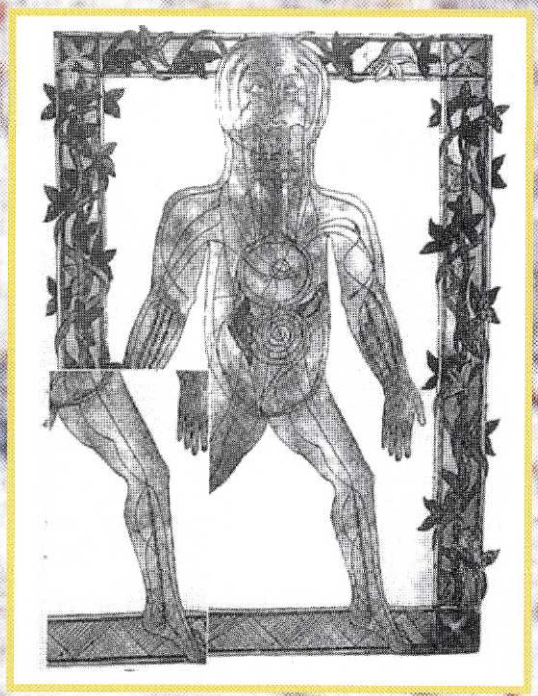
Assessment of Venous Insufficiency in Patients with Chronic Venous Leg Ulcers. Venous Hemodynamics before and after Surgery



Marie Magnusson

Göteborg 2005

Assessment of Venous Insufficiency in Patients with Chronic Venous Leg Ulcers. Venous Hemodynamics before and after Surgery

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av

Marie Magnusson

Fakultetsopponent:
Professor Bo Eklöf
American Venous Forum
Helsingborg

This thesis is based on the following papers:

I M Magnusson, P Kälebo, P Lukes, R Sivertsson, B Risberg. Colour Doppler Ultrasound in diagnosing venous insufficiency. A comparison to descending phlebography. Eur J Vasc Endovasc Surg 1995;9:437-43

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Sahlgrenska Akademin
VID GÖTEBORGS UNIVERSITET

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Department of Clinical Physiology, Cardiovascular Institute, Sahlgrenska Academy, Göteborg, Sweden

Abstract

Venous insufficiency in the legs is a common disease, which may be complicated by chronic leg ulcers in 1% among the population. Venous ulcer duration is often long compared to other aetiologies and for the patient it involves long periods of pain, discomfort and reduced quality of life. Superficial insufficiency can frequently be observed in leg ulcer patients, which makes them suitable for varicose vein surgery.

Colour Doppler ultrasound (CDU) is widely used for diagnosis of venous disease by its possibilities to localize the level of reflux both in the superficial and in the deep vein systems. Hence, less ulcer recurrence can be observed after CDU-guided varicose vein surgery in comparison to conservative treatment.

The purposes of the studies were 1) to evaluate CDU in comparison to descending phlebography, the 'golden standard' investigation of venous insufficiency, 2) to investigate common sites of insufficient vein compartments in legs with chronic leg ulcers, 3) to investigate vein surgery outcome and its relation to ulcer healing or ulcer recurrence, and 4) to describe the pathophysiology of postoperative venous ulcer recurrence in terms of venous reflux, ambulatory venous pressure and muscle pump dysfunction and to find predictive risk variables for venous ulcer recurrence.

We found a good agreement between CDU and descending phlebography. However, CDU was superior to find distal venous valve insufficiencies in cases of competent proximal ones. In leg ulcer patients with primary venous insufficiency, isolated superficial insufficiency was found in 50% and combinations with deep insufficiency was observed in 35%. In patients with secondary venous insufficiency deep reflux is common (38%), but 49% had mixed superficial and deep insufficiency. Thus, a large part of patients with leg ulcers might benefit of surgery. The ulcer recurrence rate was estimated to be 19% within a 5 year period after a median follow-up time of 2-6 years. In all patients with recurrent leg ulcers, the post-operative CDU investigation showed new insufficient or residual incompetent pathways. Long lasting ulcer disease was a significant preoperative and postoperative risk variable, which should have influence on interventional decisions and follow-up strategies. Another postoperative risk factor was axial reflux and high ambulatory venous pressure ($p<0.018$). At post-operative follow-up, venous function improved initially, but deteriorated again within a two 2 years period, especially in legs with ulcer recurrence (17%). Muscle pump function (APF%) and venous refilling times (VRT_{90}) were significant risk variables for ulcer recurrence after surgery.

In conclusion, Colour Doppler Ultrasound is reliable in diagnosing venous insufficiency and should always be used before surgical interventions. Since superficial venous insufficiency is common in legs with venous ulcers, varicose vein surgery should be considered in those cases. Correctly performed varicose vein interventions improve the muscle pump function and lower thereby the risk of ulcer recurrence. Post-operative follow-up with tests of muscle pump function is recommended in patients at risk of ulcer recurrence.

Key words: Colour Doppler Ultrasound, leg ulcer, varicose vein surgery, recurrent leg ulcers

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Cardiovascular institute, Clinical Physiology, Sahlgrenska Academy
at Göteborg University, Göteborg, Sweden

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by

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En resa på tusen mil börjar alltid med ett enda steg

Kinesiskt ordspråk

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LIST OF ORIGINAL PAPERS

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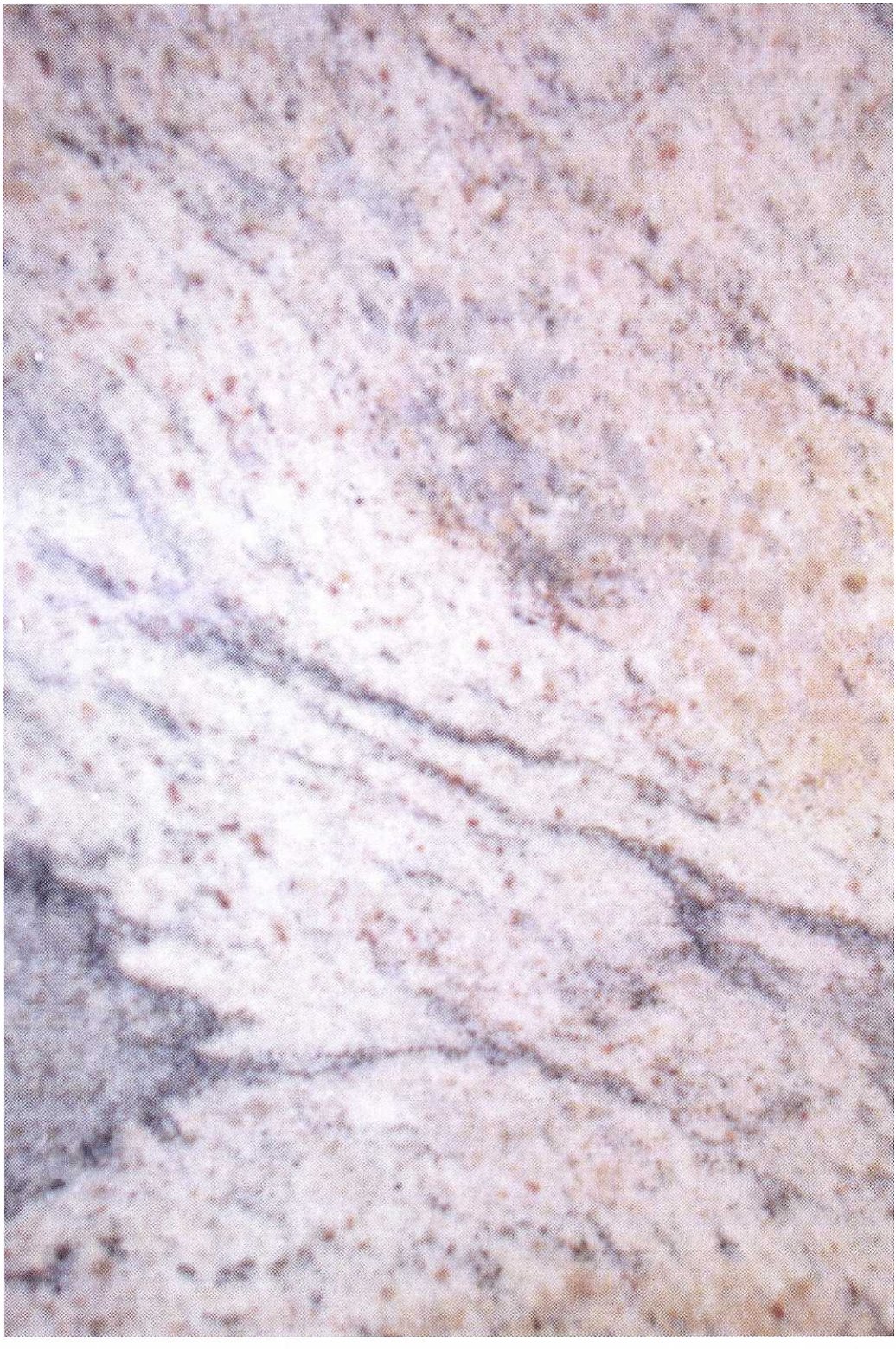
CONTENTS

ABBREVIATIONS

CDU	Colour Doppler Ultrasound
FVDS	Functional Venous Disease Score
VSDS	Venous Segmental Disease Score
AVP	Ambulatory venous pressure
VRT_{90}	Venous refilling time
APF%	Active pump fraction
VFI	Venous filling index
VV	Functional venous volume
APV	Active pump volume
APG	Air-plethysmography
VOP	Venous outflow plethysmography
CEAP	Clinical Etiology Anatomy Pathology
C_5	healed ulcer
C_6	active ulcer
S, Sr	superficial venous reflux
D, Dr	deep venous reflux
So/Do	none superficial or deep venous reflux
S+D	combined superficial and deep reflux
SEPS	subfascial endoscopic perforator surgery
GSV	great saphenous vein
SSV	small saphenous vein
FV	femoral vein
DFV	deep femoral vein
POPV	popliteal vein
PTV	posterior tibial vein
PV	peroneal vein
AK	above knee
BK	below knee
CVI	chronic venous insufficiency
DVT	deep venous thrombosis
prox	proximal
dist	distal
SBP	systolic blood pressure
DBP	diastolic blood pressure
BMI	body mass index

Man behöver inte vara alltför rädd för att
begå fel och misstag.
Det största av alla misstag är av avstå
från tillfällen att förvärva sig erfarenhet

Leonardo da Vinci



INTRODUCTORY REMARKS

The characterization of venous insufficiency is today reliable with Colour Doppler Ultrasound (CDU), which is therefore a valuable tool for the surgeon. Chronic venous insufficiency in lower leg is a common disease, which in some cases is complicated by venous leg ulcers. Conservative treatment has been used, but several studies have shown improved healing after CDU-guided varicose vein surgery. Unfortunately ulcer recurrence still occurs post-operatively.

The present studies were performed to evaluate CDU, as it is used in our hands and to describe the common sites and aetiologies of venous insufficiency in patients with chronic venous leg ulcers. In addition the surgical outcome was followed-up with special focuses on venous hemodynamics, venous reflux, ulcer healing, as well as the risk for ulcer recurrence.

vein [vein] ***n.*** **1.** blood –vessel along which blood flows back to the heart. (Cf. *artery.)* **2.** one of the ~ -like lines in some leaves or in the wings of some insects; a coloured line or streak in some kinds of stone (e.g. marble): (fig.) *There is a ~ of melancholy in his character.* **3.** crack or fissure in rock, filled with mineral or ore; lode or seam: *a ~ of gold.* **4.** mood; train of thought: *in a merry (melancholic, imaginative) ~. He writes humorous songs when he is in the (right) ~.* **veined** [veind] **adj.** having, marked with, ~s: ~ed marble.

The Advanced Learner's Dictionary of Current English, second edition, Oxford University Press, 1963

BACKGROUND

Historical aspects

"In the case of an ulcer, it is not expedient to stand; more especially if the ulcer be situated in the leg"

Hippocrates (460-377 BC)

As in many other medical events, Hippocrates gets first credit for varicose vein treatment.[1] He recommended multiple punctures and cautioned against cutting directly into the varicosity and engorged tissues. He also suggested elevation and compression bandages as appropriate treatment.[2] During the Roman time treatment of bandaging with linen was advised by Celsus (25BC-50AC) and applying wine to the ulcer was recommended by Galen (130-200AC)[3]

In 1603, just 400 years ago, *Hyeronimus Fabricius d'Acquapendente* (1533-1619) published the first treatise on the venous valves (VV) entitled *De Venarum Ostiolis*. VV had been already described in the heart and in larger veins but Fabricius was the first to describe their anatomy in the whole body.[4] He also proposed a test to evaluate VV competence that led his student, William Harvey (1578-1657), to discover the circulation of the blood and the function of the vein valves in preventing retrograde flow. Fabricius correctly described VV both in deep and superficial veins of the lower limb. Characteristic drawings from Acquapendente's work are shown in Fig. 1,2. Fabricius also discussed the correlations between VV failure, varicose veins (in which he described bi-directional flow) and venous ulcers and stated "incompetent VV cannot prevent accumulation of fecaloid humours to the lower leg that cause ulceration". In both cases, Fabricius treated varicose veins surgically by double ligature and avulsion. In order to promote ulcer healing, a 'divine favor' was invoked.

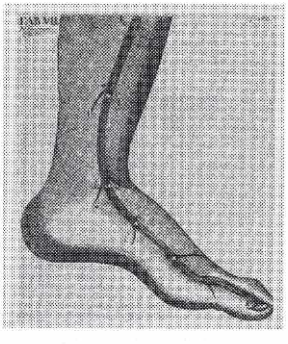


Fig. 1 Valves of the distal long (great) saphenous vein (from Aquapendente)

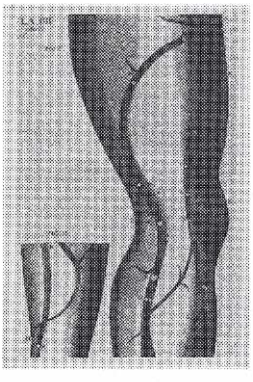


Fig. 2 Valves of a leg vein (from Aquapendente)

The term "varicose ulcer" was introduced by Wiseman, who was Sergeant-Chirurgeon to Charles II of England.[5] He realized 1676 that valvular incompetence results from venous dilatation and concluded that ulcers might be a direct result of stagnation secondary to a circulatory defect. First in the 19th century Home (1801) and Hodgson (1851) recognized the importance of vein varicosis. However in 1868, Gay and Spender discarded independently the varicose theory and proposed venous thrombosis as the major causative factor. Gay introduced the term "venous ulcer" and "arterial ulcer". Homans introduced in 1938 the therms "varicose ulcers" when associated with varicose veins, and "venous ulcers" when resulting from previous thrombosis. Several later studies stated post-thrombotic aetiologies for venous ulcers with the result, that varicose vein surgery in leg ulcer patients went gradually out of fashion, and the term "varicose ulcer" was discarded.[6] In one textbook it was clearly written that "*Incompetence in the superficial venous system does not give rise to leg ulcers*".[7] The prerequisite was seen to be either a previous deep vein thrombosis, or primary deep vein incompetence or incompetent perforating veins. Therefore, most leg ulcer patients have been treated during these years with conservative management based on graduated compression.

Venous anatomy

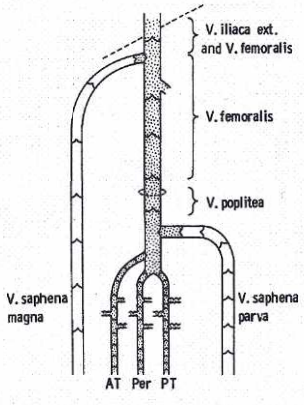


Fig. 3 The superficial (not filled) and deep venous system.

Veins of the extremities are divided into two systems, the superficial and the deep ones (Fig. 3). Deep veins are delicate structures, lying adjacent to arteries of the same name. In the forearm and calf, these veins are usually duplicated into two venous comitantes that follow the artery. The soleal sinusoids terminate in the posterior tibial and peroneal veins; and the gastrocnemial sinusoids empty in the popliteal vein. As major components of the muscle pump mechanism, these sinusoids are important physiologically; but they are also important pathologically since they represent common sites of early thrombus formation.

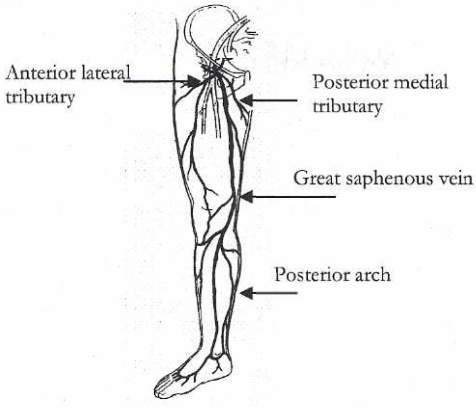


Fig. 4A The great saphenous vein (GSV) and its tributaries.

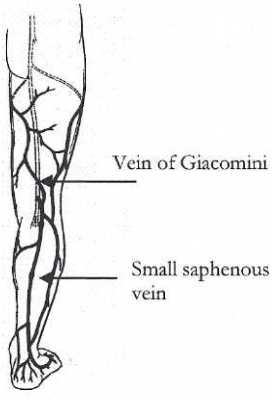


Fig. 4B The small saphenous vein (SSV)

Superficial veins (Fig. 4A,B) have no arterial analogues and are thick-walled and more muscular than deep veins. The principal superficial veins include the greater and smaller saphenous veins of the leg, the cephalic and basilic veins of the arm, and the external jugular veins of the neck. Draining into the saphenous veins, which lie on the investing fascia, are numerous tributaries that are more superficially located in the subcutaneous tissues. Perforating or communicating veins connect the deep and superficial systems. They are more numerous in the distal part of the leg.

In terms of function, the most significant feature of venous structure is the presence of bicuspid valves. The gossamer thin but extremely strong valve leaflets permit unidirectional blood flow from the periphery to the heart. In the perforating veins, valves direct blood from the superficial to the deep system in all areas except the foot, where the opposite occurs. In cardiac direction to the valve attachment to the vessel wall, the vein is dilated to form a sinus (Fig. 5). Since the cups cannot come in contact with the wall when the valve is fully open, rapid valve closure is possible when the blood flow tends to change its direction. As a rule, as more distal the vein is located, as greater is the number of valves in it. The vena cava and common iliac veins are valveless. Valves are found in about one-fourth of the external iliac veins and in two-thirds to three-quarters of the common femoral veins.

Average occurrence of Valves

Femoral vein: 1-4

Popliteal vein: 1-3

Peroneal vein: 7

Posterior and anterior veins: 9-11

Greater saphenous vein: 10-20

Smaller saphenous vein: 6-12

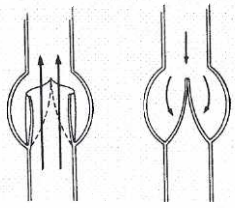


Fig. 5 Longitudinal section through a venous valve.

Venous Physiology

The veins perform many functions that are necessary for a normal blood circulation.[8] They are capable of constricting and enlarging, of storing large quantities of blood and making this blood available when it is required by the remainder of the circulation, of actually propelling blood forward by means of so called "venous-pump" and even of helping to regulate cardiac output and body temperature. Their main function is to transport blood from the capillaries to the heart, and this venous return can be passive or active.

The pressure in the right atrium is frequently called the central venous pressure. The pressure in the peripheral veins depends to a great extent on the level of this pressure, but with superposition of hydrostatic pressure components (see below). Factors that increase the tendency of venous return are 1/ increased blood volume, 2/ increased large vessel tone throughout the body with resultant increased peripheral venous pressure and 3/ dilatation of the arterioles, which decreases the peripheral resistance and allows rapid flow of blood from the arteries to the veins.

Venous pressure

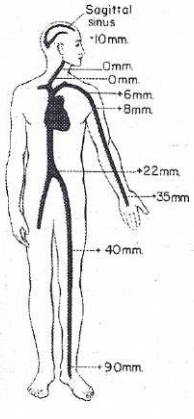


Fig. 6 Effect of hydrostatic pressure on venous pressures throughout the body.

In any body of water, the pressure at the surface of the water is equal to atmospheric pressure, but the pressure rises 1 mmHg for each 13.6 mm distance below the surface. This pressure results from the weight of the water and therefore is called hydrostatic pressure. Hydrostatic pressure also occurs in the vascular system of the human being because of the weight of the blood in the vessels. When a person is standing, the pressure in the right atrium remains approximately 0 mmHg since the heart pumps any excess blood that attempts to accumulate at this point into the arteries. However, in an adult who is standing absolutely still the pressure in the veins of the feet is approximately +90 mmHg simply because of the distance from the feet to the heart and the weight of the blood in the veins between the heart and the feet. The venous pressures at other infra cardiac levels of the body lie proportionately between 0 and 90 mmHg (Fig. 6).

The intraluminal pressure acting to distend the vein is the sum of the dynamic arterial/venous pressures due to the cardiac effect, the static filling pressure, which is constant, and hydrostatic pressure. If the first two factors remain unaltered, an increase in hydrostatic pressure will raise the intraluminal pressure, and the vein will distend.

Venous volume

Unlike the arterials, veins are collapsible, thin-walled tubes.[9] When fully distended, they have a circular cross-section; but when they are collapsed, they assume a dumbbell configuration. Between these two extremes, the lumen is elliptical (Fig. 7). In the distended state, the cross-sectional area of the veins is roughly three to four times that of the corresponding arteries. Transmural pressure refers to the difference between the intraluminal pressure distending the vein and the tissue pressure forcing the vein closed. When tissue pressure exceeds the intraluminal pressure, the transmural pressure will be low, and the vein will collapse in an elliptical fashion. Conversely, if the intraluminal pressure surpasses the tissue pressure, the vein will distend into a circular shape. Hence, changes in transmural pressure cause a large variation in cross-sectional areas and tremendous shifts in volume. The venous system is able to accommodate for these volume changes with minimal alterations of the venous pressure.

$$\textit{Vascular distensibility} = \frac{\textit{Increase in volume}}{\textit{Increase in pressure} \times \textit{Original volume}}$$

$$\textit{Vascular compliance} = \frac{\textit{Increase in volume}}{\textit{Increase in pressure}}$$

Vascular compliance or capacitance is the total distensibility, meaning the increase in volume caused by a given increase in pressure. The compliance of a vein is about 24 times that of its corresponding artery because it is about 8 times as distensible and it has a volume about 3 times as great (8x3=24). Therefore the veins or the capacitance system are frequently called the *storage areas* or the *blood reservoir* of the circulation.

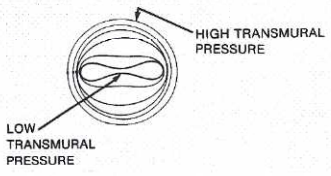


Fig. 7 Cross sections of venous lumen at various transmural pressures. From Sumner DS:Hemodynamics and pathophysiology of venous disease.

Since pressure within the veins is affected by posture, the volume of blood contained within the veins will also differ depending upon the position of the extremity in relation to the heart. It is estimated that a fluid shift of 250 ml per leg occurs upon arising from a horizontal position. The reason this volume change can be accommodated is the alteration of the cross-sectional contour brought about by hydrostatic pressure. The increase in hydrostatic pressure that cause transmural venous pressure to rise from about 10 to perhaps 80-100 mmHg at calf level from supine to standing position.

However, since the wall tension increases directly with the transmural tension times the vein radius (LaPlace law) vein dilatation result in increasing wall tensions and additional dilation, a circulus vitiosius which may end in varicose veins.

Law of LaPlace; $T_{circ} = P_{TM} \times r$ (N/m) were T_{circ} is the wall tension, P_{TM} the transmural pressure, r the vein radius.

Venous muscle pump

The muscle pump mechanism facilitates the return of blood to the heart during exercise. It has been calculated that 30% of the energy required to circulate blood during strenuous exercise is supplied by this mechanism. In addition, the muscle pump, by reducing peripheral pressures, decreases oedema in the dependent tissues and prevents the accumulation of excessive quantities of blood in the leg veins. The skeletal muscles act as the power source, and the sinusoids, deep veins and superficial veins in the order of decreasing importance, act as the bellows. As in any unidirectional pump, valves are vitally important to ensure efficient performance.

In a motionless upright subject, veins simply collect blood from the capillaries and transport it passively to the heart, the energy being supplied totally through the cardiac effect. During exercise, contraction of the calf muscles compresses the venous sinusoids directly and the other veins indirectly, forcing blood cephalad (Fig. 8). Closure of the valves in the perforating veins and in the deep veins below the calf precludes reflux of blood into the superficial tissues or down the leg. When the muscles relax, a potential space develops in the deep veins. Blood is "sucked" from the superficial veins through the perforators into the deep veins and the accumulated blood in the peripheral veins moves cephalad into the more proximal veins. Reflux down the leg is prevented by closure of the proximal valves. Closure of these valves interrupts the hydrostatic blood column so that it no longer continues unbroken from the periphery to the heart but extends for only a few centimetres above each valve to prevent over distension of the thin-walled veins. Consequently, hydrostatic pressure is markedly reduced. This reduction in venous pressure increases the pressure gradient across the capillaries, thereby augmenting blood flow. With cessation of exercise, capillary inflow gradually replenishes the blood in the deep veins, extends the hydrostatic column and returns venous pressure to its pre-exercise level. The calf muscle pump function is complex, it is reflecting venous reflux, venous patency and muscular power.

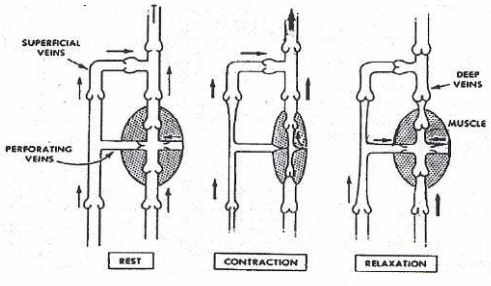


Fig. 8 Dynamics of venous blood flow in a normal limb. From Sumner DS: Venous dynamics-varicosities. Clin Obstet Gynecol 24:743-760, 1981

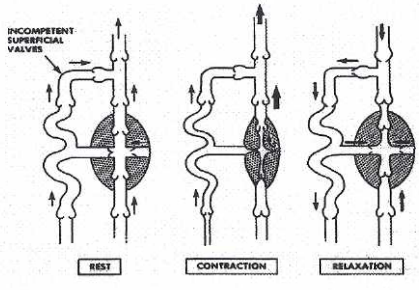


Fig. 9 Dynamics of venous blood flow in a limb with primary varicose veins. From Sumner DS: Venous dynamics-varicosities. Clin Obstet Gynecol 24:743-760, 1981

Venous hypertension

Venous hypertension is present, when the patient is unable to sufficiently reduce venous pressure by muscle pump activation. Calf muscle contraction may force blood to flow cephalad in the deep veins; but during muscle relaxation (pump diastole), regurgitation may occur through the perforators in cases of superficial vein incompetence. (Fig. 9). A portion of blood in the leg is, therefore, consigned to an inefficient circular pathway. If the valves below a pump segment are incompetent, muscle pump activation forces blood in both directions increasing the pressure in

the more distal veins. Incompetent valves above the pump segment cause fast retrograde refilling of the veins, which, contributes to the persistent venous hypertension.

Venous insufficiency

Chronic venous insufficiency (CVI) in the lower leg is a common condition of incompetent superficial and/or deep vein valves. If all degrees of varicose veins and CVI are included, the prevalence is about 50-55% in women and 40-50% in men.[10] Complicated cases of chronic venous insufficiency are also frequently found. Clinically, CVI can be classified into six different stages based on clinical findings (Table 1) in accordance with the CEAP (Clinical Etiology Anatomi Pathology)[11] C=clinical, E=primary or secondary, A=superficial, deep or perforators, P=reflux or O=obstruction. The most severely affected patients may also have development of one or more painful venous ulcers with high recurrence rates.

Table 1.—Classification of Chronic Venous Disease of the Lower Extremities: Clinical Findings

Class*	Definition
0	No visible or palpable signs of venous disease
1	Telangiectases or reticular veins
2	Varicose veins
3	Edema
4	Skin changes ascribed to venous disease (for example, pigmentation, venous eczema, lipodermatosclerosis)
5	Skin changes (as defined above) in conjunction with healed ulceration
6	Skin changes (as defined above) in conjunction with active ulceration

*The presence or absence of symptoms such as pain or aching is denoted by the addition of "s" for symptomatic or "A" for asymptomatic to modify the class category.

Primary insufficiency

Several factors may contribute to overdilation of the venous wall:

- Increased hydrostatic pressure throughout most hours of the day, as found in persons with occupations requiring prolonged standing,
- Venous congestion caused by the gravid uterus.[12] combined with
- Increased dilatability of vessels, as can be observed during pregnancy. Szotér and Cronin[13] observed increased dilatability of lower-arm veins of patients with primary varicose veins. It appears therefore that primary venous-wall weakness, as postulated also by Leu et al,[14] does play an important role. According to Reagan and Folse[15] there seems to be a hereditary disposition, towards this weakness.
- In all forms of physiologic or unphysiologic venous dilatation, the proximal incompetent valve will expose the next distal one to increasing overdilating forcess, since the hydrostatic pressure will increase stepwise in distal direction as more valves are involved.

Secondary insufficiency

A more severe chronic form of venous insufficiency (CVI) is caused by previous deep venous thrombosis (DVT). Those cases are often referred to as a post-thrombotic syndrome. Besides secondary deep venous insufficiency after recanalization the veins have often a limited lumen due to post-thrombotic wall changes or obstruction. The superficial veins are then recruited as collaterals and may dilate with the increasing postthrombotic venous pressures, and the valves will become incompetent as well. In the more severe cases with extensive venous obstruction and poor collateral development, the ambulatory venous pressure may actually rise.[16]

Venous leg ulcer

According to the Stockbridge study in Scotland[17] *, chronic leg ulcer is defined as "an open sore below the knee anywhere on the leg or foot which takes more than six weeks to heal".*

The incidence of chronic leg ulcerations is approximately 2% during the whole populations life time which might be caused by a wide range of factors where venous insufficiency is the most common reason.[18] Hence, approximately 70% of ulcers above the foot are of venous origin.[19,20] Age is a risk factor for both venous and arterial insufficiency and the leg ulcer prevalence in patients over 65 years is estimated to be about 4%.[21] Venous aetiology among recurrent ulcers is also frequent and the venous ulcer duration is longer than for ulcers of the other aetiologies.[22]

There is a general agreement that venous ulceration results from a failure to lower the venous pressure on leg exercise, which may be due to venous disease in deep veins, superficial or the perforating veins. Some controversy remains about the mechanisms of the calf muscle pump failure, but the resulting pressure abnormalities are easy to observe and measure. Venous hypertension alters the hemodynamics at the capillary level and causes a shift towards the outflow of capillary fluid and development of oedema. Excessive fluid in the interstitial spaces inhibits the exchange of nutrients and removal of metabolic degradation products. This problem is enhanced by the loss of protein into the interstitial spaces. Maintenance of these conditions for a prolonged period will result in stasis dermatitis, hemosiderin deposition and skin ulceration at the ankle region.

Venous leg ulcer patients have mainly been assigned to conservative treatment since venous ulcer has generally been ascribed to deep vein insufficiency and the post-thrombotic syndrome, including statements that "primary varicose veins never give rise to venous ulcers".[23-25] However, recent studies have shown that superficial venous insufficiency seems to be a more common cause of venous ulcer than previously believed, but the frequencies vary considerable between

these studies.[20,26-35] The reason for the variability may be different methods and study designs, as well as different patient selection.

Diagnosing venous insufficiency

Clinical diagnosis of venous incompetence has been the dominating interpretation during the years. Studies have shown little agreement between clinical diagnosis and methods diagnosing venous insufficiency.[36] There are a variety of tests available for the evaluation of venous insufficiency. None provide complete information on both morphology and venous function, and several methods provide similar information. Regarding venous morphology, contrast phlebography[37,38] is considered as the reference method, but functional tests are of major importance for evaluation of the pathophysiology. For assessment of overall venous function, ambulatory venous pressure (AVP) measurements have often been used as reference method,[39-41] by which the influence of venous reflux and obstruction on calf muscle pump efficiency is tested. The calf pump action normally reduces the venous pressure, which is lowest after leg exercise. With augmenting grades of venous hypertension the risk for leg ulcers increases too, i.e. ambulatory vein pressure measurements are important parameters for predicting the risk for development of venous ulcers.[42]

Since the venous volume and venous pressure are correlated with each other, the rate of venous return can be measured either by means of a pressure gauge or by lower leg plethysmography (using air, water or strain gauge techniques).[43-47] Plethysmography has the advantage of being noninvasive and more convenient. The function of the calf muscle pump can be assessed by the blood volume expelled from the calf during exercise. Its efficiency depends on the function of the vein valves in the deep, superficial and perforator compartments as well as on muscular power. In the presence of venous reflux, refilling of the veins becomes rapid. Thus, the refilling time either measured as venous pressure or venous volume restitution correlates to the grade of venous valve insufficiency. Especially the residual vein volume, as derived from Air-plethysmography, was found to be linear related to AVP providing an indirect and non-invasive measure of the ambulatory venous pressure.[48,49]

Continues-wave Doppler has been used extensively in the diagnosing of venous insufficiency. Since the depth control of any measurements is limited, the selection of a certain vein compartment is difficult. The investigations have to be performed blindly without visualization of the blood vessel studied. Therefore, reliable interpretations are difficult even in the hands of very experienced investigators.[50]

All levels of the venous system have to be evaluated for accurate descriptions of the role of valvular incompetence alternatively venous obstruction for clinical symptoms and events. Duplex ultrasound has considerably improved the ability to assess important blood flow information,[51] since the Doppler information from a local sample volume is combined with a real time 2D-image. In colour-coded Doppler, blood flow information from a number of sample volumes within defined areas of a real time B-mode images, is presented in colour, which is very useful in the evaluation of incompetent venous valves. With this method an instant visualization of blood flow as well as the site of the reflux can be presented.[31,52-54]

Therapeutic implications

Conservative treatment of chronic leg ulcers using compression stockings is of significant clinical value but needs a strict compliance in wearing stockings. However, ulcer recurrences are frequently seen.[55] Faster ulcer healing and less ulcer recurrence have been observed after CDU-guided varicose vein surgery.[56,57]

To correct pathophysiological aberrations associated with venous valvular incompetence, incompetent veins have to be ligated or removed. If the valvular incompetence is confined to the superficial system only, primary varicose veins are relatively easy to treat by an experienced surgeon. Interrupting the long hydrostatic column by ligation of the terminal saphenous vein is a rational procedure, but recurrent axial insufficiency can be commonly observed during follow-up. The best results will be achieved, when all tributaries are ligated, the saphenous vein is stripped and all varicosities are consequently removed.

Deep venous insufficiency is more difficult to treat. Attempts have been made to correct deep venous insufficiency by various kinds of valvuloplasty, vein transposition or by-pass procedures.[58,59] However, the clinical benefits from these interventional procedures are not proven in a long-term perspective.

"If you do what I say and follow it closely
your ulcer will heal"

Robert Linton

AIMS OF THE THESIS

The objectives of the study were:

I. To compare Colour Doppler Ultrasound outcome with descending phlebography as the "golden standard".

II. To identify common sites of venous valve incompetence in patients with chronic leg ulcers.

III. To investigate the frequencies and possible risks of ulcer recurrence after superficial vein surgery in a retrospective study design.

IV. To characterize venous hemodynamics pre- and post-operatively in patients with chronic venous leg ulcers and to correlate the post-interventional hemodynamic outcome with the ulcer recurrence.

MATERIAL AND METHODS

Patient selection

All the patients were initially referred from different outpatient surgery clinics or by general practitioners for preoperative CDU investigation at the department of clinical physiology, Östra hospital. The patients suffered of chronic leg ulcers, healed or active. One healthy control group without venous insufficiency (n=52 legs) was examined in *[paper I]*.

I. Prospective study design. During 1989-1992, 44 patients, aged 17-76 years, 22 women and 22 men (56 legs) with the clinical diagnosis of deep venous insufficiency were pre-operatively investigated for valvular surgery. Primary insufficiency was present in 35 legs and secondary insufficiency in 21 legs, which was known previously. Descending phlebography was performed (1-15 months) before the CDU examination. Both methods were evaluated independently and blindly by two different investigators. The normal control group (52 legs) was examined with CDU only in order to test CDU in legs without venous insufficiency. The age of this group ranged between 16-50 years.

II. Retrospective study design. All patients (25-88 years, median 63 years, 101 women and 85 men) with active or healed ulcers previously investigated with CDU during the years of 1990-1995 were included. Vein surgery had been performed previously in 83 legs. From the archives the patients were divided in primary, secondary or in combinations of venous and arterial insufficiency. Based on the CDU protocols of each patient, the type of venous valves incompetence within all vein compartments was studied.

III. Retrospective study design. Patients were partially recruited according to paper II (n=26) or partially enrolled as new patients being investigated between 1995-1997 (n=36). All patients were asked by a letter to participate in a CDU follow-up examination, in ambulatory venous pressure (AVP)- and venous outflow measurements as well as to answer a questionnaire at a median follow-up time of 32 months after surgery, (range 3-96 months). This procedure was prospectively followed by an interview 5.5 years post surgery (median, range 2-11 years). The patients underwent vein surgery 4 months (range 0.5-43 months) after the pre-operative CDU examination. All patients suffered of chronic primary vein

insufficiency of grade C_5 or C_6. Patients were divided in subgroups with superficial insufficiency only and with mixed superficial and deep insufficiency. The mean age in the group with superficial insufficiency was 54.5±10.2 and in mixed superficial and deep insufficiency group 57.9±13.7 years. Surgical vein correction had been performed in 38 legs (38/62, 61%) prior to the last surgical intervention. The ulcer history is presented in Table 2.

IV. Prospective study design. Patients, who were referred to the department of clinical physiology, were asked to participate in the study during the preoperative CDU investigation. CDU, AVP and Phlebo-test were performed before surgery, and at median follow-up times of 5 (range 3-12 months) and 26 months (range 13-45 months) after surgery. Venous outflow pletysmography was also performed before surgery. The patients were asked to answer a questionnaire before and after the surgical treatment. Superficial surgery was performed at a median of 6 months (range 0.5-32 months) after the preoperative CDU examination. The median total follow-up time after surgery was 4.75 (range 2-6 years) years. All patients had chronic primary insufficiency of grade C_5 or C_6. The mean age in the total group was 57.2±12.2 years. Previous surgery had been performed in 32 legs (62%). Ulcer history is presented in Table 2.

	Retrospective study, n=62	**Prospective study, n=52**
Ulcer diathesis	M=60 (range 4-336 months)	M=36 (range 8-384 months)
Ulcer duration	M=13.5 (range 1.5-120 months)	M=8.5 (range 1.5-120 months)
Ulcer episodes	M=2 (range 1-20)	M=2 (range 1-20)
Ulcer debut:		
Women Men	M=48 (range 23-63 years) M=41 (range 15-74 years)	M=50 (range 31-78 years) M=50 (range 34-77 years)
Healed/Active ulcer	*50/12*	*39/13*

Table 2. Ulcer history in retrospective group (III) and in prospective group (IV). M=median, n=legs.
Definition ulcer diathesis: the time from the first ulcer debut to the last surgical intervention.

Colour Doppler Ultrasound

The Color Doppler flow examinations were performed using computerized color flow duplex imaging with a 5 MHz linear probe (Acuson 128XP/10, Acuson Corp., Mountain View, Calif.) and all examinations are videotaped. Vein valve function was assessed by experienced examiners according to a standardized protocol described in detail and validated in *[paper I and II]*. In colour-coded Doppler flow is depicted in colour, e.g. red for flow in one direction (artery) and

blue for flow in the opposite direction (vein). The higher the frequency shift and flow velocity the paler or more white is the colour. The colour flow map is superimposed on the real time anatomical gray scale image (Fig. 10). Valvular incompetence was shown by reversed blood flow during Valsalva or calf decompression. Venous reflux in any vein was semi-quantitatively graded from the colour scale with respect to its duration and its maximum frequency shift (0=none, 1=mild, 2=moderate and 3=severe reflux). The thigh and popliteal veins were examined in a 40° head-up tilt position during repeated Valsalva manoeuvres and calf compressions. Calf veins and perforators were tested with the patient sitting on a bed with the foot in the examiner's lap using manual calf or foot compression for testing reflux. Based on patterns of reflux, venous insufficiency was classified as superficial (great and/or small saphenous vein or tributaries above or below knee), deep (femoral and/or deep femoral, popliteal and/or deep calf veins including the gastrocnemius vein) or combinations of both. Reflux grade ≥2 was the criteria for pathological reflux both in superficial and in deep veins.

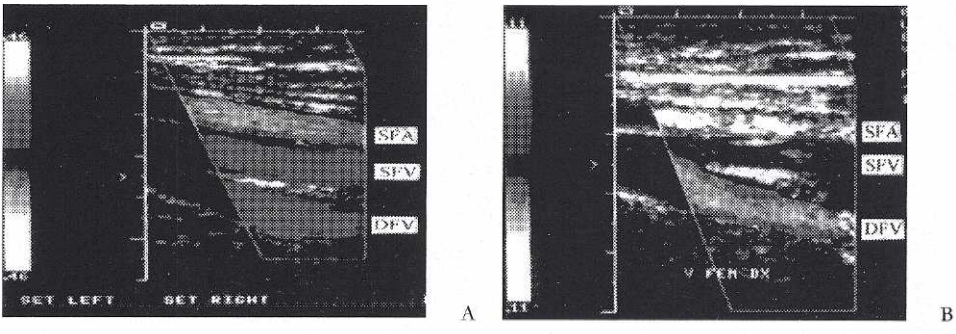


Fig. 10 Colour coded Doppler image with A: normal blood vessels. B: Valsalva-test demonstrating an incompetent deep femoral vein (DFV), (red colour).
SFA; superficial femoral artery, SFV; superficial femoral vein, DFV; deep femoral vein

The method of CDU reflux grading was evaluated in I using a healthy control group.

The results from each vein in this group are presented in Table 3. The findings in the symptom free control group demonstrated that slight degrees of venous reflux (grades 1 and 2) were seen frequently in healthy individuals.

Grading	0	1	2	3
SFV	*60*	*25*	*15*	*0*
DFV	*85*	*8*	*8*	*0*
POP	*87*	*6*	*8*	*0*
PTV	*98*	*0*	*2*	*0*
PV	*100*	*0*	*0*	*0*
GSV	*85*	*4*	*10*	*2*
SSV	*90*	*8*	*2*	*0*

Table 3. The distribution (%) of venous reflux grading 0-3 for each vein in 26 controls, examined with Colour Doppler Ultrasound.

Agreement between reflux duration in seconds ("gold standard") and our grading 0-3 (II)

To compare our mode of grading reflux with commonly accepted reflux durations in seconds as "golden standard", the reflux duration was estimated from the colour-flow reversal on the video-tapes, and our grading was evaluated by cross-tabulation. Duration >1 or ≤1s vs grading ≥2 or <2 was used to separate significant and non-significant reflux. The results are summarized in Table 4.

	Accuracy, %	n
GSV	*95*	*172*
SSV	*93*	*158*
SFV	*97*	*197*
DFV	*95*	*198*
POPL (prox)	*90*	*196*
POPL (dist)	*86*	*185*

Table 4. Accuracy of venous grading using reflux duration as golden standard. Duration >1s and reflux ≥2 was considered significant.

The reproducibility of the grading between two examiners (II)

In order to assess inter-observer variations of venous insufficiency grading, two different investigators were independently compared, using the same 69 veins (Fig. 11). In 91% inter-rater agreement between the two investigators existed, with a kappa-value of 0.88 (strength of agreement=very good, DG Altman).

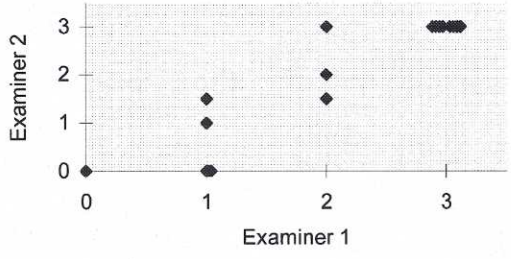


Fig. 11 Comparison between two CDU-investigators when grading the venous reflux in categories 0-3, 69 veins.

Reflux Scoring, FVDS (III and IV)

In order to compare CDU outcome before and after surgery, we calculated an individual "functional venous disease score" (FVDS) as a modification of the "venous segmental disease score"[60] which addresses the anatomical involvement of insufficient (CDU grade 2-3) venous segments (Table 5A,B). FVDS implements also the grade of venous reflux 2 or 3 when axial reflux is present (different score). FVDS includes segments of insufficient proximal and /or distal veins and insufficient tributaries above (AK) or below knee (BK). The total possible score is 16.5.

Involved Vein compartment	**FVDS** Reflux grade 2	**FVDS** Reflux grade 3
Great saphenous vein (GSV)	*2*	*3*
proximal/distal GSV	1	1
Accessory GSV	1	1
Small saphenous vein (SSV)	1	1
proximal/distal SSV	0.5	0.5
Accessory veins AK / BK	0.5	0.5

Table 5A Scoring of superficial veins.

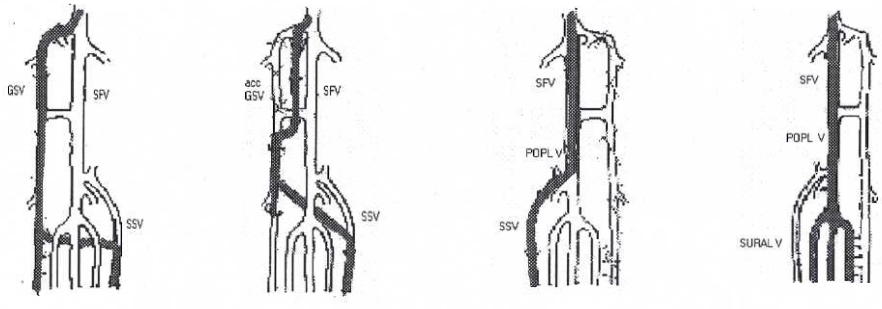
Involved Vein compartment	**FVDS** Reflux grade 2	**FVDS** Reflux grade 3
Femoral vein (FV)	1	1
proximal/distal FV	0.5	0.5
Deep femoral vein (DFV)	0.5	0.5
Popliteal vein (POPV)	1	2
proximal/distal POPV	0.5	0.5
Deep calf vein or veins	1 or 2	1 or 2
Gastrocnemius vein	0.5	0.5
Deep axial reflux	*3 or 4*	*4 or 5*
Perforators, thigh	0.5	0.5
Perforators, calf (1 or >1)	0.5 or 1	0.5 or 1

Table 5B Scoring of deep and perforator veins

Table 5A,B. Functional Venous Disease Score (FVDS) based on CDU-identified insufficient vein segments with consideration of significant venous reflux (CDU grade 2-3). Scoring with reflux grade 2 and 3 was only considered in cases of axial reflux pathways. We propose two options in scoring axial deep pathways, when one or two deep calf veins were incompetent.

Axial reflux

Axial reflux to ankle veins could be either superficial; A: Great saphenous vein (GSV, most common), B: acceccory GSV in combination with short saphenous vein (SSV), or combination of deep and superficial axial reflux: C: superficial femoral vein (SFV) + popliteal vein (POPV) + short saphenous vein (SSV), or D: deep axial reflux, SFV+POPV+deep calf veins (sural veins).



A. B. C. D.

Patient classification and definitions of residuals (III, IV)

According to the initial ultrasound examination, the patients were divided into a superficial venous insufficiency group classified as $C_{5,6}E_PA_{2\text{-}4.S}P_R$ without any deep reflux (SrDo) and a combination of superficial and deep venous insufficiency (mixed reflux, SrDr) with a CEAP classification[11] of $C_{5,6}E_PA_{2\text{-}4.S,\ 12\text{-}16.D,\ 17\text{-}18.P}P_R$.

Postoperatively we related ulcer recurrence to the outcome of the CDU re-examination by subgrouping patients in categories of residual or recurrent venous reflux (referred as residuals in this text). Superficial residuals included an incompetent great saphenous vein (GSV) and/or small saphenous vein (SSV) in the total length or in proximal or distal segments. An accessory great saphenous vein and/or tributaries above or below the knee were also included (AK or BK). Deep reflux includes incompetent deep veins in any leg compartment (SoDr). Without any reflux=SoDo.

In *[paper IV]*, legs with ulcer recurrence were divided in an early ulcer recurrence group (ulcer recurrence before 3 years) and a late ulcer group (ulcer recurrence after 5 years) and two groups without ulcer recurrence, with or without residuals.

Ambulatory venous pressure (AVP) (III and IV)

Venous pressure measurements were obtained after inserting a Venflon™ (1.0x32mm i.v. cannula) into a superficial vein on the dorsum of the foot.[48] The venous line was connected to a pressure transducer and amplifier (PC Polygraph HR, Synectics Medical). All pressure measurements were performed with reference to the heart as zero pressure level.

Continuous pressure recordings and evaluations were performed using standard computer software (Polygram, Medtronic). The resting pressure was initially recorded with the patient standing and holding onto a frame. The patient performed both a standard exercise of 10 tiptoe movements three times and than 10 knee bend three times, at the rate of one per second resulting in a more or less venous pressure drop by the leg muscle pumps.

After each exercise, the patient remained resting until the vein pressure had returned to the pre-exercise level. The time for the pressure to return to the standing pressure level after exercise was the venous refilling time (VRT) and the 90% recovery time was calculated (VRT_{90}). The AVP was defined as the lowest pressure obtained in any of three tiptoe manoeuvres or three knee bends (Fig. 12). The AVP% was calculated as the AVP fraction of the resting pressure.

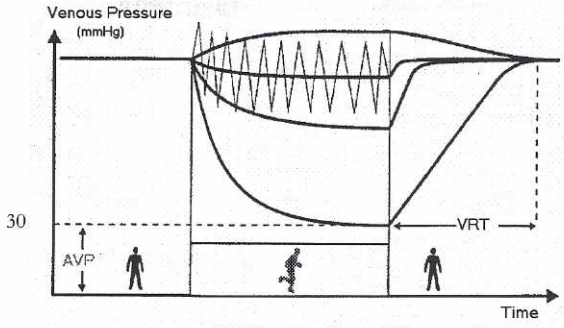


Fig. 12 Ambulatory venous pressure (AVP) showing different degree of venous insufficiency. VRT=venous refilling time. AVP below 30 mmHg is considered normal.

Strain-gauge plethysmography (Phlebo-test in VVT-mode) (IV)

The phlebo-test (Eureka Biotech AB, Sweden) of venous insufficiency is performed in analogy to Christopuolos et al[49] using computerized strain-gauge plethysmography.

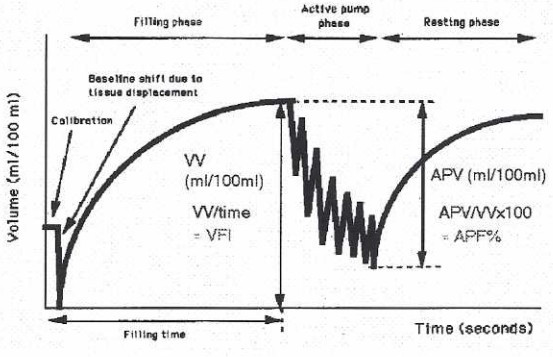


Fig. 13 Schematic presentation of a plethysmographic examination with Phlebo-test, measuring venous volume changes due to venous filling (VFI) and active muscle pump function (APF%).

The patient is placed on the tilting table in a horizontal position with elevated lower legs. Strain-gauge bands are placed around the lower leg just proximal to the ankles, and the patients were instructed not to move. The venous system of the legs is empty as a result of the venous hydrostatic pressure near zero mmHg pressures. The table is then tilted automatically into a vertical sitting position to induce refilling of the leg veins. The maximum increase in the leg volume reflects the total venous volume at that particular hydrostatic pressure (VV; functional venous volume; ml/100ml tissue). The time for the venous system to reach VV is also recorded

(VVsec). Thereafter, the patient is asked to perform dorsal flexions of both ankles following a metronome in order to emptying the leg veins by means of the activated calf muscle pump. The maximum decrease of the leg volume is recorded as the active pump volume (APV; ml/100 ml tissue). The volume increase of the lower leg after head-up tilting is due to the refilling of the veins, the arterial inflow as well as the outward capillary filtration rate. If incompetent valves are present, the refilling will be faster than normal because of the venous regurgitation volume, which is added to the arterial inflow. This is reflected by a high VFI value (venous filling index; VV/sec). An insufficient calf pump function due to regurgitation through any venous segment will result in a low relative volume of blood removed from the leg veins during the exercise (low active pump fraction; APF/VVx100 = APF%) (Fig. 13).

Venous outflow plethysmography (VOP) (III, IV)

Computerised strain gauge plethysmograph (Phlebotest, Eureka Biotech AB) measuring the venous outflow rates from the legs was used in order to exclude venous obstruction. The patient was in the supine position with thigh cuffs placed on the elevated legs. Venous volume (VV; ml/100 ml) was measured in the steady state (i.e. after approximately 4 min) with a cuff inflation pressure of 50 mmHg. Immediately after cuff deflation, when the venous outflow rate is at maximum, the venous volume decrease is recorded during the first second ($F_{1.0}$; ml/100ml/min).

Interview (III, IV)

Based on a questionnaire the patients were asked whether the ulcer had healed or whether they had any ulcer recurrences. Information about clinical symptoms such as pain and swollen legs before and after surgery was obtained on a 0-2 scale (0=asymptomatic, 1=mild and 2=moderate to severe) according to CEAP.[11] Other questions about living conditions and social life during active ulcer periods, were also asked in the interview.

Venous surgery

Surgical correction of the superficial venous system was mostly done with standard techniques, such as ligation at the sapheno-femoral junction, stripping of the great saphenous vein (GSV) from the groin to the midcalf and ligation of tributaries. Some patients underwent partial stripping of thigh or calf portions of the GSV or anterior accessory saphenous veins. In some

patients ligation at the sapheno-popliteal junction was performed followed by stripping or partial stripping of the small saphenous vein (SSV). The patients underwent open subfascial ligation of perforating veins or were treated with subfascial endoscopic perforator surgery (SEPS).

Statistics

Data was analysed on a PC using Microsoft Access, Excel, and SPSS for Windows Advanced Statistical Package (version 11.0). Results are presented as median values with corresponding ranges or mean values ± standard deviation. The Mann Whitney (2-tailed) test was used for comparison of different groups and the Wilcoxon signed ranks (2-tailed) test within groups.
The probability of 5 year ulcer recurrence was estimated by use of the general relationship between survival and hazard functions. Poisson regression (Breslow and Day) was performed in order to assess the effect of any variable on ulcer recurrence. By means of the beta coefficient for each variable a risk score was calculated for each patient after a stepwise procedure *[III+discussion]*. Fisher's permutation test *[IV]* and logistic regression were used in order to test any variable at risk for ulcer recurrence. Fisher's (2-tailed) dependent test was used for the clinical symptoms.

A model in predicting ulcer recurrence (III)

A pre- and post-operative model is presented in an attempt to predict ulcer recurrence:

- Before surgery we tested, if there is any variable available, which may indicate on high risk for ulcer recurrence guiding the surgeon in his decision whether to operate or not.
- After surgery, we aimed to identify high ulcer recurrence risk factors indicating on needs for extra care and clinical follow-up. This also included an attempt to compare different anatomical and hemodynamic scoring-systems.

RESULTS

I. Comparison of Colour Doppler Ultrasound and Descending Phlebography

The comparison between descending phlebography and Colour Doppler Ultrasound is shown in Table 6. We found good agreement for the great saphenous vein and superficial femoral vein. For the deep femoral vein the agreement between both methods was less good when a reflux grade ≥2 was (with CDU) considered. However, when using a reflux grade of ≥1 (with CDU) the agreement between the two methods was acceptable for this vein also. The reason might be that the deep femoral vein is smaller with a lower blood volume capacity and consequently the reflux volume flow will be relatively little and of short duration. Grade 1 reflux was found in 9/11 deep femoral veins (82%). We found also acceptable agreements between popliteal vein and the small saphenous vein. Hence, grade 1 reflux in the popliteal vein was detected by descending phlebography in 5 of 7 cases (71%). Discrepancies between phlebography and CDU were more pronounced when comparing calf vein outcome. However, the Valsalva-test as reflux provocation during phlebography, may be inadequate for these veins due to local incompetence combined with competent proximal vein valves. Therefore, the method of calf compression during CDU testing is probably more accurate than phlebography. The sites and frequencies of all venous insufficiencies in all patients are shown in Table 7.

	ACCURACY %		
	n	**Grade 1-3**	**Grade 2-3**
Superficial femoral vein	56	*91*	*93*
Deep femoral vein	56	*77*	*64*
Popliteal vein	56	*75*	*70*
Posterior tibial vein	38	*55*	*55*
Peroneal vein	38	*66*	*66*
Great saphenous vein	28	*82*	*86*
Smaller saphenous vein	44	*68*	*70*

Table 6. Accuracy (%) of reflux statements using Colour Doppler Ultrasound with manual calf compressions and Valsalva compared to descending phlebography outcome with Valsalva provocations.

GRADING	0	1	2	3
FV (n=56)	7	2	30	61
DFV (n=56)	27	20	41	13
POPV (n=56)	11	13	38	39
PTV (n=38)	42	11	34	13
PV (n=38)	45	21	32	3
GSV (n=28)	32	4	14	50
SSV (n=44)	39	11	18	32

Table 7. The sites and frequencies of reflux gradations 0-3 for each vein segment in 44 patients, examined with Colour Doppler Ultrasound. The reflux grades of 2 and 3 were most frequently observed, which affected mostly the femoral and popliteal veins.

Concerning the *clinical severity of the venous reflux*, classified as C_3=edema C_4=skin changes and $C_{5,6}$=ulcer (healed or active) we found 21% of the postphlebitic patients to belong to class C_3 and 63% to class $C_{5,6}$. In the contrary, 60% of the patients with primary reflux had clinical symptoms of type C_3 and only 14% of type $C_{5,6}$.

II. The sites of venous insufficiency in patients with leg ulcers

Fig. 14A represent patients with primary venous insufficiency, which involved exclusively superficial vein segments (S) in 49% and in combination with deep reflux (S+D) 35%. With subclinical thrombosis excluded (n=6) the corresponding figures were 51% and 33%. In the great saphenous vein (GSV) reflux was present in 69% and in the small saphenous vein (SSV) in 35%. In cases of incompetent and/or dilated perforators together with accessory anomalous veins, GSV and SSV were unaffected in only 5%. The deep veins were in combination of 1-3 veins, and superficial femoral vein (SFV) incompetence was seen in 35% (44/127) and popliteal vein (POP) incompetence in 34%. In this group of primary insufficiency, 45% of the patients had previously undergone varicose vein surgery and half of the patients with isolated deep reflux were treated before.

In patients with secondary venous insufficiency (Fig. 14B) isolated deep venous insufficiency was present in 38%, and when combined with superficial insufficiency, in 49%. Any kind of superficial vein incompetence, either isolated or in combination with deep reflux, was seen in 56%. Of the involved deep veins, popliteal vein incompetence was most frequent, i.e. was observed in 96% (46/48). It was more common with two or three incompetent major deep veins and calf vein incompetence was involved quit frequently. Twelve patients had previously undergone varicose vein surgery. Post-thrombotic vein abnormalities were seen in 38 of the 55 legs with history of DVT.

In patients with arterial and venous insufficiency (Fig. 14C) isolated superficial insufficiency was found in 40% and combination of superficial and deep incompetence in 27%. As in patients with primary venous insufficiency, the great saphenous vein (57%) and superficial femoral vein (37%) were involved most frequently. None significant reflux in major veins, 13%. Six patients were previously treated with surgery and five patients had diabetes. Bilateral ulcers were more common in this group (20%).

Perforators were commonly seen in all types of venous insufficiency, but more dominating in patients with combined superficial and deep incompetence (Table 8).

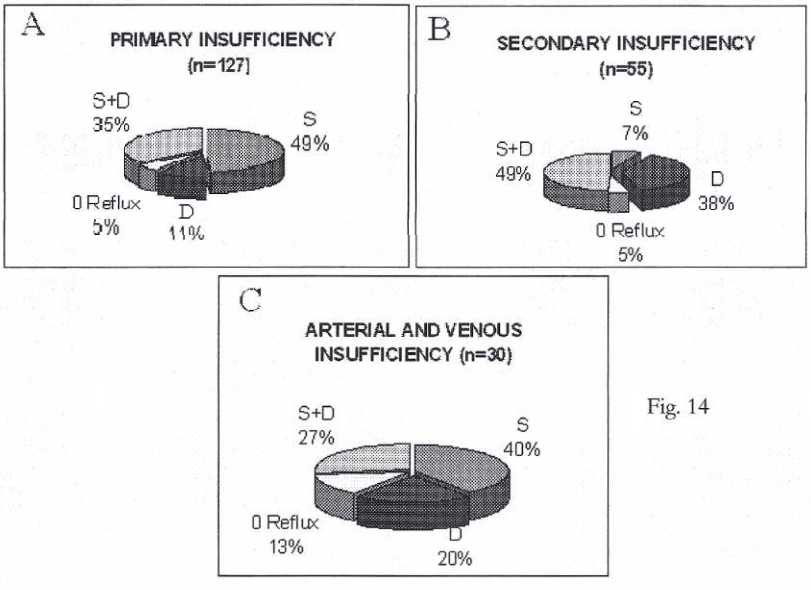


Fig. 14

Fig. 14. Sites of venous insufficiency in patients with A: Primary insufficiency, B: Secondary insufficiency and C: Combined arterial and primary insufficiency.
S=superficial venous insufficiency, D=deep venous insufficiency. S+D=combined superficial and deep venous insufficiency.

	Primary group			**Secondary group**			**Arterial and venous group**		
	S (n=62)	D (n=14)	S+D (n=45)	S (n=4)	D (n=21)	S+D (n=27)	S (n=12)	D (n=6)	S+D (n=8)
n	27	6	28	1	10	20	5	1	7
%	44	43	64	25	48	74	42	17	88

Table 8. Number of incompetent perforators in primary, secondary and arterial groups. S=superficial, D=deep and S+D=combined superficial and deep insufficiency.

III. Riskfactors for venous ulcers after superficial vein surgery

Ulcer diathesis

The inclusion criterion for this study was at least one active or healed venous ulcer due to primary venous insufficiency. However, multiple ulcers and long ulcer duration were common in the patient material (Table 2). The follow-up investigation 2-11 years after surgery (median 5.5 years) revealed that 47 out of the 62 legs (76%) were free from ulcer recurrence. The 15 legs with new post-operative ulcers had one to two ulcer episodes after the intervention (median 6 years) and the median recurrent total ulcer duration was 10 months (range 2-18 months). The ulcer diathesis was four times longer ($p<0.001$) in ulcer recurrence group than in non-ulcer group (Table 9).

	Ulcer diathesis		
Residual Reflux	Ulcer group	Non-ulcer group	p-value
axial	136.5±80.4 (n=8)	115.5±142.1 (n=2)	ns
segmental	234.8±78.3 (n=7)	62.8±70.0 (n=33)	0.001
p-value	0.05	ns	
No Residual Reflux	-	38.1±31.9 (n=12)	

Table 9. Ulcer diathesis (months) in patients with ulcer recurrence (ulcer group, n=15) and in patients with none ulcer recurrence (non-ulcer group, n=47), and its relation to venous reflux residuals after surgical intervention.

Post-operative venous insufficiency residuals and ulcer recurrence

Pre-operatively there were 42 legs with superficial (SrDo) and 20 legs with mixed insufficiency (SrDr). Post-operatively, subgroups of patients with superficial (SrDo), deep (SoDr), combined deep and superficial insufficiency (SrDr) as well as without insufficiency (SoDo) were seen (Table 10). The 15 legs without any reflux remained free from ulcers, whereas 32% of the legs with any post-operative reflux were exposed to ulcer recurrence.

After surgery	SoDo (n=15)	SrDo (n=23)	SoDr (n=4)	SrDr (n=20)	any reflux (n=47)
C_5	15	17	2	13	32
C_6	0	6	2	7	15
% (C6/[C5+C6]x100)	0	26	50	35	32

Table 10. Ulcer recurrence after surgery and any type of venous reflux residuals. C_5=healed ulcer and C_6=active ulcer recurrence.

The segmental involvement of venous insufficiency before and after the last surgical intervention can be seen in Table 11, showing that the surgical treatment was not complete in some cases or that new insufficient venous pathways developed after surgery. The total numbers of incompetent perforators decreased after surgery. However, residual and recurrences of venous insufficiency correlated well with the frequency of persistent or new perforators and a significant ($p<0.02$) larger amount of new perforators were observed in legs with superficial incompetence than without incompetence. After superficial vein surgery, fewer incompetent deep segments were identified. Of five legs with post-operative normalization of proximal popliteal valve incompetence, three legs underwent small saphenous vein stripping. Pre-operatively SrDo patients developed deep reflux in 28 segments post-operatively, mostly combined with superficial reflux.

	Before surgery	**After surgery**	
		persistent	new veins
GSV prox/dist	44/46	5/18	0
SSV prox/dist	20/26	6/9	7
Other superficial veins	25	9	44
Deep veins	47	25	44
Perforators, reflux/width	50/41	8/13	17/16

Table 11. Numbers of insufficient veins before and after surgery, n=62. GSV; great saphenous vein, SSV; small saphenous vein.

The functional venous disease score (FVDS)

As a modification of the venous segmental disease score (VSDS),[60] FVDS includes also scores of the reflux grade moderate (grade 2) or severe (grade 3) axial reflux, thus resulting in higher scores. All possible pathways for axial reflux, either by means of insufficient greater saphenous vein, deep pathways or in combination of local superficial and deep compartments coupled in series by perforators were scored according to the grade of reflux. Both scores were significantly lower ($p<0.001$) at post-operative follow-up in patients without recurrent ulcers (Table 12A-C), but not in ulcer recurrence group.

Axial reflux			
	Ulcer group	Non-ulcer group	p-value
before surgery	1.9±1.4	2.4±1.1	ns
after surgery	1.5±1.5	0.1±0.6	0.001
p-value	ns	0.001	

Table 12A

FVDS			
before surgery	3.5±1.9	3.4±1.2	ns
after surgery	3.7±1.7	1.7±1.6	0.001
p-value	ns	0.001	

Table 12B

VSDS			
before surgery	2.0±1.8	1.6±0.8	ns
after surgery	2.1±1.6	0.9±1.2	0.001
p-value	ns	0.001	

Table 12C

Table 12A-C. Axial reflux and Venous Segmental Disease Score (VSDS) and in the modification FVDS, in patients with post-operatively recurrent ulcers (n=15) and non-ulcer group (n=47).

Risk factors for recurrence of post-operative leg ulcers

Pre-operative risk factors:

Long pre-operative ulcer diathesis is a significant predictor (β=0.0124, SE=0.0027, p-value<0.001) of post-operative ulcer recurrence in a multivariate model. It shows 20% of the patients have a calculated five year probability of recurrence of more than 25%, whereas quite 40% have a probability less than 4% (Fig. 15).

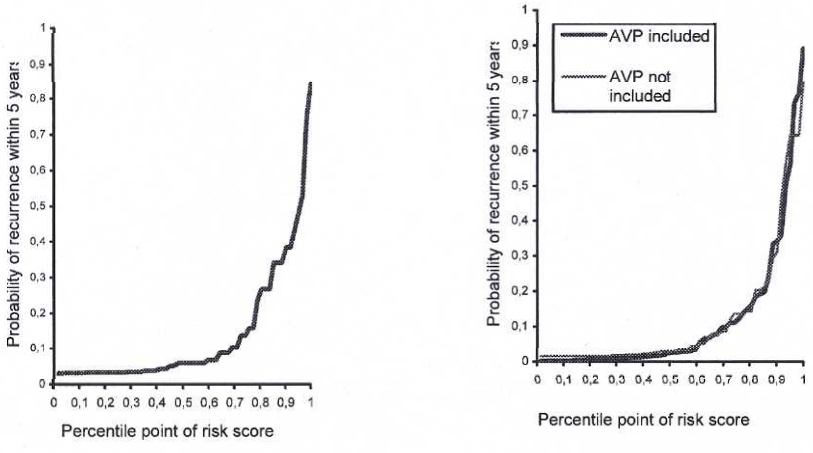


Fig. 15-16. Assessment of the risk for ulcer recurrence. By means of the beta coefficient for the variable pre-operative ulcer diathesis a pre-operative risk score for ulcer recurrence can be calculated for each patient. Analogously, the post-operative risk can be calculated on the variables ulcer diathesis, post-operative axial reflux and post-operative AVP. The score is equal to the sum of the products of the coefficient and the value of the corresponding variable. The higher the score is, the greater the risk of recurrence. x-value=0.5 corresponds to median.

Post-operative risk factors:

The variables indicating high risk for recurrent ulcers were long pre-operative ulcer diathesis (β=0.0124, SE=0.0033, p-value<0.003), axial reflux (β=0.5030, SE=0.1940, p-value<0.0095) and high post-operative AVP (β=0.0751, SE=0.0319, p-value<0.018). The multivariate analysis shows that 50% of the patients have a calculated five year probability of ulcer recurrence of less than 3%, but 13% have a probability of more than 23% (Fig. 16). The five year calculated probability of recurrence of leg ulcer did not change when excluding AVP, i.e. assessment of the pre-operative ulcer-diathesis and post-operative CDU-findings of axial reflux, are strong indicators on ulcer recurrence. Other variables considering one by one were significant risk indicators, but not in a multivariate model (Table 13).

	β	SE	P-value
VRT_{90} (s)	-0.2357	0.0738	0.0014
FVDS	0.3886	0.1263	0.0021
VSDS	0.3647	0.1427	0.0106
SBP (mmHg)	0.0229	0.0102	0.0248
DBP (mmHg)	0.0535	0.0239	0.0252
Weight (kg)	0.0286	0.0131	0.0290

Table 13. Other significant risk variables of postoperative ulcer recurrence. VRT; venous refilling time, FVDS; functional venous disease score, VDSD; venous segmental disease score, SBP; systolic blood pressure, DBP; diastolic blood pressure

Ambulatory venous pressure (AVP)

AVP was only available post-operatively. Patients with insufficient residuals (n=47) had significantly higher AVP values when compared with those patients free from (n=15) residuals (32.1±10.5 mmHg versus 20.0±11.2, p<0.001). VRT_{90} was significantly shorter in patients with residuals (10.8±5.9 sec versus 20.9±9.4 sec, p<0.001). No differences in AVP and VRT_{90} were observed when comparing superficial venous disease with the mixed ones. Patients in the superficial group, operated upon for the first time, (n=14) had no ulcer recurrences. In this group AVP was 27.4±12.4 mmHg with a VRT_{90} of 18.1±11.4 sec. Legs with superficial insufficiency and total active ulcer duration of >12 months before the last surgery had an AVP of 37.6 mmHg, compared to 26.3 mmHg (p<0.01), in patients with an ulcer duration of ≤12 months before surgery. The AVP in the corresponding patients with mixed superficial/deep insufficiency was 37.1 and 31.0 mmHg respectively (ns). In patients without ulcer recurrence AVP was normal. Patients without residuals had normal AVP and VRT_{90}.

Interview results

Despite of various grades of daily activity limitations the patients tried to live a normal life. However, during active ulcer periods, several factors and restrictions influenced their quality of life. Analgesics were required occasionally or regularly because of daily pain. Special clothing and shoes were sometimes required, or the women could not wear a skirt. The patients tried to avoid situations, which triggered more pain and they had to be careful because they were afraid of knocking the leg or ulcerated area. Most of the patients (55/62, 89%) were satisfied with the surgical outcome at follow-up. Clinical improvements of pain ($p<0.001$) and swelling of the legs ($p<0.001$) was seen after surgery in the total group. With exception of the summer period, most patients wearied compression stockings (in general class 1) regularly every day (61%) or occasionally (19%).

IV. Venous hemodynamics in patients with recurrent leg ulcers

Women/men	28/20
Age (years)	M=49.5 (range 31-78)
Weight (kg)	88.1±14.0
Height (cm)	175.3±9.0
BMI	M=24.7 (range 17.4-34)
SBP (mmHg)	142.1±20.2
DBP (mmHg)	83.5±9.1
Heredity for ulcer	20 (42%)
Heredity for varicose veins	40 (83%)
Stockings	44 (92%)
Previous surgery	32 (62%), (1-4 times)
Previous surgery both legs	24 (50%)
Working/retired	38/10

Table 14. Clinical data (mean±SD) of the patient material. 48 patients (52 legs). SBP; systolic blood pressure, DBP; diastolic blood pressure, BMI; body mass index.

Ulcer history

Table 14 shows the clinical data about the patient material.

The clinical follow-up at median 4.75 years (range 2-6 years) revealed that 43 out of the 52 legs (83%) remained free from ulcer. The 9 legs with ulcer recurrence had one ulcer episode during post-operative follow-up period and the median duration recurrence was 4 months (range 1-12 months). The ulcer history is presented in Table 2. In this material no differences in ulcer diathesis occurred between the patients with ulcer recurrence and those without. The post-

operative time to ulcer recurrence varied from one to six years, i.e., six patients got a new ulcer within 3 years and three patients first after five years.

Venous insufficiency and ulcer recurrence

Pre-operative CDU identified 34 legs with superficial insufficiency (SrDo) and 18 legs with mixed insufficiency (SrDr). Complete cured venous function was found in 7 legs (SoDo), two of these legs had mixed reflux pre-operatively. In 20% (9/45) of the legs with any type of reflux, ulcer recurrence occurred post-operatively (Table 15).

After surgery	SoDo (n=7)	SrDo (n=26)	SoDr (n=3)	SrDr (n=16)	any reflux (n=45)
C_5	7	22	3	11	36
C_6	0	4	0	5	9
% (C6/[C5+C6]x100)	0	15	0	31	20

Table 15. Ulcer recurrence after surgery in patients with either no reflux (SoDo), superficial reflux only (SrDo), deep reflux (SoDr), mixed superficial and deep reflux (SrDr) or any type of residual venous reflux. C_5=healed ulcer and C_6=active ulcer.

The pre-and postoperative distribution of incompetent vein segments are presented in Table 16 indicating on either incomplete surgical correction or development of new incompetent veins or pathways. Residual axial reflux was post-operatively observed in 12 legs, where 4 legs were complicated with early ulcer recurrence (4/6). In the whole group axial reflux decreased significantly after surgery. In 5/7 legs, venous function normalized after small saphenous vein stripping.

	Pre-op	**Post-op 1**		**Post-op 2**	
		persistent	new	persistent	new
GSV prox/dist	41/38	3/11	0	3/10	0
SSV prox/dist	13/21	2/6	3/2	4/14	4/2
Other superficial veins	13	5	24	6	45
Deep veins	44	23	16	27	30
Perforators, reflux/width	47/45	11/15	7/12	13/16	19/19

Table 16

The number of insufficient ***perforators*** correlated well with the extent of post-operative residual insufficiency. Table 17 shows a comparison of venous hemodynamics in legs with and without insufficient perforators as assessed 2 years after surgery. The muscle pump function (APF%) is lower and the venous refilling (VRT_{90} and VFI) faster in legs with superficial venous insufficiency and incompetent perforators.

	Legs with incompetent perforators (n=29)	Legs without perforators or perforators without reflux (n=23)	P
VRT_{90}	15.6±12.1	21.7±13.7	0.04
AVP%	75.6±10.5	76.0±8.8	ns
APF%	35.4±18.9	52.6±19.2	0.002
VFI	5.6±2.3	3.8±1.6	0.003

Table 17. Legs with (n=29) and without (n=23) incompetent perforators in combination of other types of venous insufficiency at two years follow-upp. VRT_{90} (venous refilling time), AVP% (ambulatory venous pressure fraction), APF% (ambulatory muscle pump fraction), VFI (venous filling index). P-value between groups.

The functional venous disease score (FVDS)

FVDS was significantly lower at both post-operativ follow-up investigations (Fig. 17A), but with exception of the legs with ulcer recurrence. The patients with early ulcer recurrence tended to have higher venous reflux scores (FVDS) varying between 1.5-6-5, approximately at the time point of the ulcer recurrence. The p-value was close to the limit of statistical significance ($p<0.07$) and might have become significant in larger patient sample size.

Ambulatory venous pressure measurements (AVP)

1. The ambulatory venous pressure fraction (AVP%) after knee bend was measured pre-and post-operatively (Fig. 17B). AVP% increased significantly ($p<0.001$) after surgery but not in ulcer group. We could not see any significant difference between the ulcer recurrence group and the cured group, neither between legs with or without insufficient residuals. The AVP (mmHg) in total group after 10 tiptoe respective 10 kneebend was 31.9±10.9 mmHg versus 24.4±10.3 ($p<0.001$) at post-op 2.
2. VRT_{90} increased significantly ($p<0.001$) after surgery but not in the legs with ulcer recurrence (Fig. 17C). Patients with late ulcer recurrence showed improved VRT_{90} at the first post-op investigation only. Legs without residuals (n=7) had normal VRT_{90} which were significantly shorter in legs with insufficient residuals (n=45) at post-op 2, (31.8±15.7 sec versus 16.0±11.4 sec, $p<0.01$).

Phlebo-test (VVT)

1. The active pump fraction, APF% increased significantly in all groups except the patients with late ulcer recurrence at the first follow-up investigation (Fig. 17D). APF% deteriorated over time and became significantly lower ($p<0.02$) in the early ulcer recurrence group (n=6) at post-op 2, when compared to the patients with insufficient residuals but without ulcer recurrence (43).
2. VFI was significantly higher in all the legs with post-operative venous insufficiency (n=45) compared with legs without residuals (n=7) (5.1±2.2 versus 3.0±0.6, $p<0.05$), (Fig. 17E). VFI improved significantly ($p<0.001$) in the legs without leg ulcer recurrence.

Significant risk variables of post-operative leg ulcer recurrence

Low active pump fraction, APF% and active pump volume, APV were significant risk variables of ulcer recurrence ($p<0.016$ and $p<0.05$ respectively) at post-op 2. Other variables of importance were venous refilling time, VRT_{90} ($p<0.016$) and heredity of leg ulcer ($p<0.01$).

Clinical symptoms

65% of the patients were satisfied with the surgical treatment when asked 2-6 years (median=4.75 years) after surgery. The clinical symptoms of pain and swelling (according to CEAP, scale F_{0-2}) improved significantly after surgery ($p<0.001$). The hemodynamic measurements in relation to the symptoms are shown in Table 18.

	Symptom free at last questionnaire (n=34)	Symptoms at last questionnaire (n=18)	P
FVDS	1.7±1.6	3.1±1.6	0.002
VRT_{90}	21.1±14.2	11.7±6.4	0.004
AVP%	75.7±10.2	75.9±8.7	ns
APF%	48.3±22.5	33.4±12.4	0.015
VFI	4.5±2.3	5.4±1.8	0.05

Table 18. Asymptomatic legs (n=34) at the follow-up of 4.75 years (range 2-6 years) and the symptomatic ones (ulcer recurrence or other symptoms, n=18), at post-op 2.
Legends as in Fig 16 A-E. P-value between groups.

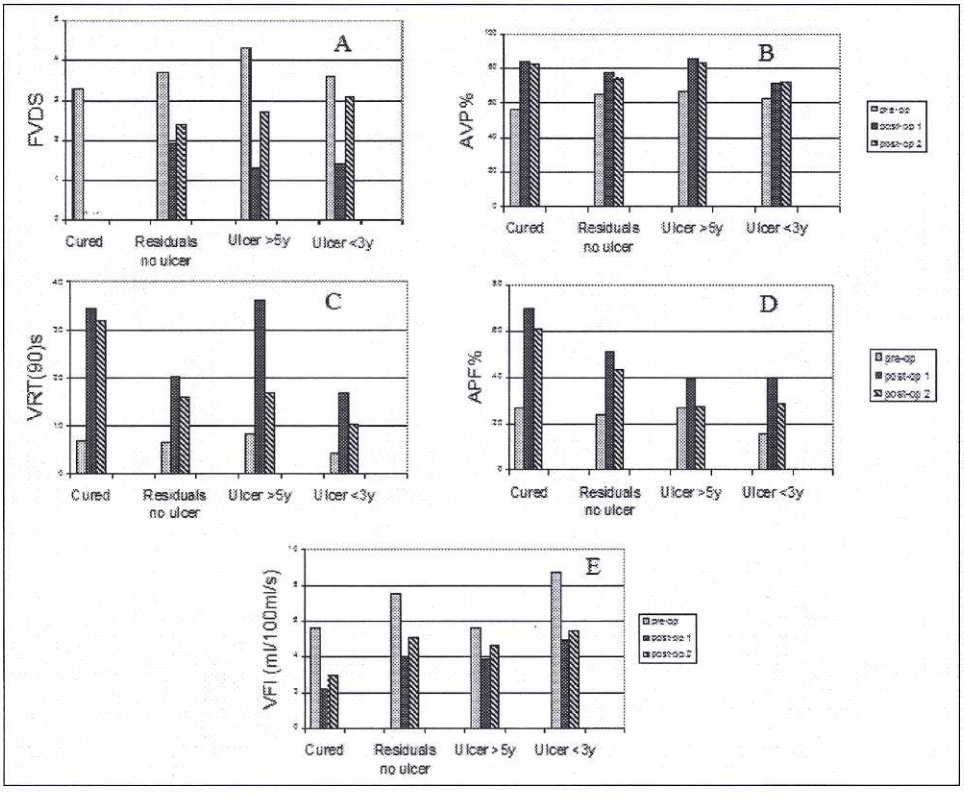


Fig. 17A-E: Venous hemodynamic measurements before (pre-op) and after surgery (5 months and 2 years post-op respectively) are presented in cured legs and in legs with residuals of venous insufficiency either with recurrent ulcer or not. Legs with ulcer recurrence are divided in early (within 3 years) and late (after 5 years) post-operative ulcer recurrence. Significant differences between the pre-operative investigation and the post-operative follow-up; *$p<0.05$, **$p<0.01$, ***$p<0.001$.
Functional venous disease score = FVDS
Ambulatory venous pressure = AVP
Venous refilling time = VRT
Active muscle pump fraction = APF%
Venous filling index = VFI

DISCUSSION

The Colour Doppler Ultrasound method

Colour Doppler Ultrasound (CDU) in diagnosing venous insufficiency was found to be as good as descending phlebography, the "golden standard", and has today become the method of choice for testing venous valvular competence within individual veins of the superficial, deep and perforating venous systems when selecting patients for surgical treatments.[52-54] CDU provides the surgeon in a better aid in planning venous surgery, it is non-invasive, reliable and better accepted by the patient. It is also well suited for follow-up studies of varicose vein recurrences. An advantage of CDU over phlebography is the possibility to detect local distal reflux when proximal valves are competent. CDU is also more sensitive in finding reflux in post-thrombotic veins. Another limitation of phlebography was the failure to find five cases with indisputable insufficient great saphenous veins, which might be explained by contrast injections distally to the saphenofemoral junction or competent proximal valves thus leading to false-negative findings. On the other hand, reflux might be induced by the heavy contrast medium, thus causing false reflux in normal veins.

Prolonged duration of venous reflux is the most used criterion, either >0.5 or >1 second.[52,61-66] In most of the healthy controls venous reflux duration was <0.5 s, except in some symptom-free individuals in whom the reflux duration was up to 1 s or even more.[52,61,62] Our control patients, who were free from symptoms of venous insufficiency, had frequently reflux grades of 1-2, (Table 3) and even 1 case with severe reflux in the great saphenous vein. This is in agreement with another study in which low grades of reflux were observed with descending phlebography in normal legs.[37] The CDU reflux grading 0-3 that we are using, is semi-quantitative and based on the colour coded flow velocity, which allows easy judgments of the velocity and the duration of the reflux and thus, makes it easier to examine the total length of each vein segment. We compared the colour Doppler gradations with the reflux durations from videotaped flow recordings and found good agreement between significant reflux durations >1 s and significant CDU reflux grades ≥2 (Table 4). The reflux duration >1 s had a slightly higher sensitivity than the significant CDU reflux grade ≥2 implying that few more statements of significant reflux will be made with measurements of the reflux duration. CDU reflux grading might have a limitation when grading deep veins with slow flow velocities, i.e. when colour coding algorithm produces

darker colours. The reproducibility between two examiners was good at our department with an agreement of 91% (Fig. 11). Reasonable reproducibility was also found by Evans et al.[67]

Venous insufficiency and venous leg ulcers

During the years different theories have been presented about the aetiology of venous leg ulcers, especially concerning its dominating reasons such as deep contra superficial, or primary contra secondary venous insufficiency. Patients with leg ulcers have been assigned to conservative treatment since venous ulcers have generally been ascribed to deep venous insufficiency. In contrary, several authors agree nowadays that superficial incompetence is important for venous ulcer development, but their results are diverging. Thus, the reported frequency of superficial reflux varies from 13% to 97% in ulcer patients.[26-34,68-71] The reasons for this variability may be different methodological study design and patient selections as well as various reflux criteria. We described our ulcer patients separately in groups of primary and secondary venous insufficiency, and found isolated primary superficial reflux in 49%, and any primary superficial reflux, mixed with deep venous insufficiency or not in 84%, which implies possible benefits from venous surgery. Deep vein reflux was more common in the post-thrombotic group, in which 38% had isolated deep reflux. Commonly, two or three major incompetent deep veins were involved, and 84% of the legs with venous ulcers had popliteal reflux compared to the 34% in the primary group. In secondary venous insufficiency, superficial incompetence was also frequent, when isolated in 7% and when combined with deep insufficiency in 49%. Therefore it might be relevant to consider varicose vein surgery in all those patients, provided venous obstruction is excluded (Scriven et al[72]). On the other hand, patients who do not have a known history of DVT might present post-thrombotic signs during CDU, which might exclude them from varicose vein surgery. Classifications in primary and secondary insufficiency may sometimes be difficult and we found in the group with "primary" insufficiency 5% having post-thrombotic non-occlusive signs without previous known DVT. We found combinations of primary venous and arterial insufficiency in 19%, and 40% of these patients had isolated superficial insufficiency. This was also in agreement with Nelzén et al[20,22] and Cornwall et al[27] with findings of 20-26% coexistent significant arterial disease in venous leg ulcer. Since compression therapy of venous insufficiency may harm the arterial circulation,[65,73] these patients might also be considered for vein surgery.

Follow-up of superficial vein surgery due to venous leg ulcers

Compared with conservative treatment, venous function may be better after CDU-guided varicose vein surgery when aimed to prevent leg ulcers.[55,56] However, surgical success rates may

vary in legs with chronic venous leg ulcers, since ulcer recurrence may occur of various reasons.[74-77]

Our retrospective study *[paper III]* of patients with venous leg ulcers was focused on ulcer healing and recurrence in a longer post-operative perspective to identify risk factors for leg ulcer recurrence. Statistical multivariate processing was aimed to present variables which 1/ may indicate on high pre-operative risk for ulcer recurrence with impact on indications for surgery or 2/ indicate on the needs for post-operative extra care and clinical follow-up.

[Paper III] was then followed up prospectively *[paper IV]* by a new cohort of leg ulcer patients aimed at investigating different hemodynamic variables with possible relevance to leg ulcer recurrence.

We found that 76% *[III]* - 83% *[IV]* of the patients were free from ulcer recurrences after 2-11 years' follow-up, and we estimated the ulcer recurrence rate to be 19% within a 5 year period *[III]*. Thus, there was a trend of better ulcer healing in *[IV]* probably due to more consequently interruption of axial reflux as well as shorter treatment intervals since ulcer diathesis was shorter, and it did not differ in length between post-operative ulcer and non-ulcer group *[IV]*. *[III]* clearly showed that residual venous incompetence with axial reflux is of great importance for recurrent ulcers. Long *ulcer diathesis* showed to be an important pre-operative risk variable ($p<0.001$) for post interventional ulcer recurrence (Fig. 15) probably due to skin changes such as lipodermatosclerosis in which skin nutrition is complicated. Investigating the rate of ulcer recurrence after surgery revealed, that long *ulcer diathesis* ($p<0.003$) and residual *axial reflux* ($p<0.01$) introduced in 13% of all patients a calculated five year probability for recurrent ulcers of more than 23% compared to 50% of all patients with a calculated five year probability of less than 3 % (Fig. 16). Axial reflux as a major contributor to increased prevalence of ulcer was previously discussed by Danielsson et al.[78]

Venous hemodynamics before and after superficial vein surgery

For pre- and post-operative comparisons we scored the extent of venous reflux by a functional venous disease scoring system (FVDS), representing a modification of an anatomical scoring system (VSDS, Rutherford et al)[60] in order to achieve a single variable representing any reflux in superficial and deep venous systems but with consideration of axial reflux grades. FVDS significantly decreased in all patients approximately 6 months after surgery *[IV]*, but deteriorated especially in patients with ulcer recurrence almost 2 years later. Opposite to the *[III]*, FVDS did not reach the statistical significance to be an independent risk factor for ulcer recurrence *[IV]*,

which might be explained by a somewhat smaller size of the patient material combined with lower frequencies of recurrent axial reflux.

CDU proven post-operative axial reflux was one of the most important risk factor for recurrent leg ulcers *[III]*, which was surprisingly not influenced by the other variables in the multivariate model (FVDS, AVP or VRT_{90}). In study *[III]*, AVP- and VRT_{90} data was only available after surgery as a complement to CDU. AVP correlated well with CDU, i.e. AVP (VRT_{90}) was significantly lower (higher) in legs without ulcer recurrences or residual venous insufficiency, implying, that higher AVP, lower VRT_{90} and higher FVDS were significantly correlated with increased risk for ulcer recurrence, when calculated as individual variables.

In study *[IV]* we followed venous hemodynamics at two occasions, 6 months and 2 years after surgery. We observed significant improvements in AVP/AVP% and VRT in legs without leg ulcer recurrences after surgery, but not in ulcer recurrence group. VRT_{90} was significantly lower in legs with residuals than without residuals at both occasions after surgery, and paralleled with higher FVDS and VFI. AVP% did not select patients with risk for ulcer recurrence, despite the fact, that it is generally accepted that increased ambulatory vein pressure is combined with increased incidence of leg ulcer[79]. Other investigators (Raju et al[80]) have also noted a lack of a consistent relationship between ambulatory hypertension and stasis ulceration and found in approximately 25% leg ulcers with normal AVP. Therefore, Raju et al proposed the refilling time (VRT_{90}) as a better indicator of calf venous pump dysfunction. Also other investigators found VRT_{90} less than 15 seconds in 79% of leg ulcers.[28] In our material *[IV]*, VRT_{90} was a significant predictor of ulcer recurrence ($P<0.016$). The most severe patients had a VRT_{90} of 10 seconds or less (Fig. 17C) and the postoperative VRT_{90} was significant shorter in patients with early ulcer recurrence than in those without postoperative residual insufficiency. Since AVP% was not significantly different between these two groups, we conclude that even though the muscle pump may lower the venous pressure to almost normal values, pathological venous reflux will rapidly establish high hydrostatic pressures again resulting in long periods of venous hypertension throughout the day. AVP might not be increased to the same degree in *[IV]* because of the shorter ulcer diathesis than in *[III]*, thus indicating on more severe venous disease. When comparing patients with shorter or longer ulcer diathesis than the median value of 36 months *[IV]*, post-operative AVP was significantly higher in patients with longer ulcer diathesis. APF% indicated on significant lower muscle pump in legs with long ulcer diathesis.

VFI (Fig. 17E), did not predict ulcer recurrence after surgery, but was significantly lower in patients with post-operative normal CDU towards those with insufficient residuals and the patients with early ulcer recurrence *[IV]*. Several studies using air plethysmography (APG)

characterized VFI as a good predictor of clinical outcome.[49,81,82] A VFI >4 ml/s was associated with an increased rate of ulcer recurrence, which together with deep reflux resulted in a 43% risk of recurrent ulceration at 1 year.[77]

Study *[IV]* identified *APF%* as the other significant risk variable for ulcer recurrence within 2-3 years after surgery (Fig. 17D). This was true also for all 2 years follow-up examinations of patients without ulcer recurrence at that time point (n=87, *study [III+IV]*). Also Araki et al[83] found calf muscle pump deficiency to be significantly related to the severity of venous ulcerations. We have no obvious hemodynamic explanation why APF% has this different pattern in comparison with AVP%. It might be possible to lower hydrostatic pressures despite of maintained large vein blood pools within dilated veins as a sign of limited volume pump capacities. The limited volume pump capacity might be a more sensitive sign in earlier stages of the venous disease than AVP, but the question arises, whether the leg muscle power is of importance to lower venous volumes.

Recurrent and residual venous incompetence after vein surgery

Varicose vein recurrence is still a problem despite skilled surgical experience. [84-87] and reasons for recurrences after adequate varicose vein surgery are discussed in the literature. One reason could be new reflux in an early post-surgery phase[88] or neovascularisation at a later stage. Turton et al. found new sites of reflux in 20% of patients with primary varicose veins. Neovascularisation starts very often with a number of smaller vessels in parallel and is today a well-established factor for recurrent venous insufficiency. [89-91] Routine stripping of GSV may reduce the tendency of neovascularisation as the cause of venous reflux recurrence (Jones et al)[92] and consequently lower the rate of re-operations (Dwerryhouse et al).[93] On the other hand, incorrect or incomplete surgery might be a more important reason for residual venous insufficiency, and "missed" tributaries in the groin are very likely to be seen when no meticulous dissection of the sapheno-femoral junction has been performed.[94-96]

All legs with residual venous incompetence (FVDS>0.5) might have a risk for ulcer recurrence, but those with signs of better ambulatory muscle pump (APF% >40) seem to be more protected (Fig. 17A,D). The risks of developing ulcer recurrence seem to be very low when the surgeon interrupted completely the superficial reflux, since no recurrent ulcers were seen in legs without incompetent veins. However, when pooling all patients in *study [III]* and *[IV]*, a total of 26% (24/92) of the patients with residual venous incompetence suffered from ulcer recurrence (Table 19). When excluding the patients with incomplete surgery, 13% (14/104) suffered of ulcer recurrence.

After surgery	SoDo (n=22)	SrDo (n=49)	SoDr (n=7)	SrDr (n=36)	any reflux (n=92)
C_5	22	39	5	24	68
C_6	0	10	2	12	24
% (C6/[C5+C6]x100)	0	20	29	33	26

Table 19. Ulcer recurrence after surgery in SoDo (no reflux), SrDo (superficial reflux), SoDr (deep reflux), SrDr (mixed superficial and deep reflux) and any type of residual venous reflux. study [III] and [IV], (n=114). C_5=no ulcer recurrence and C_6= ulcer recurrence

We found substantial recurrent or residual venous insufficiency in deep and superficial venous compartments after surgery (Table 11,16). Since the inter-observer variability is shown to be low at our department,[97] we believe that recurrent venous insufficiency might be an expression of post-operative recruitment of doubled veins over time or of development of new incompetence. Despite correct assessment of CDU results before surgery important axial reflux still remains after surgery (Table 20). We do not know the reason for the incomplete surgery and it was quite unexpected. Seven patients are waiting for new surgery and some more legs might require additional treatment. However, most of the patients with different varicose vein recurrences had no symptoms or complications.

	study [III] n=62		**study [IV] n=52**	
	no ulcer recurrence n=47	ulcer recurrence n=15	no ulcer recurrence n=43	ulcer recurrence n=9
pre-op				
axial-S	35	8	31	7
axial-S+D	5	2	3	1
axial-D	0	0	1	0
post-op				
axial-S	2	7	6	2
axial-S+D	0	0	1	1
axial-D	0	1	1	0

Table 20. Axial reflux in ulcer recurrence and none ulcer group in retrospective and prospective study, pre-and post-operatively. S=superficial axial reflux, S+D=superficial in combination of deep reflux, D=deep axial reflux.

In study *[IV]* we observed reduced venous reflux at 5 months, which increased again after around 2 years and especially in ulcer recurrence group. This increase was not seen in patients without residuals at the 2 years follow-up. Ulcer recurrence was found in only 33% with previously untreated primary valve incompetence, whereas the remaining 67% were due to

recurrent varicose veins after previous operations. Others have also observed less effective surgery of recurrent varicose veins in comparison with primary varicose veins.[89]

Could preoperative waiting times influence on the surgical outcome? The time our patients waited for surgery and for re-examination is presented in Table 21. The time between the date of surgical intervention and follow-up could be of importance for the outcome, since one reason for the development of superficial recurrences, perforators or deep reflux could be natural disease progression. Long-term observation (31-39 years) revealed 60% recurrence at the sapheno-femoral junction.[98] In our material *[III]*, the post-surgical examination was performed after 32 months (median, range 3-96 months), but this time did not differ between the groups with and without varicose vein recurrences. Others have found that even low risk groups of patients on a waiting-list (15-27 months) for varicose vein surgery developed significantly new sources of superficial reflux during the waiting time.[99]

	[III] (n=62)	[IV] (n=52)
pre-op	4 (0.5-43)	6 (0.5-32)
post-op1	-	5 (3-12)
post-op2	32 (3-96)	26 (12-45)
telephone	66 (24-132)	57 (24-72)

Table 21. Median waiting time (months, range in paranthesis) for surgery and for re-examination Pre-op; time from the first examinations to operation, post-op1 and post-op2; examinations after operation, telephone; last interview. M=median

Also the deep reflux may change pattern after varicose vein surgery. Mixed reflux involved mostly deep reflux to the knee or segmental popliteal reflux with axial superficial reflux. Only two patients had deep axial reflux to the deep calf veins. Despite of these components of deep reflux, AVP% and other hemodynamic variables increased significantly after surgery, which also is described by Padberg et al,[100] in our material, however, with the exception of the legs with ulcer recurrences.

Postoperative deep insufficiency developed in a total of 28 segments in the superficial group *[III]* (in 29% of the treated legs). In patients with mixed insufficiency, 16 new incompetent deep segments were found. New segmental deep reflux might occur when the deep venous system is exposed to higher hydrostatic blood pressure gradients after superficial venous surgery. On the other hand, deep reflux appeared to be abolished in 20 segments in the mixed group after surgery (40% of treated legs). Others have also confirmed that after GSV (SSV) surgery reflux is abolished in the SFV, (proximal popliteal vein).[101-103] The hypothesis is that superficial reflux may

maintain high blood volume flows, which dilates perforators and deep veins as an expression of flow-dependent vasodilatation or shear stress.[104] Our patients who developed deep reflux, have often a long history of ulcer disease, and there were always superficial residuals or recurrences in those legs.

Patient with superficial insufficiency *[III]* pre-operatively (n=14) and operated upon for the first time with CDU-guided surgery had normalized in AVP and VRT_{90} after surgery, and none were complicated with ulcer recurrence. Correct diagnosing of venous insufficiency and surgery with an experienced surgeon is probably of importance for successful varicose vein intervention. In study *[III]*, CDU or other objective tests were not used for evaluation of venous disease before the first surgical intervention, except of two patients, which is not an appropriate treatment strategy nowadays. Also Scriven et al[72] stated that 39% of legs with isolated superficial reflux did not have visible varicose veins. Hence, all the 38 patients without pre-operative CDU evaluation developed recurrent ulcers after previous surgery, but CDU-guided surgery succeeded in (68%) to maintain ulcer healing.

Likewise it is important to operate rapidly after the first ulcer event, since all patients with an ulcer history of <2 years had no ulcer recurrence during the post-operative 2.5-10 years follow-up.

Perforators

New incompetent perforators developed in 49% of the legs with superficial residual *[III]*. Perforators may maintain axial reflux in patients with segmental venous insufficiency in series of deep and superficial venous compartments. We also found several dilated and incompetent perforators in leg ulcer patients with primary superficial and mixed insufficiency *[paper II]*. A higher prevalence and number of perforators was also found by Rutherford et al[105] in patients with varicose vein recurrences, and Stuart et al[106] stated that, when isolated superficial reflux was abolished, the proportion of incompetent perforators decreased, whereas in legs with remaining venous reflux most of the perforators remained incompetent. Nelzén found effective ulcer healing after SEPS (subfascial endoscopic perforator surgery) with or without superficial venous surgery.[107]

Patients with varicose veins recurrences *[IV]* hade a greater number of incompetent perforators after surgery (Table 11,16) especially at 2 years follow-up, which was often combined with below knee (BK) residuals or recurrences of insufficient veins. The most used surgical approach today is stripping the GSV to the BK level, which implies, that distal superficial BK segments might still be there and further develop in time. Insufficient perforators were more frequent in legs with

ulcer recurrence (71% pooled data from *[III + IV]*) as compared to the legs with healed ulcers (41% pooled data from *[III + IV]*). Therefore perforator incompetence might complicate ulcer healing in the presence of other insufficient veins. In addition, APF% and VRT_{90} are lower and high VFI is higher in patients with incompetent perforators (*[IV]*, table 17) Hence, we found incompetent perforators to be a significant risk variable ($p<0.01$) for leg ulcer recurrence when pooling all patients within study *[III + IV]* together (n=114).

Other riskfactors of ulcer recurrence

Our patients with recurrent leg ulcers in *[III]* had higher blood pressure and they were older and heavier than non-ulcer recurrence patients. Therefore one might presume limited mobility as one reason for ulcer recurrence, especially in those three patients who suffered from knee joint disease. Besides of problems with ulcer recurrence, many patients experienced other symptoms such as difficulties in prolonged standing, hurting or heavy legs, varicose veins and hurting ankle. Thus, these symptoms might also lead to immobility which in combination with skin changes or venous hypertension might induce poor ankle motion and limited calf pump function.[108-110] Vice versa, physical training of patients with poor calf muscle pump function was shown to be of benefit for patients with chronic venous insufficiency.[111] Others found ulcer recurrence to be significantly increased in patients with deep venous insufficiency and especially in combination with high VFI (venous filling index).[77] Other significant risk factors that we found in *[III]* for ulcer recurrence were multiple ulcers ($p<0.02$) and multiple surgical interventions ($p<0.03$). Leg ulcer heredity ($p<0.005$) was another significant risk factor for ulcer recurrence found in *[IV]*.
When pooling the patients in study *[III]* and *[IV]* for a larger patient sample (n=114), the following variables were significant risk factors for ulcer recurrence: APF% ($p<0.001$), VFI ($p<0.01$), AVP ($p<0.01$), VRT_{90} ($p<0.003$), FVDS ($p<0.001$), axial reflux ($p<0.001$), ulcer diathesis ($p<0.001$), ulcer duration ($p<0.02$), BMI ($p<0.01$), incompetent perforators ($p<0.01$). SBP, DBP and heredity were not significant for ulcer recurrence. In the multivariate model (after a stepwise procedure) the most significant variables were APF% ($\beta=-0.0384$, SE=0.0138, p-value=0.0056) and axial reflux ($\beta=0.3485$, SE=0.1628, p-value=0.0323), with a Gradient of risk per 1 SD: 3.0.

Clinical symptoms

The objective hemodynamic measures (APF%, VFI, VRT_{90} and FVDS) correlated well with the patient's symptoms (Table 18). Most patients experienced clinical improvements after the last surgical intervention, 89% in *[III]* and 65% in *[IV]* after having previously suffered of long

periods of pain and discomfort. A significant improvement pain and swollen legs could be shown after surgery ($p<0.001$). However, many of the patients preferred to continue with stockings, at least at work. Continued compression therapy can postoperatively be recommended to some cases in order to decrease the progression of venous insufficiency, especially in legs with mixed reflux or remaining reflux.

In conclusion we are convinced that CDU should always be used in diagnosing and classifying venous insufficiency before surgical interventions as well as for their follow-up, which is especially important for venous ulcer treatments or risk evaluations. In order to prevent leg ulcers, it is necessary to locate and to remove or interrupt axial reflux through different superficial venous compartments. An early surgical treatment of leg ulcers seems to be of importance for long lasting ulcer healing. Additional muscle pump-test after surgery is recommended in patients with high risk for venous leg ulcers, in order to assess quantitative overall hemodynamic data for ulcer preventions. However, limited varicose vein recurrences or residuals might not be of larger hemodynamic importance.

SUMMARY AND CONCLUSIONS

- Suspected venous insufficiency of the lower extremities can be reliably investigated with Colour coded Doppler Ultrasound, with which it is possible to localize the involved vein segments, to assess the aetiology of venous dysfunction and to quantify its functional significance.
- Our studies support strongly the findings by others that primary superficial venous insufficiency are in more than 50% of the cases involved in chronic leg ulcer disease, which makes them therefore suitable for varicose vein surgery.
- However, the history of the venous leg ulcer, i.e. long ulcer diathesis is a preoperative risk factor for recurrent leg ulcers, which might have influence on the surgeons decision to operate or not.
- The surgical outcome should be evaluated by Colour coded Doppler Ultrasound, since residual axial reflux is a significant risk factor for leg ulcer recurrence and therefore an indication to re-operate the patients for consequent interruption of any remaining axial reflux.
- As other risk factors for post-operative ulcer recurrence we identified reduced muscle pump function (APF%) and pathologically decreased venous refilling times (VRT_{90}). The hemodynamic variable APF% can be assessed non-invasively by venous plethysmography, a quantitative test of venous hemodynamics and well suited for post-operative follow-up in patients with recurrent venous insufficiency.

CLINICAL RELEVANCE

Colour Doppler Ultrasound is a reliable method in diagnosing venous insufficiency and should always be used as a pre-operative test, as well as follow-up investigation, when necessary.

Since 83% of the patients with venous leg ulcers due to primary venous insufficiency have superficial insufficiency either isolated or in combination with deep vein insufficiency, venous surgery might be suitable in many cases. In the legs with secondary insufficiency, totally 56% might suffer of superficial vein insufficiency and thereby also be suitable for surgery, assuming that no venous obstruction is present.

Hence, it is important to assess a correct diagnosis of venous insufficiency with Colour Doppler Ultrasound pre-operatively, which facilitates correct vein interventions performed by experienced surgeons.

In order to improve the quality of life and to shorten ulcer diathesis, early surgical treatment of legs with ulcer is preferable since there is no reason to postpone surgery in patients with slow or none-healing ulcers.

In order to identify patients at risk for ulcer recurrence after surgery, post-operative assessment of the muscle pump function, which is an overall quantification of the venous insufficiency, is recommended.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Ultraljudsteknikens snabba utveckling har väsentligt förbättrat våra möjligheter att diagnosticera, behandla och följa upp kroniska sjukdomar i blodådrorna (s.k. venös insufficiens), eftersom det är svårt att få rätt diagnos genom kliniska undersökningar. Vi har visat en god överensstämmelse mellan ultraljud och kontraströntgen som är "guldstandard" för jämförelser av olika diagnostiska metoder (I). Fördelar med ultraljud är att metoden är non-invasiv och fri från kända biverkningar. Ultraljudsundersökningarna ger både morfologiska och funktionella bilder av blodådrorna och möjliggör en lokalisering och gradering av otäta venklaffar i benets enskilda venstammar, vilket kan drabba såväl ytliga, djupa eller perforerande (förbindelserna mellan ytliga och djupa vener) blodådror.

Venös insufficiens är vanligt förekommande bland befolkningen (ca 50%), med svårighetsgrader som sträcker sig från enkla vidgade småkärl till utbredd kronisk venös insufficiens, högt venblodtryck och venösa bensår. Dessa förekommer i ca 1% av befolkningen och leder till individuellt lidande och höga kostnader för samhället. Sårdurationen är ofta mycket lång och förenat med smärta och försämrad livskvalité. Efter en eventuell sårläkning är risken för återkommande bensår mycket hög. Behandling av venösa bensår har varit till stor del konservativ med användning av kompressionsstrumpor och/eller omlägg.

Kronisk venös insufficiens som kvarstår under längre tid utvecklar ett förhöjt venblodtryck vilket leder till förändringar i hudens mikrocirkulation med venösa bensår som följd (oftast lokaliserat på insidan av vaden). Den s.k. vadmuskelpumpen, som är aktiv vid gång, lyckas inte att hålla det venösa blodtrycket i foten tillräckligt lågt därför att blodådrorna fylls på snabbt igen. Det s.k. ambulatoriska venblodtrycket (AVP) mätes omedelbart efter knänigningar resp. tåhävningar som aktiverar muskelpumpen. Mätningarna för motsvarande venvolymsförändringar sker med hjälp av pletysmografiska metoder (s.k. Flebo-test).

Med ultraljudsmetoden har man kunnat visa att kroniska venösa bensår ofta beror på ytlig venös insufficiens, vilken är tillgänglig för kirurgi, och inte såsom man tidigare trodde enbart bero på i huvudsak djup insufficiens. Vi visade att mer än 50% av patienterna med venösa bensår har enbart ytlig venös insufficiens och att ytterligare 35% hade utöver en djup insufficiens också en ytlig klaffinkompetens som därmed är lämplig för varicer kirurgi (II). Kirurgisk sanering av ytlig venös insufficiens har rapporterats vara ett bättre alternativ till konservativ behandling genom att främja sårläkningen och att minska tendensen till sårrecidiv.

Våra studier hade som frågeställning, hur länge en kirurgisk sanering av blodådrorna kunde bestå och vad det fanns för riskfaktorer för eventuellt återkommande bensår. Först utfördes en retrospektiv studie (III) som i sin tur föranledde en prospektiv (IV) uppföljningsstudie av varicer kirurgi med ultraljud. Samtidigt mättes andra hemodynamiska variabler såsom venblodtrycket och venvolymen som mått på muskelpumpens effektivitet. Samtliga patienter hade kronisk primär venös insufficiens och venösa bensår som anledning till venkirurgi, vars uppföljning efter kirurgi sträckte sig i genomsnitt över 5.5 år.

Den retrospektiva studien visade att den totala 5-år risken för bensårrecidiv var 19% efter kirurgi. Signifikanta riskfaktorer var lång sår sjukdom med återkommande bensår innan kirurgi, samt kvarvarande ytlig venös insufficiens med långa refluxvägar och högt venblodtryck.

I den prospektiva gruppen observerades en förbättrad venfunktion under de första sex månaderna efter kirurgi men med en tydlig försämring efter 2 år hos patienter med sårrecidiv (17%). Dessa utmärktes av låg muskelpumpkapacitet, vilket var speciellt uttalad hos patienterna som fick sina sårrecidiv tidigt efter kirurgi.

Majoriteten av patienterna upplevde klara förbättringar efter kirurgi, och då speciellt minskad smärta och bensvullnad.

Sammanfattningsvis kan sägas att korrekt och radikal ytlig venkirurgi förbättrar patienternas kliniska symptom och minskar risken för sårrecidiv. Däremot ökar risken för sårreciciv med antalet kvarvarande insufficienta venvägar, varför vi vill rekommendera undersökningar med ultraljud inför alla tänkbara venkirurgiska ingrepp men även i uppföljande syfte efter kirurgi hos patienter med venösa bensår.

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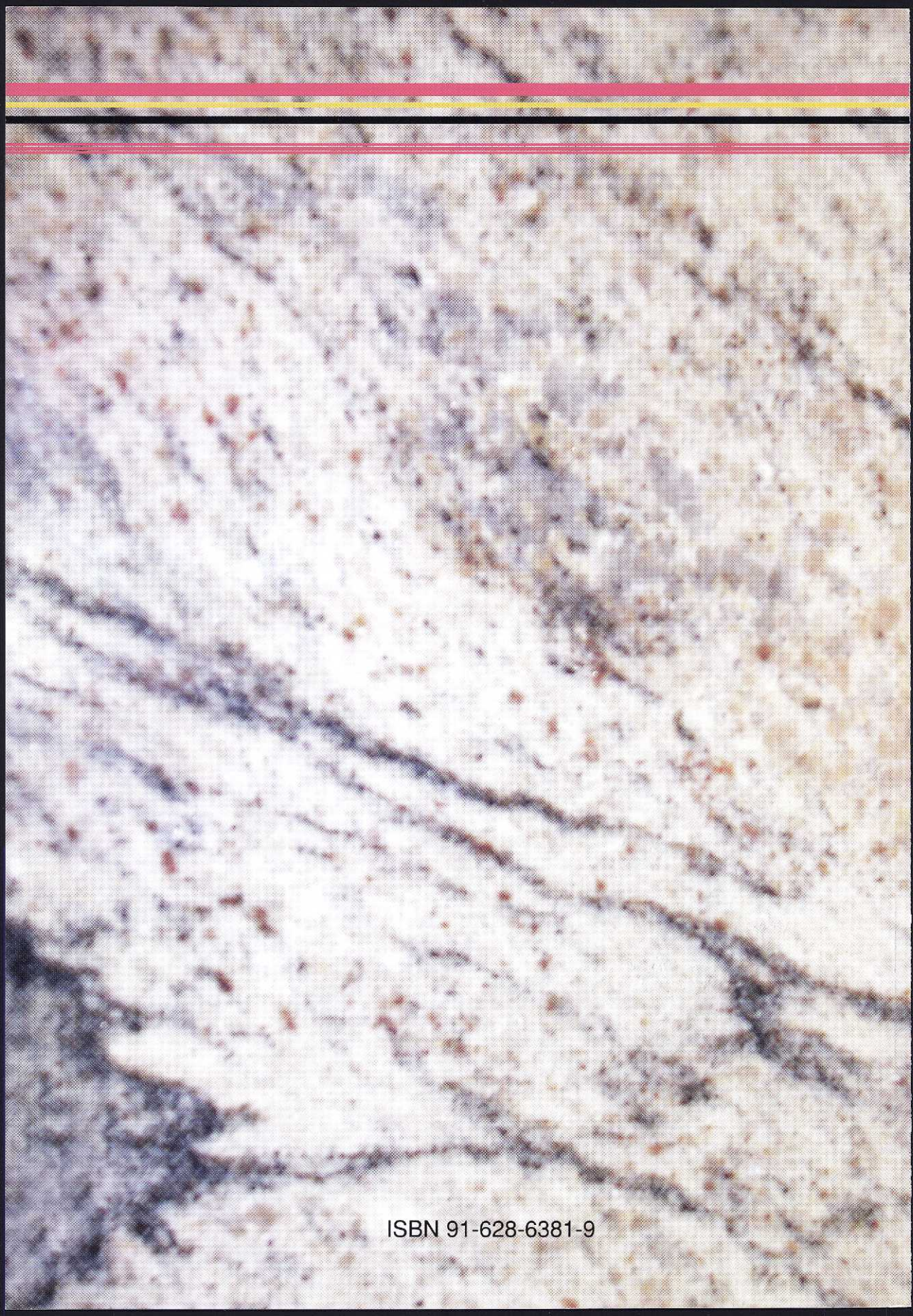

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