnormalities on DUS;
- (Congenital) venous anomalies, i.e. vena cava anomaly, to objectify venous hypertension;
- To select and follow-up therapeutic interventions. For example, in case of venous (partial) venous obstruction, i.e. venous anomaly or after a deep vein thrombosis, venous desobstruction (and stenting) may be indicated in patients with venous hypertension. The therapeutic effect after the intervention can also be monitored by AVP measurement. After the intervention AVP should be improved;
- To follow up of spontaneous course. For example, patients who have had a deep vein thrombosis. AVP measurement may be performed to assess the indication for medical elastic compression stockings, which is ambulatory venous hypertension;
- To assess the influence of interventions in the acute experiment (e.g. body position, compression, temperature).

Conclusion

AVP measurement is the "gold standard" for assessing the severity of hemodynamic abnormality of CVD in the lower extremity. Since AVP measurement has not been standardised so far, we revised AVP measurement and made some proposals how to evaluate venous pressure curves in the future.

AVP measurement will take place on a treadmill with standardised speed. Final readings are based on the mean venous pressure that is defined by the formula: (systolic pressure + 2x diastolic pressure)/ 3. After calculating the mean venous pressure, patients may be categorised into one out of three categories [normal (AVP 10-30 mmHg), intermediate venous hypertension (31-45 mmHg), severe venous hypertension (AVP >45 mmHg)].

Acknowledgements

Figures 3A and 3B are reproduced with permission from: Kolbach DN, Leffers P, Neumann HAM, Kuiper JP, Partsch H, Prins MH. Inter-observer variation in reading ambulant venous pressure from invasive venous pressure curves: the need for clear guidelines. Phlebology. 2005; 20: 110-116. Copyright (2005) Royal Society of Medicine Press, UK.

REFERENCES

1. Payne SP, London NJ, Newland CJ, Thrush AJ, Barrie WW, Bell PR. Ambulatory venous pressure: correlation with skin condition and role in identifying surgically correctible disease. Eur J Vasc Endovasc Surg 1996;11(2):195-200.
2. Becker F. Exploration de l'insuffisance veineuse. Rev Prat 1994;44(6):733-7.
3. Partsch H. Venendruckmessung in der phlebologie. Hautarzt 1981;32(2):53-8.
4. Shull KC, Nicolaides AN, Fernandes e Fernandes J, Miles C, Horner J, Needham T, et al. Significance of popliteal reflux in relation to ambulatory venous pressure and ulceration. Arch Surg 1979;114(11):1304-6.
5. Kuiper JP. Venous pressure determination (direct method). Dermatologica 1996;132:206-17.
6. Audelan J-M, Hidouche D, Vin F. Mesure de la pression veineuse. Phlébologie 1999;52:401-6.
7. Von Recklinghausen H. Unblutige Blutdruckmessung. Arch Exper Pathol Pharm 1906;13:423-5.
8. Beecher HK, Field ME, Krogh A. The effect of walking on the venous pressure at the ankle. Skand Arch Physiol 1936;73:133-41.
9. Barber RF, Shatara FI. The varicose disease. N Y State J Med 1925;31:574-80.
10. McPheeters NO, Rice CO. Varicose veins; the circulation of venous flow. Surg Gynecol Obstet 1929;49:29-32.
11. Pollack AA, Wood EH. Venous pressure in the saphenous vein in ankle of men during exercise and changes in posture. J Appl Physiol 1949;1:649-53.
12. Seiro V. Über Blutdruck und Blutkreislauf in den Krampfadern der unteren Extremitäten. Acta Chir Scand 1938;80:41-81.
13. Höjensgard JC, Stürup H. Static and dynamic pressures in superficial and deep veins of the lower extremity in man. Acta Physiol Scand 1953;27:49-67.
14. Arnoldi CC. The function of the venous pump in chronic venous insufficiency. A phlebographic study. J Cardiovasc Surg (Torino) 1961;2:116-27.
15. Kolbach DN, Leffers P, Neumann HAM, Kuiper JP, Partsch H, Prins MH. Inter-observer variation in reading ambulant venous pressure from invasive venous pressure curves: the need for clearer guidelines. Phlebology 2005;20:110-116.
16. Claes R, Thiery L, Uytterhaegen P. Videophlebography and simultaneous EMG to check the calf pump function. Paris: John Libbey Eurotext; 1992.
17. Reeder SWI, Wolff O, Neumann HAM. Comparison of ambulatory venous pressure measurement and anterior compartment pressure measurement in relation to the CEAP clinical classification of chronic venous disease. (submitted). 2011.
18. Cywinski J. The essentials in pressure monitoring. In. Boston: Martinus Nijhoff Publishers B.V.; 1980. p. 23-24.
19. Investigation of patients with deep vein thrombosis and chronic venous insufficiency. London: Med-Orion; 1991.
20. Kuiper JP. Bloedige veneuze drukmeting. In: Kuiper: Perifere veneuze drukmeting (thesis). Asten; 1966: 33-63.

Chapter 5

Comparison of ambulatory venous pressure measurement and anterior compartment pressure measurement in relation to the CEAP clinical classification of chronic venous disease

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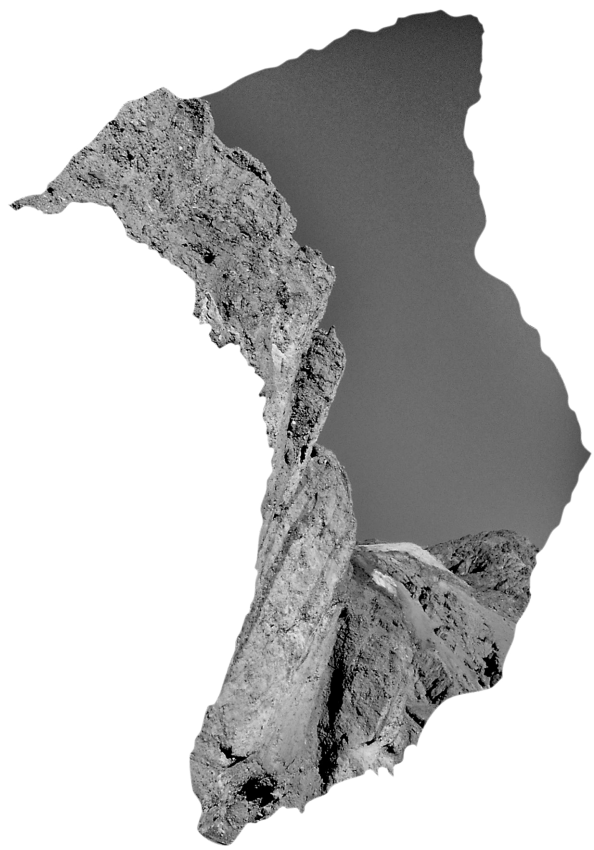
Submitted



ABSTRACT

Objectives: Retrospective descriptive study to investigate the association between CEAP-classification and ambulatory venous pressure measurement and anterior compartment pressure measurement, and the correlation between ambulatory venous pressure measurement and anterior compartment pressure measurement.

Method: Patients at various stages of chronic venous disease were scored by CEAP-classification, and investigated by ambulatory venous pressure measurement and anterior compartment pressure measurement.

Results: In total 163 legs were investigated in 89 patients. Statistically significant differences between the seven clinical categories of the CEAP-classification compared to ambulatory venous pressure measurement ($p<0.001$), for both ambulatory venous pressure and venous refill time were demonstrated.

Conclusions: Replacement of ambulatory venous pressure measurement in daily practice by CEAP clinical classification is justified, since patients with severe chronic venous disease as scored with the CEAP clinical classification have significantly higher ambulatory venous pressure and shorter venous refill time.

INTRODUCTION

Chronic venous disease (CVD) results from longstanding ambulatory venous hypertension, and may be the consequence of valvular incompetence leading to reflux, venous outflow obstruction, or a combination of both.[1] Chronic venous compartment syndrome (CVCS), not to be confused with chronic exertional compartment syndrome, is most frequently seen in patients with a post-thrombotic syndrome.[2] Not infrequently, post-thrombotic syndrome manifests itself as leg ulceration, which may be explained as follows. The venous hypertension leads to an increased capillary filtration rate with leakage of water, protein and later also erythrocytes, which gives rise to oedema and fibrosis of the skin, the subcutaneous tissue, the underlying fascia and finally results in hypoxia with consequent ulceration.[3] Ambulatory venous pressure (AVP) measurement is the gold standard for the quantitative assessment of CVD, and has both diagnostic and prognostic value.[4] The clinical significance of (anterior) compartment pressure (ACP) measurement in patients with CVD is unknown. In addition, this investigation has never been standardized and normal values have never been defined.[5]

A good correlation between high AVP and venous leg ulcers has been described.[4] However, the association between AVP measurement and the CEAP-classification has been shown to be weak.[6]

The primary aim of this study was to assess the relationship between conventional AVP measurement and the CEAP clinical classification. Secondary aims were to investigate the relation between ACP measurement and the CEAP clinical classification, and the correlation between AVP measurement and ACP measurement.

MATERIALS AND METHODS

Patients

Between 2004 and 2008, 163 limbs of 89 patients with a post-thrombotic syndrome, CVD, or unexplained leg symptoms who attended the dermatology outpatient clinic of the Erasmus Medical Center, Rotterdam, Netherlands were included. Patients attending the specialised vein clinic in this university hospital were referred by general practitioners as well as through tertiary referral because of leg complaints. In all subjects both legs were investigated. In order to allocate patients in seven clinical groups according to the CEAP-classification, two observers (S.W.I. Reeder and O. Wolff) carried out the clinical observation. All patients underwent duplex ultrasound to investigate venous dysfunction, i.e. anatomic extent and location of reflux, congenital venous disorders, and location of venous obstruction.

AVP Measurerment

This technique used was first described by Kuiper.[7] A cannula of a syringe was inserted into a dorsal vein of the patient's foot. Subsequently, a three-way tap (single [electronic pressure] transducer [Hemo 4, Model 4315961 E529U, Serial 5290891456, Siemens, Dräger Medical Netherlands B.V., Zoetermeer, the Netherlands]) and a connecting tube were attached and the system was connected to NaCl 0.9% solution. The transducer was fixed to the foot at the same level as the cannula tip (zero calibration), and subsequently connected to the recorder (MicroDAQ Data Acquisition, Fieldworks Direct, 's-Hertogenbosch, the Netherlands), which was connected to a computer. The system was calibrated for pressure increase for each leg with the patient in supine position. The system was calibrated to zero, and the patient was then helped into an upright position. The patient supported himself in the standing position by holding a frame, and the standing venous pressure (SVP) was recorded. Subsequently, the patient performed a standard exercise of 10 tiptoe movements in 15 seconds. After the last tiptoe, the patient was instructed to stand still until the pressure had reached the SVP. The tiptoe exercise was repeated and the patient was then asked to do 10 knee bends in 15 seconds.

In supine position venous pressure is between 5 and 10 mmHg and SVP is defined by the hydrostatic pressure. SVP is dependent on the patients' height and will be between 80 and 100 mmHg in the average European. Determining AVP has been a point of discussion since the introduction of AVP measurement. To define AVP we divided the deepest point of the pressure drop of the last tiptoe/knee bend (which is equal to the deepest point of the pressure drop at the end of the exercise) by the SVP and multiplied this number by 100. In this way, we calculated the percentage of the AVP (AVP%) to make the results comparable. To determine the venous refill time (RT) we determined RT90 (venous refill time to 90% of original) (Figure 1).

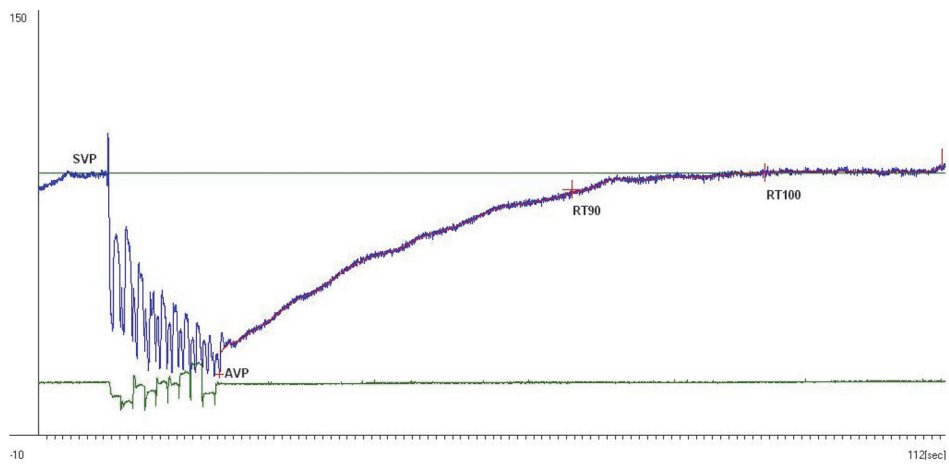
ACP measurement

The slit catheter method (Indwelling Slit Catheter Set, Intra-Compartmental Pressure Monitor System, Stryker Instruments, Kalamazoo, Michigan, USA) was used to measure the compartment pressure of the anterior compartment of the lower leg. With the patient in supine position, about 3 ml of local anaesthetic was used to infiltrate the skin, the subcutaneous tissue, and the fascia overlying the anterior tibial muscle. The fascia was pierced at a 30˚ angle to the longitudinal axis of the leg. The needle was withdrawn and the sleeve was kept in position after the catheter was inserted directly into the belly of the tibialis anterior muscle. Subsequently the catheter was connected to the transducer, filled with saline and attached to the

patient's leg. The transducer was indirectly connected to a computer that was programmed to calculate the compartment pressure. Before the measurement started, the catheter was calibrated to zero. Pressure was measured at rest with the patient in supine position. After this measurement the patient was helped into standing position, and the standing rest pressure and pressures during and after 10 tiptoe movements (twice) and 10 knee bends were recorded (See section *AVP measurement* for details). Finally, with the patient in supine position the pressure measurement was repeated.

The supine ACP was defined as the mean of the two supine pressures. In standing position, the mean of the three standing rest pressures before and after exercise was defined as ACP.

Figure 1: Normal ambulatory venous pressure (AVP) measurement and anterior compartment pressure (ACP) measurement and explanation of abbreviations. During exercise (10 tiptoe or knee bend movements) venous pressure drops from SVP to AVP. The time it takes for venous pressure to return to 90% of SVP is RT90. Anterior compartment pressure varies during exercise and returns to normal when the patient stands still. AVP measurement is marked by the blue line and ACP measurement by the green line.



SVP = standing venous pressure.
AVP = ambulatory venous pressure.
RT90 = venous refill time to 90% of original.
RT100 = venous refill time to 100% original.

Statistical analysis

The data of CEAP clinical classification (C), AVP measurement and ACP measurement were compared using Kruskal-Wallis test. Subgroup analyses were performed using a paired t-test. Spearman's test was used to estimate the correlation between AVP measurement and ACP measurement.

RESULTS

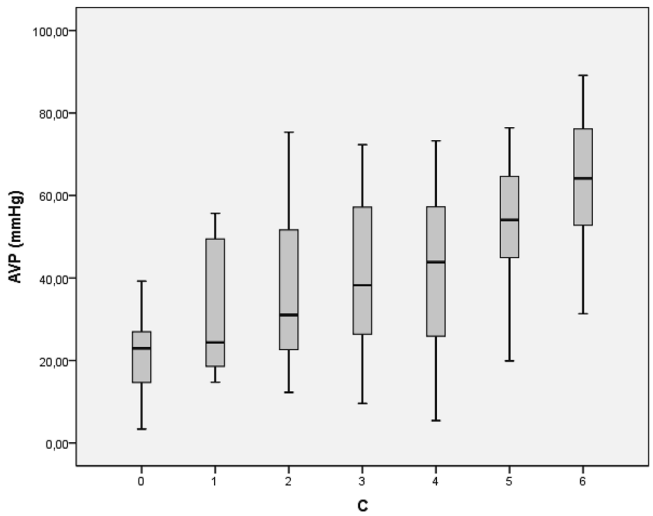
The median age of all 89 patients was 44 years (range 16-76). The 163 legs were classified as 90 female and 73 male legs. The results of the patients with regard to C, sex and age characteristics are shown in Table 1.

Table 1: CEAP clinical classification by (C), sex, age (years), and Kruskal-Wallis test of the clinical groups.

Clinical severity of venous disease	C	No. of legs	Sex (M:F)	Median age (range)
No visible or palpable signs of venous disease	0	33	11:22	35 (16-68)
Telangiectasies or reticular veins	1	8	2:6	27 (17-67)
Varicose veins	2	15	6:9	39 (20-72)
Oedema	3	27	7:20	45 (16-76)
Skin signs ascribed to venous disease (pigmentation, venous eczema, lipodermatosclerosis)	4	47	26:21	46 (25-79)
The above skin changes with healed ulceration	5	21	14:7	42 (27-74)
The above skin changes with active ulceration	6	12	7:5	60 (42-74)
Total		163	73:90	44 (16-76)

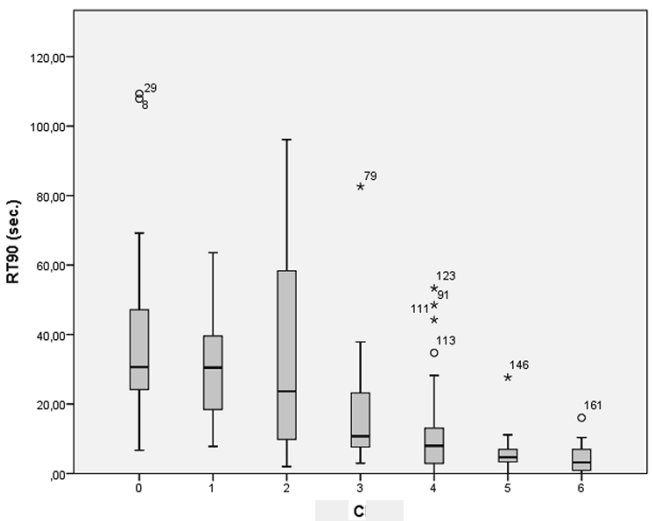
Figures 2-4 show the results of AVP measurement in the 163 legs. The Kruskal-Wallis test showed statistically significant differences between the seven groups of C compared to AVP measurement ($p<0.001$), for AVP, RT90 and AVP%. However, subgroup analyses using a paired t-test did not show significant differences between consecutive C categories. After excluding the patients who had undergone a fasciotomy or fasciectomy (n=8), we tested the relation between C and ACP measurement (Figures 5-6). We could not demonstrate a significant relation between C and supine ($p=0.212$) or standing ACP ($p=0.096$).

Figure 2: Boxplot of AVP by C.



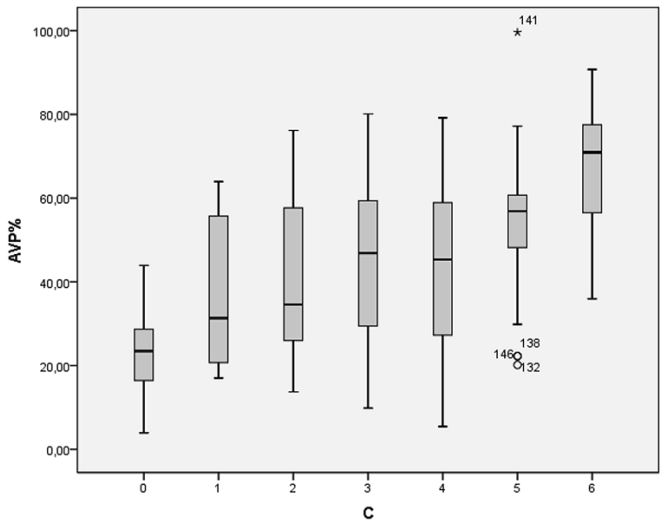
AVP = ambulatory venous pressure expressed in mmHg.
C = CEAP clinical classification.

Figure 3: Boxplot of RT90 by C.



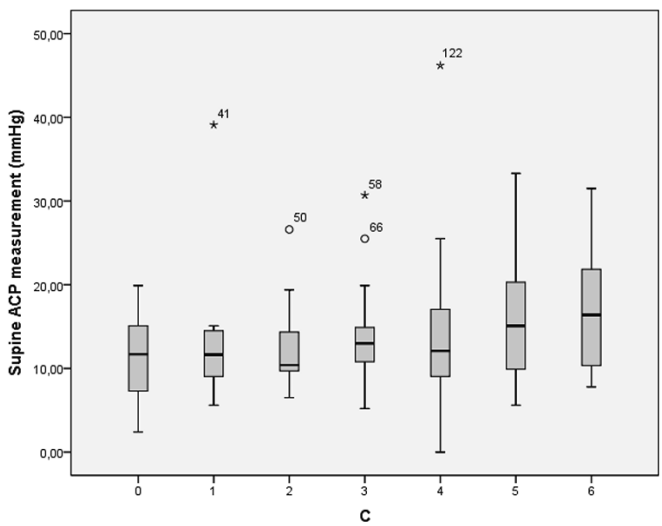
RT90 = venous refill time to 90% of original.
C = CEAP clinical classification.

Figure 4: Boxplot of AVP% by C.



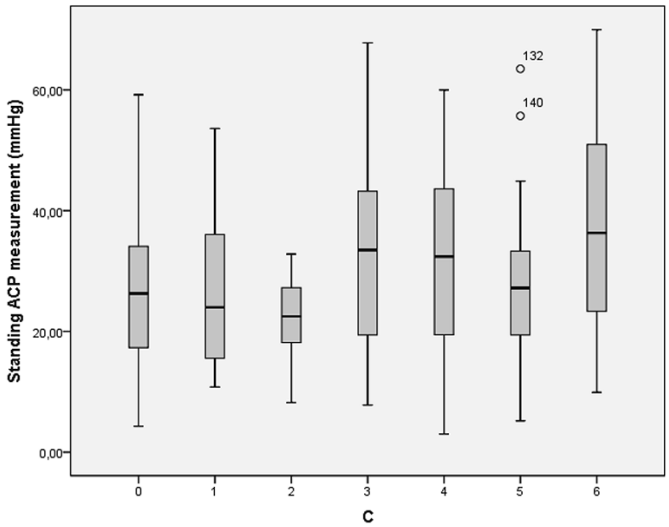
AVP% = ambulatory venous pressure : standing venous pressure x 100%.
C = CEAP clinical classification.

Figure 5: Boxplot of supine ACP measurement by C.



ACP measurement = anterior compartment pressure measurement expressed in mmHg.
C = CEAP clinical classification.

Figure 6: Boxplot of standing ACP measurement by C.



ACP measurement = anterior compartment pressure measurement expressed in mmHg.
C = CEAP clinical classification.

A poor correlation was found between AVP measurement and ACP measurement. The correlation coefficient (*r*) of supine ACP compared to AVP%, AVP and RT90 was 0.009 (*p*=0.91), 0.010 (*p*=0.896) and -0.023 (*p*=0.77), respectively. The results of Spearman's test comparing standing ACP to AVP% (*r*=-0.005, *p*=0.95), AVP (*r*=0.032, *p*=0.687) and RT90 (*r*=-0.108, *p*=0.172) showed comparable results.

Subsequently, an analysis was performed to investigate the correlation between high ACP (supine ACP≥25 mmHg and/or standing ACP≥35 mmHg, n=57).[2,5,8] Again, no correlation between AVP measurement and supine ACP could be demonstrated, with *r*=0.139 (*p*=0.303) for AVP%, *r*=0.141 (*p*=0.295) for AVP and *r*=-0.096 (*p*=0.476) for RT90. No correlation could be demonstrated between standing ACP and AVP% [*r*=-0.016 (*p*=0.906)], AVP [*r*=0.034 (*p*=0.802)] AVP and RT90 [*r*=-0.116 (*p*=0.392)] as well.

DISCUSSION

This study demonstrates a significant relation between the C of the CEAP-classification and AVP measurement, for as well AVP as RT90. In other words, the CEAP clinical classification (C) corresponds with the venous pressure in the investigated leg. Previous studies only demonstrated significant differences between mild and

severe venous disease.[6,9] Eifell et al. merged C2&C3 (mild disease) and C5&C6 (severe disease) respectively because of the small number of subjects studied (15 limbs of normal controls (C0) and 54 limbs with chronic venous insufficiency).[6] Moreover the aim of this study was different from our study, since Eifell et al. compared a new technique of AVP measurement with the gold standard we also used in our current study. Payne et al. investigated 360 legs in 212 patients. The patients in that study were divided into four clinical groups, since the CEAP-classification for CVD did not exist at that time.[9] The patients with eczema and/or hyperpigmentation were admitted to a different group (mild venous disease) than patients with lipodermatosclerosis (severe venous disease). In the current CEAP-classification these three clinical symptoms are categorised as C4a and C4b. This may explain why in the study of Payne et al. no significant differences were found between mild and severe venous disease. Besides the goal of that study was to investigate whether or no air plethysmography could replace the gold standard of ambulatory venous pressure measurement. However plethysmography is a volume measurement in stead of a pressure measurement that is AVP measurement. As the relation between volume changes and pressure is non-linear, plethysmographic techniques can not replace AVP measurement as described here.

A small number of patients with longstanding CVD will develop a CVCS, which is a severe complication of CVD. Hach showed healing of nonhealing venous leg ulcers after decompression of one of the compartments of the lower leg by fasciectomy.[10] Our study did not demonstrate a correlation between AVP measurement and high ACP. This may be explained as follows. A raised AVP leads to an increased capillary filtration rate, which leads to hyperpigmentation (by extravasation of erythrocytes) and inflammation (by extravasation of proteins). This inflammation gives rise to sclerosis of the skin, the subcutaneous fat and finally of the underlying fascia.[11,12] The fibrotic changes within the anterior compartment lead to the rise of ACP.[3] The process from a raised AVP to lipodermatosclerosis and sclerosis of the fascia may take years to develop. It is not clear whether sclerosis of the fascia develops as often as sclerosis of the skin and the subcutaneous tissue. The structure of the skin and the subcutaneous tissue is totally different from the structure of the fascia. So, it seems quite possible that only in special cases the process of sclerosis progresses to the fascia with subsequent increased compartment pressures. The CEAP-classification has no item for sclerosis of the fascia as C4b only indicates lipodermatosclerosis or white atrophy.[13] This is also true for the limited ankle mobility which seems to correlate with CVD in CVCS.[14] Using just clinical investigation as given by the CEAP-classification CVCS will be missed.

Probably our patient population with severe sclerosis was too small to demonstrate a correlation between AVP measurement and high ACP.

Unlike the acute compartment syndrome, little is known about CVCS.[10] CVCS was first described in 1990 by Pflug et al. in patients with primary varicose veins and increased resting interstitial pressure of the subfascial tissues in the supramalleolar area of the leg.[15] Most patients with CVCS have a post-thrombotic syndrome and suffer from chronic venous insufficiency for years before the diagnosis of CVCS is made. The skin and the subcutaneous tissue of the lower leg are clearly indurated and patients frequently have recurrent or persistent, often large, resistant leg ulcers.[2]

ACP measurement has never been standardized and no cut-off values exist for compartment pressure. However, in patients with acute compartment syndrome fasciotomy or fasciectomy is recommended when the compartment pressure exceeds 30-35 mmHg (using the slit catheter method) combined with appropriate clinical findings.[16] However the problem with ACP measurement, in our experience, is that, for example, a patient with a standing ACP of 40 mmHg may suffer from CVCS with typical symptoms (i.e. (ischemic) pain induced by exercise, swelling and impaired muscle function),[17] while another patient with a standing ACP of 60 mmHg does not have any symptoms at all.[10] Left to right differences may help to some extent, but will not overcome this clinical problem because CVD is often bilateral. Based on the data of Hach we suggest that pressures above 18 mmHg (supine) and 35 mm Hg (standing) should be regarded as pathological in CVCS.[10]

We conclude that in the majority of patients the CEAP clinical classification reflects the AVP well and AVP measurement will be unnecessary in diagnosing CVD. However AVP measurement is the only investigation which can quantify CVD in a precise manner because of the pressure is read out in mmHg. In special situations AVP measurement is still useful in contributing to therapeutic decisions, estimating the prognosis and the benefits of treatment, as for example in patients with severe post-thrombotic syndrome offered for venous de-obstruction and stent placement. In such cases, AVP measurement will reflect the hemodynamic result of the intervention. If CVCS is suspected ACP measurement may be used to diagnose and subsequently treat patients with this debilitating disease. The correlation between CVCS and ACP measurement should be further investigated before therapeutic guidelines may be written.

REFERENCES

1. Hosoi Y, Zukowski A, Kakkos SK, Nicolaides AN. Ambulatory venous pressure measurements: new parameters derived from a mathematic hemodynamic model. J Vasc Surg 2002;36(1):137-42.
2. Hach W. [Chronic venous compartment syndrome]. Zentralbl Chir 2001;126(6):472-5.
3. Grattenthaler C, Thoms KM, Kretschmer L. [Paratibial fasciotomy for postthrombotic leg ulcer using Vollmars fasciotome]. J Dtsch Dermatol Ges 2007;5(12):1144-5.
4. Nicolaides AN, Hussein MK, Szendro G, Christopoulos D, Vasdekis S, Clarke H. The relation of venous ulceration with ambulatory venous pressure measurements. J Vasc Surg 1993;17(2):414-9.
5. Turnipseed W, Detmer DE, Girdley F. Chronic compartment syndrome. An unusual cause for claudication. Ann Surg 1989;210(4):557-62; discussion 562-3.
6. Eifell RK, Ashour HY, Lees TA. Comparison of new continuous measurements of ambulatory venous pressure (AVP) with conventional tiptoe exercise ambulatory AVP in relation to the CEAP clinical classification of chronic venous disease. J Vasc Surg 2006;44(4):794-802.
7. Kuiper JP. Perifere veneuze drukmeting. Nijmegen: University of Nijmegen; 1966.
8. van den Brand JG, Nelson T, Verleisdonk EJ, van der Werken C. The diagnostic value of intracompartmental pressure measurement, magnetic resonance imaging, and near-infrared spectroscopy in chronic exertional compartment syndrome: a prospective study in 50 patients. Am J Sports Med 2005;33(5):699-704.
9. Payne SP, London NJ, Newland CJ, Thrush AJ, Barrie WW, Bell PR. Ambulatory venous pressure: correlation with skin condition and role in identifying surgically correctible disease. Eur J Vasc Endovasc Surg 1996;11(2):195-200.
10. Hach W, Prave F, Hach-Wunderle V, Sterk J, Martin A, Willy C, et al. The chronic venous compartment syndrome. Vasa 2000;29(2):127-32.
11. Neumann HAM, Tazelaar, DJ. Compression therapy. In: Bergan JJ, Goldman, MP, editor. Varicose veins and telangiectasias, diagnosis and treatment. St. Louis: Quality Medical Publishing Inc; 1993. p. 3-22.
12. Neumann HAM. Measurement of Microcirculation. In: Altmeyer ea, editor. Wound Healing and Skin Physiology. Berlin/Heidelberg: Springer Verlag; 1995. p. 115-26.
13. Eklof B, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, Kistner RL, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg 2004;40(6):1248-52.
14. Cavalheri G, Jr, de Godoy JM, Belczak CE. Correlation of haemodynamics and ankle mobility with clinical classes of clinical, aetiological, anatomical and pathological classification in venous disease. Phlebology 2008;23(3):120-4.
15. Pflug JJ, Zubac DP, Kersten DR, Alexander ND. The resting interstitial tissue pressure in primary varicose veins. J Vasc Surg 1990;11(3):411-7.
16. Bourne RB, Rorabeck CH. Compartment syndromes of the lower leg. Clin Orthop Relat Res 1989(240):97-104.
17. Styf J, Korner L, Suurkula M. Intramuscular pressure and muscle blood flow during exercise in chronic compartment syndrome. J Bone Joint Surg Br 1987;69(2):301-5.

Chapter 6

Varicose veins, there is more than meets the eye

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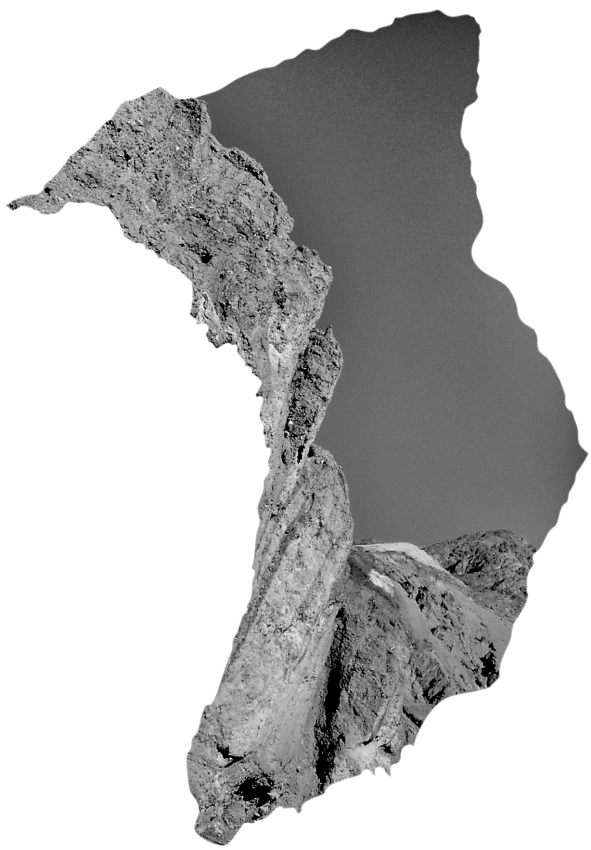


Patients with varicose veins consult a physician because of complaints, visible signs, or a combination of both. Classically, varicose veins are divided into telangiectasies, reticular veins, tributary varicose veins and saphenous varicose veins.[1] Based on duplex ultrasonography (DUS) varicose veins are divided into varicose veins inside the saphenous compartment and varicose veins outside the saphenous compartment. Varicose veins outside the saphenous compartment are frequently clinically visible as classical varicose veins and rarely lead to complaints. Varicose veins inside the saphenous compartment are rarely clinically visible varicose veins, but may lead to severe complications (C3 to C6 according to the clinical score of the CEAP-classification) if left untreated.

Fifty percent of all chronic venous leg ulcers are caused by superficial venous insufficiency (SVI) alone, which consists of a spectrum that runs from venectasia to full-blown saphenous vein incompetency. Early treatment may in time avoid nearly all of these leg ulcers. The great saphenous vein (GSV), small saphenous vein (SSV), anterior accessory saphenous vein (AASV) and their major tributaries may contribute to disturbed venous haemodynamics. In fact for the superficial venous system reflux forms the only haemodynamic disturbance, which may lead to venous hypertension and finally ulceration. In addition the terminal and preterminal valves at the saphenofemoral junction, some major perforators and the so-called "point de Gillot" may contribute to the severity of SVI. Recently Pittaluga demonstrated the relationship between incompetence of the AASV and GSV.[2]

All this means that behind the clinical diagnosis of C2 according to the CEAP-classification[3] a broad and complex situation exists regarding disturbed venous haemodynamics. Just mentioning C2 does not provide any information about the complexity of SVI in which varicose veins play the major role. Up to now an adequate classification system for varicose veins is lacking. Non-phlebologists often confuse varicose veins with chronic venous disease (CVD). However varicose veins are only in part responsible in the complex spectrum of CVD.

In 1994 the CEAP-classification was introduced as "a more precise classification of chronic venous dysfunction simple enough to encourage its universal acceptance".[4] Up to then physicians classified CVD with a vast variety of clinical, anatomical and physiological signs. Frequent adaptations of anatomical nomenclature and treatment options have made comparison of scientific studies near to impossible. The CEAP-classification almost immediately revolutionised the way in which phlebology was looked at because of its simplicity and reproducability. It made comparison between different studies possible, and has become the worldwide standard for describing the clinical features of CVD.[3] However, in many practices the CEAP-classification is reduced to only the C (grade

0 to 6). Because with the introduction of the CEAP-classification in 1994 when the Hand-Held-Doppler was the phlebologist's most important investigative tool, clinical appraisal was done by sight alone. Although DUS had been introduced in the late 80s of the last century it was still too expensive and too elaborate for every practice. Nowadays DUS is common in every phlebological practice and mandatory to perform in every patient before an intervention takes place. In addition DUS has become an essential part in both diagnosis and treatment of varicose veins since the introduction of ablative endovenous techniques such as Endovenous Laser Ablation (EVLA) and Radiofrequency Ablation (RFA) almost a decade ago. These endovascular procedures have become very popular and the focus of many with the intention to recover the disturbed venous haemodynamics. The physician is the only person who can make the right decision for the patient. The consideration to treat or not to treat is nowadays dependent on DUS findings and not on clinical appreciation alone.

A complete CEAP-classification gives a correct statement about reflux in the saphenous veins, but the use of the C alone is misleading. It can even lead to misinterpretation of the function of the saphenous veins because the C only comprises visible clinical signs. According to its definition the C is based on the physician's visual clinical appraisal of the patient. Following the complete CEAP-classification endovenous procedures may be justifiable in all C classes. However a patient without visible varicose veins (C0) or small reticular varicose veins (C1) may also have significant reflux.[5] Classifying a patient with an incompetent but invisible GSV as C0 or C1 is misleading, since this patient has more severe pathology than the clinical score suggests and may lead to undertreatment. An excellent and objective scoring system for varicose veins can also be helpful in health care insurance decisions which patients should receive reimbursements for their treatment. In other words, cosmetic varicose veins can be separated from medical varicose veins. Unfortunately reflux is not an absolute haemodynamic parameter because not all patients with reflux will develop an ulcer over time. This is illustrated by the fact that the incidence of varicose veins is much higher than the incidence of venous ulcers. We therefore propose to adjust the C in the CEAP-classification by dividing C2 into two subclasses: C2a (minor reflux) and C2b (major reflux) just as was done with C4 in 2004.[3]

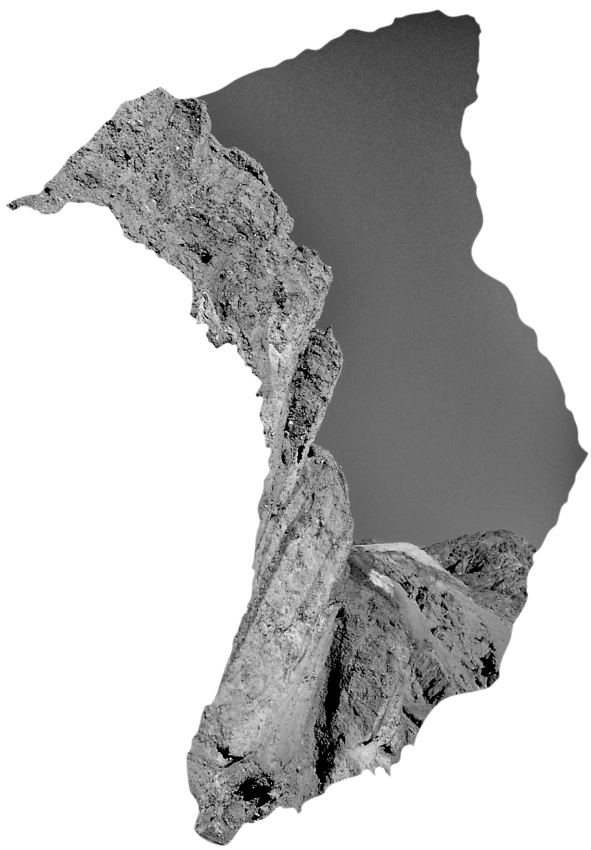
The decision to treat or not to treat should be based on medical and not on cosmetic grounds. This should depend on the risk or presence of complications of CVD. So, disturbed venous haemodynamics with significant reflux should be the criterium.[6] As an adequate study lacks we propose on theoretical grounds that a GSV with a diameter ≥5 mm measured at 15 cm distal from the saphenofemoral

junction corresponds with significant reflux, and may be classified as C2b. Such findings justify an adequate treatment which restores normal haemodynamics, takes away complaints and reduces the risk of longterm complications such as venous leg ulcers.

REFERENCES

1. Duffy DM. Small vessel sclerotherapy: an overview. In: Callen JP ea, editor. Advances in dermatology. Chicago: Mosby; 1988. p. 221-242.
2. Pittaluga P, Chastanet S, Locret T, Barbe R. The effect of isolated phlebectomy on reflux and diameter of the great saphenous vein: a prospective study. Eur J Vasc Endovasc Surg 2010;40(1):122-8.
3. Eklof B, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, Kistner RL, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg 2004;40(6):1248-52.
4. Porter JM, Moneta GL. Reporting standards in venous disease: an update. International Consensus Committee on Chronic Venous Disease. J Vasc Surg 1995;21(4):635-45.
5. Weiss RA, Weiss MA. Doppler ultrasound findings in reticular veins of the thigh subdermic lateral venous system and implications for sclerotherapy. J Dermatol Surg Oncol 1993;19(10):947-51.
6. Neumann HAM. Haut, Venen und Beine. Phlebologie 2011;40:344-355.

Therapy



Chapter 7

Venous leg ulcer recurrence

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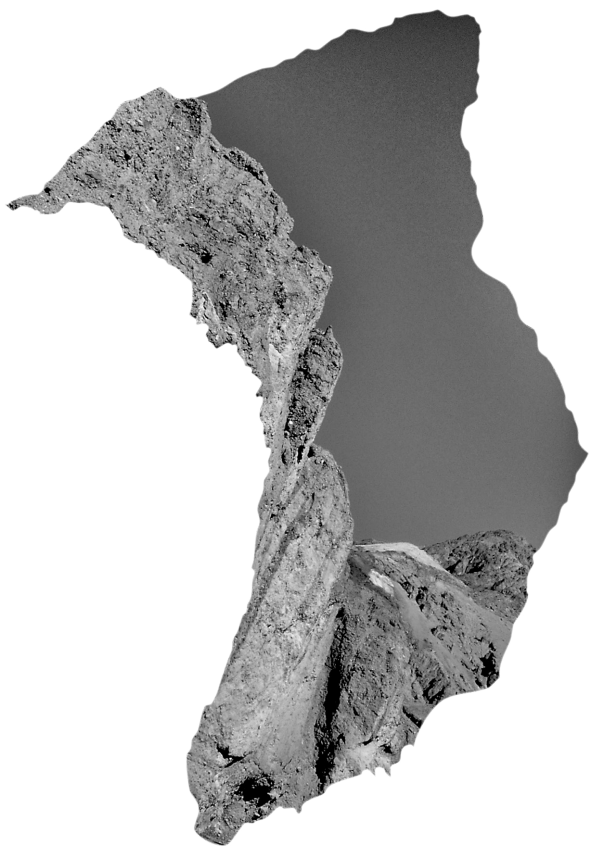
Submitted



ABSTRACT

Published literature consists of a broad range of venous leg ulcer (VLU) recurrence rates. Therefore, to assess the recurrence rate of VLUs a search and review of published data was performed using the MEDLINE OvidSP, EMBASE, Web-of-Science, PubMed publisher and Cochrane Library. The resulting data demonstrate VLU recurrence rates ranging from 0% at 6 months to 56% at 54 months. Two studies mention VLU recurrence at 60 months, with VLU recurrence rates of 19 and 48% respectively. Only three studies are comparable with regard to treatment and demonstrate VLU recurrence of 17, 17 and 25% respectively at 12 months. In conclusion, this is the first study summarising high-level evidence with regard to VLU recurrence demonstrating a tendency that even after several years recurrence rates still increase. The results of this study, high recurrence rates indicate the need for new strategies after a VLU has healed.

INTRODUCTION

Chronic venous disease (CVD) of the lower extremity is a very common medical condition caused by venous hypertension as a consequence of reflux, obstruction, or a combination of both.[1] Besides the socioeconomic problem CVD gives rise to disability and loss of quality of life.[2] Studies on incidence and prevalence differ depending on the age range of the study population since the strongest indicator for CVD is age. One of the latest epidemiological studies on CVD is the Bonn Vein Study which forms a representative cross-section of the community.[3] According to the clinical score in the CEAP-classification the investigated study population with an age range of 18 to 79 years the prevalence of CVD was 90.4% and divided as follows: C0 9.6%, C1 59.1%, C2 14.3%, C3 13.4%, C4 2.9%, C5 0.6% and C6 0.1%. Primary CVD is far more prevalent than secondary CVD, the former accounting for about three-quarters of lower extremities with this disorder.[4] Leg ulceration is the severest manifestation of CVD and is present in up to 0.5% and between 0.6 and 1.4% has healed venous leg ulcers (VLUs).[5] Fifty percent of VLUs will heal within 12 weeks, but about 8% of the treated ulcers do not heal after 5 years.[6,7] VLU recurrence rates after healing are high. However, there is a large variation in published recurrence rates.

METHODS

Therefore, to assess the recurrence rate of VLUs a review of published data was performed. We performed a search using the MEDLINE OvidSP, EMBASE, Web-of-Science, PubMed publisher and Cochrane Library with the Medical Subject Headings (MeSH) *varicose ulcer* and *recurrence*. The search was performed from inception to February 5, 2013. Based on titles and abstracts we then independently limited the search by two authors (S.W.I.R. and C.E.) to: one of four languages (English, German, French and Dutch); human studies published from 1996 to February 5, 2013; venous leg ulcer recurrence; and studies that included more than 20 patients with (recently healed) venous leg ulcers. Subsequently the full-text articles of all the remaining studies were read independently by two authors (S.W.I.R. and C.E.) to determine eligibility of the report to be included. Disagreements were adjudicated by an independent third reviewer (M.B.M.-V.). To be included, studies needed to fulfil the following criteria: prospective study design; diagnosis made by CEAP-classification and/or by using duplex ultrasound; and leg ulcer recurrence expressed as recurrence at a certain time.[8] EndNote software (version X5; Thomson Reuters) was used to manage and deduplicate all identified references.

RESULTS

The initial search yielded 1022 articles. After review of all titles and abstracts, 140 articles were chosen for further review. Twelve articles were excluded during deduplication. Of the remaining 128 articles 20 met the inclusion criteria (Table 1).

Table 1: Venous leg ulcer recurrence. All prospective studies included between 1996 and 2013, on condition that recurrence rates and duration were mentioned/ estimated.

	Number of VLUs			VLU recurrence	
	C5	C6	C5+C6	%	at time (months)
Nelzén et al. (1997)[11]	-	206	206	56[a]	54
Ghauri et al. (1998)[14]	-	176	176	21[b]	6
				23[b]	12
Rhodes et al. (1998)[18]	20	22	42	7[c]	12
				12[c]	24
				30[c]	36
Gloviczki et al. (1999)[17]	21	101	122	16[d]	12
				28[d]	24
				39[d]	36
Barwell et al. (2000)[23]	101	512	613	25[e]	12
				31[e]	24
				38[e]	36
Barwell et al. (2000)[24]	-	633	633	38[e]	36
Ghauri et al. (2000)[19]	-	336	336	13[e]	6
				17[e]	12
Sybrandy et al. (2001)[25]	-	39	39	13#[f]	48
				17#[g]	48
McDaniel et al. (2002)[21]	-	99	99	37[h]	36
				48[h]	60
Zamboni et al. (2003)[26]	-	47	47	9[i]	31.7*
				38[j]	31.7*
Gohel et al. (2005)[22]	320	1004	1324	17[e]	12
Van Gent et al. (2006)[27]	-	196	196	22[j]	24
				23[c]	24
Nelzén et al. (2007)[20]	44	53	97	19[c]	60
Gohel et al. (2007)[10]	159	341	500	31[l]	48
				56[j]	48
Darvall et al. (2009)[16]	-	28	28	7[l]	12
Nael et al. (2010)[12]	-	29	29	17[l]	0.23*
				20[l]	2.8*
				26[j]	5.5*

	Number of VLUs			VLU recurrence	
	C5	C6	C5+C6	%	at time (months)
Christenson et al. (2011)[13]	-	91	91	14[m]	36
Kulkarni et al. (2012)[28]	163	37	200	4.7[l]	12
				28.1[l]	48
Clarke-Moloney et al. (2012)[15]	100	-	100	16.1[i]	12
Harlander-Locke et al. (2012)[9]	21	-	21	0[n]	6
				4.8[n]	12
				4.8[n]	18

* Original data calculated to months.
# Read out from Kaplan-Meier curve.
[a] Observational study, conservative treatment or any surgical treatment.
[b] Compression therapy with or without venous surgery (saphenous vein(s) and/or perforators).
[c] Subfascial endoscopic perforator surgery (SEPS) with or without superficial venous surgery.
[d] SEPS with or without superficial venous surgery and/or split-thickness skin grafting.
[e] Compression therapy with or without superficial venous surgery.
[f] SEPS.
[g] Linton procedure.
[h] Compression therapy with or without venous surgery (superficial veins, perforators, and/or deep veins).
[l] Compression therapy.
[j] Compression therapy with venous surgery (superficial veins and/or perforators).
[k] Superficial venous surgery plus compression therapy.
[l] Ultrasound-guided foam sclerotherapy.
[m] Para-tibial subcutaneous fasciotomy plus compression therapy with or without meshed skin grafting.
[n] Compression therapy plus endovenous ablation of superficial veins and/or perforators.

Our data demonstrate VLU recurrence rates ranging from 0% at 6 months to 56% at 54 months.[1,2,6-19] Two studies mention (estimated) VLU recurrence at 60 months, with VLU recurrence rates of 19 and 48% respectively.[20,21] However these outcomes are hard to compare, since the patients in the first study were primary treated surgically and the patients in the second study with compression therapy. Only three studies are comparable with regard to treatment – compression therapy with or without superficial venous surgery – and demonstrate VLU recurrence of 17, 17 and 25% respectively at 12 months.[19,22,23]

Conclusions

As far as we know, this is the first study that summarises high-level evidence (randomised controlled trials and prospective cohort studies) with regard to VLU recurrence. The included studies vary largely with regard to number of patients, treatment as well as duration of (estimated) VLU recurrence, what makes it difficult to make a clear statement based on these outcomes. However, there is a tendency demonstrating that even after several years recurrence rates still increase. Although a meta-analysis would result in the highest level of evidence on this topic, this will be hard to achieve because of the number of variables. The results of this study, high recurrence rates indicate the need for new strategies after a VLU has healed.

REFERENCES

1. Bergan JJ, Schmid-Schonbein GW, Smith PD, Nicolaides AN, Boisseau MR, Eklof B. Chronic venous disease. N Engl J Med 2006;355(5):488-98.
2. Beyth RJ, Cohen AM, Landefeld CS. Long-term outcomes of deep-vein thrombosis. Arch Intern Med 1995;155(10):1031-7.
3. Maurins U, Hoffmann BH, Losch C, Jockel KH, Rabe E, Pannier F. Distribution and prevalence of reflux in the superficial and deep venous system in the general population–results from the Bonn Vein Study, Germany. J Vasc Surg 2008;48(3):680-7.
4. Labropoulos N, Gasparis AP, Pefanis D, Leon LR, Jr., Tassiopoulos AK. Secondary chronic venous disease progresses faster than primary. J Vasc Surg 2009;49(3):704-10.
5. Gloviczki P, Comerota AJ, Dalsing MC, Eklof BG, Gillespie DL, Gloviczki ML, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg 2011;53(5 Suppl):2S-48S.
6. Moffatt CJ, Doherty DC, Smithdale R, Franks PJ. Clinical predictors of leg ulcer healing. Br J Dermatol 2010;162(1):51-8.
7. Nicolaides AN, Cardiovascular Disease E, Research T, European Society of Vascular S, Organization TIASAC, International Union of A, et al. Investigation of chronic venous insufficiency: A consensus statement (France, March 5-9, 1997). Circulation 2000;102(20):E126-63.
8. Beebe HG, Bergan JJ, Bergqvist D, Eklof B, Eriksson I, Goldman MP, et al. Classification and grading of chronic venous disease in the lower limbs. A consensus statement. Eur J Vasc Endovasc Surg 1996;12(4):487-91.
9. Harlander-Locke M, Lawrence P, Jimenez JC, Rigberg D, DeRubertis B, Gelabert H. Combined treatment with compression therapy and ablation of incompetent superficial and perforating veins reduces ulcer recurrence in patients with CEAP 5 venous disease. J Vasc Surg 2012;55(2):446-450.
10. Gohel MS, Barwell JR, Taylor M, Chant T, Foy C, Earnshaw JJ, et al. Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): Randomised controlled trial. Br Med J 2007;335(7610):83-87.
11. Nelzen O, Bergqvist D, Lindhagen A. Long-term prognosis for patients with chronic leg ulcers: A prospective cohort study. Eur J Vasc Endovasc Surg 1997;13(5):500-508.
12. Nael R, Rathbun S. Effectiveness of foam sclerotherapy for the treatment of varicose veins. Vasc Med 2010;15(1):27-32.
13. Christenson JT, Prins C, Gemayel G. Subcutaneous fasciotomy and eradication of superficial venous reflux for chronic and recurrent venous ulcers: mid-term results. Phlebology 2011;26(5):197-202.
14. Ghauri ASK, Nyamekye I, Grabs AJ, Farndon JR, Whyman MR, Poskitt KR. Influence of a specialised leg ulcer service and venous surgery on the outcome of venous leg ulcers. Eur J Vasc Endovasc Surg 1998;16(3):238-244.
15. Clarke-Moloney M, Keane N, O'Connor V, Ryan MA, Meagher H, Grace PA, et al. Randomised controlled trial comparing European standard class 1 to class 2 compression stockings for ulcer recurrence and patient compliance. Int Wound J 2012 Oct 19. doi: 10.1111/j.1742-481X.2012.01108.x. [Epub ahead of print].
16. Darvall KAL, Bate GR, Adam DJ, Silverman SH, Bradbury AW. Ultrasound-guided foam sclerotherapy for the treatment of chronic venous ulceration: a preliminary study. Eur J Vasc Endovasc Surg 2009;38(6):764-769.

17. Gloviczki P, Bergan JJ, Rhodes JM, Canton LG, Harmsen S, Ilstrup DM, et al. Mid-term results of endoscopic perforator vein interruption for chronic venous insufficiency: Lessons learned from the North American Subfascial Endoscopic Perforator Surgery registry. J Vasc Surg 1999;29(3):489-502.
18. Rhodes JM, Gloviczki P, Canton LG, Rooke T, Lewis BD, Lindsey JR. Factors affecting clinical outcome following endoscopic perforator vein ablation. Am J Surg 1998;176(2):162-167.
19. Ghauri ASK, Taylor MC, Deacon JE, Whyman MR, Earnshaw JJ, Heather BP, et al. Influence of a specialized leg ulcer service on management and outcome. British Journal of Surgery 2000;87(8):1048-1056.
20. Nelzen O, Fransson I. True Long-term Healing and Recurrence of Venous Leg Ulcers Following SEPS Combined with Superficial Venous Surgery: A Prospective Study. Eur J Vasc Endovasc Surg 2007;34(5):605-612.
21. McDaniel HB, Marston WA, Farber MA, Mendes RR, Owens LV, Young ML, et al. Recurrence of chronic venous ulcers on the basis of clinical, etiologic, anatomic, and pathophysiologic criteria and air plethysmography. J Vasc Surg 2002;35(4):723-728.
22. Gohel MS, Taylor M, Earnshaw JJ, Heather BP, Poskitt KR, Whyman MR. Risk factors for delayed healing and recurrence of chronic venous leg ulcers - An analysis of 1324 legs. Eur J Vasc Endovasc Surg 2005;29(1):74-77.
23. Barwell JR, Taylor M, Deacon J, Ghauri ASK, Wakely C, Phillips LK, et al. Surgical correction of isolated superficial venous reflux reduces long-term recurrence rate in chronic venous leg ulcers. Eur J Vasc Endovasc Surg 2000;20(4):363-368.

Chapter 8

E-survey on venous leg ulcer among Dutch dermatologists

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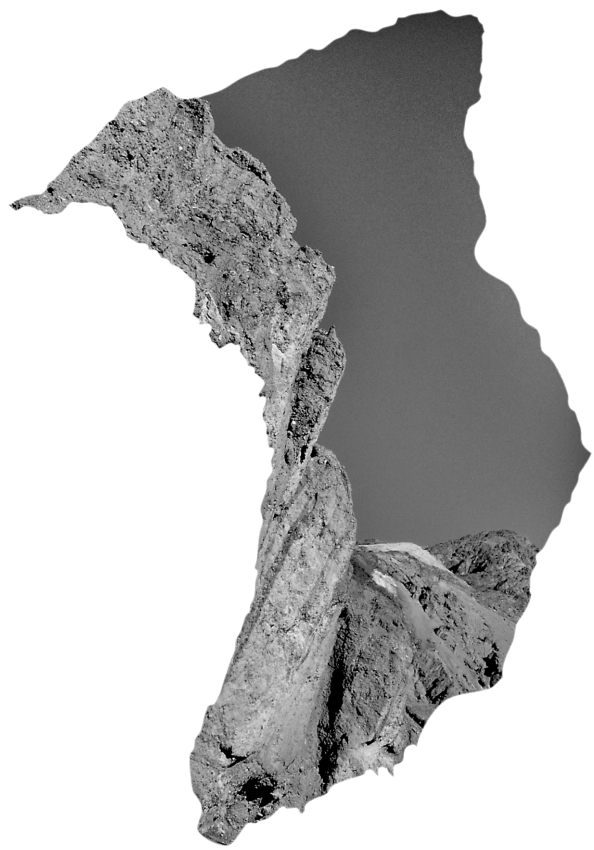

SUMMARY

Aim: To get insight into the frequency of venous leg ulceration in the Dutch dermatologic practice, and into how this profession treats this disease.

Design: E-survey.

Methods: To all Dutch dermatologists and residents dermatology an email was sent with an online link to a questionnaire on venous leg ulcers.

Results: The overall response was 30%. 83.5% of the doctors usually treat their patients according to the guideline. The dermatologic practice consists on average of 73 patients (range 0-500; SD 93) with leg ulceration, and yearly 54 new leg ulcer patients (range 0-300; SD 50) are seen. 65% of the patients are women, 80% is more than 45 years of age and 55% is older than 65. Of all ulcers, 77% has a venous aetiology, of which 59% has a primary cause. Mean time to heal is 74 days (range 4-200; SD 39). Per year, dermatologists admit on average 7 patients (range 0-50; SD 11) because of leg ulceration. Eventually, 47% of the admitted patients are treated by skin transplantation.

Conclusions: This questionnaire gives a good insight in the epidemiology, and the diagnostic and therapeutic regimen for patients with venous leg ulcers in Dutch dermatologic practice.

ZUSAMMENFASSUNG

Ziel der Untersuchung war, einen Einblick in die Häufigkeit und Behandlung venöser Ulzera in der niederländischen dermatologischen Praxis zu verschaffen.
Entwurf des Internetfragebogens.

Methoden: Alle niederländischen Dermatologen und Assistenzärzte im Fachbereich Dermatologie habben eine E-Mail im Oktober 2008 zugeschickt bekommen. Diese Email war verknüpft mit einem Online-Fragebogen über das venösen Ulcus cruris.

Ergebnisse: 30% aller Fragebogen wurden beantwortet. Die Dermatologen, die den Fragebogen ausgefüllt haben waren alle mit der niederländischen Leitlinie für Ulcus cruris vertraut. 83,5% der Ärzte behandeln in der Regel ihre Patienten nach dieser Leitlinie. Eine durchschnittliche dermatologische Praxis behandelt im Schnitt 73 Patienten (0-500, SD: 93) mit Beinulzerationen und jährlich werden 54 neue Patienten mit einem Ulcus cruris (0-300; SD 50) gesehen. 65% der Patienten sind Frauen, 80% sind älter als 45 Jahre und 55% älter als 65 Jahre. Dreiviertel aller Beinulzerationen haben eine venöse Ätiologie, von denen die venöse Ätiologie in 59% die primäre Ursache ist. Eine zusätzliche erweiterte Untersuchung wurde bei fast jedem Patienten durchgeführt. Die Behandlung erfolgte in allen Fällen mit ambulanter Kompressionstherapie. Die durchschnittliche Zeit zur vollständigen Heilung betrug 74 Tage (Bereich 4-200; SD 39). Im Jahresdurchschnitt werden 7 Patienten (SD 11 0-50) stationär behandelt und 59% dieser Patienten is bettlägerig, und die Hälfte wird mit Vacuum Assisted Closure (VAC®-Therapie) behandelt. Letztendlich wurden 47% der stationären Patienten mit einer Hauttransplantation behandelt.

Schlussfolgerung: Dieser Internetfragebogen erschafft einen Einblick in die Epidemiologie, Diagnose und die therapeutischen Strategien von Patienten mit einem Ulcus cruris im niederländischen dermatologischen Alltag.

INTRODUCTION

Chronic venous disease, i.e. varicose veins, post-thrombotic syndrome and chronic venous insufficiency belongs to the most prevalent diseases in the Western world. Venous leg ulcers (VLUs) have a lifetime prevalence of one to two percent and the prevalence of active VLUs ranges from 0.045%-0.7% depending on the age category investigated.[1-4] Several German studies have demonstrated that this prevalence is 4 to 5% in people over 80 years of age.[5,6] VLUs occur 2 to 3 times more frequent in women and had a relation with belonging to lower socio-economic class.[7] Chronic VLUs under 60 years of age are unusual and half of VLUs are caused by superficial venous insufficiency.[8]

Although the treatment goal of VLUs is complete healing within a reasonable period of time prognosis is poor. About 50% of adequately treated VLUs heal within 3 months, but after 2 and 5 years 20 and 8% have not healed respectively.[9, 10] After healing recurrence rates are high.[11] The average yearly VLU recurrence rates are estimated between 6 to 15% and in the first year after healing these rates are even (30 to 75%). Moreover most VLUs recur more than once.[12]

The commonest cause of leg ulceration is venous insufficiency. Other causes such as arterial insufficiency, diabetes mellitus, vasculitis, malignancy and other, less frequent causes of ulceration may accompany venous insufficiency. In many patients venous insufficiency is caused by post-thrombotic syndrome. Estimates vary but on average 1 out of 3 patients who suffered from deep vein thrombosis will develop post-thrombotic complications such as leg ulcer in the first 5 years.[13] The prevalence of chronic venous insufficiency after a deep vein thrombosis decreases if medical elastic compression stockings are worn, which may contribute to diminished incidence of VLUs.[14]

Since 2001 the Guidelines Committee of the Dutch Society of Dermatology and Venereology has appointed a working group "Ulcus Cruris Venosum" and originated to the multidisciplinary guideline "Diagnosis and treatment of venous leg ulcer" published by the Quality Institute for Healthcare CBO in 2005.[15] This multidisciplinary guideline constitutes guidance for medical specialists dealing with the diagnosis and treatment of VLUs in daily practice. As guidelines are important instruments to improve the quality of healthcare as well as to improve cost-effectiveness it is important that the workers in the field implement the guidelines in their daily practice. Information is needed on how professionals treat their patients to survey this process from knowledge to written guidelines and subsequently implementing and acting according to the guideline for the benefit of the patients. As VLUs are a social as well as a financial burden, guidelines help to improve the quality of care and as a consequence will lead to improvement of the patients' quality of life and a reduction of the costs.

Written surveys to Dutch dermatologists have been performed previously to collect information on diagnosis and treatment of basal cell carcinoma and psoriasis.[16, 17] E-surveys are quite new to the medical profession and to date have not been used for scientific purposes in the Dutch Dermatology Society. In other branches such as legal, trade and industry professionals are much more used to e-surveys by their fraternity to gather information.[18]

We performed an e-survey to gain insight to VLUs in the Dutch dermatological practice. This e-survey had multiple goals. First, recent epidemiological data are lacking with regard to VLUs. Second, no data exist to which extent supplementary investigations are performed by Dutch dermatologists. How will these patients subsequently be treated? Finally, this e-survey was performed to investigate the feasibility and response of the medical profession to this kind of questionnaire.

METHODS

In October 2008 the Dutch Society of Dermatology and Venereology sent an email to all Dutch dermatologists and residents dermatology whose email addresses were provided. This email contained a request to collaborate to an e-survey on VLUs as well as a link to the e-survey itself. After the first mailing two reminders were sent. The e-survey consisted of eighteen questions with regard to diagnostics, treatment and aftercare of VLUs. The questions were predominantly multiple-choice questions with two open questions on the treatment of VLUs (Table 1). The e-survey finished with two background questions (Table 2).

Table 1: Questions of e-survey.

Investigative questions	Answers
1. How many patients do attend to you each year?	...
2. How many patients are treated in your practice at this time?	...
3. 3. What is the age of the patients with a leg ulcer in your practice?	a. 0 – 18 years b. 19 – 34 years c. 35 – 45 years d. 56 – 65 years e. 66 – 75 years f. Over 75 years
4. Which percentage of the patients with leg ulcer is male?	..%
5. Which percentage of leg ulcers in your practice has a venous etiology?	..%
6. Which percentage of venous leg ulcers is primary (primary varicose veins) and which percentage is secondary (post-traumatic, post-thrombotic)?	..%

Investigative questions	Answers
7. In which part of patients with a leg ulcer supplementary investigation is performed?	..%
8. What does supplementary investigation consist of (multiple answers possible)?	See table 4
9. What is the average time to healing of venous leg ulceration?	.. weeks
10. Who are responsible for the treatment of venous leg ulceration?	a. General nurse b. Home care c. Patients themselves d. Wound nurse e. Treating doctor f. Other
11. Are you familiar with the CBO guideline Venous Leg Ulcer?	a. Yes, I know and have read the guideline b. Yes, I know the guideline and have read it superficially c. Yes, I have heard of it d. No
12. Do you treat patients with a venous leg ulcer according to the CBO guideline Venous Leg Ulcer?	a. Yes, always b. Yes, usually c. Sometimes d. No
13. What is standard care for venous leg ulceration in your practice?	…
14. Which medical specialties are involved in the treatment of leg ulceration in your practice?	a. Dermatology b. Vascular surgery c. General surgery d. Internal medicine e. Rehabilitation medicine f. Other specialties, that are …
15. Do you have joint consultations with other specialties?	a. Yes b. No c. No answer
16. How many patients are admitted to the hospital for treatment of leg ulceration?	…
17. Which percentage of patients receives medical elastic compression stockings for aftercare of venous leg ulceration?	..%
18. Which treatment modality do you use for in-hospital treatment of venous leg ulceration?	…

Table 2: Background questions of the e-survey.

Background questions	Answers
1. What does apply to you?	a. I am a resident dermatology b. I have been a dermatologist less than 5 years c. I have been a dermatologist between 5 and 15 years d. I have been a dermatologist for over 15 years e. No answer
2. What is the last recertification you have followed?	a. Benelux Society b. European Academy of Dermatology and Venereology c. Dutch Society of Dermatology and Venereology d. Workshop AZM at Vaeshartelt e. Workshop EVLT at Erasmus MC, Rotterdam f. Cabourg, France 2007 g. None of the above
3. These were all of our questions. If you appreciate receiving a summary of the results you may state this below.	a. Yes, I would like to receive a summary of the results b. No, I do not appreciate receiving the results

RESULTS

One hundred and thirty-four of 452 (30%) dermatologists and residents in dermatology whose email addresses were registered at the office of the Dutch Society of Dermatology and Venereology responded. Of the respondents 17% was resident and 83% dermatologist. Several respondents did not respond to all questions. As demonstrated in Table 3, most respondents (87%) replied within 2 weeks after the first email.

All 92 respondents are familiar with the Dutch guideline Venous Leg Ulcer, 61% (n=56) has read this guideline and 35% (n=32) has read it superficially. Treatment of VLUs takes place according to this guideline: always in 8.8% (n=8), usually in 83.5% (n = 76) and sometimes in 7.7% (n=7).

On average 54 (range 0-300) new leg ulcer patients are attended to the Dutch dermatologists each year. The average Dutch dermatologic practice counts 73 (range 0-500) patients with a leg ulcer. Leg ulceration is more prevalent in women as compared to men (65 versus 35%). Eighty percent of the patients are over 45 years of age and 55% is older than 65 years of age. 77% of the leg ulcer has a venous aetiology (range 15-100%). The cause of venous insufficiency is primary (primary varicose veins) in 59% (range 5-100%) and secondary (post-traumatic, post-thrombotic) in 41% (range 10-95%).

Table 3: Response to e-survey per week.

Week	41	47,7%
	42	39,2%
	43	7,7%
	45	3,8%
	46	0,8%
	49	0,8%
		Total 134

In nearly every patient supplementary investigation takes place (Table 4). The care profile of Dutch health insurance companies is added in table 4 for comparison. Besides dermatology several specialties are involved in the treatment of leg ulceration: vascular surgery (82%), internal medicine (20%), rehabilitation medicine (18%), general surgery (5%), orthopaedic surgery (1%) and anaesthesiology (pain team) (1%). Sixteen percent of respondents have joint consultations for patients with leg ulceration.

Table 4: This table shows the percentages of patients supplementary investigation takes place in diagnosing VLUs compared to the care profile of Dutch insurers.

Supplementary investigation	**E-survey (%)**	**Care profile Dutch insurers (%)**
Duplex ultrasound	95	100
Ankle brachial pressure index	85	50
Laboratoy investigation	68	-
Microbiologic investigation	68	35
Biopsy	59	5
Arterial doppler	51	-
Others: lymphoscintigraphy, allergy testing	3	

Ambulatory compression therapy is standard care and the most important treatment modality in the outpatient treatment of VLUs.[19] All respondents answered that ambulatory compression therapy whether or not in combination with local wound care is used in the outpatient treatment of VLUs. The mean time to healing of the outpatient treated VLUs is 74 days (range 4-200).

On average the respondents admit 7 patients to the hospital because of VLUs (range 0-50). Various answers were given to the open question on used treatment

modalities in patients admitted to the hospital because of leg ulceration. Fifty-nine percent of the patients are treated with bed rest, whether or not in combination with VAC® therapy (47%). Creating a clean wound bed is the main goal of local wound care, which is reached by for example compresses with sodium chloride 0.9% or sodium hypochlorite (eusol). Occasionally the wound is cleaned by surgical debridement or seldom maggot therapy. Finally 47% of the patients receive skin transplantation during their hospital stay, mainly consisting of punch grafts (Reverdin) or, less frequently, split-thickness skin grafts.

DISCUSSION

We performed an e-survey to obtain information on the prevalence and treatment of leg ulceration in the Dutch dermatological practice and to compare these results with the existing Dutch guideline. This is the first e-survey gathering information on this subject in the Netherlands for scientific use. All respondents are familiar with the Dutch guideline "Venous Leg Ulcer" and most dermatologists treat patients with VLU according to this guideline. It is surprising that all respondents are familiar with the guideline. This may be explained by the fact that before the actual introduction of the guideline all Dutch dermatologists and residents were invited to respond on the concept text and the guideline was discussed after its release on one of the meetings of the Dutch Society of Dermatology and Venereology. The wide range of number of ulcers in the different practices is remarkable. This may be explained by the fact that not all dermatologists are focussed on venous diseases. In a country with a high density of dermatological practices and good access to dermatological care for nearly all inhabitants, the general practitioner refers the patient – which is mandatory in the Dutch healthcare system – and refers to an appropriate clinic for leg ulcer care. VLUs is more prevalent in women and its prevalence is age-related which corresponds to the existing literature.[1,9]

The mean time to healing varies in the existing literature. However with adequate ambulatory compression therapy a time to healing of 3 months is realistic in 50% of VLU patients.[20] This corresponds to the results of our e-survey (2.5 months). From this we may conclude that the great majority follows the guideline the Dutch dermatologists confirm the expectations of good clinical leg ulcer care.

According to the respondents on average 7 VLU patients are yearly admitted to the hospital. It would have been interesting to know the reasons for hospital admission. Our own experience is that the patients admitted are most frequently patients with a non-healing VLU.[21] However other reasons for hospital admission were mentioned by some of the respondents and consisted mainly of wound infection requiring intravenous antibiotics, pain management, analysis of the leg

ulcer before treatment and facilitating consultation by other physicians. During hospital admission 47% of the patients are treated by VAC® therapy. VAC® therapy speeds up wound preparation before grafting compared to conventional wound care techniques.[22] Moreover wound healing is presumably progressed by this therapy. The treatment modality consisting of VAC® therapy to prepare the wound for consecutive grafting in combination with VAC® therapy for graft adherence seems to be popular among the Dutch dermatologists. This may be explained by the fact that this therapeutic option is part of the Dutch guideline.[15]

Before the existence of the guideline a Dutch study has demonstrated that expert centres perform better with regard to compression therapy than ordinary centres.[23] It seems that the guideline has contributed to improvement of the quality of care for VLU patients because the average healing time is conform what may be expected according to the guideline.

Besides leg ulceration itself we were interested in how the dermatologic profession would respond to an e-survey, because a comparable questionnaire has never been distributed before among Dutch dermatologists. A response of almost 30% seems low, especially compared to written questionnaires (46% for psoriasis,[17] 76% for basal cell carcinoma[16]), but corresponds to comparable e-surveys to for instance the business and legal profession.[18] Comparable data for the medical profession however are lacking. The risk of a low response is the possibility of selection bias by the non-respondents.[24] Selection bias does not seem to apply for our e-survey since the results correspond to the international literature.[24] Besides, a sample of 30% is very reliable. The proportion of dermatologists and residents represent a characteristic part of the target group has taken part in the e-survey.

Previous research has demonstrated that response to e-surveys is lower than response to written questionnaires.[25] Another study showed that if people have the possibility to choose between a written questionnaire and an e-survey only one in four prefer a paper questionnaire over a digital.[26] Finally, a large Dutch study in which 8 large European countries participated demonstrated low responses in the Netherlands and United Kingdom.[27]

In conclusion, although the response to our e-survey was lower than the response to a written questionnaire the response is valuable and comparable to similar surveys. This current e-survey gives a good insight in the epidemiology, diagnosis and treatment of VLUs in the Dutch dermatological practice. It is more easy to organise and less expensive than a conventional paper questionnaire. This is an important conclusion since it paves the way for researchers and even policymakers to regularly approach a specific profession to obtain insight in their activities. Policy and guidelines may get aligned with their use in daily practice and

will contribute to better implementation of guidelines which as we have proven for VLUs improves the quality of care to the desired high level of care according to the guideline.

REFERENCES

1. Callam MJ, Ruckley CV, Harper DR, Dale JJ. Chronic ulceration of the leg: extent of the problem and provision of care. Br Med J (Clin Res Ed) 1985;290(6485):1855-6.
2. Dissemond J, Korber A, Grabbe S. [Differential diagnoses in leg ulcers] Differentialdiagnosen des Ulcus cruris. J Dtsch Dermatol Ges 2006;4(8):627-34.
3. Ghauri AS, Taylor MC, Deacon JE, Whyman MR, Earnshaw JJ, Heather BP, et al. Influence of a specialized leg ulcer service on management and outcome. Br J Surg 2000;87(8):1048-56.
4. Moffatt CJ, Franks PJ, Doherty DC, Martin R, Blewett R, Ross F. Prevalence of leg ulceration in a London population. QJM 2004;97(7):431-7.
5. Rabe E, Pannier-Fischer, F., Bromen, K. et al. Bonner Venenstudie der Deutschen Gesellschaft für Phlebologie. Epidemiologische Untersuchung zur Frage der Häufigkeit und Ausspägung von chronischen Venenkrankheiten in der städtischen und ländlichen Wohnbevölkerung. Phlebologie 2003;32:1-14.
6. Etufugh CN, Phillips TJ. Venous ulcers. Clin Dermatol 2007;25(1):121-30.
7. Abbade LP, Lastoria S, de Almeida Rollo H, Stolf HO. A sociodemographic, clinical study of patients with venous ulcer. Int J Dermatol 2005;44(12):989-92.
8. Magnusson MB, Nelzen O, Risberg B, Sivertsson R. A colour Doppler ultrasound study of venous reflux in patients with chronic leg ulcers. Eur J Vasc Endovasc Surg 2001;21(4):353-60.
9. Callam MJ. Epidemiology of varicose veins. Br J Surg 1994;81(2):167-73.
10. Moffatt CJ, Doherty DC, Smithdale R, Franks PJ. Clinical predictors of leg ulcer healing. Br J Dermatol 2010;162(1):51-8.
11. Gohel MS, Barwell JR, Taylor M, Chant T, Foy C, Earnshaw JJ, et al. Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): Randomised controlled trial. Br Med J 2007;335(7610):83-87.
12. Vowden KR, Vowden P. Preventing venous ulcer recurrence: a review. Int Wound J 2006;3(1):11-21.
13. Pesavento R, Villalta S, Prandoni P. The postthrombotic syndrome. Intern Emerg Med 2010;5(3):185-92.
14. Kakkos SK, Daskalopoulou SS, Daskalopoulos ME, Nicolaides AN, Geroulakos G. Review on the value of graduated elastic compression stockings after deep vein thrombosis. Thromb Haemost 2006;96(4):441-5.
15. Richtlijn Diagnostiek en behandeling van het ulcus cruris venosum. In. Utrecht: CBO; 2005.
16. Thissen MR, Neumann HA, Berretty PJ, Ideler AH. [The treatment of basal cell carcinoma patients by dermatologists in Netherland]
17. De behandeling van patienten met basalecelcarcinomen door dermatologen in Nederland. Ned Tijdschr Geneeskd 1998;142(27):1563-7.
18. Wakkee M, Lugtenberg M, Spuls PI, de Jong EM, Thio HB, Westert GP, et al. Knowledge, attitudes and use of the guidelines for the treatment of moderate to severe plaque psoriasis among Dutch dermatologists. Br J Dermatol 2008;159(2):426-32.
19. 18.Http://www.bna.nl/Nieuws/Nieuwsoverzicht/Nieuwsdetail/825/Verdiepingsonderzoek-hoge-deelname-en-belangrijke-cijfers.
20. O'Meara S, Cullum N, Nelson EA, Dumville JC. Compression for venous leg ulcers Review. Cochrane Database Syst Rev 2012;11:CD000265.

21. O'Meara S, Tierney J, Cullum N, Bland JM, Franks PJ, Mole T, et al. Four layer bandage compared with short stretch bandage for venous leg ulcers: systematic review and meta-analysis of randomised controlled trials with data from individual patients. BMJ 2009;338:b1344.
22. Reeder S, de Roos KP, de Maeseneer M, Sommer A, Neumann HA. Ulcer recurrence after in-hospital treatment for recalcitrant venous leg ulceration. Br J Dermatol 2013;168(5):999-1002.
23. Vuerstaek JD, Vainas T, Wuite J, Nelemans P, Neumann MH, Veraart JC. State-of-the-art treatment of chronic leg ulcers: A randomized controlled trial comparing vacuum-assisted closure (V.A.C.) with modern wound dressings. J Vasc Surg 2006;44(5):1029-37; discussion 1038.
24. van Gent WB, Hop WC, van Praag MC, Mackaay AJ, de Boer EM, Wittens CH. Conservative versus surgical treatment of venous leg ulcers: A prospective, randomized, multicenter trial. J Vasc Surg 2006;44(3):563-571.
25. Fleming CM, Bowden M. Web-based surveys as an alternative to traditional mail methods. J Environ Manage 2009;90(1):284-92.
26. Leece P, Bhandari M, Sprague S, Swiontkowski MF, Schemitsch EH, Tornetta P, et al. Internet versus mailed questionnaires: a controlled comparison (2). J Med Internet Res 2004;6(4):e39.
27. Kroth PJ, McPherson L, Leverence R, Pace W, Daniels E, Rhyne RL, et al. Combining web-based and mail surveys improves response rates: a PBRN study from PRIME Net. Ann Fam Med 2009;7(3):245-8.
28. Lombarts MJ, Rupp I, Vallejo P, Sunol R, Klazinga NS. Application of quality improvement strategies in 389 European hospitals: results of the MARQuIS project. Qual Saf Health Care 2009;18 Suppl 1:i28-37.

Chapter 9

A prospective open study on treatment of venous leg ulcers in the Dutch community; implications for patient referral

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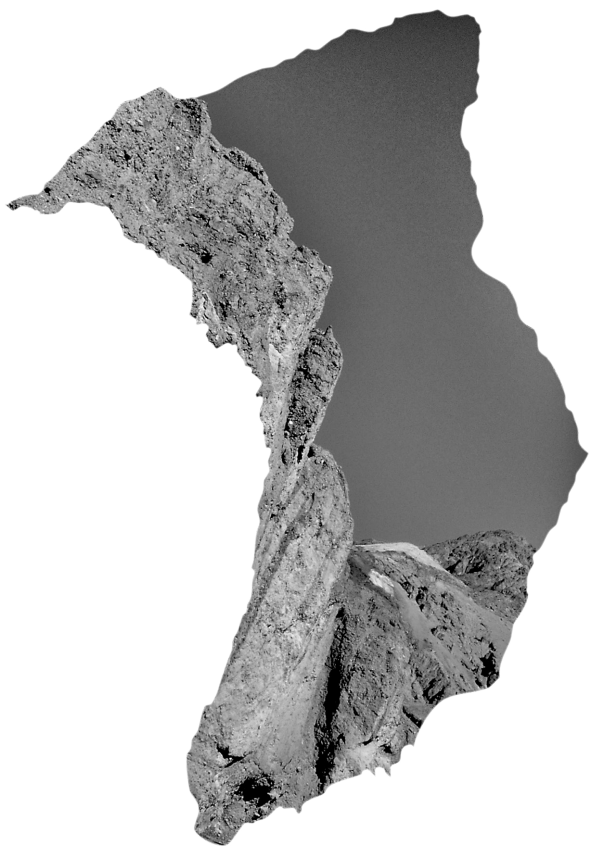
Submitted



ABSTRACT

Background: Chronic venous disease is one of the most common medical conditions and venous leg ulceration is one of its most severe manifestations. With standard care consisting of ambulatory compression therapy 50% of these ulcers will heal in 3 months. The primary aim of this study was to investigate venous leg ulcer healing in a Dutch population using the existing venous leg ulcer guideline.

Methods: A multicentre, prospective, open study was performed in patients with venous leg ulceration receiving outpatient treatment by ambulatory compression therapy at the dermatology department. In the course of 5 months, patients were examined by taking a photograph ulcer area, digital planimetry was performed to obtain an initial ulcer size and after 12 weeks ulcers are classified as healed or unhealed.

Results: A total of 56 patients were included, with a median age of 71.38 years (SD 13.8) and the group consisting of 23 (41.1%) males and 33 (58.9%) females. The median initial ulcer size was calculated to be 2.82 cm^2 (± 11.16). The twelve-week healing rate was 51.8% (n=29), with a median closure time of 38.0 days (± 35.68). The initial ulcer size was significantly smaller in the healed ulcers compared to the unhealed ulcers (p=0.001).

Conclusion: The results of this study correspond with the existing literature with regard to 3-month ulcer healing. Application of the existing evidence-based (S3) guideline is possible in the dermatological practice and will fulfil the expectations in optimising evidence-based healthcare. Besides, initial ulcer size is an indicator for healing.

INTRODUCTION

Chronic venous disease may lead to leg ulceration, the severest manifestation of this debilitating condition. In the adult Western population venous leg ulcers (VLUs) have a lifetime prevalence of 1% and a prevalence of active VLUs of 0.3%.[1,2] Standard treatment for VLUs consists of ambulatory compression therapy with bandages or special ulcer stockings.[3] With adequate compression therapy only 50% of all VLUs heal within 3 months.[4] The other half will heal very slowly or not at all. Even after five years 8% of all VLUs will not have healed.[2,4] In the last decade more evidence has become available for guiding the treatment of VLUs. In 2005 a Dutch (evidence-based, S3) guideline for VLUs was published to provide evidence-based healthcare.[5] This guideline also formed the template for the VLUs guideline of the European Dermatology Forum in 2006.[6] Currently both guidelines are under revision.

We performed a prospective study to evaluate the effectiveness of the treatment of VLUs in the Netherlands. The main goal of this study was to investigate VLU healing based on treatment according to the Dutch guideline. With this study we intend to demonstrate whether VLU healing rates are in accordance with the existing literature, which is 50% within 3 months.[4]

PATIENTS AND METHODS

A multicentre, prospective open study of patients with VLUs visiting the outpatient clinics after referral by their general practitioner was conducted from 7 January 2011 to 27 May 2011. Patients with VLUs were collected from six rural hospitals (Lievensberg Ziekenhuis, Bergen op Zoom; Amphia Ziekenhuis, Breda; Franciscus Ziekenhuis, Roosendaal; Maasstad Ziekenhuis, Rotterdam; Ruwaard van Putten Ziekenhuis, Spijkenisse; and Albert Schweitzer ziekenhuis, Zwijndrecht) and one university hospital (Erasmus Medical Center, Rotterdam). Patients that visited the hospital regularly because of VLUs were included and were followed for 12 weeks. The diagnosis of VLU was made – according to the Dutch guideline VLU[5] – by a dermatologist – based on patient history, clinical investigation and duplex ultrasound. Serious arterial incompetence was ruled out with ankle-brachial index (cut-off point 0.7). Upon first contact with the patient an ulcer size was measured by taking a digital picture of the ulcer after which digital planimetry was performed. Using Adobe® Photoshop® 7.0 the number of pixels in the ulcer were counted and subsequently divided by the square number of pixels on 1 cm of a ruler, resulting in an ulcer size expressed in cm^2 (Figures 1a-g).[7, 8]

Figure 1a: Step 1: Photograph of the circumference of the VLU.

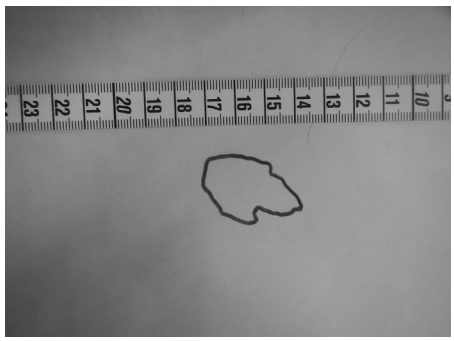


Figure 1b: Step 2: Counting the number of pixels per 10 centimetres (3073.15, as demonstrated in the upper right corner of the picture).

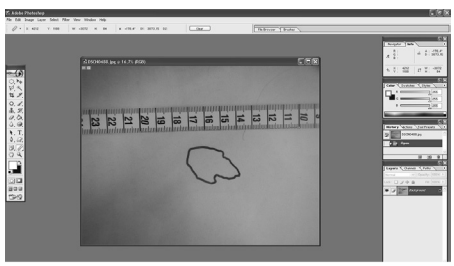


Figure 1c: Step 3: The circumference of the VLU is drawn.

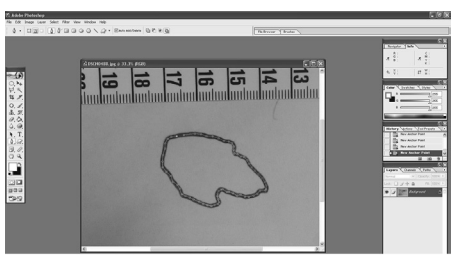


Figure 1d: Picture of the VLU after drawing.

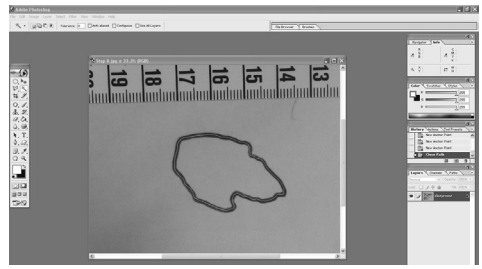


Figure 1e: Step 5: The surface within the drawn VLU circumference is blackened.

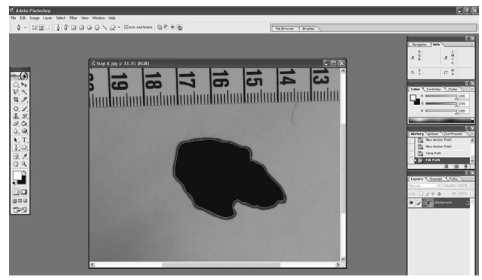


Figure 1f: Step 6: the surface outside the drawn VLU circumference is whitened.

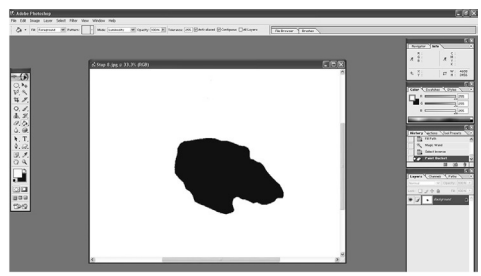
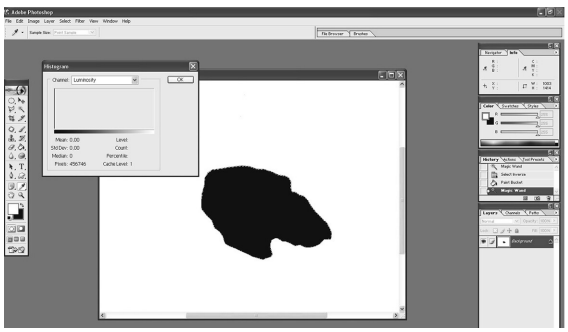


Figure 1g: Step 7: The histogram shows the number of pixels per colour, these are the black pixels inside the drawing of the VLU. In this case the black surface consists of 456746 pixels. Subsequently the surface of the VLU expressed in cm^2 is calculated as follows:
3073,15 pixels/10 cm = 3073,15 / 10 = 307,315 pixels/1 cm
307,315 x 307,315 = 94442,51 pixels / cm^2
456746 / 94442 = 4,84 cm^2



According to the Dutch guideline the treatment of all VLU patients consisted of local wound care in combination with ambulatory compression therapy using short-stretch bandages. Local wound care consisted of debridement (surgical or enzymatic) and/or an alginate dressing. All patients were treated by specialised nurse practitioners either in an outpatient setting at one of the participating clinics or at home. All nurses were instructed in the application of the Dutch guideline on ambulatory compression therapy.[9] Non-conservative treated patients were excluded from participating in the study.

After 12 weeks, VLUs were classified by dermatologists as healed, or unhealed. If a VLU had already healed before the established 12 weeks, the date of the hospital visit when the closure of the VLU was first documented was used for data-analysis. Data were analysed by Mann-Whitney U test, chi-square test and Fisher's exact test using SPSS® 17.0, a p-value <0.05 was considered to be statistically significant.

RESULTS

A total of 56 patients were included in this study. All of whom could be evaluated. Of these 56 patients 41.1% (n=23) were male and 58.9% (n=33) were female (Table 1). Mean age was 71.38 years (SD 13.8) and the VLUs were most frequently located in the pretibial area (42.9%, n=24), the medial malleolus (39.3%, n=22) and the lateral malleolus (8.9%, n=5) (Table 2). After 12 weeks 51.8% (n=29) of the VLUs were

completely healed, 48.2% (n=27) were still open. The median closure time in days was 38.0 (SD 35.68).

Median initial VLU size of all patients was calculated to be 2.82 cm^2 (SD 11.16), for the healed group 1.48 cm^2 (SD 2.82) and for the unhealed group 5.17 cm^2 (SD 15.11). We used the Mann-Whitney U test to evaluate the differences between the healed and unhealed group related to initial VLU size; a significant difference was found (p=0.001).

Table 1: Overview of patient and wound characteristics, grouped by final status of the VLU.

	Healed n = 29	**Unhealed n = 27**	**p-value**
Gender, n (%)			
– Male (SD) : female (SD)	13 (44.8) : 16 (55.2)	10 (37.0) : 17 (63.0)	0.554
Mean age in years (SD)	71.9 (13.2)	70.7 (14.6)	0.761
Median initial VLU size in cm^2 (SD)	1.48 (2.82)	5.17 (15.11)	0.001

Table 2: Location of the VLUs.

Location of VLU	**N (%)**
Pretibial	24 (42.8)
Medial malleolus	22 (39.3)
Lateral malleolus	5 (8.9)
Foot	2 (3.6)
Calf	2 (3.6)
Heel	1 (1.8)
Total	56 (100)

DISCUSSION

This study demonstrates that in following the Dutch guideline on VLU 52% of the initial VLUs will have healed within 12 weeks of treatment and confirms earlier published data.[2,4] As most studies on the treatment of VLUs have been performed in dedicated (dermatological) centres it may be expected that these centres perform significantly better in ulcer care we may conclude that guidelines for the treatment of VLUs improve the quality of care and makes it more cost-effective by optimising healing rates and by avoiding unnecessary investigations treatment options.[10]

To our knowledge there are no data on healing rates of VLUs by general practitioners (GP's). We therefore cannot compare our results with that of GP's. In their Guideline GP's in the Netherlands advise to refer patients to a dermatologist if a VLU does not show *'a healing tendency'* within two months.[11] It is therefore reasonable to assume that our patients had VLUs that existed for at least this period of time.

In the current study we found a significant delayed wound healing related to the initial VLU size. These data are also found in the literature but not in the Dutch guideline however.[12,13] As GP's will almost exclusively diagnose VLUs based on clinical grounds after excluding serious arterial incompetence with ankle-brachial index, ulcer size will be an easy and reproducible parameter for immediate referral. As smaller VLUs heal easier these ulcers should also heal within 3 months with outpatient care, e.g. through ambulatory compression therapy by a district nurse. In addition, in case small VLUs that have not healed within 3 months these patients should be referred to a dermatologist for further evaluation. The cut-off point for direct referral of VLU patients based on ulcer size seems to be 5 cm^2 according to this current study (Table 1).

Conclusion

The evidence-based guideline VLU of the Dutch Society of Dermatology and Venereology has given the physician – frequently the dermatologist – good information about healing expectations. In the revision of the Dutch guideline the difference of ulcer size should be incorporated to separate simple uncomplicated from complex decelerated healing VLUs, since we have demonstrated that VLUs smaller than 5 cm^2 will heal within 3 months.

Monitoring the healing rate of VLUs is an excellent quality parameter to evaluate quality of healthcare for VLU patients by GP's as well as by dermatologists. Ulcers that have not healed within three months should always be re-evaluated, including duplex ultrasound investigation and often additional treatment. However, in our view this care is best given in the second line, e.g. by a dermatologist.

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We are grateful to all the physicians and nurses of the Departments of Dermatology of the participating hospitals for their dedication and contribution to this study:
Lievensberg Ziekenhuis, Bergen op Zoom;
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Ruwaard van Putten Ziekenhuis, Spijkenisse;
Albert Schweitzer ziekenhuis, Zwijndrecht.

REFERENCES

1. Callam M. Prevalence of chronic leg ulceration and severe chronic venous disease in Western countries. Phlebology 1992;7(suppl):6-12.
2. Nicolaides AN, Cardiovascular Disease E, Research T, European Society of Vascular S, Organization TIASAC, International Union of A, et al. Investigation of chronic venous insufficiency: A consensus statement (France, March 5-9, 1997). Circulation 2000;102(20):E126-63.
3. Amsler F, Willenberg T, Blattler W. In search of optimal compression therapy for venous leg ulcers: a meta-analysis of studies comparing diverse [corrected] bandages with specifically designed stockings. J Vasc Surg 2009;50(3):668-74.
4. Moffatt CJ, Doherty DC, Smithdale R, Franks PJ. Clinical predictors of leg ulcer healing. Br J Dermatol 2010;162(1):51-8.
5. Richtlijn Diagnostiek en behandeling van het ulcus cruris venosum. In. Utrecht: CBO; 2005.
6. Guidelines for Diagnostics and treatment of Venous Leg Ulcers. European Dermatological Forum. Version 2.1, December 2006, pag 1-47.
7. Johnson M, Miller R. Measuring healing in leg ulcers: practice considerations. Appl Nurs Res 1996;9(4):204-8.
8. Mayrovitz HN, Soontupe LB. Wound areas by computerized planimetry of digital images: accuracy and reliability. Adv Skin Wound Care 2009;22(5):222-9.
9. Kwaliteitsinstituut voor de Gezondheidszorg CBO. Richtlijn Diagnostiek, preventie en behandeling van veneuze trombo-embolie en secundaire preventie van arteriële trombose. Alphen aan den Rijn: Van Zuiden Communications B.V.; 2008.
10. van Gent WB, Wilschut ED, Wittens C. Management of venous ulcer disease. BMJ 2010;341:c6045.
11. NHG-Standaard Ulcus cruris venosum (Tweede herziening). Van Hof N, Balak FSR, Apeldoorn L, De Nooijer HJ, Vleesch Dubois V, Van Rijn-van Kortenhof NMM. Huisarts Wet 2010:53(6):321-33.
12. Hjerppe A, Saarinen JP, Venermo MA, Huhtala HS, Vaalasti A. Prolonged healing of venous leg ulcers: the role of venous reflux, ulcer characteristics and mobility. J Wound Care 2010;19(11):474, 476, 478 passim.
13. Margolis DJ, Berlin JA, Strom BL. Risk factors associated with the failure of a venous leg ulcer to heal. Arch Dermatol 1999;135(8):920-6.

Chapter 10

Ulcer recurrence after in-hospital treatment for recalcitrant venous leg ulceration

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Br J Dermatol 2013;168(5):999-1002

ABSTRACT

Background: Leg ulceration caused by chronic venous disease occurs in 1% of the adult Western population. A majority of these patients are successfully treated in the outpatient setting. A minority of patients is hospitalised, most frequently because of the lack of healing tendency. The literature provides recurrence rates for ulcer disease, but lacks specific data on recurrence rates after in-hospital treatment of recalcitrant venous leg ulcers.

Objectives: To investigate time to ulcer recurrence after in-hospital treatment of venous leg ulceration.

Methods: A multicentre, retrospective cohort study of patients admitted for leg ulceration between 1996 and 2007 was conducted.

Results: Data could be collected for 107 of the patients. Of these, 27 patients had a conservative treatment (bed rest, local wound care, pain management) and 48 patients underwent surgical ulcer treatment with (n=19) or without (n=29) initial vacuum-assisted closure (VAC) treatment. Treatment method was 'miscellaneous' in the remaining 32 patients. Median admission time was 30 days, median percentage of closure at discharge was 95%, and median time to ulcer recurrence 60 days. Mann-Whitney U-test showed significant differences between the conservative group and the surgery group, the latter having a longer length of hospital stay ($P<0.0001$) and a higher percentage of ulcer closure ($P<0.0001$) but there was no difference in time to ulcer recurrence ($P=0.273$). Comparable differences were demonstrated between the conservative group and the VAC plus surgery group. No significant differences could be demonstrated between the surgically treated patients and those treated by VAC and surgery.

Conclusions: Hospital stay is significantly shorter in cases of surgical treatment of recalcitrant venous leg ulcers. Most ulcers recur within 2 months after hospital discharge. Recurrence of venous leg ulcers after hospital admission is independent of method of treatment and cause of ulceration.

INTRODUCTION

Chronic venous disease may lead to leg ulceration, the severest manifestation of this debilitating condition. In the adult Western population venous leg ulceration has a lifetime prevalence of 1% and a prevalence of active ulceration of 0.3%.[1,2]

The majority of patients with venous ulcers are treated in an outpatient setting. On average 50% of the ulcers heal within 12 weeks, but about 8% of the treated ulcers have not healed after 5 years.[2,3] There is a high recurrence rate of up to 70%.[4] The majority of the recurrences occur within three months of healing. These recurrence rates decrease to 23-32% after two years and 32-39% after five years if compression therapy is continued after ulcer healing.[5]

A minority of patients are admitted to hospital because of leg ulceration, most frequently because of nonhealing tendency. The recent literature lacks information on such recalcitrant venous leg ulcers with respect to the effect of hospitalization on healing rate and recurrence rate after discharge.

The present study was performed to investigate the value of in-hospital treatment for recalcitrant venous leg ulceration. The primary aim of the study was to investigate time to ulcer recurrence after in-hospital treatment of patients with venous leg ulceration. Secondary aims investigated were: the duration of hospital stay; percentage of closure at discharge; the difference between ulcers based on primary venous insufficiency and those based on secondary (post-thrombotic) venous insufficiency; and the correlation between ulcer duration before hospital admission and ulcer recurrence.

MATERIALS AND METHODS

A multicentre, retrospective cohort study of patients admitted for leg ulceration between 1996 and 2007 was conducted. Patients with venous leg ulceration were collected from three academic (Erasmus Medical Centre, Rotterdam, the Netherlands; University Hospital of Antwerp, Antwerp, Belgium; Maastricht University Medical Centre, Maastricht, Netherlands and one rural hospital (Bernhoven Hospital, Veghel, Netherlands). The following main data were collected from medical charts and reports to the referring physician: sex, date of birth, year of admission, length of hospital stay, cause of ulceration (primary or secondary chronic venous disease, therapy, percentage of ulcer closure at discharge, and time to ulcer recurrence. Only patients with ulcers based on chronic venous disease as the major cause of ulceration were included.

Patients were divided into four treatment groups: conservative (local wound management, bed rest and pain management), ulcer surgery (split-thickness skin graft or pinch grafting), ulcer surgery in combination with vacuum-assisted

closure (VAC) and miscellaneous treatments. None of these patients underwent additional venous surgery or foam sclerotherapy during hospitalization. Patients were excluded for statistical analysis if any significant data were missing.

Ulcer healing and recurrence was calculated using Kruskal-Wallis test. Different treatment regimens were compared using Mann-Whitney U-test. All analyses were carried out using SPSS for Windows version 13.0.1, with $P<0.05$ considered significant.

RESULTS

For 107 patients (81 women; median age 75 years; range 30-92 years) all significant data could be collected (Table 1). The overall mean time from first ulcer episode to hospital admission was 13 years (SD 14.2, median 6.5). Median admission time was 31 days (range 1-365), median percentage of closure at discharge was 95 % (range 0-100), and median time to ulcer recurrence 60 days [interquartile range (IQR) 19-338]. Patients were divided into four main treatment groups: conservative (n=27), surgery (n=29), VAC in combination with surgery (n=19) (Figure 1a-c), and miscellaneous treatment method (n=32). Mann-Whitney U-test showed significant differences between the conservative group and the surgery group, the latter having a longer length of hospital stay ($P<0.0001$) and a higher median percentage of ulcer closure (in the surgery group 100 % vs. 50 % in the conservative group; $P<0.0001$), but there was no difference in time to ulcer recurrence ($P=0.273$). Comparable differences were demonstrated between the conservative group and the VAC plus surgery group for length of hospital stay ($P<0.0001$), percentage of ulcer closure (median closure in the VAC plus surgery group 95%; $P<0.0001$), and time to ulcer recurrence ($P=0.790$). No significant differences could be demonstrated between the surgically treated patients and the patients treated with VAC plus surgery. In patients treated with skin transplantation, time to follow-up ranged from 1 to 9 years. Data comparing primary (n=44) to secondary (n=61) causes of venous ulceration showed no significant differences for length of hospital stay, percentage of ulcer closure at discharge and time to ulcer recurrence.

To estimate the correlation between time from first ulcer appearance to hospital admission and ulcer recurrence, we first calculated whether there were significant differences between the treatment groups regarding the time from ulcer appearance (in years). There were no significant differences between the different treatment groups calculated with Kruskal-Wallis test ($P=0.221$). Subsequently we estimated the correlation between time from ulcer appearance to hospital admission and time to ulcer recurrence of the overall patients group. No correlation could be demonstrated (Pearson $r=0.05$, $P=0.708$).

Table 1: Patient characteristics defined by the different treatment modalities.

	Conservative (n = 27)	**Surgery (n = 29)**	**VAC + Surgery (n = 19)**	**Miscellaneous (n = 32)**	Overall (n = 107)
Sex					
– men : women	7 : 20	8 : 21	3 : 16	7 : 25	25 : 82
Age (years)					
– median	80.5	74.0	76.0	72.5	75.0
– SD*	16.1	11.8	14.5	16.7	15.1
– range	39 – 92	41 - 90	46 - 84	30 - 90	39 - 92
Hospital admission (days)					
– median	19.0	49.0	39.0	21.0	30.0
– SD*	19.0	64.3	29.9	18.3	41.0
– range	7 – 75	10 – 365	21 - 120	1 – 80	1 - 365
Cause of venous ulcer					
– primary : secondary	12 : 15	13 : 16	9 : 10	10 : 22	44 : 63
Closure at discharge (%)					
– median	50.0	100	95.0	100	95.0
– SD*	40.8	17.8	25.4	15.9	34.3
– range	0 - 100	50 - 100	0 - 100	50 -100	0 - 100
Time of recurrence (days)					
– median	82.5	120.0	65.5	35.0	60.0
– IQR**	0 - 593	14 - 540	14 - 135	30 - 180	19.3 – 337.5
Patients with recurrent or persisting ulcer (%)	26/27 (96.3)	22/27 (81.5)	15/19 (78.9)	18/22 (81.8)	81/95 (85.3)
– lost to follow-up	0/27	2/29	0/19	5/32	7/107
– died during hospital stay	0/27	0/29	0/19	5/32	5/107

* SD = standard deviation.
** IQR = inter quartile range.

Figure 1a: Venous leg ulcer after debridement and before pinch grafting.

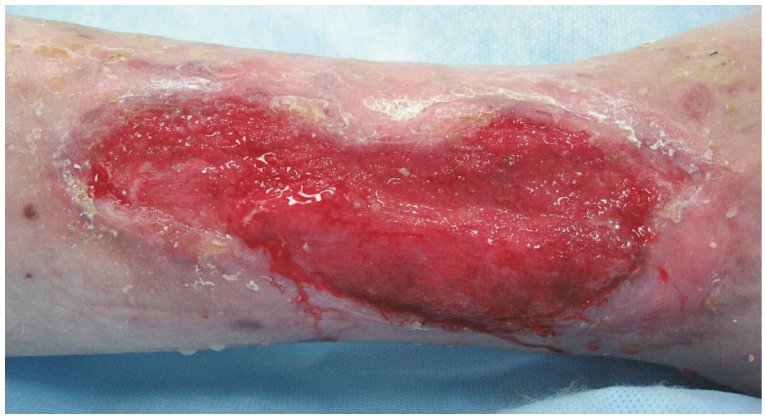


Figure 1b: Five days after pinch grafting over 50% of the graft has settled.

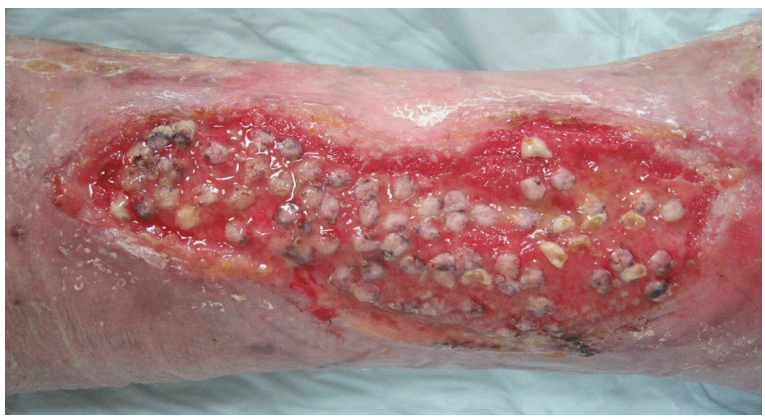
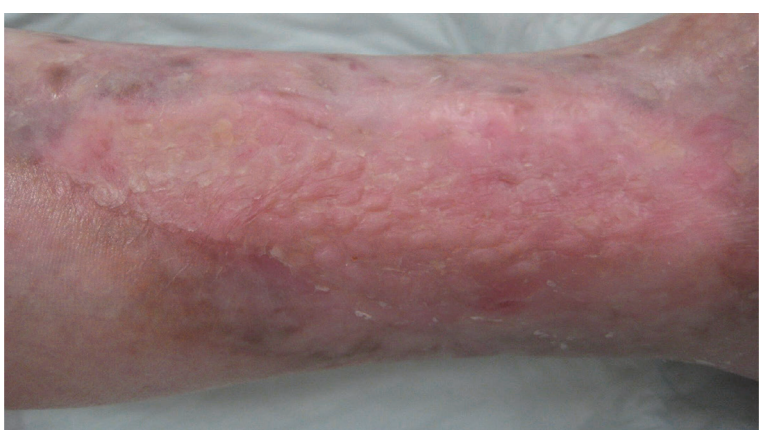


Figure 1c: No signs of ulcer recurrence during follow-up in this patient.



DISCUSSION

In this study, 2 months after hospital discharge 85.3% of venous leg ulcers had already recurred. Compared with the existing literature the overall recurrence rate in our study was high. The few studies published on recurrence rates after in-hospital treatment of patients with (venous) leg ulcers have shown recurrence rates between 23 and 62%,[6,7] with comparable time to follow-up. In the study of Sebastian[6] on patients treated with skin transplantation, time to follow-up was comparable with the present study (1-9 years vs. 2-13 years). In our study, although there was no statistically significant difference, the conservatively treated group had the highest recurrence rate (96.3%), compared with 81.5% and 78.9% in the surgery and VAC plus surgery groups, respectively.

We could not find any data in the literature on time to ulcer recurrence after hospital admission. However, after outpatient treatment of venous leg ulcer with compression bandages recurrence rates of 26 to 69% have been reported.[5] Most of the recurrences occur in the first 3 months after healing.[8] A median recurrence time of 2 months in our study corresponds well with these data.

The percentage of ulcer closure at hospital discharge was significantly higher in the patients treated with surgery or a combination of VAC plus surgery compared with the conservatively treated patients. This may be explained by the beneficial effect of skin grafts. Most ulcers that had been covered with grafts were scored as having closure of (almost) 100% at discharge. However, skin grafting did not result in better outcome with regard to time to ulcer recurrence. It is noteworthy that, of the conservatively treated patients, only four patients had 100% closure at hospital discharge. In this group of non-surgical patients, primary and secondary causes were equally divided in those patients who had 100% healing and those who did not heal.

Most patients with ulcers treated in hospital are admitted because of the lack of healing tendency. In most of these patients it is not evident why the ulcers have not healed in an outpatient setting. Up to a few years ago only limited literature existed on risk factors for delayed wound healing and ulcer recurrence. Recent studies have demonstrated contradicting as well as supporting data regarding risk factors.[3, 9-11] Presence of lipodermatosclerosis, long-standing ulceration and history of deep vein thrombosis have all been claimed as risk factors for delayed wound healing, while the same studies reported conflicting data on other risk factors such as obesity and ulcer size.

With regard to ulcer recurrence, duration of the first ulcer episode for more than two years before hospital admission as well as incompetence of the deep venous system have been indicated as risk factors.[10] In the present study the overall

mean time from first ulcer episode to hospital admission was long (13 years) which confirms the fact that long-standing ulceration is a risk factor for ulcer recurrence.[12] Another risk factor for ulcer recurrence is persisting superficial venous reflux as has been shown by Gohel et al. in the ESCHAR study, a randomized controlled trial comparing surgical correction of superficial venous reflux with conservative treatment (compression).[13] They demonstrated a significant reduction of ulcer recurrence and a greater proportion of ulcer-free time after surgery for correction of superficial venous reflux than after compression bandaging alone. It should be noted that in the present study none of the patients had undergone surgery or foam sclerotherapy to correct superficial reflux during their hospital stay, and this may have contributed to the high ulcer recurrence rate. It was not always clear from the charts why superficial reflux had been left untreated. From the data of the ESCHAR study (which were unknown at the moment of treatment of patients included in the present retrospective study) it should be clear that whenever correction of superficial venous reflux is possible, this should be the treatment of choice to reduce recurrence rate more successfully.[11] Currently, this can be easily performed either by foam sclerotherapy, endovenous thermal ablation or surgery.

In our study, we expected that venous leg ulcers secondary to post-thrombotic syndrome would have a worse outcome with regard to recurrence time than primary venous leg ulcers, related to superficial reflux only. However, we could not demonstrate any significant differences between these two groups. No literature could be found on this specific topic, but apparently the aetiology of chronic venous disease was not a predictive factor for the outcome of venous leg ulcers.

Only a minority of patients are hospitalized because of leg ulceration, usually because of lack of healing tendency. A Dutch database registered 12 164 leg ulcers in 2008 of which 514 (4.2%) were admitted to hospital (http://www.vektis.nl). The term recalcitrant venous ulcer (or the so-called 'ulcère rebelle' in French literature) used to be applied to nonhealing ulcers. In our opinion this term may also be used for venous leg ulcers that recur early after successful treatment. These ulcers are in some way different from the ulcers that generally heal within a few months in the outpatient setting. Therefore it is necessary to study in more detail the aetiology and pathophysiology of recalcitrant ulcers, in order to enlarge therapeutic options and improve final outcome.

In conclusion, our study shows that recurrence of venous leg ulcers after hospital admission is independent of ulcer treatment and cause of ulceration. Hospital admission as such does not seem to be successful and other treatment strategies should be considered. Besides time since the first episode of ulceration

other risk factors for delayed wound healing and ulcer recurrence should be further investigated to be able to develop better treatment strategies in the future.

Acknowledgements
The authors want to thank the medical secretaries of the four participating hospitals for their practical help in providing patients' charts.

REFERENCES

1. Callam M. Prevalence of chronic leg ulceration and severe chronic venous disease in Western countries. Phlebology 1992;7(suppl):6-12.
2. Nicolaides AN, Cardiovascular Disease E, Research T, European Society of Vascular S, Organization TIASAC, International Union of A, et al. Investigation of chronic venous insufficiency: A consensus statement (France, March 5-9, 1997). Circulation 2000;102(20):E126-63.
3. Moffatt CJ, Doherty DC, Smithdale R, Franks PJ. Clinical predictors of leg ulcer healing. Br J Dermatol 2010;162(1):51-8.
4. Etufugh CN, Phillips TJ. Venous ulcers. Clin Dermatol 2007;25(1):121-30.
5. Nelson EA, Bell-Syer SE, Cullum NA. Compression for preventing recurrence of venous ulcers. Cochrane Database Syst Rev 2000(4):CD002303.
6. Sebastian G. Die Rolle der Hauttransplantation im Behandlungsplan venoser (postthrombotischer) Ulcera cruris. Wien Med Wochenschr 1994;144(10-11):269-72.
7. Gruen RL, Chang S, MacLellan DG. Optimizing the hospital management of leg ulcers. Aust N Z J Surg 1996;66(3):171-4.
8. Palfreyman SJ, Lochiel R, Michaels JA. A systematic review of compression therapy for venous leg ulcers. Vasc Med 1998;3(4):301-13.
9. Brizzio E, Amsler F, Lun B, Blattler W. Comparison of low-strength compression stockings with bandages for the treatment of recalcitrant venous ulcers. J Vasc Surg 2010;51(2):410-6.
10. Abbade LPF, Lastória S, de Almeida Rollo H. Venous ulcer: clinical characteristics and risk factors. Int J Dermatol 2011;50:405-411.
11. van Gent WB, Hop WC, van Praag MC, Mackaay AJ, de Boer EM, Wittens CH. Conservative versus surgical treatment of venous leg ulcers: a prospective, randomized, multicenter trial. J Vasc Surg 2006;44(3):563-71.
12. Barwell JR, Ghauri ASK, Taylor M, Deacon J, Wakely C, Poskitt KR, et al. Risk factors for healing and recurrence of chronic venous leg ulcers. Phlebology 2000;15(2):49-52.
13. Gohel MS, Barwell JR, Taylor M, Chant T, Foy C, Earnshaw JJ, et al. Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial. BMJ 2007;335(7610):83.

Chapter 11

The recalcitrant venous leg ulcer, a never ending story?

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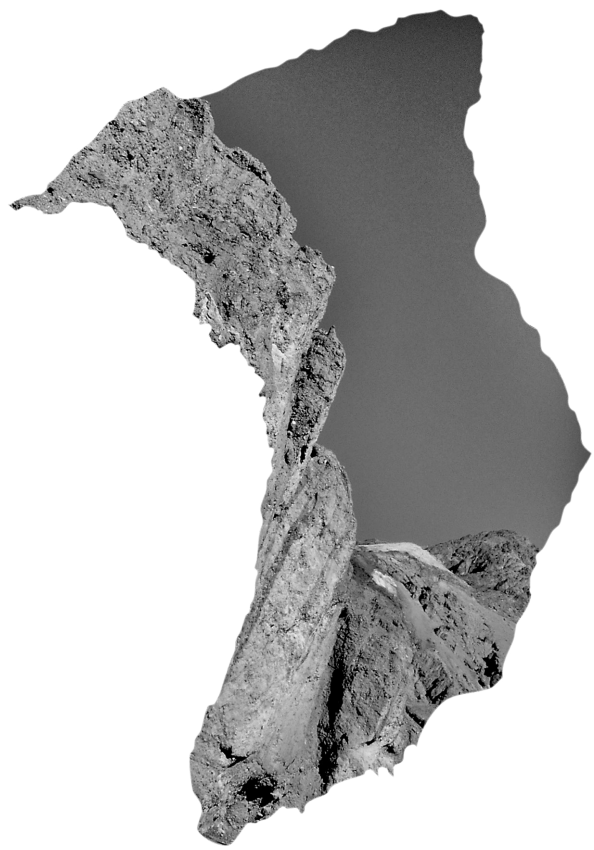
Submitted



SUMMARY

Introduction: In general, four particular causes of recalcitrant venous leg ulcers may be distinguished. These are foot pump insufficiency, chronic venous compartment syndrome and non-re-canalized popliteal vein thrombosis. The fourth cause of recalcitrant venous leg ulcers is lipodermatosclerosis as a symptom of severe chronic venous insufficiency.

Methods: We reviewed the literature and based on this we describe four main causes of recalcitrant venous leg ulcers and their specific treatment.

Results: Foot pump insufficiency arises when the plantar foot veins are not able to empty. Treatment should consist of physical therapy, a mechanical foot pump device and an insole. Lipodermatosclerosis may be treated by excision and split-thickness skin grafting (Vigoni procedure). Chronic venous compartment syndrome is usually caused by post-thrombotic syndrome and treatment consists of a fasciectomy, but is rarely used nowadays. Patients with non-re-canalized popliteal vein thrombosis may be supported by intermittent pneumatic compression, walking exercises, alternate standing and walking with lying down. All patients with recalcitrant venous leg ulcers must wear medical elastic compression stockings with high stiffness and high compression lifelong.

Conclusions: Patients with recalcitrant venous leg ulcers are challenging. More specific treatment will heal more of these ulcers.

ZUSAMMENFASSUNG

Chronische Venenerkrankung kommt häufig vor und führt zu Ulzerationen in 1% der Westlichen Bevölkerung. Venöse Beinulzerationen können in drei Gruppen eingeteilt werden: unkompliziert, persistierend und rezidivierend. Es gibt vier Ursachen für persistierende Beinulzerationen: Insuffizienz der Muskel-Venen-Pumpe des Fußes, Lipodermatosklerose, chronisch-venöse Kompartmentsyndrom und nicht-rekanalizierte Thrombose der Vena Poplitea.

Methode: Wir haben die Literatur durchsucht und beschreiben vier Hauptursachen für persistierende Beinulzerationen und Ihre Behandlung.

Resultaten: Die Insuffizienz der Fußpumpe entsteht, wenn die Venen der Fußsohle sich niet entleeren können; die Behandlung besteht deswegen aus Physiotherapie, eine mechanische Fußpumpe und eine Einlegsohle. Lipodermatosklerose wird behandelt mit ambulanter Kompressionstherapie, Exzision des Ulkus und Spalthauttransplantation (Verfahren von Vigoni). Das chronisch-venöse Kompartmentsyndrom wird meistens verursacht durch das postthrombotische Syndrom, das zur Erhöhung des venösen Drucks führen kann. Die Behandlung besteht aus einer Fasziotomie. Patienten mit einer nicht-rekanalizierten Thrombose der Vena Poplitea können unterstützt werden durch intermittierende pneumatische Kompression, Gehübungen und abwechselnd stehen, laufen und liegen. Patienten mit persistierenden venösen Beingeschwüren sollten Lebenslang medizinische Kompressionsstrumpfe mit hoher Steifigkeit tragen.

Schlussvolgerungen: Einsicht in der zugrundeliegenden Pathologie von persistierende venöse Beinulzerationen ist entscheidend, um die Behandlung von dieser diagnostisch und therapeutisch anspruchsvolle Patienten zu optimieren. Die sorgfaltige Analyse der verschiedenen Ursachen und eine zielgerichtete Behandlung wird die Ergebnisse verbessern und der Anzahl der erfolgreich behandelten Ulzerationen erhöhen.

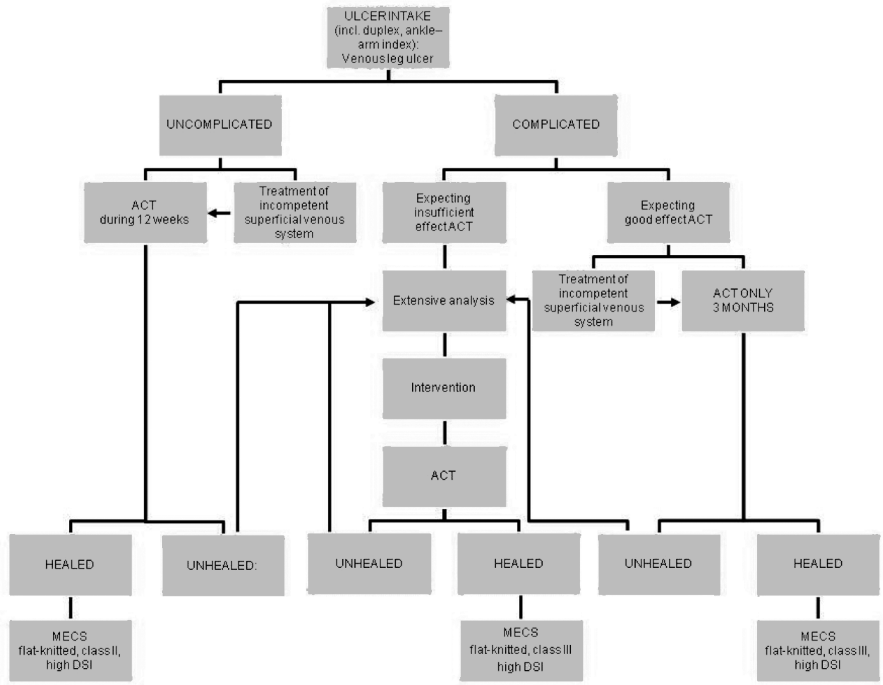
INTRODUCTION

Chronic venous disease (CVD), e.g. varicose veins and post-thrombotic syndrome (PTS) is one of the most common medical conditions. In 1994, the so-called CEAP-classification was introduced "as a more precise classification of chronic venous dysfunction simple enough to encourage its universal acceptance".[1] Chronic venous disease has a worldwide prevalence of 83.6% in the adult population with 63.9% of the subjects ranging from C1 to C6 in the CEAP clinical classification and 19.6% being C0s subjects.[2] In the adult Western population, the prevalence of varicose veins is higher than 20% (range, 21.8%-29.4%) and about 5% of the population (range, 3.6%-8.6%) has venous edema, skin changes or venous leg ulcers (VLUs). Active VLUs are present in up to 0.5% and between 0.6% and 1.4% have healed VLUs.[3,4] Duplex ultrasound is the method of choice to confirm or to exclude the presence of venous dysfunction, although it lacks information on true venous hemodynamics.[5,6] We investigated the value of the CEAP clinical classification in relation to direct ambulatory venous pressure measurement since the severity of CVD depends on the severity of the ambulatory venous hypertension. In a previous study [7] we reported a statistically significant relationship between the two, justifying the replacement of the ambulatory venous pressure measurement with the CEAP clinical classification.

Ambulatory compression therapy (ACT) with bandages or medical elastic compression stockings (MECS) is the gold standard treatment modality.[8] Optimally, this should be combined with the correction of the existent venous insufficiency, since treatment of insufficient veins decreases the recurrence rate (Figure 1).[9] On average, 50% of the VLUs heal within 12 weeks with adequate ACT, but about 8% of the treated VLUs still have not healed after 5 years.[10] The reason for this is not always clear. Even with adequate ACT not all VLUs will heal. Moreover, most of the VLUs that have not healed within one year will also not heal within 5 years.[11] A minority of the patients with VLUs is admitted to the hospital in most cases, because of the non-healing tendency. During hospitalization, nearly all VLUs will heal because of the fact that patients are confined to their beds minimizing the negative influence of gravity. In other words, venous pressure will be between 5 and 10 mmHg in supine position.[12] During hospital admission various treatment modalities such as conservative, surgical and Vacuum Assisted Closure© combined with surgery may be used. However, irrespective of the therapy used, most VLUs will recur within two months after hospital discharge, even with adequate ACT (flat-knitted customized class II-III MECS with a high dynamic stiffness).[13] Although all VLUs result from a disturbed skin microcirculation induced by venous hypertension, these non-

healing VLUs differ in underlying complexity from VLUs that are successfully treated in the outpatient setting with ACT.[14]

Figure 1: Flowchart diagnosis and treatment of VLUs.



Since various studies[4,0] reported that not all VLUs healed easily with ACT and many ulcers recurred, one cannot lump them together. Subdividing VLUs should help to customize the treatment in the healing phase as well as after the VLU has healed. We propose three categories for this:

1. Uncomplicated VLU: the first ulcer that usually heals within 3 months with ACT;
2. Recurrent VLU: an ulcer that recurs more than twice;
3. Recalcitrant VLU: a VLU that does not heal within 1 year or recurs more than twice.

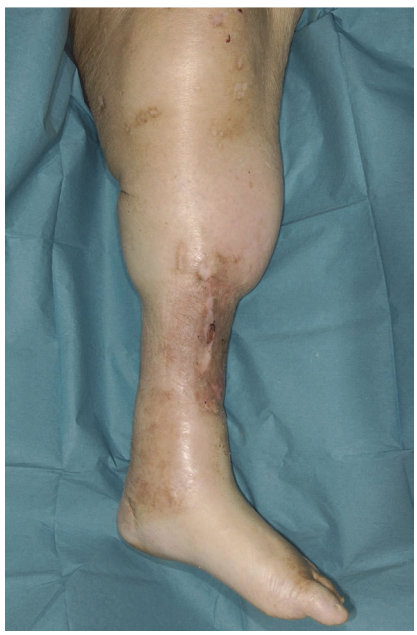
All these recalcitrant VLUs ("ulcère rebelle" in French literature) are based on a disturbed venous return from the leg to the heart causing high ambulatory venous

pressure (venous hypertension), which is also the hallmark of CVD.[10] Failure of the calf muscle pump is the most common cause of inadequate venous return. Other factors playing a role in recalcitrant VLUs may be obesity, mixed arterial-venous disease, infection, inadequate diagnosis, inadequate treatment and genetic factors like disturbances of the clotting system. However, these causes of a disturbed VLU healing are beyond the scope of this article because we focused on factors directly correlated to CVD and for which a treatment modality exists. We distinguish the following four specific causes of the recalcitrant VLUs to clarify the problem:

1. Foot pump insufficiency;
2. Lipodermatosclerosis (Figure 2);
3. Chronic venous compartment syndrome;
4. Non-re-canalized thrombosis.

We postulate that by treating the underlying disorder these VLUs will have a higher chance of healing and recurrence will be lower than that with standard treatment with ACT alone.

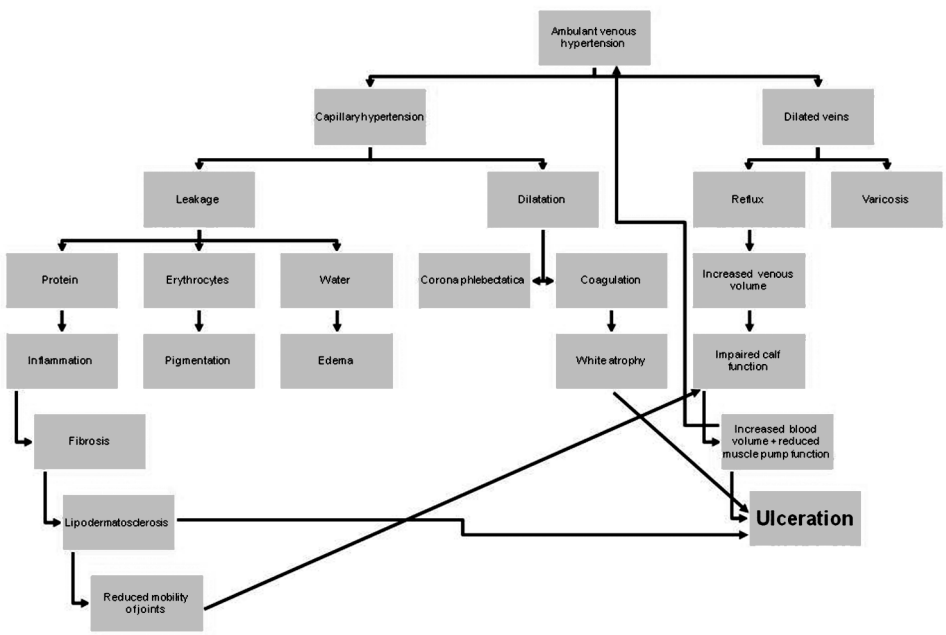
Figure 2: Lipodermatosclerosis.



UNDERLYING ETIOLOGY OF RECALCITRANT VLUS

Since the heart is a pressure pump and not a suction pump, mechanisms other than the human heart are responsible for the venous return. Of all physiological mechanisms available for the venous return, the venous muscle pumps are by far the most important. They consist of the foot pump, the calf muscle pump and the muscle pump of the upper leg. These pumps together overcome a pressure of around 90 mmHg in still standing position to a pressure of around 20 mmHg when walking. Venous pressure will be lower only in the supine position. Failure of one of these pumps because of valve dysfunction in the veins, venous obstruction in the deep proximal venous system and/or any form of dependency will lead to venous hypertension, which is the main cause of CVD.[15] The pathophysiological mechanism in which the incompetence of larger veins leads to a decompensated microcirculation responsible for all the clinical signs of CVD such as edema, lipodermatosclerosis, white atrophy and VLUs is very complex.[16] In recalcitrant VLUs, the microcirculation of the skin is seriously compromised leading to chronic changes in the extracellular matrix. Eventually, these changes are irreversible and normal healing is disabled (Figure 3). Even the application of external growth factors and all kinds of modern wound dressings will not be able to improve the alterations in the microcirculation and the extracellular matrix.[17]

Figure 3: The Rotterdam model.



Not all skin changes will contribute to this problem equally. White atrophy and lipodermatosclerosis need our attention. Although white atrophy is not unique to CVD, venous incompetence is considered to be the most common cause. Under the influence of the high ambulatory venous pressure, the total density of capillaries not only diminishes, but the remaining capillaries become much more tortuous, the so-called glomerulus-like structures.[18] Microthrombosis occurs due to standstills in the capillaries and an extremely low local skin oxygen pressure.[19] The surrounding extracellular matrix homogenises and the tissue becomes vulnerable and finally a very painful VLU occurs. Although VLUs in white atrophy are very painful and show a slow healing tendency, they generally heal within a year and are therefore, not considered to be recalcitrant. Lipodermatosclerosis has had many aliases, is unique for CVD and a precursor of most VLUs.[20] The skin becomes thicker and the walls of the capillaries become thickened by collagen IV formation.[21] The sclerosis of the dermis extends to the subcutis, subcutaneous fat, and finally to the fascia. Lipodermatosclerotic skin is also vulnerable and therefore, prone to VLUs.[22] For a rational treatment of this complex ulcer we first need to analyze the four given factors in each patient.

1. FOOT PUMP INSUFFICIENCY

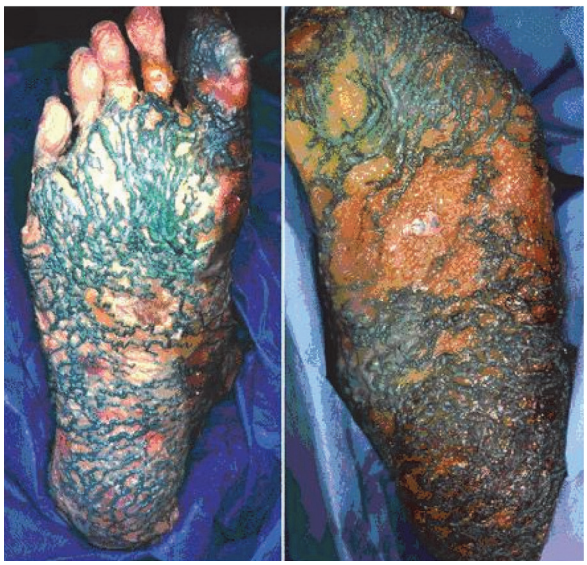
The venous system of the foot is the most distal venous system and as a consequence is influenced the most by gravity. Moreover, it is a very complex venous system. The central part is a venous reservoir under the plantar fascia, known as Lejars' plantar venous sole (Figure 4).[23] The great saphenous vein (GSV) as well as the small saphenous vein (SSV) originate from the dorsal venous arch (Hunter), which has many valveless perforators.[24] There are perforating veins along the base of the foot that connect the venous reservoir to the superficial venous system. Valves in these veins are directed outwards and prevent inwards flow. Therefore, blood is directed outwards when pressure is applied on the foot. A venous foot pump was first postulated by Le Dentu already in 1867, but never received the attention it deserved.[25]

During normal walking the combined action of the plantar venous pump and the calf muscle pump initiate venous return. Three phases of the venous foot pump can be described during walking:[26]

1. During the weight-bearing phase, placement of the foot on the ground gives direct compression of the venous reservoir in the sole of the foot;
2. The flexion of the toes fixes the forefoot on the ground resulting in compression in the musculo-tendinous plane in the impulse phase;

3. In the suspension phase, the foot is lifted off the ground, which allows refilling of the plantar veins.

Figure 4. Sole of Lejars. Very important dilatation of all the veins of the sole due to CVD.[26]

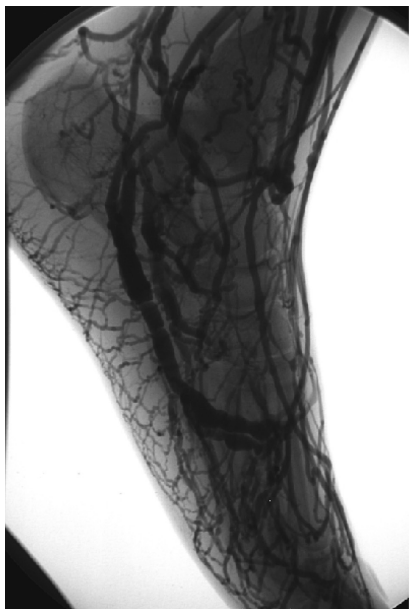


The plantar venous pump is the only venous pump up to the level of the calf. At this level, the soleus muscle and more proximally the gastrocnemius muscle take over its action. This makes the foot pump the essential first step for venous return in the leg. Incompetence of this pump is rare and often associated with the immobility of the ankle joint. This explains why venous foot ulcers occurring in the skin changes also known as 'pseudo-Kaposi sarcoma', 'acroangiodermatitis of Mali-Kuiper' or 'dermite d'ocre de Favre et Chaix', are much less common than VLUs related to the incompetence of the GSV or SSV located on the medial or the lateral side of the ankle, respectively.[27] Nonetheless, VLUs of the forefoot and the toes have also been described to be associated with reflux in the foot portion of the GSV, SSS and the anterior arch veins of the foot dorsum.[28]

Muscle contraction of the calf muscles in persons with a normal gait leads to emptying of the calf muscle veins.[29] Patients with an abnormal gait, for example those who have reduced ankle joint mobility or static foot disorders (hollow feet, flat feet) are not able to empty the plantar foot veins and subsequently the calf muscle

veins sufficiently, which may ultimately lead to CVD.[30] Another reason for the muscle pump failure and the secondary VLU is the arthrogenous stasis syndrome, which is caused by regional lipodermatosclerosis.[31] In addition to the VLUs, further symptoms include recurvation in the knee joint and fixed talipes equinus. The arthrogenous stasis syndrome differs from the chronic venous compartment syndrome in that the intra-compartmental structures are not altered. Venous foot pump insufficiency may be diagnosed with dynamic phlebography of the foot (Figure 5).

Figure 5: Phlebography of the sole of Lejars.



An insole should correct static foot disorders and patients with reduced ankle mobility or immobilization should use a mechanical foot pump device – a device that mimics the movement of the foot during ambulation – on a daily basis. Basic treatment should consist of placing a pad at the base of the toes of the forefoot, added customized inlays combined with MECS with a sufficiently high stiffness. Patients should be trained by a physical therapist to properly unwind the foot in combination with daily walking exercises. In addition, if possible, all incompetent leg veins should be treated.

2. LIPODERMATOSCLEROSIS

Lipodermatosclerosis is classified as C4b in the clinical score of the CEAP-classification and is considered a high risk factor for developing VLUs, persistent VLUs and VLUs recurrence.[22] In 1958, Vigoni described a surgical excision technique for the treatment of ulcers in lipodermatosclerotic skin in which all the sclerotic skin is removed.[32] He treated his patients with ACT before the surgical excision of the involved site. Ambulatory compression therapy does not only correct edema, but also initiates the healing process of the reversible part of lipodermatosclerotic skin ulcers. It ends when a steady state has been reached and no further improvement is to be expected. The lesions were grafted with split-thickness skin grafts after excision. This Vigoni procedure was revived during the last decade of the last century and is now also known as the Schmeller procedure.[33] The result of this procedure is influenced by the extent of the lipodermatosclerosis, whether or not ACT was used before the intervention and the presence of obesity. Nevertheless, patients with non-healing VLUs in an area with lipodermatosclerosis should be seriously considered for treatment with the Vigoni procedure. This will improve the prognosis with regard to the healing time and the recurrence rate of VLUs. Long-term healing rate of 88% was reported by Schmeller and Gaber.[33]

3. CHRONIC VENOUS COMPARTMENT SYNDROME

In 1990, Pflug et al described a group of patients with both varicose veins and an increased interstitial resting pressure of the subfascial tissues in the malleolar area of the leg.[34] Most of these patients also had a PTS and had suffered from CVD for years before they developed other symptoms. They called it: "chronic venous compartment syndrome" (CVCS) because the increased pressures were measured in the venous compartment.

Venous hypertension causes a protein-rich edema that leads to inflammation and thus fibrosis and sclerosis of the skin, subcutaneous tissue and underlying fascia.[35] Patients frequently have large recurrent or persistent VLUs. The fibrotic changes in the fascia and within the anterior compartment of the lower leg may lead to an increased pressure within the compartment.

Patients with a CVCS not only suffer from VLUs, but may also have other symptoms such as exercise induced (ischemic) pain, swelling, impaired muscle function and paraesthesia.[36] The diagnosis is made by measuring the pressure in one of the compartments of the lower leg, usually the anterior compartment.[7] However, unlike the compartment pressures in the acute compartment syndrome, anterior compartment pressure measurement has never been standardized for the diagnosis CVCS. To establish the diagnosis CVCS, one should measure the pressure

in both legs and relate the symptoms and signs to the measured pressures. Hach et al published a study in which they reported the results of decompression in CVCS in which the pressure fell significantly, but never normalized (Table 1).[37] Perhaps these pressures may guide physicians in their decision making. Based on the data by Hach et al, we suggest that pressures above 18 mmHg (supine) and 35 mm Hg (standing) should be regarded as pathological in CVCS.

The treatment of CVCS consists of fasciectomy. Fasciectomy in which a part of the fascia is removed seemed to be superior to fasciectomy in which the fascia was only incised. After fasciectomy most of the VLUs will heal with ACT and patients will be relieved of their symptoms.[37]

Table 1. Mean compartment pressures (range) in mmHg in healthy subjects and patients with chronic venous compartment syndrome (CVCS) before and after treatment.[37]

	Healthy subjects	Patients with CVCS	Patients after crural fascia resection and grafting
Supine	13.6 (9-17)	21.1 (8-47)	15.5 (5-24)
Upright	29.9 (15-42)	62.5 (33-87)	34.5 (10-58)

4. NON-RE-CANALIZED THROMBOSIS

A PTS will develop in 50% of the patients after a deep vein thrombosis.[38] Based on the underlying disturbance in the venous hemodynamics, PTS may be divided into three different types:[39]

- Reflux type: recanalization and destruction of valves leading to venous hypertension;
- Obstructed type: persistent occlusion causing high venous resistance;
- Mixed type: combining the negative effects of reflux and obstruction on the venous hemodynamics.

Reflux type PTS is generally less severe than the other two types and these patients may be treated with MECS. In patients with the obstructed type PTS, venous claudication is not uncommon. Venous claudication is defined by thigh and/or leg pain and tightness on vigorous exercise, which subsides in rest.[40] The symptomatology of venous claudication is different from that of intermittent claudication. The pain in venous claudication is described as congestion and pressure and is felt more in the proximal part of the leg and often caused by proximal pelvic vein obstruction. With regard to the PTS, it is important to subdivide

the obstructed type into proximal obstruction, e.g. femoral and iliac vein and distal occlusion, e.g. popliteal vein, because of the therapeutic implications and the different clinical picture. In general, persistent obstruction is more common in the proximal veins than in the popliteal vein where reflux is the main outcome.

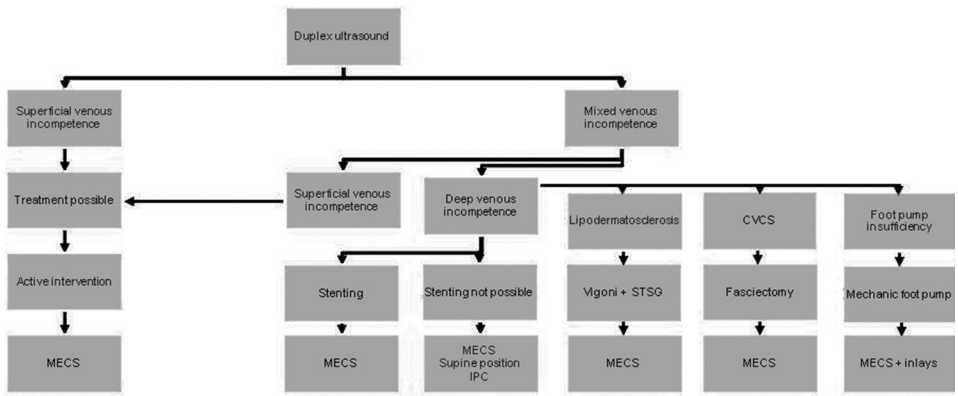
In popliteal vein thrombosis, the vein will either (partially) re-canalize with almost always subsequent reflux due to valve destruction or less frequently the vein will remain obstructed. This obstruction is the result of fibrosis within the vein during the process of resolution of the thrombus. This fibrosis ("obstruction") causes a high venous resistance with increasing pressure during ambulation. During walking, the venous transport capacity is too small for the venous debit. The result will be venous claudication and venous hypertension. One of the most important factors for increased ambulatory venous pressure and thus the severity of CVD in PTS limbs is the condition of the popliteal valves as reported by Neglen et al.[41] That study also reported that VLUs occurred in 75% of the patients at some time in the limbs with incompetent popliteal valves. Reflux in the popliteal vein causes venous hypertension and subsequently the non-healing tendency of VLUs. There is no satisfying treatment available to correct popliteal reflux because the results of valve repair and replacements are poor and are only performed at a few specialized centers.[42] These patients must wear MECS lifelong to reduce venous hypertension. However, deep venous incompetence is much less susceptible to ACT than superficial venous incompetence.[43]

Persistent obstruction of the popliteal vein causes a more severe problem because at this venous level there is no deep venous bypass to drain the venous blood. The superficial veins inevitably drain the blood. However, MECS should be worn in order to lower the ambulatory venous pressure. In these patients, wearing MECS impedes the venous return through the superficial venous system, which leads directly to worsening of the symptoms. Patients with an obstructive PTS pose a medical challenge and form the group with the most severe PTS, because this disorder is incompatible with standing upright. Besides wearing MECS, these patients should alternate standing and walking with lying down, because in the horizontal position venous pressure approximates 4 mmHg in the femoral vein. Moreover, they need to do walking exercises to stimulate collateral venous circulation and venous return. Patients may be helped with an intermittent pneumatic compression, especially for reducing edema, although most patients do not tolerate this therapy very well.

Proximal obstruction is associated with more complaints of pain, heaviness and swelling and venous claudication occurs frequently. If possible, these patients may be treated by de-obstruction and venous stenting.[44] Sometimes venous

pressure profiles normalize after this intervention in patients with a patent popliteal vein. The obstructed type PTS is converted into a reflux type PTS in other cases. Most patients will benefit from this procedure, because the complaints will diminish significantly, especially those of venous claudication. The consequent reflux may be compensated by wearing MECS.

Figure 6: Flowchart of the diagnosis and the treatment of recalcitrant VLUs.



DISCUSSION

All patients with a leg ulcer suspected of venous incompetence should – irrespective of the duration of the ulcer – be investigated by duplex ultrasound. Duplex ultrasound gives an accurate information on the anatomy, the reflux and the obstruction in the venous system. Therefore, it has become the gold standard in the investigation of CVD.[5,6] The superficial, the perforating and the deep venous system should be carefully investigated from the common iliac vein to the foot. Obstruction, reflux, abnormal flow and anatomy should be carefully noted in a schematic drawing.[5] Since the venous pressure in the standing position only drops when the leg muscles are used, the dynamics of the joints and muscles of the leg as well as the unwinding of the foot should be investigated. By doing this, the physician may separate the true venous disease due to venous incompetence from musculoskeletal dysfunction. Even small alterations in the walking pattern may lead to dysfunction in the venous return either by diminishing the muscle pump activity, reducing the foot pump function or even widening of the soleus veins.

Although most VLUs will heal within 6 months with adequate ACT, 8% of the VLUs have not healed after 5 years.[10] These can be categorized as non-healing VLUs. These patients should be identified as soon as possible because extra investigation and additional treatment is mandatory. Since most VLUs will heal during hospitalization and nearly all these ulcers will recur after discharge from the hospital, it remains an unsatisfactory solution for this problem.[13]

After the correct diagnosis is made the algorithm as shown in Figure 5 may be followed. Non-healing VLUs or VLUs that have recurred more than twice should be re-examined and treated accordingly. Many causes of recalcitrant VLUs such as foot pump insufficiency and CVCS may be treated adequately. However, occlusion of the popliteal vein is not (yet) treatable. Treatment of these patients is supportive and theoretically consists, besides physical therapy, of permanently placing the patient in supine position, which is not very practical in daily life.

Besides the four described pathological conditions for recalcitrant VLUs, one should be aware that also recirculation loops, gastrocnemic- and soleus vein incompetence may contribute in the severity of CVD. Additional treatment for these conditions may be necessary to obtain optimal treatment results in such complicated cases.

In our opinion, many more leg ulcers can be healed without recurrence provided the physician is able and willing to consider the problem of chronic VLUs not just as a local wound healing problem, but as a problem of disturbed venous hemodynamics, severe skin changes and changes of the subcutaneous tissue and dysfunction of the musculoskeletal structures. The diagnostic analyses and the treatment of recalcitrant VLUs deserve a "dynamic" perspective including all the venous return mechanisms and the complex foot unwinding movement.

Conclusion

Venous leg ulcers are a common medical problem. Most patients will be cured with standard care consisting of wound treatment and ACT. However 8% of patients have a non-healing or recalcitrant VLU.[10] These patients merit a closer examination to determine whether their VLU may be caused by:

1. Foot pump insufficiency;
2. Lipodermatosclerosis;
3. Chronic venous compartment syndrome;
4. Non-re-canalized thrombosis.

As a result of the differences in underlying pathology, these ulcers may only heal with specific treatment of the underlying disorder regardless of either ACT with

inelastic bandages or MECS with high stiffness and high compression. Depending on the underlying pathology, these patients may benefit from:

1. Mechanical foot pump device;
2. Vigoni procedure;
3. Fasciectomy;
4. Walking exercises, intermittent pneumatic compression, balance between standing and recumbent position.

Treatment of VLUs is an important and challenging area of phlebology. The diagnoses described in this article will offer more satisfactory therapeutic options for the patients with recalcitrant VLUs and make their treatment ever so rewarding.

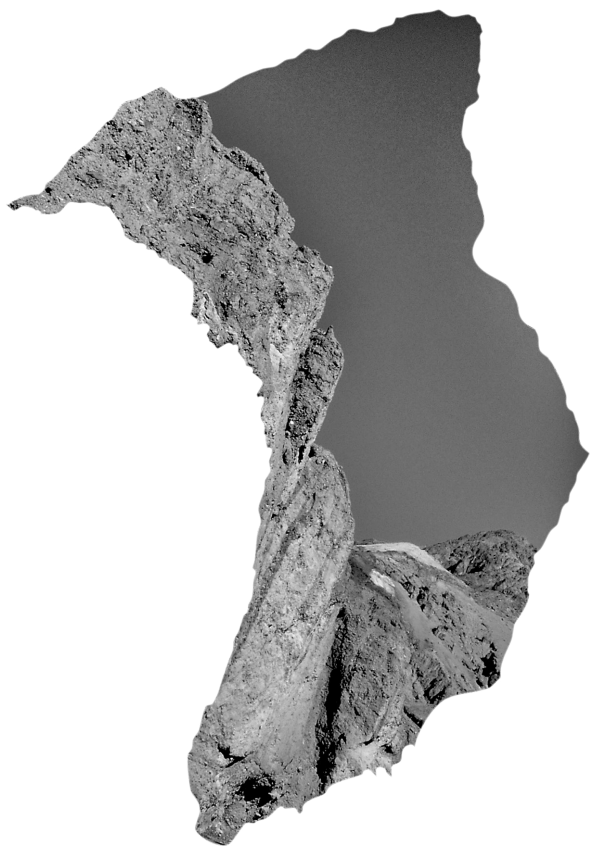
REFERENCES

1. Beebe HG, Bergan JJ, Bergqvist D, Eklof B, Eriksson I, Goldman MP, et al. Classification and grading of chronic venous disease in the lower limbs. A consensus statement. Eur J Vasc Endovasc Surg 1996;12(4):487-91.
2. Rabe E, Guex JJ, Puskas A, Scuderi A, Fernandez Quesada F. Epidemiology of chronic venous disorders in geographically diverse populations: results from the Vein Consult Program. Int Angiol 2012;31(2):105-15.
3. Gloviczki P, Comerota AJ, Dalsing MC, Eklof BG, Gillespie DL, Gloviczki ML, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg 2011;53(5 Suppl):2S-48S.
4. Deutsche Gesellschaft für Phlebologie. Guidelines for diagnosis and therapy of venous ulcers (version 8 2008). ICD10: 183.0 (without inflammation) and 183.2 (with inflammation). Phlebologie 2008;37:308-329.
5. Coleridge-Smith P, Labropoulos N, Partsch H, Myers K, Nicolaides A, Cavezzi A. Duplex ultrasound investigation of the veins in chronic venous disease of the lower limbs–UIP consensus document. Part I. Basic principles. Eur J Vasc Endovasc Surg 2006;31(1):83-92.
6. Cavezzi A, Labropoulos N, Partsch H, Ricci S, Caggiati A, Myers K, et al. Duplex ultrasound investigation of the veins in chronic venous disease of the lower limbs–UIP consensus document. Part II. Anatomy. Vasa 2007;36(1):62-71.
7. Reeder SWI, Wolff, O, Neumann HAM. Comparison of ambulatory venous pressure measurement and anterior compartment pressure measurement in relation to the CEAP clinical classification of chronic venous disease. Submitted 2013.
8. O'Meara S, Cullum N, Nelson EA, Dumville JC. Compression for venous leg ulcers. Cochrane Database Syst Rev 2012;11:CD000265.
9. Gohel MS, Barwell JR, Taylor M, Chant T, Foy C, Earnshaw JJ, et al. Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial. BMJ 2007;335(7610):83.
10. Nicolaides AN, Cardiovascular Disease E, Research T, European Society of Vascular S, Organization TIASAC, International Union of A, et al. Investigation of chronic venous insufficiency: A consensus statement (France, March 5-9, 1997). Circulation 2000;102(20):E126-63.
11. Margolis DJ, Berlin JA, Strom BL. Which venous leg ulcers will heal with limb compression bandages? Am J Med 2000;109(1):15-9.
12. Reeder SWI, Wolff O, Partsch H, Nicolaides AN, Mosti G, Cornu-Thenard A, et al. Expert consensus document on direct ambulatory venous pressure measurement. Int Angiol 2013: In press.
13. Reeder S, de Roos KP, de Maeseneer M, Sommer A, Neumann HA. Ulcer recurrence after in-hospital treatment for recalcitrant venous leg ulceration. Br J Dermatol 2013;168(5):999-1002.
14. Neumann HAM. Haut, Venen und Beine. Phlebologie 2011;40:344-355.
15. Araki CT, Back TL, Padberg FT, Thompson PN, Jamil Z, Lee BC, et al. The significance of calf muscle pump function in venous ulceration. J Vasc Surg 1994;20(6):872-7; discussion 878-9.

16. Pappas PJ, Brajesh, KL, Padberg Jr., FT, Zickler, RW, Duran, WN. Pathophysiology of Chronic Venous Insufficiency. In: Bergan JJ, editor. The Vein Book. San Diego: Elsevier Academic Press; 2007. p. 89-102.
17. Palfreyman SJ, Nelson EA, Lochiel R, Michaels JA. Dressings for healing venous leg ulcers. Cochrane Database Syst Rev 2006(3):CD001103.
18. Maessen-Visch MB, Koedam MI, Hamulyak K, Neumann HA. Atrophie blanche. Int J Dermatol 1999;38(3):161-72.
19. Neumann HA, van den Broek MJ, Boersma IH, Veraart JC. Transcutaneous oxygen tension in patients with and without pericapillary fibrin cuffs in chronic venous insufficiency, porphyria cutanea tarda and non-venous leg ulcers. Vasa 1996;25(2):127-33.
20. Blaauw GH, Neumann HA, Berretty PJ. La lipodermatosclerose et l'epaisseur dermale. Etude preliminaire. Phlebologie 1993;46(1):25-31.
21. Neumann HA, Van den Broek MJ. Increased collagen IV layer in the basal membrane area of the capillaries in severe chronic venous insufficiency. Vasa 1991;20(1):26-9.
22. Burnand KG, Whimster I, Naidoo A, Browse NL. Pericapillary fibrin in the ulcer-bearing skin of the leg: the cause of lipodermatosclerosis and venous ulceration. Br Med J (Clin Res Ed) 1982;285(6348):1071-2.
23. Lejars F. Les veines de la plante du pied. Archives de physiologie. 5° série, 1890.
24. De Roos KP, Neumann HA. Muller's ambulatory phlebectomy for varicose veins of the foot. Dermatol Surg 1998;24(4):465-70.
25. Le Dentu A. Circulation veineuse du pied et de la jambe. Paris: Adrien Delahaye; 1867.
26. Uhl JF, Gillot C. Anatomy of the foot venous pump: physiology and influence on chronic venous disease. Phlebology 2012;27(5):219-30.
27. Mali JW, Kuiper JP, Hamers AA. Acro-angiodermatitis of the foot. Arch Dermatol 1965;92(5):515-8.
28. van Bemmelen PS, Spivack D, Kelly P. Reflux in foot veins is associated with venous toe and forefoot ulceration. J Vasc Surg 2011;53(2):394-8.
29. Thiery L. Physiology of the muscular veins. In: Raymond-Martimbeau F, Prescott, R., Zummo, M., editor. Phlébologie 92. Paris: Éditions John Libbey Eurotext; 1992. p. 82-4.
30. Uhl JF, Chahim M, Allaert FA. Static foot disorders: a major risk factor for chronic venous disease? Phlebology 2012;27(1):13-8.
31. Hach W. Das arthrogene Stauungssyndrom. Gefässchirurgie 2003;8:227-233.
32. Vigoni M. Au sujet du traitement de l'hypodermite sclereuse du membre inferieur. Acta Chir Belg 1958;57(3):232-9; discussion 240-1.
33. Schmeller W, Gaber Y. Surgical removal of ulcer and lipodermatosclerosis followed by split-skin grafting (shave therapy) yields good long-term results in "non-healing" venous leg ulcers. Acta Derm Venereol 2000;80(4):267-71.
34. Pflug JJ, Zubac DP, Kersten DR, Alexander ND. The resting interstitial tissue pressure in primary varicose veins. J Vasc Surg 1990;11(3):411-7.
35. Grattenthaler C, Thoms KM, Kretschmer L. Paratibiale Fasziotomie beim Ulcus cruris postthromboticum mit dem Fasziotom nach Vollmar. J Dtsch Dermatol Ges 2007;5(12):1144-5.
36. Styf J, Korner L, Suurkula M. Intramuscular pressure and muscle blood flow during exercise in chronic compartment syndrome. J Bone Joint Surg Br 1987;69(2):301-5.
37. Hach W, Prave F, Hach-Wunderle V, Sterk J, Martin A, Willy C, et al. The chronic venous compartment syndrome. Vasa 2000;29(2):127-32.
38. Wentel TD, Neumann HA. Management of the postthrombotic syndrome: the Rotterdam approach. Semin Thromb Hemost 2006;32(8):814-21.

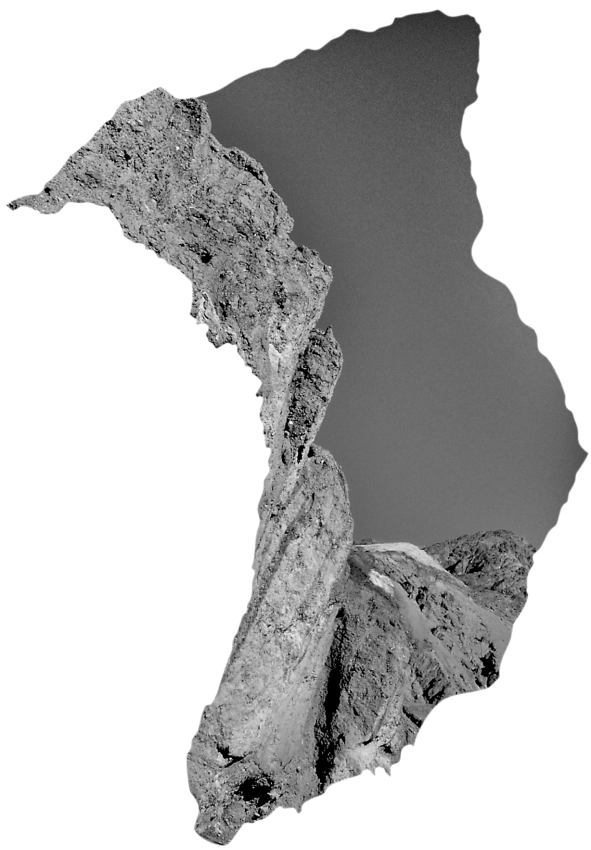
39. Kolbach DN, Neumann HA, Prins MH. Definition of the post-thrombotic syndrome, differences between existing classifications. Eur J Vasc Endovasc Surg 2005;30(4):404-14.
40. Delis KT, Bountouroglou D, Mansfield AO. Venous claudication in iliofemoral thrombosis: long-term effects on venous hemodynamics, clinical status, and quality of life. Ann Surg 2004;239(1):118-26.
41. Neglen P, Egger JF, 3rd, Olivier J, Raju S. Hemodynamic and clinical impact of ultrasound-derived venous reflux parameters. J Vasc Surg 2004;40(2):303-10.
42. Galanaud JP, Kahn SR. The Post-Thrombotic Syndrome: A 2012 Therapeutic Update. Curr Treat Options Cardiovasc Med 2013.
43. Nelson EA, Bell-Syer SE. Compression for preventing recurrence of venous ulcers. Cochrane Database Syst Rev 2012;8:CD002303.
44. Meissner MH, Eklof B, Smith PC, Dalsing MC, DePalma RG, Gloviczki P, et al. Secondary chronic venous disorders. J Vasc Surg 2007;46 Suppl S:68S-83S.

General discussion and summary



Chapter 12

General discussion and future perspectives



GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Introduction

Diseases of the veins and especially chronic venous disease (CVD) are very common worldwide.[1] Although the last two decades many different new diagnostic and treatment modalities have been introduced compression therapy is still the cornerstone in the treatment of CVD itself as well as supplementary to other treatment modalities like sclerotherapy, endovascular thermal ablation and venous surgery.[2]

One of the most precarious complications from patients' perspective as well as from socio-financial perspectives is a venous leg ulcer (VLU). Although half of VLUs will heal in 3 months, 20% has not healed after 2 years of adequate ambulatory compression therapy (ACT).[3] Even after 5 years 8% of all VLUs have not healed which is a dramatic situation for the patient. The failure of ACT may be compensated for by hospitalization. In supine position nearly all VLUs will heal. However after discharge even when adequate ACT is continued nearly all ulcers recur.[4] The combination of a high incidence, significant percentage of non-healing ulcers and high recurrences make VLUs a serious medical challenge. As 2% of the healthcare costs is spent on VLUs society pays a lot for this problem.[5]

In contrast to the incidence, loss of quality of life and costs of CVD have the interest of the medical profession in CVD, the medical specialty of phlebology, which is not recognized by the UEMS[b]. So a wide variety of physicians treat those patients. Phlebology is still in its infancy with regard to evidence based medicine and guidelines are scarce. Worldwide there are only a few university centres that perform high quality phlebological research. This is a pity because there is a great need for new treatment strategies.

In this thesis we studied several aspects of VLUs with the aim to translate these research results to improvements in daily care. One of the aims of translating research in medicine is to improve the quality of life of patients and to keep healthcare affordable. When we translate this to CVD there is still a long road to travel. Major aspects we are faced with are:
prevention;

1. who needs treatment;
2. optimal treatment of varicose veins;
3. treatment of VLUs;
4. prevention of VLU recurrence.

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[b] Union Européenne des Médecins Spécialistes.

Symptoms and signs

It is well-known that medical elastic compression stockings (MECS) and even light MECS reduce several and generally subjective symptoms of chronic venous disease (CVD) in healthy individuals (athletes) as well as specific populations (passengers on long-haul flights).[6-8] Even 'placebo' stockings (6 mmHg) have shown some effects.[9] As light MECS are much more comfortable and cosmetically more acceptable for patients than real MECS more research is needed to understand the effectiveness of light MECS. We investigated the effect of light MECS in a group of people sharing the same hobby, which is singing in a choir. As choristers stand these people benefit from wearing light MECS during a rehearsal. Edema is the first clinical sign of de-compensation of the venous system.[10] Normally the positive effects of ACT are explained by the effect of interface pressure and due to Pascals' law this pressure influences the tissue pressure as well as the capillaries. Standing humans all have a high venous pressure in the lower limb. Pressure multiplied by time will even in healthy individuals lead to edema formation, which explains the complaints of choristers during their standing rehearsals. This reduction of complaints may be attributed to lowering the capillary filtration rate and thus to prevent edema, which we proved with plethysmography for ulcer kit MECS (light-weight stocking plus compression class II stocking).

Nowadays, light MECS and support panty hoses are sold without prescription in many department stores. Although many people buy these stockings no research has demonstrated their effectiveness. Since light MECS have proved their effect we would like to suggest and promote department stores to sell light MECS in stead of support stockings as well as support panty hoses. However, people should be convinced to buy light MECS. As our own study showed, people recognize the effect of these MECS on subjective symptoms of CVD and are willing to wear these MECS, but people do not want to buy them themselves because of the costs, €34.51 for one pair of light MECS we used in the study with the choristers. This duality may be explained as follows: the Dutch got used to reimbursement of nearly all medical supplies by insurance companies and MECS are reimbursed from compression class II (CEN[c] 23-32 mmHg). However, this does not count for light MECS (compression classes A and I, CEN 10-14 and 15-21 mmHg respectively) for which no reimbursement exists based on governmental reimbursement criteria. During the last years, compensation for medical expenses has declined and will decline further in the future, because cost reduction is the one ways of overcoming the economic recession.[11] So, we should try to change the mindset of the Dutch in

[c] Comité Européen de Normalisation.

such a way that they will buy light MECS as they buy cloths, i.e. not reimbursed. On the other hand it is difficult to explain research to the public to convince them.

Diagnostics

Ambulatory venous pressure (AVP) measurement is the "gold standard" for assessing the severity of hemodynamic abnormality of CVD in the lower extremity.[12,13] Since this gold standard had not been standardised so far, we revised AVP measurement and made some proposals how to evaluate venous pressure curves in the future.[14] Although AVP measurement has largely been replaced by the non-functional investigation duplex ultrasound (DUS), it still has its diagnostic importance and supplementary value in complex cases of CVD and is performed on a small scale worldwide. It is the only investigation that gives exact figures of CVD. Time will tell whether the consensus document will lead to a proper and correct interpretation of AVP measurement pressure curves.

AVP measurement has been performed for over a century and the relation between AVP measurement pressure curves and the clinical score of the CEAP-classification - which has been introduced in 1994 – is excellent.[15,16] In other words, the physicians' clinical score corresponds to AVP and thus the severity of CVD. However, the CEAP-classification is not flawless, since it lacks DUS. The CEAP-classification was introduced in a time were Hand-Held-Doppler was the phlebologists' most important investigative tool. DUS had been introduced in the late 80s of last century and it was still too expensive and too elaborate for every practice in the 90s. Nowadays DUS is the most used investigative tool of the phlebologist and even mandatory to perform in a patient before an intervention takes place. However, the worldwide used CEAP-classification focuses on the visible clinical signs of CVD in stead on the disturbed venous haemodynamics as visible with DUS. Due to Dutch governmental healthcare decisions patients eligible for reimbursement should at least have C3 according to the clinical score in the CEAP-classification.[17] However, C3 does not even contain varicose veins, since C3 only stands for edema. In other words, C3 varicose veins do not even exist. So, to our opinion CVD should be treated on medical grounds, i.e. disturbed venous haemodynamics with significant reflux. As an adequate study lacks we propose on theoretical grounds that a great saphenous vein with a diameter ≥ 5 mm measured at 15 cm distal from the saphenofemoral junction corresponds with significant reflux.[18] Such findings justify an adequate treatment which restores normal haemodynamics, takes away complaints and reduces the risk of complications, such as venous leg ulceration and will be cost-effective.

Therapy

CVD may lead to leg ulceration as the end stage of CVD. In the adult Western population venous leg ulceration has a lifetime prevalence of 1% and a prevalence of active ulceration of 0.3% in the population over 18 years of age.[19,20] As CVD is as well a societal as a financial burden new ways have to open to manage this problem. In addition, CVD is highly correlated with age. The most recent epidemiological study demonstrated a prevalence of superficial venous insufficiency in 12.6% of men and women aged 17-39 years. This prevalence is 23.7% in men and 39.1% in women aged 60-80 years respectively.[21] In an aging Dutch population this cost aspect is neglected.

The first step forward should be prevention. Primary prevention of varicose veins is nearly impossible due to genetic backgrounds and evolution. Only severe obesity and small working area in standing professions are detected as risk factors.[22-24] On the contrary, prevention of deep vein thrombosis (DVT) is common and moreover excellent guidelines are available.[25] Although DVT prevention seems to be adequate in the Netherlands still 1 to 2 per 1000 inhabitants will develop a DVT annually.[26] As 50% of the patients will develop a PTS after DVT and PTS is reduced to dramatically wearing MECS at until 2 years after the DVT, more attention should be given to supplying and wearing MECS after a DVT.[27] No data are available on the effectiveness of wearing MECS after 2 years after the DVT.[28] Further research in this field is mandatory.

Prevention of VLUs is a challenge. As 50% of the VLUs are based on superficial venous incompetence in theory these leg ulcers may be prevented by adequate treatment of the incompetent saphenous vein(s) in time.[29] However, do we have to treat all varicose veins to avoid these VLUs? Actually, we do not think so. Only severe reflux will lead to venous hypertension. As ambulatory venous pressure measurement in all patients with varicose veins is impossible we propose to use a diameter of the incompetent saphenous vein of ≥ 5 mm as an absolute treatment indication.[18] Secondary prevention consisting of treatment of varicose veins as well as wearing MECS after a DVT will reduce the incidence of VLUs.

Once a patient presents himself with a VLU the patient as well as the physician is confronted with a great problem. We promote an active regimen based on clinics and duplex ultrasound investigation.[30] Close cooperation in healthcare between the first line and second line should lead to shortened healing times and less recurrences. The physician is confronted with an even larger problem if the VLU does not heal or recurs despite adequate treatment. It has been demonstrated these patients do not benefit from hospital admission as most VLUs recur within two months after hospital discharge.[4] Early identification of these so-called recalcitrant

VLUs or "ulcères rebelles" is essential and these patients should not only be treated with ACT but should also receive adequate treatment of the underlying problem, e.g. a Vigoni procedure in lipodermatosclerosis and a fasciectomy in chronic venous compartment syndrome. All this will lead to increased ulcer healing percentages and lower recurrence rates.

An underestimated aspect of patients with CVD and especially patients with VLUs is limited ankle joint mobility which leads to an abnormal gait and impairment of unwinding the foot. Additional physical therapy to wearing MECS may contribute to improve the walking pattern.

The effectiveness of light MECS is underestimated. As many patients only visit their physician because of in general subjective complaints without serious venous reflux and reimbursement of active treatment decreases more and more light MECS offer a cheap option for the treatment of these so-called venous complaints. All professionals dealing with CVD should realize that this disease progresses in time, which was recently demonstrated by Pannier et al.[31] C1 will progress to C2 and consequently to C3 or C4 etcetera. Insignificant reflux today may progress to serious reflux with consequently venous hypertension in years and patients should be warned for this and be investigated with certain intervals.

CVD is one of the most common human conditions. Nevertheless it is still underestimated by professionals as well as decision makers. This omission is one of the facts that CVD is very expensive for society.

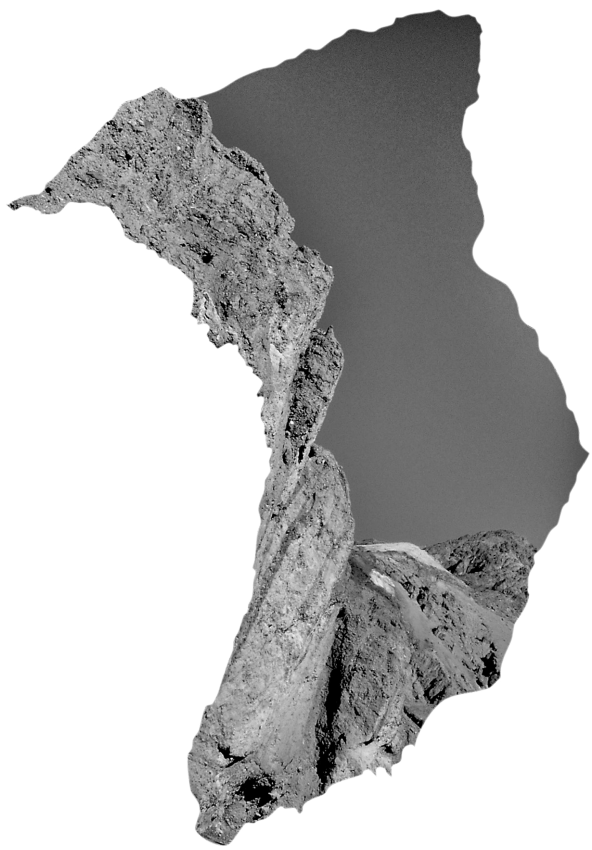
REFERENCES

1. Pannier-Fischer F, Rabe E. [Epidemiology of chronic venous diseases]]. Hautarzt 2003;54(11):1037-44.
2. Reeder SWI, de Roos, K-P. Compressietherapie nog steeds de hoeksteen in de flebologie. Themabijlage Compressietherapie Elsevier November 2008:6-8.
3. Callam MJ, Harper DR, Dale JJ, Ruckley CV. Chronic ulcer of the leg: clinical history. Br Med J (Clin Res Ed) 1987;294(6584):1389-91.
4. Reeder S, de Roos KP, de Maeseneer M, Sommer A, Neumann MH. Ulcer recurrence after in-hospital treatment for recalcitrant venous leg ulceration. Br J Dermatol 2012.
5. Oostenbrink J, Rutten, FFH. Handleiding voor kostenonderzoek; methoden en richtprijzen voor economische evaluatie in de gezondheidszorg. iMTA/CvZ Amstelveen. 2000. In.
6. Weiss RA, Duffy D. Clinical benefits of lightweight compression: reduction of venous-related symptoms by ready-to-wear lightweight gradient compression hosiery. Dermatol Surg 1999;25(9):701-4.
7. Ali A, Caine MP, Snow BG. Graduated compression stockings: physiological and perceptual responses during and after exercise. J Sports Sci 2007;25(4):413-9.
8. Scurr JH, Machin SJ, Bailey-King S, Mackie IJ, McDonald S, Smith PD. Frequency and prevention of symptomless deep-vein thrombosis in long-haul flights: a randomised trial. Lancet 2001;357(9267):1485-9.
9. Jonker MJ, de Boer EM, Ader HJ, Bezemer PD. The oedema-protective effect of Lycra support stockings. Dermatology 2001;203(4):294-8.
10. Michel CC. Microvascular permeability, venous stasis and oedema. Int Angiol 1989;8(4 Suppl):9-13.
11. Mladovsky P, Srivastava, D, Cylus, J, Karanikolos, M, Evetovits, T, Thomson, S, McKee, M. Health policy responses to the financial crisis in Europe. In. Copenhagen: WHO Regional Office for Europe; 2012. p. 1-132.
12. Von Recklinghausen H. Unblutige Blutdruckmessung. Arch Exper Pathol Pharm 1906;13:423-5.
13. Kuiper JP. Bloedige veneuze drukmeting. In: Kuiper: Perifere veneuze drukmeting (thesis). Asten; 1966: 33-63.
14. Reeder SWI, Wolff, O, Partsch, H, Nicolaides, AN, Mosti, G, Cornu-Thenard, A, Obermayer, A, Weingard, I, Neumann, HAM. Expert consensus document on direct ambulatory venous pressure measurement. Int Angiol 2013:Accepted for publication.
15. Reeder SWI, Wolff O, Neumann HAM. Comparison of ambulatory venous pressure measurement and anterior compartment pressure measurement in relation to the CEAP clinical classification of chronic venous disease. Submitted.
16. Beebe HG, Bergan JJ, Bergqvist D, Eklof B, Eriksson I, Goldman MP, et al. Classification and grading of chronic venous disease in the lower limbs. A consensus statement. Eur J Vasc Endovasc Surg 1996;12(4):487-91.
17. Staal P, de Vaan, HHC, Gaasbeek Janzen, HM, Ligtenberg, G. Varices: medisch noodzakelijke versus cosmetische behandelingen. In. Diemen: College voor zorgverzekeringen; 2011. p. 1-70.
18. Neumann HAM. Haut, Venen und Beine. Phlebologie 2011;40:344-355.
19. Callam MJ, Ruckley CV, Harper DR, Dale JJ. Chronic ulceration of the leg: extent of the problem and provision of care. Br Med J (Clin Res Ed) 1985;290(6485):1855-6.
20. Nicolaides AN. Investigation of chronic venous insufficiency: A consensus statement (France, March 5-9, 1997). Circulation 2000;102(20):E126-63.

21. Maurins U, Hoffmann BH, Losch C, Jockel KH, Rabe E, Pannier F. Distribution and prevalence of reflux in the superficial and deep venous system in the general population–results from the Bonn Vein Study, Germany. J Vasc Surg 2008;48(3):680-7.
22. Krijnen RM, de Boer EM, Ader HJ, Bruynzeel DP. Venous insufficiency in male workers with a standing profession. Part 1: epidemiology. Dermatology 1997;194(2):111-20.
23. Krijnen RM, de Boer EM, Ader HJ, Bruynzeel DP. Venous insufficiency in male workers with a standing profession. Part 2: diurnal volume changes of the lower legs. Dermatology 1997;194(2):121-6.
24. Krijnen RM, de Boer EM, Bruynzeel DP. Epidemiology of venous disorders in the general and occupational populations. Epidemiol Rev 1997;19(2):294-309.
25. Kwaliteitsinstituut voor de Gezondheidszorg CBO. Richtlijn Diagnostiek, preventie en behandeling van veneuze trombo-embolie en secundaire preventie van arteriële trombose. Alphen aan den Rijn: Van Zuiden Communications B.V.; 2008.
26. Prandoni P, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta M, et al. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med 1996;125(1):1-7.
27. Brandjes DP, Buller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet 1997;349(9054):759-62.
28. Wentel TD, Neumann HA. Management of the postthrombotic syndrome: the Rotterdam approach. Semin Thromb Hemost 2006;32(8):814-21.
29. Magnusson MB, Nelzen O, Risberg B, Sivertsson R. A colour Doppler ultrasound study of venous reflux in patients with chronic leg ulcers. Eur J Vasc Endovasc Surg 2001;21(4):353-60.
30. Reeder SWI, Esteve Cuevas, L, Munte, K, de Roos, K-P, Neumann, HAM. A prospective open study on treatment of venous leg ulcers in the Dutch community; implications for patient referral. Submitted. 2013.
31. Pannier F, Rabe E. The relevance of the natural history of varicose veins and refunded care. Phlebology 2012;27 Suppl 1:23-6.

Chapter 13

Summary/Samenvatting



Summary

In **chapter 1** we provide a general introduction of this thesis. Chronic venous disease (CVD) is a common medical condition that affects 2-64% of the worldwide population and leads to leg ulcers in 1% of the Western population. Venous leg ulceration (VLU) has an unfavorable prognosis with regard to non-healing and recurrence rates. Annually 6% of the total healthcare costs are spent on the treatment of venous diseases. CVD results from ambulatory venous hypertension and is the consequence of valvular incompetence, venous outflow obstruction, or a combination of both, and may be divided in primary CVD and secondary CVD. However, the venous microcirculation is very complex and multifactorial. CVD is associated with multiple and subjective symptoms and objective clinical signs. Nowadays the diagnosis CVD is made by duplex ultrasound and in special situations other diagnostic tools may be used. Compression therapy is the cornerstone in the treatment of CVD, as treatment modality as well as supplement to another treatment. We end this introduction by stating the aims of this thesis.

In **chapter 2** we investigate the effect of light medical elastic compression stockings (light MECS) (Proleg®) on leg symptoms in a choir after a standing rehearsal. We performed a case-control study, in which the cases wore light MECS during the rehearsal, and the controls did not wear any MECS. Preceding the rehearsal all the subjects filled in a questionnaire. After the rehearsal the effect of the stockings was evaluated by a second questionnaire. A part of the questions was answered by visual analogue scores. Wearing light MECS led to significant improvement of symptoms of leg fatigue ($P<0.01$). Improvement of symptoms of leg swelling, leg cramp, and restless legs was demonstrated, but this improvement was not significant. In conclusion, light MECS are very effective in preventing symptoms of leg fatigue during sustained standing. Moreover they reduce symptoms of restless legs, leg swelling, and leg cramp.

In **chapter 3** we investigate the use of compression ulcer stockings with regard to reduction of the capillary filtration rate (CFR). We used plethysmography to measure the CFR in both legs of 17 subjects, 6 with chronic venous insufficiency and 11 healthy subjects. The CFR was measured with both (day and night) stockings, only the night stocking and without stockings. The reduction of the CFR was significant ($P<0.0001$) for the total population in the group wearing two stockings versus one stocking (CFR=0.019 vs. 0.084 ml/100ml/min), one stocking versus no stockings (CFR=0.149 vs. 0.084 ml/100ml/min) and two stockings versus no stockings (CFR=0.019 vs. 0.149 ml/100ml/min). In conclusion, compression

ulcer stockings are highly effective in reducing the CFR and thus reducing edema formation, which leads to improved healing of venous ulcers.

Ambulatory venous pressure (AVP) measurement has never been fully standardised. In **chapter 4** we invite experts on AVP measurement to discuss this investigation and reach consensus on AVP measurement. After committing to participate to the consensus meeting during the UIP World Congress in Monaco 2009, each expert received statements and questions concerning the pitfalls in standardising AVP measurement by email. They also received the protocol of AVP measurement of the department of dermatology in Rotterdam, the Netherlands. From here, this protocol was revised. A list of questions was sent out beforehand based on which several proposals for future evaluations of venous pressure curves were formulated at the meeting. The most important change of the previous non-standardised protocol on AVP measurement is that AVP measurement should be performed on a treadmill at a speed of 2 km/h and with an elevation of 8˚. If no treadmill is available tiptoe or knee bending exercises may be used. It is proposed to define AVP as mean AVP [(systolic venous pressure + 2 x diastolic venous pressure)/ 3]. Venous refill time (RT) should not be routinely used as outcome measure. The conclusion of AVP measurement may be: normal (no venous hypertension), intermediate ambulatory venous hypertension or severe venous hypertension. The related pressure ranges obtained by the proposed mode of evaluation should be validated in future studies. AVP measurement is the "gold standard" to quantify the severity of hemodynamic abnormality of CVD in the lower extremity. Several proposals concerning a standardized evaluation of venous pressure measurements have been formulated.

In **chapter 5** we investigate the association between CEAP clinical classification and AVP measurement and ACP measurement, and the correlation between AVP measurement and ACP measurement. In a retrospective descriptive study, patients with various causes and at various clinical stages of CVD were examined. Severity of venous disease was scored by the CEAP clinical classification and patients were investigated by AVP measurement and ACP measurement. In total 163 legs were investigated in 89 patients (median age 44 years, range 16-79). These were classified as 90 female and 73 male legs. The legs were categorized in accordance with CEAP clinical classification: C0 n=33; C1 n=8; C2 n=15; C3 n=27; C4 n=47; C5 n=21; C6 n=12. Statistically significant differences between the seven groups of CEAP clinical classification compared with AVP measurement (p<0.001), for both AVP and RT were demonstrated. No significant relation was demonstrated between CEAP clinical classification and supine ACP (p=0.165) or standing ACP (p=0.148). A poor correlation was found between AVP measurement and ACP

measurement (r<0.10). In conclusion, patients with severe CVD as scored with CEAP clinical classification have significantly higher AVP and shorter RT. No relations were observed between CEAP clinical classification and ACP measurement, as well as between AVP measurement and ACP measurement, presuming that AVP and ACP represent different stages and/or complications of CVD. Replacement of AVP measurement in daily practice by CEAP clinical classification is justified. However in special situations where quantification of CVD is required, i.e. in post-thrombotic syndrome, AVP measurement is still practical. If chronic venous compartment syndrome (CVCS) is suspected by the patients' symptoms, ACP measurement may be used irrespective of CEAP clinical classification and AVP. However the correlation between high ACP and chronic venous hypertension determined by as well CEAP clinical classification as high AVP could not be proved. This lack of correlation between CVD and CVCS may be explained by the fact that tissue interaction by the decompensated microcirculation leading to fibrosis seems to be different in the skin, the subcutaneous tissue and the compartment. Up to now we have no predictable criterion for the development of CVCS in relation to CVD.

In **chapter 6** we discuss the use of the CEAP-classification. Since the introduction of the CEAP-classification in 1994 most published phlebological literature only mention the CEAP clinical classification (indicated by the C in the CEAP-classification), which is a clinical appraisal of the physician and not an interpretation of duplex ultrasound.The CEAP-classification was introduced in an era when the hand-held-Doppler was the phlebologist's most important investigative tool and clinical appraisal was done by sight alone. Nowadays duplex ultrasound is common in every phlebological practice and mandatory to perform in every patient before an intervention takes place. The decision to treat patients should be based on the expectation to recover the disturbed venous haemodynamics. The use of just the CEAP clinical classification may lead to misinterpretation of the function of the saphenous veins because the CEAP clinical classification only comprises visible clinical signs. We therefore proposed to adjust the CEAP clinical classification by dividing C2 into two subclasses: C2a (minor reflux) and C2b (major reflux) just as was done with C4.

In **chapter 7** we perform a systematic search to summarize the evidence-based literature with regard to VLU recurrence, because of the large variation in published VLU recurrence rates. A review of published data was performed using the MEDLINE OvidSP, EMBASE, Web-of-Science, PubMed publisher and Cochrane Library with the Medical Subject Headings (MeSH) *varicose ulcer* and *recurrence*. To be included, studies needed to fulfil the following criteria: prospective study design; diagnosis made by CEAP-classification and/or by using duplex ultrasound;

and leg ulcer recurrence expressed as recurrence at a certain time. Our data demonstrated VLU recurrence rates ranging from 0% at 6 months to 56% at 54 months. Two studies mention VLU recurrence at 60 months, with VLU recurrence rates of 19 and 48% respectively. Only three studies are comparable with regard to treatment and demonstrate VLU recurrence of 17, 17 and 25% respectively at 12 months. This was the first study summarising high-level evidence with regard to VLU recurrence demonstrating a tendency that even after several years recurrence rates still increase. A more systematic approach of organising the evidence of VLU recurrence might lead to the final answer. The results of this study, high recurrence rates indicate the need for new strategies after a VLU has healed.

In **chapter 8** we execute an internet survey to get insight into the frequency of VLUs in the Dutch dermatologic practice, and into how this profession treats this disease. To all Dutch dermatologists and residents dermatology an email was sent in October 2008, with an online link to a questionnaire on venous leg ulcers. The overall response to the internet survey was 30%. All responders are familiar with the Dutch guideline on Venous Leg Ulcer. 83.5% of the doctors usually treat their patients according to this guideline. The dermatologic practice consists on average of 73 patients (range 0-500; SD 93) with leg ulceration, and yearly 54 new leg ulcer patients (range 0-300; SD 50) are seen. 65% of the patients are women, 80% is over 45 years of age and 55% is over 65. Of all ulcers, 77% has a venous aetiology, of which 59% has a primary cause. Supplementary examination is performed in almost every patient. The outpatient treatment in all cases consists of ambulatory compression therapy. Mean time to heal is 74 days (range 4-200; SD 39). Per year, dermatologists admit on average 7 patients (range 0-50; SD 11) because of leg ulceration. A majority of the admitted patients (59%) are confined to bed, and half of these patients are treated by vacuum-assisted closure (VAC) therapy. Eventually, 47% of the admitted patients are treated by skin transplantation. We conclude that this questionnaire gives a good insight in the epidemiology, and the diagnostic and therapeutic regimen for patients with VLUs in Dutch dermatologic practice.

In **chapter 9** we perform a prospective open study to investigate VLU healing in a Dutch population using the existing guideline on VLUs. The study was performed in patients with VLUs receiving outpatient treatment at the dermatology department in one of the five contributing hospitals. In the course of five months, patients were examined by taking a photograph of the ulcerated area, digital planimetry was performed to obtain an initial ulcer size and after 12 weeks ulcers were classified as healed or unhealed. A total of 56 patients were included, with a median age of 71.38 years (SD 13.8) and the group consisting of 23 (41.1%) males and 33 (58.9%) females. The median initial ulcer size was calculated to be 2.82 cm^2 (± 11.16). The

twelve-week healing rate was 51.8% (n=29), with a median closure time of 38.0 days (± 35.68). The initial ulcer size was significantly smaller in the healed ulcers compared with the unhealed ulcers (p=0.001). We concluded that the results of this study correspond with the existing literature with regard to 3-month ulcer healing and application of the existing guideline is possible in the dermatological practice and will fulfil the expectations in optimising evidence-based healthcare. Besides, initial ulcer size is an indicator for healing.

In **chapter 10** we investigate time to VLU recurrence after in-hospital treatment of VLUs in a multicentre, retrospective cohort study of patients admitted for leg ulceration between 1996 and 2007. Of 107 patients data could be collected. Of these, 27 patients had a conservative treatment (bed rest, local wound care, pain management) and 48 patients underwent surgical ulcer treatment with (n = 19) or without (n=29) initial VAC treatment. Treatment method was 'miscellaneous' in the remaining 32 patients. Median admission time was 30 days, median percentage of closure at discharge was 95%, and median time to ulcer recurrence 60 days. Mann-Whitney U-test showed significant differences between the conservative group and the surgery group, the latter having a longer length of hospital stay (P<0.0001) and a higher percentage of ulcer closure (P<0.0001) but there was no difference in time to ulcer recurrence (P=0.273). Comparable differences were demonstrated between the conservative group and the VAC plus surgery group. No significant differences could be demonstrated between the surgically treated patients and those treated by VAC and surgery. In conclusion, hospital stay was significantly shorter in case of surgical treatment of recalcitrant VLUs. Most ulcers recurred within 2 months after hospital discharge. Recurrence of VLUs after hospital admission is independent of method of treatment and cause of ulceration.

VLUs may be divided into three categories: uncomplicated, recurrent and recalcitrant. In general four particular causes of recalcitrant venous leg ulcers may be distinguished: foot pump insufficiency, lipodermatosclerosis, chronic venous compartment syndrome and non-recanalized popliteal vein thrombosis. In **chapter 11** we review the literature and describe the four main causes of recalcitrant VLUs and their specific treatment besides wearing lifelong MECS with a high stiffness. Foot pump insufficiency arises when the plantar foot veins are not able to empty, as a consequence treatment should consist of physical therapy, a mechanic foot pump device and an insole. Lipodermatosclerosis may be treated by excision and split-thickness skin grafting (Vigoni procedure). Chronic venous compartment syndrome is usually caused by post-thrombotic syndrome, which may result in increased pressure. Treatment consists of decompression through a fasciectomy. Patients with non-recanalized popliteal vein thrombosis may be supported by

intermittent pneumatic compression, walking exercises, alternating standing and walking with lying down. Only a few patients will be suitable for venous stenting. We may conclude that patients with recalcitrant VLUs are challenging, with regard to diagnosis as well as to treatment. More specific treatment will heal more of those ulcers.

In **chapter 12** the main findings from studies presented in this thesis are discussed and placed into a broader perspective.

Samenvatting

In **hoofdstuk 1** geven we een algemene inleiding van dit proefschrift. Chronische veneuze insufficiëntie (CVI) is een veel voorkomende aandoening die 2-64% van de wereldwijde populatie treft. Het leidt tot ulcera crurum in 1% van de Westerse populatie. Veneuze ulcera crurum hebben een ongunstige prognose voor wat betreft genezingstendens en kans op recidief. Jaarlijks wordt 6% van het totaal aan kosten voor de gezondheidszorg uitgegeven aan de behandeling van veneuze ziekten. Het belangrijkste kenmerk van CVI is veneuze hypertensie ten gevolge van klepinsufficiëntie, veneuze uitstroomobstructie, of een combinatie van beide en kan worden ingedeeld in primaire en secundaire chronische veneuze ziekte. Daarentegen is de veneuze microcirculatie erg complex en multifactorieel. CVI is geassocieerd met multipele en subjectieve symptomen en objectieve klinische tekenen. Tegenwoordig wordt de diagnose CVI gesteld met behulp van duplex sonografie en in bijzondere situaties zijn andere aanvullende onderzoeken nodig. Compressietherapie is de hoeksteen in de behandeling van CVI, zowel als behandeling op zich als aanvulling op een andere therapie. We eindigen deze introductie met het stellen van de doelen van dit proefschrift.

In **hoofdstuk 2** onderzoeken we het effect van lichte therapeutisch elastische kousen (Proleg®) op beenklachten in een koor na een staande repetitie. We verrichtten een case-control studie waarin de cases de lichte therapeutisch elastische kousen droegen tijdens de repetitie en de controles deze kousen niet droegen. Voorafgaand aan de repetitie vulden alle deelnemers een enquête in. Na de repetitie werd het effect van de kousen geëvalueerd door middel van een tweede enquête. Een deel van de vragen werd beantwoord door het invullen van een visueel analoge schaal. Het dragen van lichte therapeutisch elastische kousen leidde tot een significante verbetering van klachten van vermoeide benen ($P<0.01$). Tevens werd verbetering van klachten van beenzwelling, krampen en rusteloze benen aangetoond, maar dit was niet significant. Concluderend, lichte therapeutisch elastische kousen zijn erg effectief in het voorkomen van symptomen van vermoeide benen tijdens langdurig staan. Daarnaast verminderen deze kousen de klachten van rusteloze benen, beenzwelling en krampen.

In **hoofdstuk 3** onderzoeken we het effect van ulcus compressiekousen op afname van de capillaire filtratiesnelheid (CFR). We gebruikten plethysmografie om de CFR in beide benen te meten in 17 personen, van wie 6 met CVI en 11 gezonde proefpersonen. CFR werd gemeten met beide compressiekousen (dag- en nachtkous), alleen de nachtkous en zonder compressiekousen. De afname in CFR was significant ($P<0.0001$) voor de totale populatie in de groep

die beide compressiekousen droeg versus één compressiekous (CFR=0.019 versus 0.084 ml/100ml/min), één compressiekous versus geen compressiekous (CFR=0.149 versus 0.084 ml/100ml/min) en twee compressiekousen versus geen compressiekousen (CFR=0.019 versus 0.149 ml/100ml/min). Concluderend, ulcus compressiekousen zijn zeer effectief in het reduceren van de CFR en dus in het reduceren van oedeem, wat leidt tot een betere wondgenezing.

Ambulante veneuze drukmeting (AVP meting) is nooit volledig gestandaardiseerd. In **hoofdstuk 4** nodigen we experts uit op het gebied van AVP meting om te discussiëren en consensus te bereiken. Na toezegging aan deelname tijdens de consensusbespreking tijdens het UIP World Congress in Monaco in 2009 ontving iedere expert per email stellingen en vragen betreffende de valkuilen in het standaardiseren van AVP meting. Ook ontvingen zij het protocol van AVP meting van de afdeling dermatologie in Rotterdam en vanuit hier werd het protocol gereviseerd. Gebaseerd op een lijst met vragen werd op voorhand een vragenlijst verzonden waarop tijdens de bijeenkomst verschillende voorstellen werden gedaan voor toekomstige evaluaties van veneuze drukcurves. De belangrijkste wijziging ten opzichte van het bestaande, niet gestandaardiseerde protocol is dat AVP meting op een loopband met een snelheid van 2 km/u en met een helling van 8˚ zou moeten worden verricht. Indien geen loopband aanwezig is, kunnen op de tenen lopen en kniebuigoefeningen worden gebruikt. Voorgesteld werd om AVP te definiëren als de gemiddelde AVP [(systolische veneuze druk + 2 x diastolische veneuze druk) / 3]. Veneuze hervulllingstijd zou niet routinematig moeten worden gebruikt als uitkomstmaat. De conclusie van AVP meting kan zijn: normaal (geen veneuze hypertensie), matige veneuze hypertensie of ernstige veneuze hypertensie. De gerelateerde drukranges bij deze voorgestelde indeling zou in toekomstige studies moeten worden geëvalueerd. AVP meting is de goudstandaard om de ernst van hemodynamische afwijkingen bij CVI in het been te kwantificeren. Verschillende voorstellen betreffende een gestandaardiseerde evaluatie zijn geformuleerd.

In **hoofdstuk 5** onderzoeken we associatie tussen de CEAP-classificatie en AVP meting en voorste compartimentdrukmeting (ACP meting), en de correlatie tussen AVP meting en ACP meting. In een retrospectieve studie werden patiënten onderzocht met CVI door diverse oorzaken en in verschillende klinische stadia. De ernst van de CVI werd gescoord met behulp van de CEAP-classificatie en patiënten werden onderzocht met zowel AVP meting als ACP meting. In totaal werden 163 benen onderzocht in 89 patiënten (leeftijd mediaan 44 jaar, range 16-79). Dit waren 90 vrouwen- en 73 mannenbenen. De benen werden ingedeeld volgens de CEAP-classificatie: C0 n=33, C1 n=8, C2 n=15, C3 n=27, C4 n=47, C5

n=21, C6 n=12. Statistisch significante verschillen tussen de zeven klinische groepen van de CEAP-classificatie vergeleken met AVP meting (P<0.001), voor zowel AVP als veneuze hervullingstijd (RT) werden aangetoond. Geen significante relatie werd aangetoond tussen CEAP-classificatie en staande (P=0.165) en liggende (P=0.148) compartimentdruk. Een slechte correlatie werd gevonden tussen AVP meting en ACP meting (r<0.10). Concluderend, patiënten met ernstige CVI volgens de CEAP-classificatie hebben significant hogere AVP en kortere RT. Geen relatie kon worden aangetoond tussen de CEAP-classificatie en ACP meting en tussen AVP meting en ACP meting, waardoor wij aannemen dat AVP en ACP verschillende stadia en/of complicaties van CVI representeren. Vervanging van AVP meting door de CEAP-classificatie is in de dagelijkse praktijk gerechtvaardigd. Echter in bijzondere situaties, waar kwantificering van CVI vereist is, bijvoorbeeld in post-trombotisch syndroom, is AVP meting nog steeds praktisch. Als op basis van het klachtenpatroon een chronisch veneus compartimentsyndroom wordt vermoed, kan ACP meting worden gebruikt onafhankelijk van de CEAP-classificatie en de AVP meting. De correlatie tussen hoge compartimentdrukken en chronische veneuze hypertensie bepaald door zowel de CEAP-classificatie als hoge AVP kon niet worden bewezen. Deze slechte correlatie tussen CVI en chronisch veneus compartimentsyndroom kan mogelijk worden verklaard door het feit dat weefselinteractie door de gedecompenseerde microcirculatie leidend tot fibrose verschillend lijkt in de huid, het subcutane weefsel en het compartiment. Tot nu toe hebben we geen voorspellend criterium voor het ontwikkelen van chronisch veneus compartimentsyndroom in relatie tot CVI.

In **hoofdstuk 6** bespreken we het gebruik van de CEAP-classificatie. Sinds de introductie van de CEAP-classificatie in 1994 wordt in de meeste wetenschappelijke literatuur alleen de CEAP klinische classificatie (aangeduid als de C in de CEAP-classificatie) gebruikt, wat een klinische beoordeling door de arts is en niet een interpretatie van duplex sonografie. De CEAP-classificatie was geïntroduceerd in een tijd dat het aanvullend onderzoek van de fleboloog voornamelijk bestond uit hand-held-Doppler en de klinische beoordeling werd gedaan op het zicht. Tegenwoordig is duplex sonografie gemeengoed in elke flebologische praktijk en een verplicht onderzoek bij iedere patiënt die een invasieve behandeling ondergaat. Het behandelen van een patiënt moet afhankelijk zijn van de verwachting dat de behandeling de verstoorde veneuze hemodynamiek zal herstellen. Het gebruik van enkel de C van de CEAP-classificatie kan leiden tot misinterpretatie van de functie van de v. saphena magna en de v. saphena parva, omdat het gebruik van enkel de klinische score van de CEAP-classificatie alleen zichtbare tekenen van CVI omvat. We stellen voor om de CEAP-classificatie aan te

passen door C2 op te splitsen in C2a (`minor reflux') en C2b (`major reflux') zoals eerder werd gedaan voor C4.

In **hoofdstuk 7** verrichten we een systematisch literatuuronderzoek met als doel het samenvatten van de evidence-based literatuur met betrekking tot het recidiveren van veneuze ulcera crurum, vanwege de grote spreiding van recidiefpercentages in de bestaande literatuur. Om de recidiefpercentages van het veneuze ulcus cruris te onderzoeken werd gebruikt gemaakt van MEDLINE OvidSP, EMBASE, Web-of-Science, PubMed publisher en Cochrane Library met de Medical Subject Headings (MeSH) *varicose ulcer* and *recurrence*. De studies moesten voldoen aan de volgende criteria: prospectieve studie, diagnose gesteld met CEAP-classificatie en/of met duplex sonografie en recidief veneus ulcus cruris uitgedrukt als recidief op een bepaald moment. Onze data toonden recidiefpercentages tussen 0% op 6 maanden en 56% op 54 maanden. Twee studies vermeldden recidiefpercentages van het veneuze ulcus cruris op 60 maanden, te weten 19 en 48%. Slechts 3 studies zijn vergelijkbaar voor wat betreft behandeling en toonden recidiefpercentages van 17, 17 en 25% op 12 maanden. Dit was de eerste studie waarin `high-level evidence' werd opgesomd met betrekking tot het recidiveren van het veneuze ulcus cruris en laat de tendens zien dat zelfs na een aantal jaren de recidiefpercentages nog altijd toenemen. Een meer systematische benadering van het bewijs van het recidiveren van het veneuze ulcus cruris zal moeten leiden tot het verlossende antwoord. De hoge recidiefpercentages uit onze studie tonen de noodzaak aan tot nieuwe behandelstrategieën als veneuze ulcera crurum genezen zijn.

In **hoofdstuk 8** verrichten we een online enquête om inzicht te krijgen in het voorkomen van het veneuze ulcus cruris in de Nederlandse dermatologische praktijk en hoe de dermatologische professie deze aandoening behandelt. In oktober 2008 werd een email verzonden aan alle dermatologen en arts-assistenten in opleiding tot dermatoloog met een online link naar een vragenlijst over veneuze ulcera crurum. De respons was 30%. Alle respondenten zijn bekend met de Nederlandse richtlijn Ulcus Cruris Venosum. Het overgrote merendeel van de artsen (83.5%) behandelt zijn patiënten meestal volgens de bestaande richtlijn. De dermatologische praktijk bestaat gemiddeld uit 73 patiënten met een ulcus cruris (range 0-500; SD 93) en jaarlijks worden 54 nieuwe patiënten met een ulcus cruris gezien (range 0-300; SD 50). 65% van de patiënten zijn vrouwelijk, 80% is ouder dan 45 jaar en 55% is ouder dan 65 jaar. Van alle ulcera heeft 77% een veneuze etiologie en hiervan is de oorzaak primair in 55% van alle gevallen. Aanvullend onderzoek wordt in vrijwel iedere patiënt verricht. De poliklinische behandeling bestaat in ieder geval uit ambulante compressietherapie. De

gemiddelde genezingsduur is 74 dagen (range 4-200; SD 39). Jaarlijks nemen de dermatologen gemiddeld 7 patiënten op vanwege ulcus cruris (range 0-50; SD 11). Meer dan de helft van de opgenomen patiënten (59%) wordt behandeld met bedrust en de helft van deze patiënten wordt behandeld met vacuum-assisted closure (VAC) therapie. Uiteindelijk wordt 47% van de patiënten behandeld met een huidtransplantatie. Concluderend geeft deze enquête goed inzicht in de epidemiologie, de diagnostiek en therapeutisch regime voor patiënten met een veneus ulcus cruris in de Nederlandse dermatologische praktijk.

CVI is één van de meest voorkomende aandoeningen en het veneuze ulcus cruris is één van de ernstigste manifestatie. Met de standaard behandeling bestaande uit ambulante compressietherapie zal 50% van deze ulcera genezen binnen 3 maanden. In **hoofdstuk 9** doen we een open prospectieve studie om genezing van het veneuze ulcus cruris in de Nederlandse populatie te onderzoeken gebruik makend van de richtlijn Ulcus Cruris Venosum. De studie werd verricht onder patiënten met een veneus ulcus cruris die ambulant werden behandeld op de polikliniek dermatologie van één van de zeven deelnemende ziekenhuizen. Patiënten werden in de loop van vijf maanden onderzocht door middel van het maken van een foto van het ge-ulcereerde gebied, digitale planimetrie werd verricht voor het verkrijgen van de initiële grootte van het ulcus. Na 12 weken werden de ulcera geclassificeerd als genezen of niet genezen. In totaal werden 56 patiënten geïncludeerd met een mediane leeftijd van 71.38 jaar (SD 13.8). De groep bestond uit 23 (41.1%) mannen en 33 (58.9%) vrouwen. De initiële grootte van het ulcus werd berekend op mediaan 2.82 cm^2 (SD 11.16). De genezing op 12 weken was 51.8% (n=29) met een mediane genezingsduur van 38.0 dagen (SD 35.68). De grootte van het initiële ulcus was significant kleiner in de groep met genezen ulcera in vergelijking met de groep van niet genezen ulcera (p=0.001). We concluderen dat de resultaten van deze studie overeenkomen met de bestaande literatuur met betrekking tot de genezing van het veneuze ulcus cruris op drie maanden. De toepassing van de bestaande richtlijn in de dermatologische praktijk is mogelijk en voldoet aan de verwachtingen evidence-based gezondsheidszorg te optimaliseren. Daarnaast is initiële grootte van het ulcus een parameter voor genezing.

In **hoofdstuk 10** onderzoeken we de recidieftijd van ulcera na ziekenhuisopname vanwege een veneus ulcus cruris in een multicenter, retrospectieve cohort studie met patiënten die werden opgenomen vanwege het ulcus cruris tussen 1996 en 2007. Van 107 patiënten kon data worden verzameld, waarvan 27 een conservatieve behandeling kreeg (bedrust, lokale wondbehandeling en pijnbestrijding) en 48 patiënten ondergingen een chirurgische behandeling

met (n=19) of zonder (n=29) initiële VAC behandeling. De behandeling was onbekend bij de overige 32 patiënten. De mediaan opnameduur was 30 dagen, het mediaan sluitingspercentage bij ontslag was 95% en de mediaan recidieftijd was 60 dagen. Statistische analyse toonde significante verschillen tussen de conservatieve en de chirurgische groep, waarbij de patiënten in de laatste groep significant langer opgenomen lagen (P<0.0001) en een hoger sluitingspercentage hadden (P<0.0001), maar er was geen verschil in recidieftijd (P=0.273). Vergelijkbare verschillen werden aangetoond tussen de conservatieve groep en de VAC plus chirurgie groep. Geen significante verschillen konden worden aangetoond tussen de chirurgische groep en de VAC plus chirurgie groep. Concluderend, ziekenhuisopname is significant korter bij chirurgische behandeling van recalcitrante veneuze ulcera. De meeste ulcera recidiveren binnen twee maanden na ontslag uit het ziekenhuis. Recidiveren van veneuze ulcera crurum na ziekenhuisopname is onafhankelijk van de behandeling en oorzaak van ulceratie.

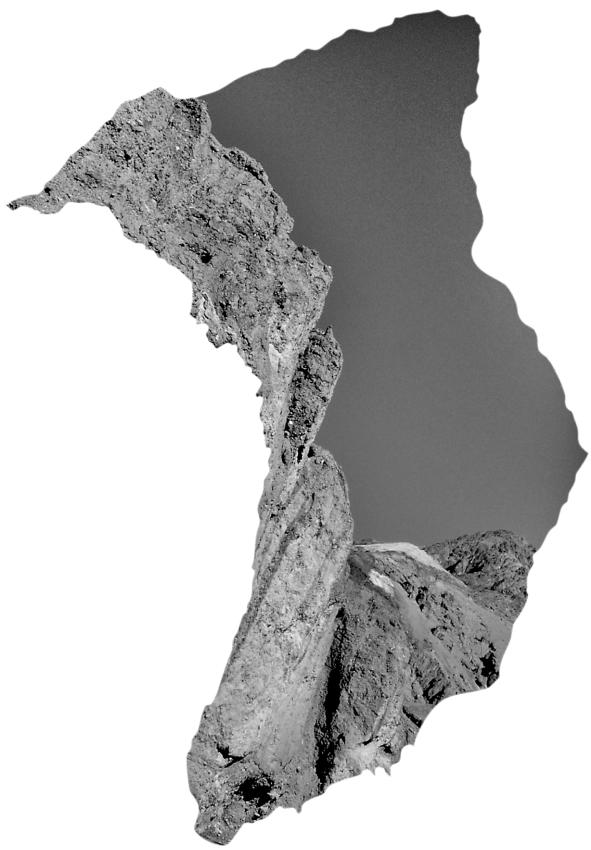
Veneuze ulcera crurum kunnen worden ingedeeld in drie categorieën: ongecompliceerd, recidiverend en recalcitrant. In het algemeen kunnen vier specifieke oorzaken van recalcitrante veneuze ulcera crurum worden onderschreven: voetpomp insufficiëntie, dermato- et liposclerose, chronisch veneus compartimentsyndroom en niet-gerekanaliseerde vena poplitea trombose. Met behulp van de bestaande literatuur beschrijven we in **hoofdstuk 11** deze vier oorzaken van recalcitrante veneuze ulcera crurum en hun specifieke behandeling naast het levenslang dragen van therapeutische elastische kousen met een hoge stiffness. Voetpomp insufficiëntie ontstaat als de plantaire voetvenen niet meer kunnen ledigen. De behandeling dient te bestaan uit fysiotherapie, een mechanische voetpomp en inlegzolen. Dermato- et liposclerose kan worden behandeld door excisie van het gehele gebied gevolgd door split-thickness skin grafting (Vigoni procedure). Chronisch veneus compartimentsyndroom wordt meestal veroorzaakt door een post-trombotisch syndroom dat op termijn kan leiden tot een verhoogde compartimentsdruk. De behandeling bestaat uit decompressie door middel van een fasciectomie. Behandeling van patiënten met een niet-gerekanaliseerde trombose van de vena poplitea is enkel ondersteunend, omdat een totale occlusie van de vena poplitea niet verenigbaar is met rechtop staan. Patiënten kunnen worden geholpen door middel van intermitterende pneumatische compressie, loopoefeningen en het alterneren van staan, wandelen en liggen. Slechts enkele patiënten zijn geschikt om aan te bieden voor stentplaatsing. We concluderen dat patiënten met recalcitrante veneuze ulcera crurum uitdagend zijn met betrekking tot diagnose en behandeling. Specifieke

behandeling van de onderliggende pathologie zal tot genezing van meer ulcera leiden.

In **hoofdstuk 12** worden de belangrijkste bevindingen van dit proefschrift besproken en in perspectief geplaatst. Daarnaast worden de limitaties van de studies besproken en suggesties gegeven voor toekomstig onderzoek.

Chapter 14

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



Appendix

In this thesis apparently conflicting epidemiological data on chronic venous disease (CVD), varicose veins and venous leg ulcer (VLU) are used. This may be explained by the fact that CVD is age-dependent and not all epidemiological data are age-dependent since most research is performed in a specific population. Three references may be regarded as key references. The Basle study performed by Widmer et al. demonstrated a perfect correlation between age and CVD among 3766 male factory workers.[1] Krijnen et al. investigated 387 male workers with a standing profession.[2] They demonstrated chronic venous insufficiency in 29% of the workers and a correlation regarding age, weight and duration of standing has been demonstrated. The most recent epidemiological study of CVD is the Bonn Vein study, but not all data have been published yet.[3] The great advantage of the last study is that a cross-section of the general population of 3072 people aged 18 to 79 is used.

A summary of the most frequently used data of prevalence of CVD, varicose veins and VLU is given.

Chronic venous disease

Author	Prevalence
Evans et al. (1997)[4]	♂:♀ = 9°:7
Criqui et al. (2003)[5]	27.9%
Maurins et al. (2008)[3]	90.4% (C0 9.6, C1 59.1, C2 14.3, C3 13.4, C4 2.9, C5 0.6, C6 0.1)
Rabe et al. (2012)[6]	83.6% (C0s 19.7, C1-C6 63.9)

Varicose veins

Author	Prevalence
Coon et al. (1973)[7]	♂:♀ = 1°:2
Abramson et al. (1981)[8]	♂:♀ = 1°:3
Brand et al. (1988)[9]	♀ <30 years = <10% ♀ ≥70 years = <77%
Weindorf et al. (1990)[10]	10.2%
Evans et al. (1999)[4]	♂:♀ = 4°:3
Criqui et al. (2003)[5]	23.3%

Venous leg ulcer

Author	Prevalence (%)	
	Active VLU	Healed VLU
Callam et al. (1985)[11]	0.15	Not mentioned
Cornwall et al. (1986)[12]	0.38	Not mentioned
Nicolaides et al. (2000)[13]	0.3	Not mentioned
Ghauri et al. (2000)[14]	0.15 0.21	Not mentioned
Margolis et al. (2002)[15]	4-5	Not mentioned
Pannier-Fischer et al. (2003)[16]	0.1	0.6
Moffatt et al. (2004)[17]	0.045	Not mentioned
Dissemond et al. (2006)[18]	0.7	Not mentioned
Gloviczki et al. (2011)[19]	0.5	0.6-1.4

REFERENCES

1. Widmer LK, Madar, G, Leu, HJ, Kamber, V, Münst, G, Wandeler, JM, Stähelin, HB, Käch, K Venenprojekt. Varikosis und chronisch-venöse Insuffizienz. In: Widmer LK, Stähelin, HB, Nissen, C, da Silva, A, editor. Venen-, Arterien-Krankheiten, koronare Herzkrankheit bei Berufstätigen. Prospektiv-epidemiologische Untersuchung Basler Studie I-III 1959-1978. Bern: Verlag Hans Huber; 1981. p. 59-136.
2. Krijnen RM, de Boer EM, Ader HJ, Bruynzeel DP. Venous insufficiency in male workers with a standing profession. Part 1: epidemiology. Dermatology 1997;194(2):111-20.
3. Maurins U, Hoffmann BH, Losch C, Jockel KH, Rabe E, Pannier F. Distribution and prevalence of reflux in the superficial and deep venous system in the general population–results from the Bonn Vein Study, Germany. J Vasc Surg 2008;48(3):680-7.
4. Evans CJ, Fowkes FG, Ruckley CV, Lee AJ. Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population: Edinburgh Vein Study. J Epidemiol Community Health 1999;53(3):149-53.
5. Criqui MH, Jamosmos M, Fronek A, Denenberg JO, Langer RD, Bergan J, et al. Chronic venous disease in an ethnically diverse population: the San Diego Population Study. Am J Epidemiol 2003;158(5):448-56.
6. Rabe E, Guex JJ, Puskas A, Scuderi A, Fernandez Quesada F. Epidemiology of chronic venous disorders in geographically diverse populations: results from the Vein Consult Program. Int Angiol 2012;31(2):105-15.
7. Coon WW, Willis PW, 3rd, Keller JB. Venous thromboembolism and other venous disease in the Tecumseh community health study. Circulation 1973;48(4):839-46.
8. Abramson JH, Hopp C, Epstein LM. The epidemiology of varicose veins. A survey in western Jerusalem. J Epidemiol Community Health 1981;35(3):213-7.
9. Brand FN, Dannenberg AL, Abbott RD, Kannel WB. The epidemiology of varicose veins: the Framingham Study. Am J Prev Med 1988;4(2):96-101.
10. Weindorf N, Schultz-Ehrenburg U. Le developpement de la varicose chez les enfants et les adolescents. Phlebologie 1990;43(4):573-7.
11. Callam MJ, Ruckley CV, Harper DR, Dale JJ. Chronic ulceration of the leg: extent of the problem and provision of care. Br Med J (Clin Res Ed) 1985;290(6485):1855-6.
12. Cornwall JV, Dore CJ, Lewis JD. Leg ulcers: epidemiology and aetiology. Br J Surg 1986;73(9):693-6.
13. Nicolaides AN, Cardiovascular Disease E, Research T, European Society of Vascular S, Organization TIASAC, International Union of A, et al. Investigation of chronic venous insufficiency: A consensus statement (France, March 5-9, 1997). Circulation 2000;102(20):E126-63.
14. Ghauri ASK, Taylor MC, Deacon JE, Whyman MR, Earnshaw JJ, Heather BP, et al. Influence of a specialized leg ulcer service on management and outcome. British Journal of Surgery 2000;87(8):1048-1056.
15. Margolis DJ, Bilker W, Santanna J, Baumgarten M. Venous leg ulcer: incidence and prevalence in the elderly. J Am Acad Dermatol 2002;46(3):381-6.
16. Pannier-Fischer F, Rabe E. Epidemiologie der chronischen Venenerkrankungen. Hautarzt 2003;54(11):1037-44.
17. Moffatt CJ, Franks PJ, Doherty DC, Martin R, Blewett R, Ross F. Prevalence of leg ulceration in a London population. QJM 2004;97(7):431-7.

18. Dissemond J, Korber A, Grabbe S. [Differential diagnoses in leg ulcers] Differential-diagnosen des Ulcus cruris. J Dtsch Dermatol Ges 2006;4(8):627-34.
19. Gloviczki P, Comerota AJ, Dalsing MC, Eklof BG, Gillespie DL, Gloviczki ML, et al.The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg 2011;53(5 Suppl):2S-48S.

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List of publications

Michiels JJ, Reeder-Boertje SWI, van den Bos RR, Wentel TD, Neumann HAM. Prospective studies on the diagnosis and management of deep vein thrombosis (DVT) and the post-thrombotic syndrome: filling the gap. Part 2: post-thrombotic syndrome: Rotterdam approach. Cercetãri Experimentale & Medico-Chirurgicale 2007;2-3:92-97.

Michiels JJ, Reeder-Boertje SWI, van den Bos RR, Wentel TD, Neumann HAM. Prospective studies on the diagnosis and management of deep vein thrombosis (DVT) and the post-thrombotic syndrome: filling the gap. Part 1: deep-vein thrombosis (DVT): Rotterdam approach. Cercetãri Experimentale & Medico-Chirurgicale 2007;2-3:86-91.

Reeder SWI, Wentel TD, Neumann HAM. A new approach to the post-thrombotic syndrome. Phlebology Digest 2007;20(3):4-8.

Reeder SWI, Roos K-P de. Compressietherapie nog steeds de hoeksteen in de flebologie. Themabijlage Compressietherapie Elsevier; November 2008; 6-8.

Reeder SWI, Neumann HAM. Functional tests in venous disease. In: Wittens C. Innovative treatments of venous disorders. Turijn: Edizioni Minerva Medica 2009, pp. 87-97.

Reeder SWI, Middelburg TA, Neumann HAM. Een zeer pijnlijk ulcus op het onderbeen. Ulcus arteriolosclerоticum van Martorell. Ned Tijdschr Geneeskd 2009;153:B421.

Vuerstaek JDD, Reeder SWI, Neumann HAM. Arteriolosclerotic ulcer of Martorell. An uncommon but severe vascular leg ulcer. J Eur Acad Dermatol Venereol 2010;24(8):867-74.

Bullens-Goessens YIJM, Reeder SWI. Zwangerschap en veneuze pathologie. In: Neumann HAM, Langendoen SI, de Maeseneer M, Wittens CHA. Handboek flebologie; diagnostiek en behandeling van veneuze ziekten. 1st ed. Houten: Prelum uitgevers; 2011. p. 121-41.

Reeder SWI, Maessen-Visch MB, van Asten WNJC, Neumann HAM. Overige technieken. In: Neumann HAM, Langendoen SI, de Maeseneer M, Wittens CHA. Handboek flebologie; diagnostiek en behandeling van veneuze ziekten. 1st ed. Houten: Prelum uitgevers; 2011. p. 211-7.

Reeder SWI, De Roos K-P, Neumann HAM. Bas élastiques thérapeutiques Classe I (bas Proleg®): des jambes moins fatiguées dans le choeur. Une mélodie en forme? Phlébologie 2011;64:59-64.

Wolff O, Wentel TD, Reeder SWI, Neumann HAM. The effect of compression ulcer stockings on the capillary filtration rate and the formation of edema. Phlebologie 2011;40(5):245-50.

Reeder SWI, Neumann HAM, de Maeseneer MGR. Bloedige veneuze drukmeting en compartimentdrukmeting. Ned Tijdschr Dermatol Venereol 2012;22(1):67-70.

Reeder SWI, de Roos K-P, de Maeseneer MGR, Sommer A, Neumann HAM. Ulcer recurrence after in-hospital treatment for recalcitrant venous leg ulceration. Br J Dermatol 2013;168(5):999-1002.

Reeder SWI, Wolff O, Partsch H, Nicolaides AN, Mosti G, Cornu-Thenard A, Obermayer A, Weingard I, Neumann HAM. Consensus: ambulatory venous pressure measurement. Int Angiol 2013. In press.

Curriculum Vitae

Suzanne Wilhelmina Ida Boertje werd op 29 augustus 1979 geboren te Alkmaar. In 1998 behaalde zij haar vwo-diploma aan het Petrus Canisius College te Alkmaar. Datzelfde jaar werd zij ingeloot voor de studie geneeskunde aan de Universiteit van Amsterdam. Na haar reguliere co-schappen in het Academisch Medisch Centrum te Amsterdam liep zij haar oudste co-schap op de afdeling Dermatologie in hetzelfde ziekenhuis. Het doctoraaldiploma werd behaald in november 2002 en het artsdiploma in november 2004. Aansluitend werkte zij tot april 2006 als arts-assistent op de afdeling Interne Geneeskunde in het Zaans Medisch Centrum te Zaandam, waarna zij van april 2006 tot juni 2007 als arts-assistent op de afdeling Dermatologie in het Waterlandziekenhuis te Purmerend heeft gewerkt. Sinds mei 2007 is zij werkzaam als arts-assistent op de afdeling Dermatologie in het Erasmus MC, waar zij sinds 1 januari 2008 het tot stand brengen van het huidige proefschrift onder supervisie van prof.dr. H.A.M. Neumann en dr. K-P. de Roos combineert met de opleiding tot dermatoloog. Zij trouwde op 5 september 2005 met Igor Reeder en zij zijn de trotse ouders van Isis en Tristan.

PhD Portfolio

Summary of PhD training and teaching activities

Name PhD student : Suzanne Wilhelmina Ida Reeder
PhD period : January 2008 – September 2013
Erasmus MC Department : Dermatology
Promotor : Prof.dr. H.A.M. Neumann
Supervisor : Dr. K-P. de Roos

	Year	Workload (Hours/ ECTS)
1. PhD training		
General academic skills		
– DOO course: Samenwerking	2009	8 hours
– Biomedical English Writing and Communication	2010	4 ECTS
– Implementatie Modernisering Medische Vervolgopleidingen, Desiderius School, Rotterdam	2010	8 hours
– DOO course: Ethiek	2010	8 hours
– Supervised intervision	2010-present	1 ECTS
– DOO course: Communicatie	2011	8 hours
– DOO course: Teach the Teacher	2012	16 hours
Presentations		
– Symposium oedeemtherapeuten, Oosterhout. "Wetenswaardigheden uit Monaco, Compressiezorg van A tot Z".	2009	1 ECTS
– World meeting of the Union Internationale de Phlébologie, Monaco. "The relation between CEAP and the gold standard AVPM".	2009	1 ECTS
– European Venous Forum, Antwerpen. "Hospital admission for venous leg ulcers: What is it worth?"	2010	1 ECTS
– Congress of the European Academy of Dermatology and Venereology, Lissabon. "Venous pressure measurement".	2011	1 ECTS
– Congres Cabourg IV, Frankrijk. "De v. ovarica, pathofysiology en kliniek", "Chronisch compartimentsyndroom", "Het ulcère rebelle".	2011	3 ECTS
– European Vascular Course, Maastricht. "Compression stockings class I in a choir: a perfect melody?"	2011	1 ECTS
– Wetenschappelijke vergadering van de Nederlandse Vereniging voor Dermatologie en Venereologie, Rotterdam. "Bloedige veneuze drukmeting en compartimentsdrukmeting".	2012	1 ECTS
– European Vascular Course, Maastricht. "Compression for Everyone".	2012	1 ECTS
– Workshop Op ontdekking in het diep veneus systeem, Rotterdam. "Veneuze Drukmeting, hoe doen we dat?"	2012	1 ECTS

	Year	Workload (Hours/ ECTS)
International conferences		
– 12ème Conférence Nationale des Plaies et Cicatrisations, Paris, France (27-29 January).	2008	1 ECTS
– European Venous Forum, Barcelona, Spain (26-28 June).	2008	1 ECTS
– Deutsche Gesellschaft für Phlebologie, Bochum, Germany (15-18 October).	2008	1 ECTS
– European Vascular Course, Maastricht, the Netherlands (26-28 February).	2009	1 ECTS
– World meeting of the Union Internationale de Phlébologie, Monte Carlo, Monaco (31 August-4 September).	2009	1 ECTS
– European Venous Forum, Antwerp, Belgium (24-26 June).	2010	1 ECTS
– Deutsche Gesellschaft für Phlebologie, Aachen, Germany (10-13 November).	2010	1 ECTS
– European Vascular Course, Maastricht, the Netherlands (2-4 March).	2011	1 ECTS
– Cabourg IV: Wij gaan endovasculair. Cabourg, France (5-9 April)	2011	1 ECTS
– Congress of the European Academy of Dermatology and Venereology, Lisbon, Portugal (20-24 October).	2011	1 ECTS
– European Vascular Course, Maastricht, the Netherlands (10-13 March).	2012	1 ECTS
National conferences		
– 9e Wetenschappelijke vergadering van de Nederlandse Vereniging voor Experimentele Dermatologie, Lunteren, the Netherlands.	2008	1 ECTS
– Nederlandse Vereniging voor Dermatologie en Venereologie – Nascholing Wondgenezing, Basaalcelcarcinoom en Varices, Amsterdam, the Netherlands.	2008	1 ECTS
– Dermatologendagen, Papendal, the Netherlands.	2012	1 ECTS
– Dermatologendagen, Papendal, the Netherlands.	2013	1 ECTS
Seminars and workshops		
– Dermatologie, discussiepunten in de praktijk.	2008	4 hours
– There's no excuse for writing unreadable scientific articles! by David Alexander.	2008	1 hour
– Publishing and Acceptance Criteria for Scientific Journals, by Ian Cressie.	2009	2 hours
– Star Academy "Overtuigend Presenteren".	2009	1 ECTS
– Star Academy "Afgestemd Communiceren en Onderhandelen".	2010	1 ECTS
– CPO symposium: Methodologie van Patiëntgebonden Onderzoek en Voorbereiding van Subsidieaanvragen.	2013	7 hours

	Year	Workload (Hours/ ECTS)
Other		
– Organisation and programm coordinator of Multicenter Flebologie Overleg.	2010-2011	1 ECTS
– Organisation of Cabourg IV.	2011	1 ECTS
2. Teaching activities		
– Nascholing internisten, Erasmus MC, Rotterdam. "Het wordt moeilijk…"	2009	1 ECTS
– Nascholing doktersassistenten, U-consultancy, Bunnik. "Psoriasis".	2010	1 ECTS
– Nascholing oedeemtherapeuten en fysiotherapeuten, Utrecht. "Flebologie en lymfologie".	2010	1 ECTS
– Opleiding Flebologie, Utrecht. "Module Diagnostiek" and "Module Pathofysiologie".	2012	2 ECTS
– Nascholingsavond voor de praktijk, Dermapark, Uden. "Bloedige veneuze drukmeting en compartimentdrukmeting".	2012	1 ECTS
– Workshop Op ontdekking in het diep veneus systeem, Rotterdam. Supervising hands-on workshop duplex ultrasound.	2012	
– COCOM Dermato-chirurgie, lasers en flebologie, Rotterdam. Supervising hands-on workshop laser.	2013	

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List of frequently used abbreviations

AASV, anterior accessory saphenous vein
ACP, anterior compartment pressure
ACT, ambulatory compression therapy
AVP, ambulatory venous pressure
AVP%, percentage of ambulatory venous pressure
BMC, bas médicaux compressifs
CEN, Comité Européen de Normalisation
CFR, capillary filtration rate
CVCS, chronic venous compartment syndrome
CVD, chronic venous disease
CVI, chronic venous insufficiency
DUS, duplex ultrasound
DVT, deep vein thrombosis
MAP, mean arterial pressure
MECS, medical elastic compression stockings
PTS, post-thrombotic syndrome
RT, venous refill time
RT90, 90% of venous refill time
SVI, superficial venous incompetence
SVP, standing venous pressure
UEMS, Union Européenne des Médecins Spécialistes
UIP, Union Internationale de Phlébologie
VAC, vacuum-assisted closure
VLU, venous leg ulcer