VENOUS ELASTICITY AND CALF MUSCLE PUMP FAILURE

THEIR MEASUREMENT AND ROLE IN VENOUS DISEASE

Simon Philip Kent Payne MB ChB (Leic.), FRCS (Eng.)

Thesis submitted for the degree of Doctorate of Medicine at the University of Leicester, United Kingdom

1997

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Statement of Originality

This work was performed by myself in the Department of Surgery at the University of Leicester. The work is original except where stated and cited in the text.

Signed,

_____

Simon PK Payne

Date:

_____

ABSTRACT

The aims of this thesis were firstly to review several techniques used to assess venous calf muscle pump function and to establish the relative importance of venous incompetence in different sites. Secondly to investigate venous elasticity in varicose limbs using a new method and thirdly to examine the effect of compression stockings on venous elasticity and venous valvular function.

Ambulatory venous pressure measurement showed strong agreement with the clinical severity of venous disease. The use of narrow tourniquets in combination with this technique was not helpful however in predicting the effect of venous surgery, indeed the technique did not differentiate deep from superficial reflux. Duplex scanning demonstrated that the tourniquets did not obstruct superficial venous flow as previously claimed. Air-plethysmography failed to distinguish between patients with venous disease of varied severity nor did the volume measurements agree with pressure measurement as previously claimed.

Statistical analysis of reflux patterns in 274 limbs found popliteal reflux to have the greatest clinical importance, followed by long saphenous reflux. Venous elasticity measurement showed reduced elasticity in varicose limbs at low distension pressures. Major surgery did not alter venous elasticity, but compression stockings produced an improvement. Duplex scanning showed that compression stockings reduced venous reflux but did not restore competence to incompetent veins.

In conclusion, ambulatory venous pressure remains the reference standard test of venous calf muscle pump function. The addition of tourniquets is unhelpful as is air-plethysmography. The popliteal and the long saphenous veins are the most important when considering a mixed pattern of venous reflux. Varicose veins show a defect in venous elasticity which is improved by elastic compression stockings, however in spite of reducing reflux the stockings do not restore venous valves to competence.

SYNOPSIS

In spite of the prevalence of varicose veins and venous ulceration there remain large gaps in our knowledge of the pathophysiology of venous insufficiency. A thesis on the subject might examine a number of questions ranging from the aetiology of varicose veins right through to the cellular interactions surrounding the endpoint of venous insufficiency; venous ulceration.

A clear understanding of venous disease holds the concept of the venous calf muscle pump described by Professor Sir Norman Browse to be the central focus of venous physiology. Venous pathophysiology may be however divided into three stages. The first concerns the aetiology of the varicose process, the second is failure of the venous calf muscle pump and the final stage concerns the relationship between venous hypertension and venous ulceration.

As Vascular Surgeons we are concerned with assessing and attempting to improve the second stage of the venous insufficiency - the calf muscle pump. In this thesis I have examined this stage in more detail. The work described is divided into five sections:

The first addresses the clinical significance of venous calf muscle pump failure as measured by ambulatory venous pressure (AVP) monitoring. This study demonstrated in 360 limbs a linear trend towards more severe skin damage with increasing ambulatory venous pressure. Ulceration was associated with more severe calf muscle pump dysfunction than were lipodermatosclerosis, eczema or pigmentation. Duplex scanning was then used to dissect the relative contribution to the clinical picture from incompetence in each of the major veins in the leg. In 274 limbs popliteal reflux was shown to have most influence over the clinical condition of the limb. Long saphenous reflux also significantly influenced whether a limb exhibited skin damage or ulceration.

The use of AVP measurement combined with tourniquets to assess patients for venous surgery was then examined in the second section: In 48 limbs AVP / tourniquet assessment was shown to be inaccurate in selecting between long saphenous stripping

and sapheno-femoral ligation without stripping. Tourniquet testing was then compared with Duplex scanning to differentiate deep from superficial reflux in 234 limbs - there was no agreement between the two methods. The effect of the tourniquets on deep and superficial venous blood flow was then studied with Duplex in 10 limbs. The tourniquets were not reliable in obstructing superficial venous blood flow which may explain their lack of predictive value in venous assessment.

In the third section the air-plethysmograph was compared with Duplex scanning and AVP measurement as a method of assessing venous function in 113 limbs. The air-plethysmography results showed considerable scatter within groups of clinically similar limbs and substantial overlap between groups of clinically different limbs. The previously claimed correlation between residual venous volume measured with the air-plethysmograph and ambulatory venous pressure was not demonstrated.

Venous elasticity measurement is examined in the fourth section using the air-plethysmograph to record limb volume changes in combination with direct venous pressure measurement. Close agreement between air-plethysmography and strain gauge plethysmography when used to measure limb volume changes was shown in 20 limbs. Venous elasticity measurement was shown to be reproducible in a sample of 30 limbs. A comparison between 58 subjects with venous insufficiency and 45 subjects without venous disease showed a loss of elasticity in the limbs with venous disease at low distension pressures compared with normal limbs. The effect of major abdominal surgery on venous elasticity was assessed in 11 subjects, finding no significant effect from the surgery.

The final section concerns the effect of compression hosiery on both venous elasticity and venous valvular function. The effect of wearing compression stockings for four weeks on venous elasticity was measured in 20 limbs. At low distension pressures the stockings increased venous elasticity and also decreased the resting volume of the limbs. One week after removing the stockings and these changes were no longer evident. Finally from the above observations it is reasonable to postulate that compression

stockings improve venous calf muscle pump function by restoring competence to dilated incompetent venous valves. However the function of identifiable incompetent segments of vein were studied underneath compression stockings. Only one of 31 segments was restored to competence although venous diameter and reflux flow through each venous segment was reduced, suggesting that compression stockings do not act by restoring competence to dilated, incompetent venous valves. The beneficial effects of compression stockings may be mediated via a reduction in venous reflux or by normalising the transmural pressure across the vein and capillary wall allowing the veins and the microcirculation to function more effectively.

This thesis is dedicated to my wife, companion and the mother of our two children; Thomas and Olivia

Sarah Jayne

ACKNOWLEDGEMENTS

Mr. William Barrie who kindled my interest in venous disease and then supported these endeavours with the use of the Vascular Studies Unit at the Leicester General Hospital together with ongoing advice, guidance and inspiration throughout.

Mr. Nicholas London for his continued guidance, criticism and advice throughout this work, and for his enthusiasm in encouraging me to pursue the project to completion.

Professor Peter Bell who nurtured my interest in vascular surgery then supporting that by allowing me to work in his department, supervising and encouraging me in this work through to completion.

Dr. Elizabeth Watkin, Dr. Carol Newland, Mrs Janet Brookes, Ms. Abigail Thrush, Mr. Mike Asher for their technical expertise and instruction in performing this work and for their enthusiasm and assistance with the project.

TABLE OF CONTENTS

SECTION I

INTRODUCTION AND BACKGROUND

CHAPTER ONE

VENOUS DISEASE, AN HISTORICAL PERSPECTIVE

The first mention of "certain serpentine windings" (varicose veins) advises against surgical treatment for this condition because that would be "head upon the ground" (ie fatal) (Major, 1954). This advice is taken from the papyrus of Ebers (c 1550 BC), possibly the first publication in the venous literature. A votive tablet at the foot of the Acropolis in Athens on the site of the temple of the Hero Doctor Amynos depicts a dilated and tortuous long saphenous vein on the leg of a god which is being examined by a mortal (4th century BC). The figure appears to be performing a modification of the Brodie-Trendelenberg test used today in clinical assessment of varicose veins. This is the first known illustration of venous disease (see Figure 1.1).

It was not until the time of Hippocrates (460 - 377BC) that anatomical dissection was performed for research, prior to then knowledge of the cardiovascular system was very scant. Hippocrates however refers many times in his works to the vascular system. In De Carnibus he mentions arteries and veins, which both arise from the heart. In De Ulceribus he discusses venous ulceration, stating that "in the case of an ulcer it is not expedient to stand, more especially if the ulcer be situated in the leg" (Hippocrates,1886). Varicose veins were believed to be due to the posture adopted during horse riding, with the feet dependent. The association between varicose veins and venous ulceration was made at this time.

Current Hippocratian thinking was that an ulcer should remain open to release evil humors; "Varicose veins or haemorrhoids appearing in a case of madness put an end to it". He advised the use of compression bandaging and small venous punctures for cases of venous ulceration in order to let out these evil humours (Majno,1975).

Galen (AD 130-200) combined Hippocrates ideas with his own thoughts regarding the to and fro movement of blood. He was a prolific writer who used the information from earlier work on the cardiovascular system, together with his own studies of anatomical dissection producing approximately four hundred treatises. He attributed the varices to the weight of stagnant "gross" blood on the walls of the veins (Galen,1562). Menstruation was thought of as release of "gross" blood, suppression of which, for example in pregnancy, would result in it's collection in the legs, where it becomes stagnant causing varicose veins and ulceration. Ulceration was thought to be the natural means by which the body rids itself of this stagnant blood and thus should not be encouraged to heal (Ettmulleri,1688). Galen treated varicose veins by incision and tearing out with a blunt hook. He treated venous ulcers by venesection (to release the "gross" blood) and application of dressings soaked in wine (Walsh,1934). This thinking persisted as late as 1822 when Buchan wrote "If an ulcer conduces to the patient's health, from whatever cause it proceeds, it ought not to be healed; but if on the contrary, it wastes the strength, and consumes the patient by a slow fever, it should be healed as soon as possible."(Buchan,1822)

Early developments in surgery allowed simple operations to be performed, including operations for varicose veins. About 270 BC, the Egyptians (Herophilos and Erasistratos) invented artery forceps which they used to ligate blood vessels (Majno,1975), they also noted that the heart contained valves to prevent reflux of blood (Lonie,1973). Ligation of bleeding veins, division of veins between ligatures and the avulsion of varicose veins were described by Calcus in De Medicina (AD 25).

The Roman tyrant Caius Marius who died in 86 BC underwent surgical treatment of his severe varicose veins. The tyrant was reported to endure the procedure (performed without anaesthetic) silently without changing countenance. A Surgeon of the day who also was afflicted with varicose veins decided against operation, saying "I see the cure is not worth the pain."(Clough,1859). Surgery had improved since the days of the Papyrus of Ebers but still had little to recommend it.

Although the idea that venous ulcers were allowing stagnant blood to escape was still popular this did not suppress the (correct) use of compression bandaging. Maitre Henri de Mondeville (1306) described the use of compression bandages to treat venous ulcers although he was using them to expel the evil humours that Hippocrates had subscribed to. Ambroise Pare (1510 - 1590) who was employed as surgeon to Henri II, cured the ulcer of his captor Lord Vandeville by regular bandaging from foot to knee. He also described the ligation of the long saphenous vein in the thigh, although he still believed (of varicose veins) "It is best not to meddle with such as are inveterate; for of such being cured there is to be feared a reflux of the melancholy bloud to the noble parts, whence there may be imminent danger of malign ulcers, a cancer, madness or suffocation."

The theory that venous ulcers were acting as a "safety valve" to release evil influences was renounced in 1859 by Hunt who remarked that although many patients still believed that the ulcer was salutary, and that it could not be healed without risk of damage to the general health, it was an unfounded and now almost obsolete prejudice (Hunt,1859). The theory was put to rest, however the logical explanation was to wait another 70 years for the discovery of the circulation of blood.

Advances in the understanding of venous disease could only be made following greater study of the anatomy and physiology of the vascular system. A period during which anatomical dissection was prohibited for religious reasons was followed by a resurgence of interest in the vascular system. During The Renaissance venous anatomy was studied in detail by great minds such as Leonardo da Vinci who, in 1452, in addition to his works as an artist and inventor produced some masterful drawings of the venous system of the arm and leg.

The basis of venous physiology, the venous valve was discovered long before it's true function was realised. From 1547 to 1551 Gianbattista Canano and Amatus Lusitanus were in dispute over who first described venous valves; Canano described valves in the azygos, renal and sacral veins, claiming this to be the first description, but Amatus stated that he had shown many times that the veins contained valves. Amatus published his

findings, unlike Canano. The credit is usually given to Canano, then Professor of Anatomy at Ferrara. Vesalius, in 1555 also described the venous system in detail but was unable to find venous valves and therefore denied their existence, although had been told of their discovery by Canano when they met in consultation at the bedside of Duke Francis of Este in Regensburg (Cockett,1991).

Vesalius's book, De Humani Corporis Fabrica was of great importance at the time. The plates were prepared by the greatest artists in Titians studio. The book established Vesalius as the dominant figure in surgery and anatomy, so when he denied the existence of venous valves Canano felt unable to compete and promptly destroyed his own work on the muscles of the arm.

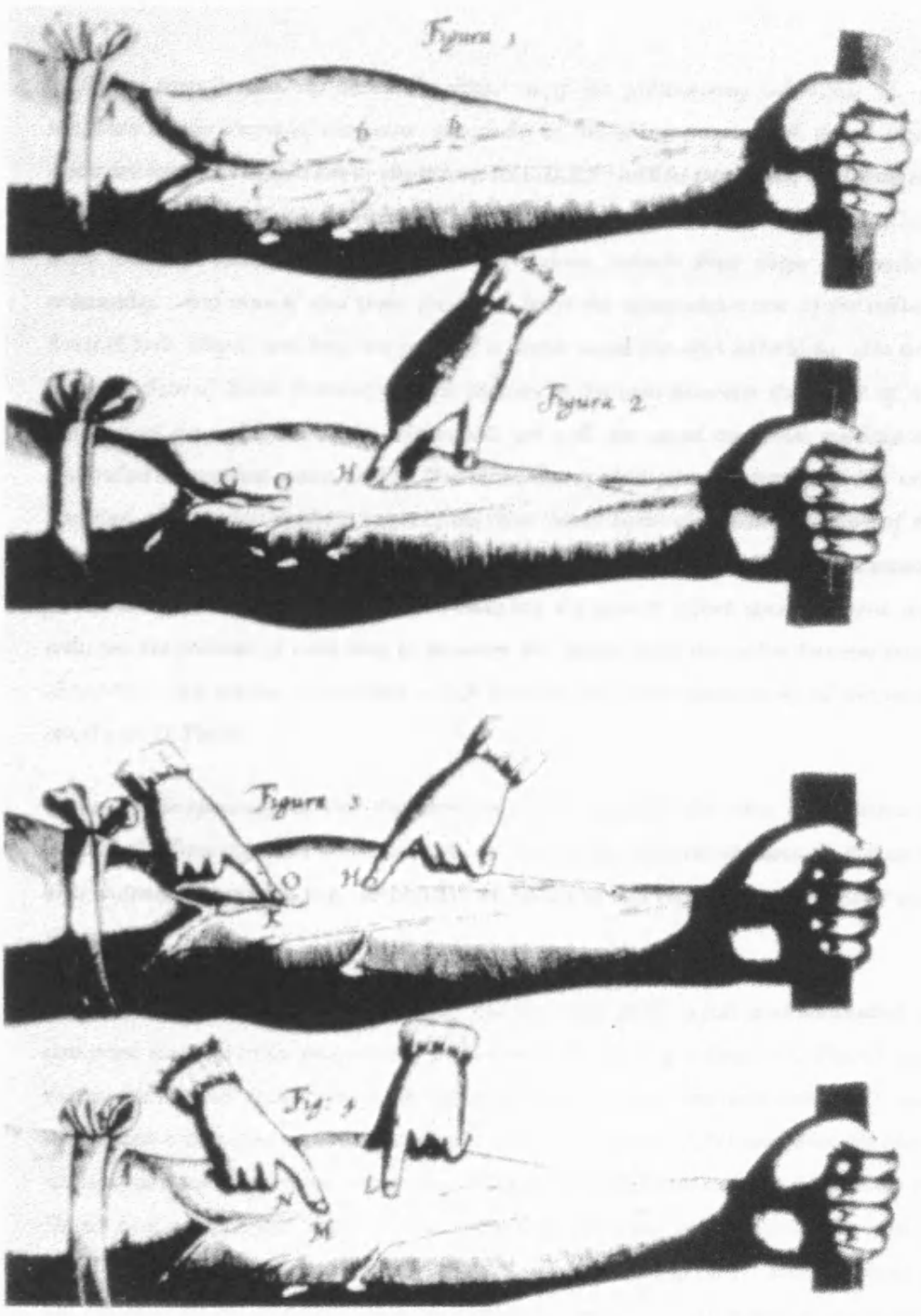
The venous valves were again described in great detail by Hieronymus Fabricius of Aquapendente in 1579 although he did not deduce that the blood circulated. At that time the blood was thought to ebb and flow, a theory described by Galen. Fabricius, who succeeded Vesalius as Professor of Anatomy and Surgery at Padua, stated in his book De Venarum Osteolis ("The little doors in veins") that the purpose of venous valves was "to delay the blood to some extent, and to prevent the whole mass of it flooding into the feet, or hands and fingers, and collecting there.....to ensure a really fair general distribution of the blood for the nutrition of the various parts" (Fabricius,1986).

It was in 1628 that Fabricius's English student of 1599 - 1603, William Harvey in Exercitatio anatomica de motu cordis et sanguinis in animalibus ("Anatomic treatise on the motion of the heart and the blood in animals"), demonstrated that the valves in the veins were to ensure unidirectional blood flow and deduced that the blood circulated (Harvey,1628). The proof that blood flows from the arteries to the veins was only supplied after Harveys death by Marcello Malpighi, who observed blood corpuscles transferring from the arterioles to the venules via the capillaries. Harvey's classic illustration of the function of venous valves is readily demonstrable as Figure 1.2 shows. The foundation of venous physiology was thus established.

Figure 1.1

Votive tablet depicting a dilated and tortuous long saphenous vein on the leg of a God. The leg is being examined by a mortal. This tablet lies at the foot of the Acropolis in Athens at the site of the temple of the hero Doctor Amynos.

Figure 1.2



William Harveys classic demonstration of the circulation of blood (see text overleaf)

Harvey's original description of his test demonstrating the circulation of the blood.

"..Let an arm be tied up above the elbow as if for phlebotomy (A,A,Fig 1). At intervals in the course of the veins, especially in labouring people and those whose veins are large, certain knots or elevations (B,C,D,E,F) will be perceived, and this not only at the places where a branch is received (E,F), but also where none enters (C,D): these knots or risings are all formed by valves, which thus show themselves externally. And now if you press the blood from the space above one of the valves, from H to O, (Fig 2) and keep the point of a finger upon the vein inferiorly, you will see no influx of blood from above; the portion of the vein between the point of the finger and the valve O will be obliterated: yet will the vessel continue sufficiently distended above that valve (O,G). The blood being thus pressed out, and the vein emptied, if you now apply a finger of the other hand upon the distended part of the vein above the valve O (Fig 3), and press downwards, you will find that you cannot force the blood though or beyond the valve; but the greater effort you use, you will only see the portion of vein that is between the finger and the valve become more distended, that portion of the vein which is below the valve remaining all the while empty (H,O, Fig 3).

It would therefore appear that the function of the valves in the veins is the same as that of the three sigmoid valves which we find at the commencement of the aorta and pulmonary artery, viz., to prevent all reflux of the blood that is passing over them.

Further, the arm being bound as before, and the veins looking full and distended, if you press at one part in the course of a vein with the point of a finger (L, Fig.4), and then with another finger streak the blood upwards beyond the next valve (N), you will perceive that this portion of the vein continues empty (L,N) and that the blood cannot retrograde, precisely as we have already seen the case to be in Fig.2; but the finger first applied (H, Fig. 2, L, Fig. 4), being removed, immediately the vein is filled from below, and the arm becomes as it appears at D,C, Fig. 1. That the blood in the veins therefore proceeds from inferior or more remote to superior parts and towards the heart, moving in these vessels in this and not in the contrary direction, appears most obviously.."

CHAPTER TWO

EPIDEMIOLOGY OF VARICOSE VEINS AND VENOUS ULCERATION

It is difficult to find a satisfactory definition of varicose veins upon which a consensus has been reached. Arnoldi's definition that "any dilated, elongated or tortuous vein" may be termed varicose is the most frequently used (Arnoldi,1957). However papers on venous disorders do not universally apply this definition, often applying their own or use a clinical grading of severity. When known, I have drawn attention to the definition used. Unfortunately the venous literature is scattered with different definitions and thus it is difficult to draw comparisons between studies.

2.1 Varicose veins

The prevalence of varicose veins ranges from 0.9% to 76.8% according to which study one reads (see below). It is clear that in addition to true changes in the prevalence of varicose veins the literature reflects the application of different definitions and different selection procedures. Thus it is important when looking at any study of the epidemiology of varicose veins to be clear what definition was used and how the sample was selected, otherwise all we can say is that we are almost certain that the prevalence of varicose veins is greater than 0.9% and less than 76.8%!

In 1942 Lake et al. studied 536 subjects age 40 years or more who worked in a large department store (Lake *et al.* 1942). The subjects were stratified according to the nature of their work (standing , walking, sitting or climbing stairs). 40.7% of men and 73.2% of women were found to have "visible varicose veins". This difference was still apparent when those women who had been pregnant were removed from the statistics. Those women with standing or walking occupations had a higher incidence of varicose veins

than those sitting or climbing stairs. The presence of varicose veins was associated with a higher incidence of arterial disease in men.

Arnoldi's study of 293 female hospital admissions demonstrated an increase in prevalence with advancing age, from 35.9% in women age 20-29 to 65.4% in women over 60. Unfortunately some of these women had been admitted for varicose vein surgery thus biasing the results so no other conclusions may be drawn from this study.

Other studies have used patient groups as the study cohort but have avoided the bias of using attendances for treatment of varicose veins. Drury, in a personal survey of 4,983 patients who were attending for routine examination in General Practice showed a prevalence of 8% in women and 5% in men (Drury,1965). Examining 1000 outpatients in Munich, Eberth-Willhausen and Marshall found a prevalence of varicose veins of 50%, 25% had clinically unimportant, 10% clinically relevant and 15% pathological venous disease, no sex bias was detected, however the prevalence increased with advancing age (Eberth-Willerhausen and Marshall,1984). In a Study of 1755 patients presenting with random complaints Maffeii et al. found a prevalence in men of 37.9% and 50.9% in women (non-pregnant), the overall prevalence was 47.6% (Maffei *et al.* 1986).

The prevalence of venous disease in the community has been addressed by a number of large studies in Tecumseh, Tubingen in Germany, Jerusalem and Basle. The Tecumseh study found a prevalence of varicose veins in men age 20 - 29 of 0.9% which rose to 56.8% for the over 70's. In women the prevalence rose from 8% at age 20 - 29 to 76.8% in the over 70's (Coon *et al.* 1973). The Tubingen study of 4530 patients attending for their statutory X-ray examinations found a prevalence of varicose veins of 23% in men and 49% of women over the age of eighteen (Fischer,1981). In Jerusalem a prevalence of 29% in women and 10% in men over the age of 15 was found which rose to 39% in men and 42% in women over the age of 75 (Abramson *et al.* 1981). Small distended veins were ignored in this study but otherwise the definition used was that of Arnoldi.

The Basle study failed to demonstrate a sex bias; varices were found in 48.7% of a workforce population, with an equal sex distribution. Varicose veins were classified as considerable in 13% of workers and no increase in prevalence with age was demonstrated (Abramson *et al.* 1981). Using a workforce population as the study group may be responsible for the lack of sex or age bias demonstrated. A large study in Shangai examined 30,712 peasants and workers from both heavy and light industries. Varicosity of the superficial veins in the lower extremities was found in 2,577 (8.4%). Risk factors identified for developing varicose veins included hard labour, body mass, standing, pregnancy and sitting (Sun,1990).

The Framingham study also addressed risk factors such as obesity and amount of exercise taken. Varicose veins were found to be commoner in females who are overweight, who take little exercise and are hypertensive (Brand *et al.* 1988). Weddell studied a random sample of 289 people in South Wales and found varicose veins in 6% of men and 17% of women. There was a considerable discrepancy between the history of varicose veins or otherwise given by the patient and the findings on clinical examination. The only risk factors that were significantly associated with varicose veins were pregnancy and heavy lifting (Weddell,1969).

One study has looked at which leg is more commonly affected; Cornu examined 843 limbs undergoing surgery for varicose veins and found an equal distribution between the two limbs (Cornu *et al.* 1986).

Table 2.1 is drawn from a recent literature review of the epidemiology of varicose veins (Callam,1994). From these studies the mean prevalence is 38%. The prevalence of varicose veins increases with advancing age. The risk of developing varicose veins appears to be approximately twice as high in women compared with men. Other risk factors include obesity, standing occupation and pregnancy. The influence of race on prevalence of varicose veins is addressed below.

2.2 Racial Variation

There has been some dispute over whether venous disease is more common in certain races or climes. Several reports from the 1970's indicated that varicose veins were less common in third world countries (Barker,1964; Coles,1974; Dalrymple and Crofts, 1975; Worsfold,1974; Williams,1974). Burkitt was perhaps the most notable of these quoting a prevalence of varicose veins among Central African women of only 0.12% (Burkitt,1972). However Rougement found a 10.9% prevalence in Mali women (Rougement,1974) and Daynes and Beighton found a 7.7% prevalence in African women over the age of eighteen (Daynes and Beighton,1973). What was also apparent was that most of the women with varicose veins denied any symptoms, which may explain the low prevalence found in some studies. The Jerusalem study however found a lower prevalence of varicose veins in women from North Africa compared with other racial groups (Abramson *et al.* 1981). In other parts of the world this pattern has been repeated (Beaglehole *et al.* 1976; Maffei *et al.* 1986; Mekky *et al.* 1969). The Jerusalem study examined all patients in a common environment but from different racial backgrounds, indicating that the predisposition to varicose veins is in part racially determined.

2.3 Venous ulceration

Leg ulceration may be regarded as the end point of venous disease, although Harman (Harman,1974) reported a series of 23 deaths due to bleeding from varicose veins. Aside from the inconvenience and discomfort the patient with venous ulceration suffers, the condition is also expensive to treat. A recent estimate of the annual cost to the National Health Service of treating leg ulcers is £600 000 000 (Harding,1991) (as discussed below the majority of leg ulcers are due to venous disease). The annual cost per ulcer has been estimated as £2000 - 4000, most of this expense being in community nursing (Bosanquet,1992). This degree of venous disease is quite disabling and is also

self perpetuating since mobility is limited by the ulcer and therefore venous stasis is compounded. For these reasons much more attention has been paid to venous ulceration than the earlier stages of the disease.

Venous ulceration is easier to define than varicose veins, however other causes of ulceration, such as arterial insufficiency or rheumatoid disease should be excluded. In addition it is important to be clear whether one is dealing with active ulcers (prevalence) or those limbs which have been ulcerated at some time (incidence, if the time span is also quoted). Most studies quote the number of limbs which have been ulcerated at some time although it is not always clear what the time span surveyed is (this obviously varies with the age of the patients).

What is clear from most studies is that venous ulcers are common and are expensive to treat. In an address given before the Medical Society of London in 1931, Dickson-Wright, assistant Director of Surgery at St Mary's Hospital estimated the prevalence of venous ulcer to be 0.5% among the population of Great Britain (Dickson-Wright,1931). Gjores, in an opening address to a conference on venous leg ulcers summarised estimates produced by a number of eminent Surgeons of the number of leg ulcers. (see Table 2.2). I have appended the population estimates (million) for these countries in order to gain an approximation of prevalence (per million) from these estimates. Lofgren stated that venous disease is the commonest cause of leg ulceration, arterial disease coming second (Lofgren,1984). This is in agreement with the findings of the Forth Valley Leg Ulcer Study, see below.

Table 2.1 Studies of varicose vein prevalence

Author	Year	No. of subjects	Prevalence (%) Men	Women	Total	Age (yrs)
Maffei	1986	1755	37.9	50.9	47.6	>15
Lake	1942	536	41	74	57	>40
Arnoldi	1958	1981	18	38	28	>25
Berge & Feldthusen	1963	1354	50			50
Berge & Feldthusen	1963		10			20
Recoules-Arche	1965	5424			14	16-54
Mekky *et al.*	1969	504		32.1		15-74 (Engl)
Mekky *et al.*	1969	467		5.8		15-74 (Egypt)
Miyauchi	1913	50 000	0.6			18
Bobek *et al.*	1966	15 060	6.6	14.1	11	>15
Prior *et al.*	1970	232	25	42		>20
Stanhope	1975	728	5	0.1		20-70
Malhotra	1972	354	6.8			18-65 (Nth India)
Malhotra	1972	323	25.1			18-65 (Sth India)
Abramson	1981	4802	10.4	29.5		>15
Richardson & Dixon	1977	1259	4.8	4.1	4.5	
Hirai	1990	541		45		>15
Guberan *et al.*	1973	610		29		15-70
Coon *et al.*	1973	6389	12.9	25.9	19.7	>10
Wright *et al.*	1989	1338			25	20-75
Leipnitz *et al.*	1989	2821	14.5	29	20.2	45-65
Widmer	1978	4529	56	55	55	25-74
Rudofsky	1988	14 000			15	>15
Weddell	1969	100			15	>15

The community varicose vein studies also looked at the problem of venous ulceration. As with varicose veins the Tecumseh study demonstrated an increase in ulcer prevalence with increasing age. No ulcers were found in the 20 - 29 age group, whereas 0.6% of men and 2.1% of women in the 60-69 year age group had ulcers (Coon *et al.* 1973). This female preponderance of venous ulcers was also shown in the Tubingen study which found 2% of men and 3% of women to have a leg ulcer (Fischer,1981). The Munich outpatients survey of 1000 patients found that 4% of adults had experienced a leg ulcer either previously or currently (Eberth-Willerhausen and Marshall, 1984). Maffeii, in his survey of out patients found that 2.3% of men and 4% of women had an active or healed ulcer (3.6% of all patients) (Maffei *et al.* 1986).

Table 2.2 Estimates of leg ulcers (per country).

year		no of ulcers		pop (million)	prevalence (ulcers/million)
1937	Denmark	5,000 - 15,000	Roholm	5	1000-3000
1942	Sweden	1,000 - 3,000	Bauer	8	125-375
1951	England	1- 200,000	L-Mummery	46	2000-4000
1952	Great Britain	250,000	Boyd	55	4500
1952	USA	3- 400,000	Linton	210	1500-2000
1956	Sweden	31,000 - 42,000	Gjores	8	4000-5000
1985	Scotland	140,000	Ruckley	5	28000

Table 2.3 The Lothian and Forth Valley Leg Ulcer Study.

Evidence of deep venous insufficiency	70 %
Arterial impairment (ABPI < 0.9)*	21 %
Rheumatoid arthritis	9 %
Diabetes	5.5 %

(*Resting ankle/brachial systolic pressure index, using Doppler)

The Forth Valley Leg Ulcer Study showed an incidence of leg ulceration of 1.48 per 1000 population with a female to male ratio of 2.8:1 on postal survey (Callam *et al.* 1985) of which 1.12 per 1000 were subsequently found on examination to be of venous aetiology (Callam *et al.* 1987). Dale et al. in the same study demonstrated an increase in the incidence of leg ulceration with advancing age. Ten per 1000 adults (1%) and 36 per 1000 (3.6%) of the over 65's had experienced chronic leg ulceration by postal survey (Dale *et al.* 1983). (This part of the study was directed at patients over the age of 65 from a single practice.)

Table 2.3 shows the aetiological factors contributing to the leg ulcers identified in this study. As mentioned above, venous disease accounts for the vast majority of them.

Bobek, in a survey of over 15,000 adults found that 1% had active or healed ulceration (Bobek *et al.* 1966). This figure of 1% is reinforced by Kamber's study in factory workers (Kamber *et al.* 1991).

Several studies have carefully excluded patients without current ulceration, therefore measuring the true prevalence. In a comprehensive survey of leg ulceration, Cornwall *et al.* found a prevalence of leg ulceration of 0.18% of the population, or 0.38% of those aged over 40 years. Once ulcers from other causes had been excluded, those due to

venous disease were found to have a prevalence of 0.11% (Cornwall *et al.* 1986). In a large Australian metropolitan survey Baker at al found a prevalence of active venous ulceration of 0.16 per 1000 (Baker *et al.* 1991).

Although the two more recent surveys were careful to ensure that only active, true venous ulcers were included it has been suggested that the incidence of venous ulceration is falling. This is supported by the Skaraborg study from Sweden. In 1974 the prevalence of leg ulceration was 0.26% in the over 25's, and ten years later in 1984 the prevalence had dropped to 0.19% (Hallbook,1988). Explanations offered for this include advances and enthusiasm for deep venous thrombosis prophylaxis, thus truly reducing the incidence, and a greater awareness with facilities for assessing the arterial component to these ulcers in 1984 compared to 1974, thus reducing the number that are falsely atributed to venous insufficiency. A later study from Skaraborg found a point prevalence of true venous ulcers of 0.16% (95% ci: 0.15 - 0.18), 54% of the ulcers examined in this study were concluded to be of venous origin (Nelzen *et al.* 1994).

Thus it appears that between 2 and 3% of adults will experience chronic leg ulceration at some time in their life. The majority of these will be due to venous disease, however the prevalence of active venous ulceration at any one time in the population is nearer 0.1%. The risk of developing a venous ulcer is higher in women and rises with advancing age. Venous ulcers are common, are costly to treat and quite miserable for the patient who suffers them. However there is some hope that the incidence is falling, and certainly there is more enthusiasm for treating venous ulceration actively.

CHAPTER THREE

PATHOPHYSIOLOGY OF VENOUS DISEASE

3.1 Classification of venous disease

In order to focus our therapeutic endeavours and direct both teaching and research in venous disease it is necessary to have some form of classification. This was addressed in a consensus document published by the American Venous Forum (American Venous Forum, 1994). The classification proposed was based on the acronym CEAP (Clinical condition, Etiological mechanism of the condition, Anatomic distribution of the disease and Pathophysiological mechanism of the problem). An example using this classification would be C: leg ulcer, E: post-thrombotic, A: superficial and deep, P: reflux. This classification is straightforward to use, provides a clear framework upon which to plan investigation and treatment and therefore is rapidly gaining acceptance. Kistner (Kistner 1996, Kistner *et al.* 1996) has recently reported two series in which this classification has been used. He states that the system is useful in "sorting out patients for surgery and other treatment.....and affords the opportunity to interrelate the clinical, anatomic, etiologic and pathophysiologic phenomena of CVD to each other."

3.2 Functional anatomy

The function of veins is to convey deoxygenated blood from the periphery back to the heart. The veins of the lower limb may be divided on both an anatomical and functional basis into deep and superficial systems, the deep fascia of the leg separates the two. Ninety percent of the blood returning from the legs flows through the deep veins (Arnoldi,1989).

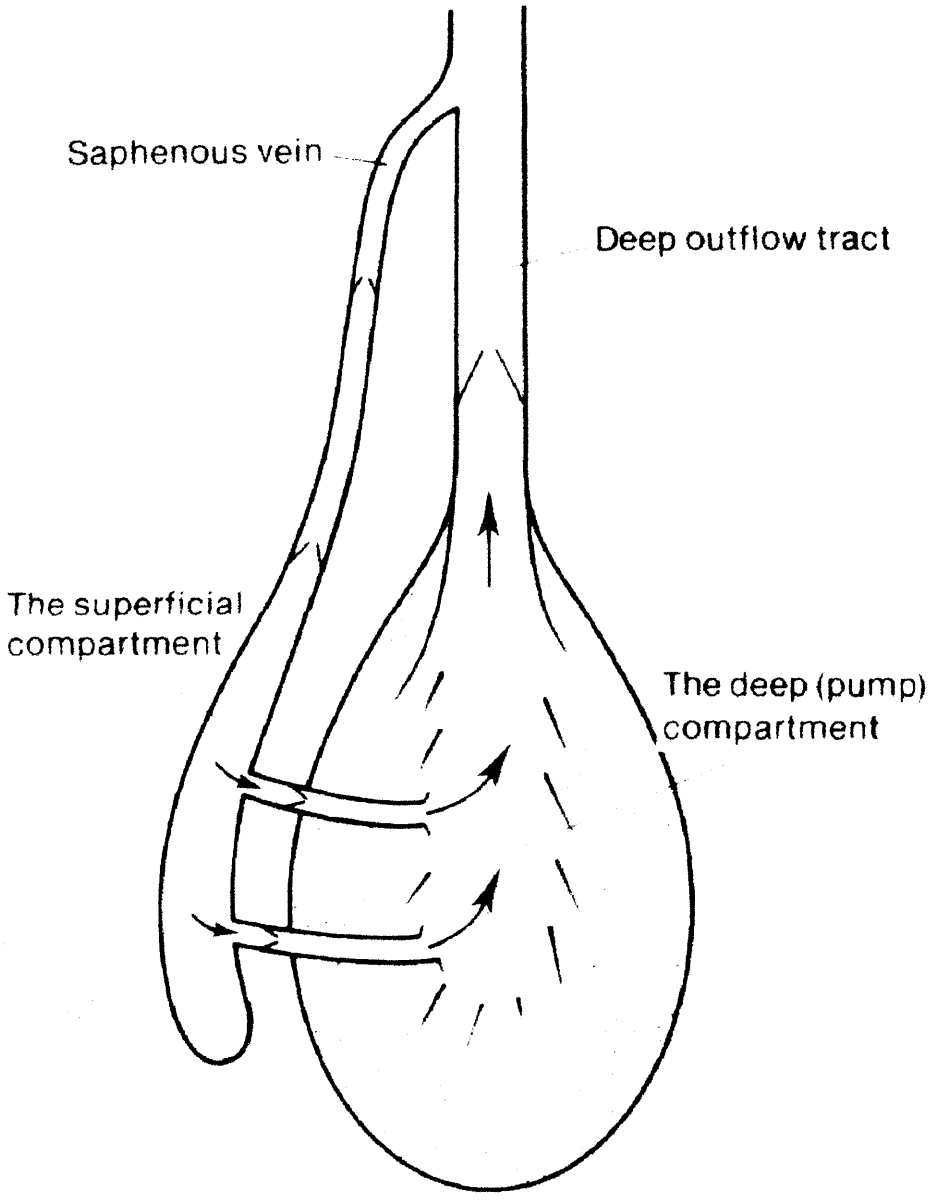
The superficial veins comprise the long and the short saphenous veins (saphenous = visible, Greek), together with their numerous tributaries. These drain into the deep

system through the sapheno-femoral and sapheno-popliteal junctions. In addition the tributaries may drain directly into the deep system via perforating veins. These are usually described eponymously according to their site; Dodd's perforators are located in the thigh, Boyd's just below the knee, Cockett's in the calf and May's posterior to the medial malleolus.

The deep system below the knee comprises the soleal sinuses and gastrocnemius veins within the muscles, and the posterior tibial, anterior tibial and peroneal veins between the muscles. These all drain, together with the short saphenous vein into the popliteal vein which becomes the superficial femoral vein as it enters the deep compartment of the thigh.

The superficial veins act as a venous reservoir which collects blood from the skin and dermal plexus of veins and drains into the deep system. Bicuspid valves in the veins ensure blood flows into the deep compartment and thence proximally towards the heart. Figure 3.1 shows diagramatically this system of venous drainage. It can be seen that as the calf muscles contract, blood will be forced from the deep chamber proximally into the popliteal vein towards the heart. Venous valves will prevent retrograde flow via the perforators. On relaxing the calf muscles, the pressure in the deep chamber will fall allowing blood to flow in again from the superficial system. This mechanism is known as the 'calf muscle pump'. The venous calf muscle pump should maintain venous outflow equal to the arterial inflow during exercise, without undue dilatation and with low pressure of the veins of the leg (Arnoldi,1964).

Figure 3.1 The Venous Calf Muscle Pump



The venous calf muscle pump, arrows indicate the direction of normal blood flow.

(Browse and Burnand,1988)

3.3 The aetiology of varicose veins

The most effective way of treating any disorder is to direct therapy toward the primary abnormality. Unfortunately in Medicine so often the primary abnormality is either unknown or untreatable, and so we treat the consequences of the disease process as they arise. Varicose veins and venous ulceration fall into this category and thus the mainstays of treatment are the removal of superficial veins which have become varicose and the interruption of sites where deep to superficial incompetence is found. Nevertheless in order to improve treatment the pursuit of the aetiology of varicose veins must continue.

Several theories have been postulated to explain the aetiology of varicose veins. The theories of descending valvular incompetence and the theory of congenital vein wall weakness are the two most accepted theories, however arterio-venous communication and turbulance have also been speculated to be the underlying factors responsible.

Arterio-venous fistula theory

This was suggested in 1938 by Holling (Holling *et al.* 1938) and also by Piulachs and Vidal-Barraquer in 1953 (Piulachs and Vidal-Barraquer, 1953) as a pathological mechanism for the development of varicose veins. Evidence in support of this theory is that the femoral vein in patients with varicose veins or ulceration contains blood with higher oxygen content than normal controls (Scott *et al.* 1990; Fontaine,1957; Blumoff and Johnson, 1977; Blalock,1929), indeed it had been noted almost 100 years previously that blood from varicose veins was sometimes as red as that from arteries (Pigeaux,1843). An arterial injection of contrast medium appears in the venous circulation much quicker in patients with venous disease than normals, suggesting arterio-venous shunting in those patients with varicose veins (Haimovici,1976; Haimovici *et al.* 1966; Vogler,1954). In addition many patients with arteriovenous fistulae, either congenital or acquired, develop varicose veins in the vein that drains the

fistula. The Klippel-Trenauney syndrome is an example of the association between congenital arterio-venous fistula and varicose veins. Ryan and Copeman (Ryan and Copeman, 1970) pointed out that arterio-venous shunting may be the result rather than the cause of venous disease; they suggested that prolonged venous hypertension opened up the normal arterio-venous connections in the leg which are normally responsible for temperature regulation.

This theory was examined critically by Partsch and his colleagues (Löfferer *et al.* 1969; Lindemayr *et al.* 1972) who used radiolabelled albumin macroaggregates to quantify arterio-venous shunting in normal limbs and those with venous ulceration Instead of increased shunting they demonstrated trapping of the aggregates in the limbs with ulceration. Since then the theory of arterio-venous shunting has found few proponents, the only recent paper supporting this hypothesis is the work of Schalin (Schalin,1989).

Theory of turbulance

Fegan and colleagues (Fegan and Kline, 1972) have performed several studies examining flow in the long saphenous vein of patients with varicose veins and postulated that turbulant blood flow in the vein is a principle cause of varicose vein formation. Turbulance was measured using a modified audiofrequency turbulance detector and demonstrated to be occuring at the same time as retrograde blood flow. Those areas of the vein where turbulance was detected were subsequently shown to exhibit histological varicose changes. Turbulance alone however was not found to be associated with the symptoms of venous disease or the skin sequelae of calf pump failure. They concluded that turbulant blood flow caused varicose changes in the long saphenous vein but that incompetent perforating veins were responsible for calf pump failure and thus the syptoms and signs of venous insufficiency. In my opinion it is not possible to determine from these studies whether turbulance causes varicose veins or vice-versa. It seems much more likely that turbulance is secondary to the vein becoming tortuous and dilated

as part of the varicose process. No other workers to my knowledge have suggested that turbulance is a cause of varicose veins.

Theory of progressive valvular incompetence

This theory states that as the uppermost valves in the leg fail, so the next set of valves are exposed to increased pressure, leading to their failure. The process continues down the leg, usually in the distribution of the long saphenous vein (Ludbrook,1963; Ludbrook,1966). Several studies supported this theory by demonstrating iliofemoral incompetence in the contralateral limb of patients with unilateral varicose veins and in family members of a patient with varicose veins (Reagan and Folse, 1971; Folse,1970). Ludbrook (Ludbrook and Beale, 1962) used femoral vein pressure measurements to examine the ilio-femoral venous segment, demonstrating that all patients with varicose veins had an incompetent ilio-femoral segment. This compared to 75% of normal control limbs having iliofemoral incompetence. He concluding that this increase in the incidence of ilio-femoral reflux was the underlying causal factor in the development of varicosis. There are a small group of patients with congenital aplasia of the venous valves, if this theory of valvular incompetence causing varicose veins then this is a most interesting group of patients since they represent the most severe end of this spectrum of inherited valvular hypoplasia. Bollinger (Bollinger,1971) studied 19 cases, the majority of these patients presented with swollen legs and venous ulcers. The condition (congenital valvular aplasia) has been demonstrated to be hereditary by Lindval and Lodin (Lindval and Nodin, 1961) and also by Plate et al. (Plate *et al.* 1983) who studied three generations, postulating that the inheritance was autosomal dominant.

Vein wall defect hypothesis.

The theory of descending valvular incompetence however does not explain a number of observations (Rose and Ahmed, 1986);

1. The long saphenous vein often becomes varicose in small sections separated by areas with normal valves. Lateral "blow outs" do not always occur below an incompetent valve.

2. Normal veins do not become varicose when subjected to increased pressure, such as when they are used as an arterial conduit even if all the valves are rendered incompetent.

3. The varicose veins of pregnancy often disappear after parturition.

4. Quite large varicose veins can develop without being connected to either an incompetent perforator or long saphenous trunk.

A recent study (Abu-Own *et al.* 1994) of 190 limbs with long saphenous reflux found that 63 of these limbs had a competent saphenofemoral junction and of those only 5 were found to have an incompetent perforator (although it may be difficult to be certain that duplex scanning has excluded any incompetent perforating veins).

The "vein wall defect" theory was advanced to explain these findings. This theory is based on the hypothesis that there is an underlying (congenital) defect in the vein wall of patients prone to develop varicose veins. This weakness allows abnormal venous distension at normal pressures, rendering the valves incompetent since the valve cusps will no longer be apposable.

Studies of the valve cusps from patients with primary (non-thrombotic) varicose veins supports this contention. Edwards and Edwards (Edwards and Edwards 1940) studied 59 normal valves and 106 valves from patients with varicose veins. Leu and coworkers

(Leu *et al.* 1979) also came to this same conclusion. They demonstrated that the valves in the varicose group were normally formed but had become dilated and baggy.

Zsotér *et al.* investigated venous distensibility of sections of long saphenous vein taken from limbs with varicose veins and from control patients without varicose veins. Sections of varicose vein and also macroscopically normal vein from the "varicose" limbs were studied. Veins were mounted in an organ bath bathed in a physiological salt solution and distended by infusion of a salt solution under pressure (measured by connection to a pressure transducer). They found that both the varicose sections and the "macroscopically normal" veins were more distensible than the veins from control patients (Zsotér *et al.* 1967). Since it is believed that these sections of macroscopically normal vein would become varicose in time it is therefore reasonable to suppose that this increased distensibility is a causal factor in developing varicose veins.

Zsoter and Cronin (Zsotér and Cronin 1966) also looked at the distensibility of forearm veins (varicose veins do not affect the upper limb) in patients with varicose veins and normal controls. Sections of vein approximately 3cm in length without tributaries were isolated and cannulated with a 23 gauge needle. In the same manner as the previous experiment these sections of vein were distended with a physiological salt solution as the pressure was monitored. The sections of vein belonging to patients with varicose veins in the leg were more distensible than the control veins suggesting that the vein wall defect causing varicose veins is a generalised condition. Presumably the low venous pressure in the arm allows these veins to remain unaffected by varicose changes.

Clarke et al. (Clarke *et al.* 1989) looked at venous elasticity measured using a combination of venous pressure recording and strain gauge plethysmographic venous volume recording. They calculated venous elasticity from the equation; elasticity = stress/strain. Stress they defined as a change in venous pressure and strain a change in venous volume as measured by the strain gauge plethysmograph. In order to standardise their recordings of strain the venous pressure volume curve was measured at a point where a constant gradient had been reached and a straight line used to extrapolate the

curve back to read a volume for pressure = 0mmHg. Unfortunately the strain gauge plethysmograph already expresses volume change as a percentage of initial volume, therefore this calculation is flawed (for further explanation see below). Four groups of patients were studied; normal controls, patients with superficial varicose veins, patients with deep venous insufficiency, and patients deemed to be at high risk of developing varicose veins (determined by the presence of risk factors). Using this method the venous elasticity of all veins in the calf were studied. They were able to demonstrate an abnormality in venous elasticity in limbs with varicose veins compared to the controls, which confirmed a previous report from Eiriksson and Dahn (Eiriksson and Dahn 1968). Of greater interest however they also showed that a group of patients thought to be at high risk of developing varicose veins were shown to have a similar modulus of venous elasticity as those with either deep or superficial venous incompetence, which is different to the normal controls. This is good evidence that the precurser to varicose veins and venous incompetence is an abnormality in the vein wall affecting venous distensibility or elasticity.

Eiriksson also investigated venous distensibility of patients who had undergone removal of their superficial varices. These limbs still demonstrated abnormal distensibility, showing that the deep veins are similarly affected (Eiriksson,1968). The evidence from these studies is that varicose veins and deep venous incompetence is caused by a defect in venous elasticity which affects all veins. Only the veins in the leg become varicose since these are subjected to higher pressure than the veins in the arm.

Varicose changes in the deep veins are often noted at operation, particularly of the popliteal vein during short saphenous disconnection. Valvular incompetence in these veins is more difficult to correct surgically and is more likely to result in venous ulceration (O'Donnell,1991). Therapeutic manoeuvres should therefore be directed at improving vein wall function as early in the disease process as possible, thus preventing the dilatation that causes varicose veins and venous valvular incompetence.

3.4 Calf muscle pump failure

Failure of the calf muscle pump described above results in an increase in the venous pressure after exercise (ambulatory venous pressure) which is thought to be the central factor in the pathogenesis of venous ulceration. This pressure abnormality is simple to measure by cannulating a pedal vein. The resting pressure is in the region of 80 - 100 mmHg when the subject stands erect. On exercise the calf muscle pump reduces this pressure to 0 - 20mmHg and normally takes longer than 20 seconds to return to the resting pressure when exercise ceases, unless venous insufficiency is present.

It is helpful when considering calf muscle pump failure to draw comparisons with failure of the left ventricle (Browse and Burnand 1988).

a. Neuro/muscular weakness. This will cause pump failure just as ischaemic heart disease causes heart failure. The condition is self perpetuating because the changes of venous insufficiency in turn cause stiffening of the ankle joint and thus atrophy of the muscles.

b. Pump chamber contraction or dilatation. Deep venous thrombosis may cause either a decrease in the size of the pumping chamber or may block the outflow thus causing dilatation of the pumping chamber.

c. Communicating vein incompetence. This is analogous to mitral regurgitation; when the muscle pump is in systole, blood is able to regurgitate back into the venous reservoir (the superficial veins).

d. Outflow tract incompetence. This is akin to aortic incompetence; during diastole, blood regurgitates back into the pumping chamber which eventually dilates causing "congestive" pump failure.

e. Isolated superficial venous incompetence. Reflux in the superficial venous system is common in patients with varicose veins who often have no skin sequelae.

However the pumping mechanism may be overloaded just as in deep venous reflux, and may cause secondary perforating vein incompetence or "congestive" type pump failure.

A number of workers have demonstrated good correlation between ambulatory venous pressure and the incidence of venous ulceration, concluding that ambulatory venous hypertension was the key factor in the pathogenesis of ulceration (Arnoldi,1966; Ludbrook,1966; Nicolaides and Zukowski 1986; Pollack *et al.* 1949; Tyson and Goodlett 1945; Warren *et al.* 1949). Other workers have found substantial overlap in the ambulatory venous pressure recording between patients with normal skin and those with ulcers (Lewis *et al.* 1973; Hoare *et al.* 1982; Randhawa *et al.* 1984). This suggests the influence of one or more other factors causing ulceration. Raju et al. also measured the venous pressure rise that Valsalva manoeuvre produces and found that incorporating this measurement and the ambulatory venous pressure into a 'reflux index' gave a better indication of the risk of ulceration (Raju and Fredericks 1991).

The clinical state of venous disease seems to be more advanced (ie. there is a much higher chance of ulceration) in limbs which have deep venous reflux compared to those with superficial incompetence only (O'Donnell,1991). This is supported by the observation that venous pressure after exercise (AVP) is higher in limbs with popliteal reflux than in limbs with superficial venous incompetence (Shull *et al.* 1979).. A follow-up study of 111 limbs with proven deep venous thrombosis (Milne *et al.* 1994) established that the development of reflux was necessary to cause the "post-phlebitic syndrome" but that reflux could develop without necessarily causing symptoms, suggesting that other factor(s) are also involved.

3.5 Theories on the cause of venous ulceration.

Although consensus seems to have been reached that the haemodynamic effect of calf muscle pump failure is central to the pathogenesis of ulceration there is heated discussion regarding the final common pathway.

The two 'front runners' for this title are the fibrin cuff hypothesis (Browse and Burnand 1982) and the white cell trapping hypothesis (Thomas *et al.* 1988; Coleridge-Smith *et al.* 1988).

The fibrin cuff hypothesis

The fibrin cuff hypothesis is based on the idea that oxygen delivery from the capillaries is hindered in patients with lipodermatosclerosis by a peri-capillary cuff of fibrin.

This fibrin cuff had been observed histologically (Browse and Burnand 1982) and was thought to have leaked from the capillaries as fibrinogen, along with other plasma proteins due to the excessive intracapillary pressure. The fibrinogen polymerised as fibrin causing the classical signs of lipodermatosclerosis. In a dog model of venous hypertension it was also possible to demonstrate the appearance of peri-capillary fibrin cuffs and decrease in fibrinolytic activity by creating an arteriovenous fistula in the leg (Leach,1984). Persistence of this fibrin cuff was explained by reduced fibrinolytic activity in the blood and vein wall of patients with venous disease (Browse *et al.* 1977; Hach *et al.* 1986). Clearance of radio-labelled fibrin has been shown to be reduced in limbs with lipodermatosclerosis (Leach and Browse 1986). The blood levels of fibrinogen and fibrin antigens are also raised in patients with venous disease (Falanga *et al.* 1991).

The transcutaneous partial pressure of oxygen has been shown to be reduced in the legs of limbs with venous disease compared to normals (Clyne *et al.* 1985; Stacey *et al.* 1987; Falanga *et al.* 1991), thus supporting the concept of reduced tissue oxygenation causing ulceration. The TcPO2 however does not predict the rate of healing as one might expect if a decrease in TcPO2 was directly responsible for ulceration (Nemeth *et al.* 1989). In addition, using direct needle electrodes to measure oxygen tension Schmeller *et al.*. (Schmeller *et al.* 1992). found only a modest reduction in oxygen tension in limbs with lipodermatosclerosis.

There has been some criticism of these studies of TcPO2; the measurements of TcPO2 were taken with the transducer at 40°C, Dodd et al. have repeated this experiment with the transducer at 37°C and found that the TcPO2 values were higher in the legs with venous disease than the normal controls (Dodd *et al.* 1985). They conclude that there may be a failure of capillary dilatation with increase in temperature in the limbs with venous disease which would explain these paradoxical results. Coleridge-Smith *et al.* have shown no abnormality in the clearance of xenon, a molecule larger than oxygen, by the skin microcirculation (Coleridge-Smith *et al.* 1991). Since Xenon is a larger molecule than oxygen they argue that this suggests the lack of any diffusion barrier to oxygen in these limbs, thus contradicting the fibrin cuff diffusion barrier hypothesis.

The fibrin cuffs persist during treatment of venous ulceration and are still present when the ulcer has healed (Falanga *et al.* 1992), from which it is concluded that they may not be the final pathway directly responsible for ulceration. Michel (Michel 1990) has used the Krogh-Erlang equation to consider oxygen diffusion from capillary blood to the surrounding tissue. He concluded that oedema is unlikely to significantly affect oxygen delivery and that fibrin cuffs would have to be composed of >50% fibrin to present a significant diffusion block.

The white cell trapping hypothesis

The white cell trapping hypothesis was advanced to explain the finding that limbs with venous disease appear to "trap" white blood cells when dependent for a period of 40 minutes. Moyes *et al.* and Thomas *et al.* have both shown that blood samples taken from the long saphenous vein in limbs with venous disease show an increase in red cell count when the limbs are dependent but that the white cell count does not increase. Samples taken when the legs are again supine show a "wash out" effect as the white cell count increases. Legs with venous disease "trapped" 30% of white cells and normals "trapped" 7% (Moyses *et al.* 1987; Thomas *et al.* 1991; Thomas *et al.* 1988). Skin biopsies of

limbs with venous ulcers or lipodermatosclerosis show an increase in the number of white cells, suggesting that these play a part in mechanism of venous ulceration (Scott *et al.* 1991). Plasma elastase, a marker of neutrophil degranulation, is elevated in limbs with venous disease compared with normal controls (Shields *et al.* 1994). Elevating venous pressure for 30 minutes in healthy controls causes neutrophil degranulation and increased expression of adhesion molecules responsible for neutrophil adhesion (Shields *et al.* 1994).

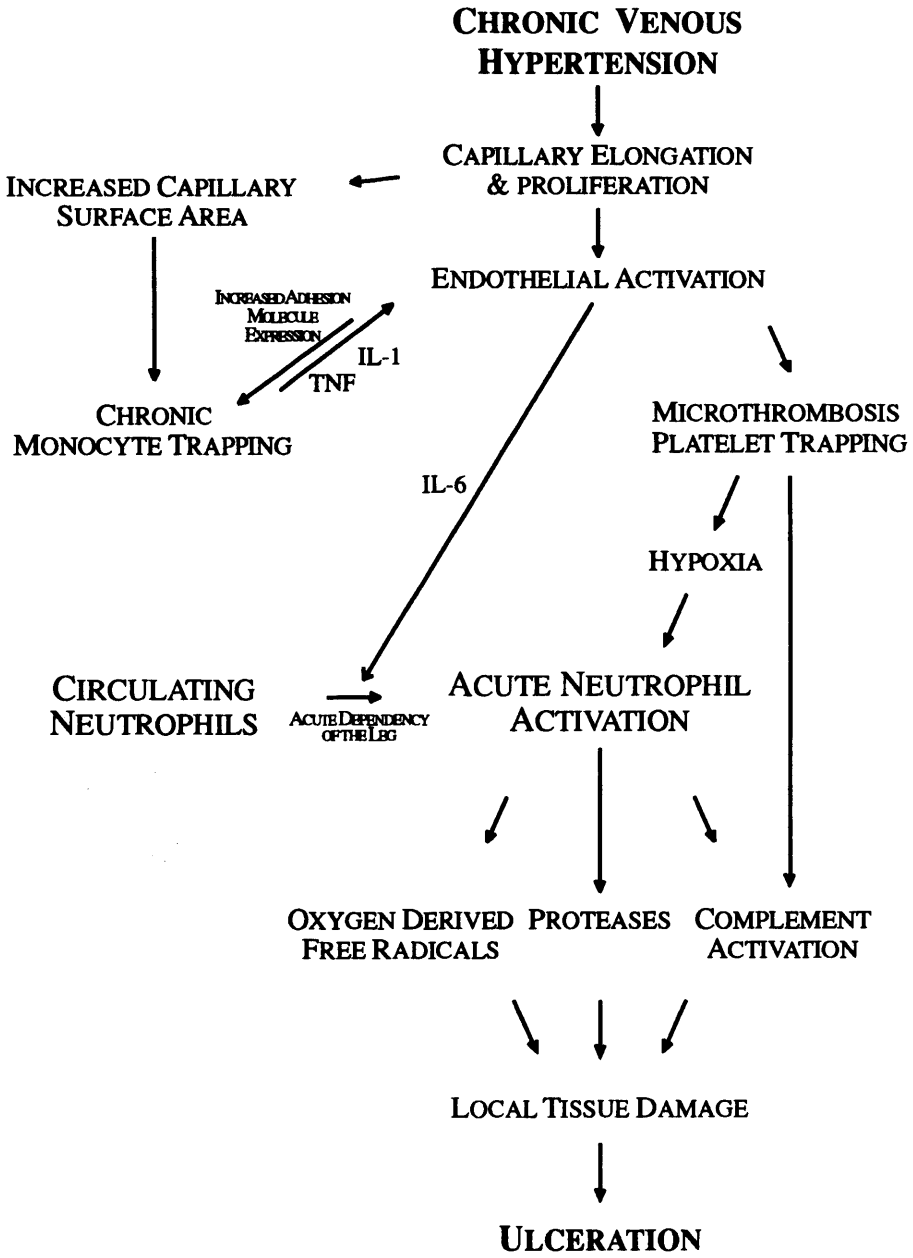
The skin microcirculation has been studied by a number of groups. Coleridge-Smith *et al.* (Coleridge-Smith *et al.* 1988) showed a decrease in the number of functioning capillary loops after dependency in limbs with chronic venous insufficiency, this is thought, by those who support this hypothesis, to be where the white blood cells are "trapped". Belcaro *et al.* (Belcaro *et al.* 1988) used a laser-Doppler to look at capillary blood flow in the skin of limbs with chronic venous insufficiency; they were able to show that at rest the blood flow was increased compared to normals but that as the limb was left dependent the veno-arteriolar reflex which normally reduces blood flow by constricting arterioles was defective. It is difficult to reconcile this finding with the results demonstrating a reduction in the number of functional capillary loops.

White cell trapping and activation could produce many of the changes seen in limbs with lipodermatosclerosis and ulceration. Inflammatory mediators may be released causing increased permeability of endothelial cells and the production of tissue plasminogen activator may be reduced through the effect of Interleukin-1 on plasminogen activator inhibitor-1. The neutrophils in patients with chronic venous disease have been shown to inappropriately produce more oxygen derived free radicals (Whiston *et al.* 1994). Bradbury *et al.* (Bradbury *et al.* 1993) have reviewed these studies and produced a diagram (see Figure 3.2) which summarises a number of hypotheses regarding the final pathway of venous ulceration.

Although the issue is not resolved these theories have sparked some new therapeutic ideas. The steroid drug Stanozolol has been used as an adjunct to compression hosiery in

the treatment of venous ulceration and lipodermatosclerosis with some benefit, thought to be due to it's fibrinolytic enhancement (Burnand *et al.* 1980). Pentoxyphylline, which antagonises the effects of Tumour Necrosis Factor and IL-1 on polymorphonuclear neutrophils thus reducing their adhesiveness and activation, has also been used to help venous ulcer healing. In a randomised study of 80 patients with venous ulcers, Colgan (Colgan *et al.* 1990) demonstrated healing over a 6 month period in 64% of the group treated with pentoxyphylline compared with 34% of a control group. Both groups received compression bandaging in addition. This increase in healing was statistically significant ($p = 0.03$).

Figure 3.2 Venous hypertension and ulceration (Bradbury *et al.* 1993)



CHAPTER FOUR

TREATMENT OF VENOUS DISEASE

The sequelae of venous disease are caused by failure of the calf muscle pump to reduce venous pressure adequately during exercise. Therapy may be directed towards improving any aspect of this pathological pathway, from the varicose dilatation that causes valvular incompetence through to the manipulation of the microcirculation and cellular events that are thought to cause ulceration.

4.1 General measures

Preliminary advice to patients with venous disease usually includes, losing weight, taking more exercise, avoiding standing still and elevating the legs wenever possible. These simple measures will improve symptoms and reduce the chances of developing the sequelae of venous disease.

a. Lose weight. Obesity contributes to the development of venous ulceration (Ryan,1983). It has also been found in both the Shangai study (Sun,1990) and the framingham study (Brand *et al.* 1988) to be a risk factor for the development of varicose veins and therefore it is sensible to lose weight if there is any evidence of venous disease.

b. Take more exercise. In addition to the effect on obesity that this will have, exercise will improve muscle tone and therefore make the calf muscle pump more effective. The Framingham study (Ryan,1983) found that patients who take little exercise were more likely to develop varicose veins.

c. Do not stand still. Patients who have a standing occupation often complain that their symptoms are exacerbated by their work. This is not surprising when one considers the mechanism of the (normal) calf muscle pump which reduces venous pressure from 80-

100 mmHg when standing still to 0-20 mmHg after ten tiptoe exercises. Even a subject with normal calf pump function will experience symptoms if made to stand still. Lake *et al.* (Lake *et al.* 1942) found a standing occupation to be a risk factor in the development of varicose veins.

d. Elevate foot of the bed. Since elevated venous pressure has been implicated in the development of the sequelae of venous disease any opportunity to lower it should reduce the risk of skin changes and ulceration. Almost one third of each day is spent in bed, therefore the simple measure of elevating the foot of the bed will improve the venous drainage for this period of time. This is especially important to those patients who have developed ulceration. Elevation has been shown using laser-Doppler to increase skin blood flow which may be beneficial (Abu-Own *et al.* 1994).

4.2 Compression therapy.

History of compression treatment.

Celsus in AD25 described the use of compression plasters and linen bandages in the treatment of venous ulceration (Celsus,1756). As mentioned previously, the use of compression bandaging was seen extensively throughout historical records. The reasoning behind it's use however was erroneous until the venous circulation was described. Until that time compression bandaging was thought to expel evil humours. In 1676 Richard Wiseman introduced his leather laced stocking (Wiseman,1676). This was the forerunner of todays elastic compression stocking. The lacing could be adjusted to give the required compression at each level (see Figure 4.1). In 1891 the concept of elastic compression was introduced by Martin. He wrote a letter to the British Medical Journal describing the use of Indiarubber bandages for the treatment of leg ulcers (Martin,1878). At about this time Unna (Unna,1896), a German dermatologist was using rigid paste dressings; the "Unna boot". Dickson-Wright used an adhesive elastic

bandage in 1930 (Dickson-Wright,1930), the familiar elastic webbing bandages were introduced in 1948 by Bisgaard (Bisgaard,1948).

Scientific principles and the invention of graduated compression.

It is logical to assume that the sequelae of venous insufficiency are due to the elevated transmural pressure across the vein wall. Ideally this should be treated by reducing the intraluminal pressure (by abolishing reflux and rendering the calf muscle pump more effective). If this is not possible, then increasing the extraluminal pressure will also reduce the transmural pressure. Elastic compression is thought to act in this way (although there are also studies which demonstrate a reduction in the intraluminal pressure when elastic compression is used (Browse and Burnand 1988). Modern compression stockings exert a greater pressure at the ankle than at the knee. This concept was introduced by the engineer Conrad Jobst (Bergan,1985) who invented graduated compression stockings to treat his own venous ulcers. His clinical notes written by Dr Laurence Fallis (Chief of Surgery) state on Feb 15 1949 "Legs in good condition. Patient has invented elastic stocking. Nylon rubber, which is an improvement on existing appliance. It applies uniform and graded pressure from below up." the next year the clinical record states "Mr Jobst has been wearing a special elastic stocking for a period of a year now. There is remarkable improvement in the legs. The induration and thickening of the tissues has practically disappeared. Even the veins seem to have regressed." The idea is said to have come to him whilst bathing in a swimming pool. Jobst often swam since the pressure of the water on his legs gave him great relief. His idea was to produce a stocking which would provide the same external compression as the water in the swimming pool. He reasoned that the water was providing a counteractive hydrostatic pressure to the venous pressure within the leg. Since this decreases from below upwards the stockings were designed to also apply graduated compression. Stemmer has also more recently calculated the ideal external compression force that should be applied based on the premise that the external compression should

match the increase in intraluminal pressure which calf pump failure has produced (Stemmer *et al.* 1980). Todays modern elastic stockings are ready made graduated compression garments. Usually a compression of 30 - 40 mmHg at the ankle is sufficient although pressures up to 50mmHg have been shown to be acceptable (Chant *et al.* 1985).

Studies on the use of compression.

It is unclear whether compression stockings act by improving the calf muscle pump, by improving the microcirculation, or by reducing exudate and stimulating fibrinolysis. There is evidence to support each of these concepts.

a. Graduated compression stockings provide symptomatic relief.

Compression stockings may be used for the relief of symptoms such as aching when due to varicose veins. Browse and Burnand (Browse and Burnand 1988) have described this as a diagnostic test. Relief of the discomfort is good evidence that it is of venous origin. Chant et al. (Chant *et al.* 1985) have provided patients on a varicose veins waiting list with compression stockings and demonstrated that in addition to the stockings being acceptable a large number of the patients felt the improvement sufficient that they withdrew from the surgical waiting list.

b. Graduated compression stockings improve calf muscle pump activity.

Several workers (Gjores and Thulesius 1977; Jones *et al.* 1980; Partsch,1984) have investigated the effect of graduated compression on calf pump activity using water bath plethysmography. They were able to show that the use of compression improved the volume of blood expelled from the foot during knee-bend exercises. Jones *et al.* in addition demonstrated that the greater the degree of compression applied, the greater was this effect. More recently using gamma scintigraphy the resting blood volume has been shown to be reduced by wearing compression stockings (Sparrow *et al.* 1995)

The new method of air-plethysmography holds promise for the evaluation of different types of compression stocking since the stocking may be worn underneath the plethysmograph. Christopoulos has shown using air-plethysmography an improvement in the fraction of blood ejected from the calf and a decrease in the amount of venous reflux when a compression stocking is worn (Christopoulos *et al.* 1987).

The photoplethysmograph has been used by Evander et al. (Evander *et al.* 1984) to investigate the effect of compression hosiery; they demonstrated an improvement (prolongation) of the venous refilling time, showing that the stockings reduce venous reflux in addition to their beneficial effects on the calf pumping mechanism.

Somerville *et al.* (Somerville *et al.* 1974) measured ambulatory venous pressure in 12 patients with varicose veins. A clear improvement in ambulatory venous pressure was demonstrated when the stockings were used. This improvement correlated with the improvement in patients symptoms. When the stockings were discarded the ambulatory venous pressure returned to the pre-treated level. Horner *et al.* (Horner *et al.* 1980) compared graduated and non-graduated compression. They demonstrated that only the graduated stockings were able to reduce ambulatory venous pressure, the greater the graduation the greater the fall in ambulatory venous pressure. Christopoulos *et al.* (Christopoulos *et al.* 1991) demonstrated a decrease in venous reflux (measured by air-plethysmography) and an improvement in ambulatory venous pressure after a period of one month wearing compression stockings. Mayberry *et al.* (Mayberry *et al.* 1991) however, were unable to demonstrate any improvement in calf pump haemodynamics when graduated compression stockings were used, concluding that the beneficial effects of these stockings must be mediated through another mechanism. Consensus seems to be that compression stockings potentiate the efficacy of the venous calf muscle pump and that graduated compression has a greater effect than non-graduated. Whether this is mediated by reducing venous diameter, thus allowing incompetent dilated valves to coapt correctly has not been resolved. A recent paper by Sarin *et al.* (Sarin *et al.* 1992) addresses this question using duplex scanning through a water filled variable pressure

cuff. As the pressure in the cuff was increased 26% of the veins examined became competent at a pressure lower than that required to occlude the veins. They concluded that this shows that compression stockings act by allowing valve cusp apposition in dilated, incompetent valves. The number of veins which became competent at a pressure of 40mmHg at the knee was only 5 of 57 (9%). Most compression stockings prescribed for venous insufficiency have a pressure at the ankle of 30-40 mmHg which decreases towards the knee. In my opinion this study demonstrates that compression stockings do not restore valvular competence to dilated valves.

c. graduated compression may improve the microcirculation and stimulate fibrinolysis.

Burnand, as part of a controlled trial investigating the effect of the drug stanazolol, has demonstrated a decrease in lipodermatosclerosis when adequate compression is used (Burnand *et al.* 1980). There was a further improvement when the fibrinolytic drug was also used. He suggests that it is possible that compression stockings improve the release of fibrinolytic activator from the venous endothelium (Browse and Burnand 1988), however Berridge *et al.* were unable to demonstrate any improvement in fibrinolytic activity in 17 subjects with lipodermatosclerosis when stockings exerting 30-40mmHg pressure at the ankle were used (Berridge *et al.* 1989).

Using a laser-doppler flowmeter Belcaro (Belcaro *et al.* 1988) has examined the capillary microcirculation in patients with venous insufficiency. The responses of the microcirculation were improved following a period of one month wearing compression stockings. The veno-arteriolar reflex was restored which is usually lost in limbs with chronic venous hypertension.

4.3 Sclerotherapy

Injection sclerotherapy was first used to treat varicose veins in 1853 when Chassaignac (Chassaignac, 1855) injected ferric chloride into varicose veins. It was in 1967 however

that the technique was carefully described and popularised by Fegan (Fegan, 1967), whose name has become synonymous with the procedure. The technique has subsequently been shown to have a high recurrence rate when reflux is present in the saphenous systems (Hobbs,1974. Jakobsen,1979). The technique can also result in skin ulceration if the sclerosant is injected outside the vein lumen. For these reasons injection sclerotherapy has become less popular in recent years. A few centres however have modified the injection technique by using duplex scanning to guide injection, including sclerotherapy of the saphenofemoral junction. An improved recurrence rate comparable with some surgical series is claimed (Kanter and Thibault, 1996) using this method.

4.4 Surgery.

Babcock, in 1907 is quoted as saying "..as for the veins of the leg, the area involved is so extensive, the anastomoses so free, and the other factors so prejudicial that the problem of surgical treatment is a more difficult one, and the passing years have left a trail of obsolete operations." (Bergan,1991).

Surgical treatment of venous disease may be divided into superficial venous surgery (long and short saphenous), surgery to the perforating veins and deep venous surgery.

Surgery of the superficial veins

a. Superficial venous surgery owes a great deal to Trendelenberg who, in 1891, described ligation of the long saphenous vein in the thigh to treat long saphenous vein incompetence (Trendelenberg,1891). This procedure however was attended by an unacceptably high recurrence rate (Bier *et al.* 1917). To improve these results Homans (Homans,1917) advocated that the long saphenous vein should be ligated flush with the femoral vein and combined with excision of the distal varices. Keller, in 1905 (Keller,1905) introduced stripping of the long saphenous vein using a flexible

intraluminal stripper. This was followed by the introduction by Mayo (Mayo,1906) of the extraluminal stripper (since abandoned) and by Babcock (Babcock,1907) of the familiar stiff intraluminal stripper with acorn shaped tip.

Of patients presenting with varicose veins approximately 85% of them have long saphenous system varices (Mitchell and Darke 1987) and between 12% (Thibault *et al.* 1990) and 15% (Almgren and Eriksson 1990) have short saphenous system incompetence. Compression sclerotherapy has an unacceptably high recurrence rate in the presence of reflux (63% at 3 years (Hobbs,1974) and 93% at 6 years (Jakobsen,1979)) and therefore long saphenous surgery is carried out in the majority that require treatment.

In both the long and the short saphenous systems the surgeon is faced with a choice of whether to strip the vein out or merely to ligate and divide the connection with the deep system. The argument over long saphenous stripping persists. Several papers testify that saphenofemoral ligation without stripping is an incomplete operation which gives an unacceptably high recurrence rate (Munn *et al.* 1981; Myers,1957; Jakobsen,1979; Darke and Penfold 1992). They state that the more extensively an incompetent venous system is removed, the lower is the recurrence rate. In addition the long saphenous vein has been found to be present in 73% (Bradbury *et al.* 1994) and 74% (Khaira *et al.* 1996) of limbs with recurrent varicose veins. Large (Large,1985) has found however that routine stripping does little to improve the results of saphenofemoral disconnection and avulsions. This is supported by the work of Hammarsten et al. (Hammarsten *et al.* 1990) who found that saphenofemoral disconnection with selective perforator ligation gave similar clinical and haemodynamic results when compared to long saphenous stripping. Using duplex scanning they were also able to demonstrate that the saphenous vein in the thigh which remains when saphenofemoral disconnection is carried out is suitable for use as an arterial bypass conduit 5 years later, similar findings are also reported by Fligelstone et al. (Fligelstone *et al.* 1995). This is countered by a randomised trial of 89 limbs which demonstrated improved PPG refill times, less

recurrence and improved patient satisfaction in the group randomised to long saphenous stripping in addition to saphenofemoral disconnection and avulsions (Sarin S *et al.* 1994). This opinion is reinforced by Bergan in two recent reviews (Bergan 1996, Bergan 1996)

It seems sensible to strike a balance. In those patients who would prefer a quicker operation, more suited to day case surgery, with a quicker recovery and who may require arterial grafting in the near future (ie. elderly patients) it is worthwhile performing saphenofemoral disconnection in selected patients. Those younger patients who have (potentially) much more time in which to develop a recurrence of their venous disease may be better served by stripping the long saphenous vein (at least to just below the knee). The critical question if one employs a selective policy towards saphenofemoral disconnection is whether there is incompetence in the thigh (Hunterian) perforating vein. Clinical selection has been shown by McMullin at al. (McMullin *et al.* 1991) to be inadequate at making this selection; many cases treated by saphenofemoral disconnection having residual long saphenous reflux detected on duplex postoperatively. It is possible that duplex scanning or ambulatory venous pressure testing preoperatively would select cases more effectively.

One technique, practised mainly in France is an ambulatory conservative approach based entirely on precise Duplex mapping of venous incompetence. The technique, introduced by Franceschi (French acronym;*CHIVA*) involves ligation of incompetent sections of the superficial veins (mapped with Duplex) through tiny stab incisions (Zamboni *et al.* 1995). The procedure may be performed under local anaesthesia and also has the attraction of preserving potentially useful saphenous vein, should it be needed for future bypass surgery. The Duplex maps produced in planning this surgery should convince proponents of the theory of descending valvular incompetence that the varicose process is a progresive weakening vein wall, causing incompetence secondarily. This however begs the question whether the technique is likely to fail in the longer term as the veins left behind dilate and become incompetent (as has been demonstrated after saphenofemoral

ligation). A major disadvantage with the technique is that the Duplex maps are time consuming (therefore expensive) to produce which limits it's potential in the U.K health care system.

Sporadic reports of external venous valvuloplasty of the saphenofemoral junction (Corcos *et al.* 1992; Zamboni and Liboni 1991; Corcos *et al.* 1989) may also be found although the technique has not found widespread acceptance. One study compares this technique of external valvuloplasty using a dacron band with saphenofemoral ligation. Both techniques were effective in controlling varices in the short term. 12 of the 15 were patent and competent, one was incompetent and the remaining 3 occluded. In 16 limbs undergoing Saphenofemoral ligation 1 demonstrated reverse flow in the LSV after the operation (Schanzer and Skladany 1994).

Surgery of the perforating veins.

The names of Cockett and Linton have both become eponymously linked with operations designed to correct perforating vein incompetence.

Cockett (Cockett,1955) described the ligation of enlarged incompetent perforating veins superficial to the deep layer of investing fascia through a posterior longitudinal incision. He published a series of 201 limbs treated by this operation. Over two-thirds of the limbs had evidence of perforating vein incompetence and no limb treated by the Cockett's operation had recurrence of ulceration over a short term follow-up.

Dodd published in 1957 (Dodd *et al.* 1957) a series of 174 limbs treated by ligation of incompetent perforating veins at the ankle. He initially treated limbs by extrafascial ligation but became convinced of the advantages of subfascial ligation. Of 96 patients treated by subfascial ligation and followed for 2 years or more 90% had a "satisfactory" result ("satisfactory" = no recurrence of the ulcer).

Linton's operation (Linton,1938) of subfascial ligation of medial communicating veins in the calf is easier to perform since the extrafascial tissue is very fibrotic and is also interlaced with a network of dilated veins which bleed easily in the limbs upon which this operation is thought to be indicated.

The importance of perforating vein ligation is questioned by some: Åkesson and Plate (Åkesson *et al.* 1990) have examined the haemodynamic effect of ligating incompetent communicating veins, using foot volumetry and ambulatory venous pressure assessment. They found that this operation produced no haemodynamic benefit, in contrast to stripping the long saphenous vein which reduced venous reflux and ambulatory venous hypertension. This finding is supported by Stacey (Stacey *et al.* 1988) who showed that perforator surgery does not normalise venous function tests. Bradbury *et al.* have shown that the presence of popliteal venous reflux is strongly associated with ulcer recurrence after thorough superficial venous surgery including perforator ligation (Bradbury *et al.* 1993; Bradbury *et al.* 1993). Darke and Penfold (Darke and Penfold 1992) showed healing rates of 90% of ulcers in patients with both perforator and long saphenous reflux treated by saphenofemoral ligation alone. To date there has been no clinical trial of perforator surgery.

Perforator ligation has recently become less invasive with the development of subfascial endoscopic perforator ligation originally described by Hauer (Hauer,1985) and popularised by Fischer (Fischer *et al.* 1993). This technique employs a small scope, originally a modified proctoscope but now a dedicated instrument, which is introduced through a relatively small incision in the upper calf. Using this scope the subfascial space is explored and perforators clipped as they are seen and divided. Some early reports have been encouraging (Jugenheimer and Junginger 1992) and certainly the technique has been received with considerable interest as shown by several recent publications describing minor modifications to the original technique (Kok *et al.* 1997, Paraskeva *et al.* 1996, Phillips and Fleischl 1996). It will be possible, using this technique to answer the question of the clinical and haemodynamic significance of the

perforating veins without the compounding problem of the extensive dissection and wound of the Linton or Cockett procedure.

Surgery of the deep veins.

Surgery to the deep veins of the leg may be divided into two further groups; those performed when a valve is still present and those performed when the valve is absent (either congenitally or as a result of thrombosis).

When the valve is still present (primary valvular incompetence) the mechanism of valve failure is due to laxity and failure of apposition of the valve cusps, therefore surgery should be directed towards tightening the valve cusps and allowing them to appose normally. The first successful repair of incompetent valves was performed by Kistner in 1968 (Kistner,1978). The technique he used was to open the vein through the valve commissure and valvuloplasty accomplished by suture placement at the valve commissures (Figure 4.2). This technique has since been modified by Raju (Figure 4.3) (Raju, 1985) and by Sottiurrai (Figure 4.4) (Sottiurai,1988). Table 4.1 shown below summarises the results achieved with these techniques of internal venous valvuloplasty.

These four series show that between 63 and 80% of patients remained free of ulceration during 4 year follow-up and that 30% of these patients were able to discard elastic compression stockings. It should be remembered however that these are the results of enthusiasts for these techniques. In addition many of these patients also underwent superficial or perforator ligation preventing a truly objective analysis of the results.

Table 4.1 The results of internal venous valvuloplasty

	Raju	Sottiurai	Eriksson	Kistner
No. performed	61	29	12	32
Good results	63%	76%	67%	80%
Mean follow-up (months)	24	56	36	72

Two external techniques of valvuloplasty have recently been developed. The first involves placing a series of sutures along the decussating margin of the valve insertion, the first at the valve commissure and subsequent sutures placed more distally (Figure 4.5) (Kistner,1991). The second technique involves placing a silastic cuff around the vein thus reducing the luminal size and allowing the valve cusps to appose (Jessup and Lane 1988). The results of external valvuloplasty have yet to be reported. The angioscope has also been used to guide external venous valvuloplasty, although easier to use to plicate the long saphenous vein it has been used to perform this task to the superficial femoral vein valve cusps (Hoshino v 1993).

In the absence of valve cusps it is necessary to transpose or transplant a segment of valve bearing vein. Another possibility is the creation of a new valve.

Vein segment transposition was devised in 1977 (Kistner,1991). Many possibilities exist for transposition, the most frequent is the anastomosis of the (incompetent) superficial femoral vein to the (competent) profunda femoris vein. Results however have been mixed (Eriksson and Almgren 1986; Johnson *et al.* 1981; Queral *et al.* 1980; Ferris and Kistner 1986; Raju,1985) and the procedure has not gained widespread acceptance.

Valve transplantation is an attractive concept; a competent valve is excised with a segment of vein from the axillary vein and is inserted into an incompetent popliteal vein after a similar length has been excised. This technique was developed to overcome the situation

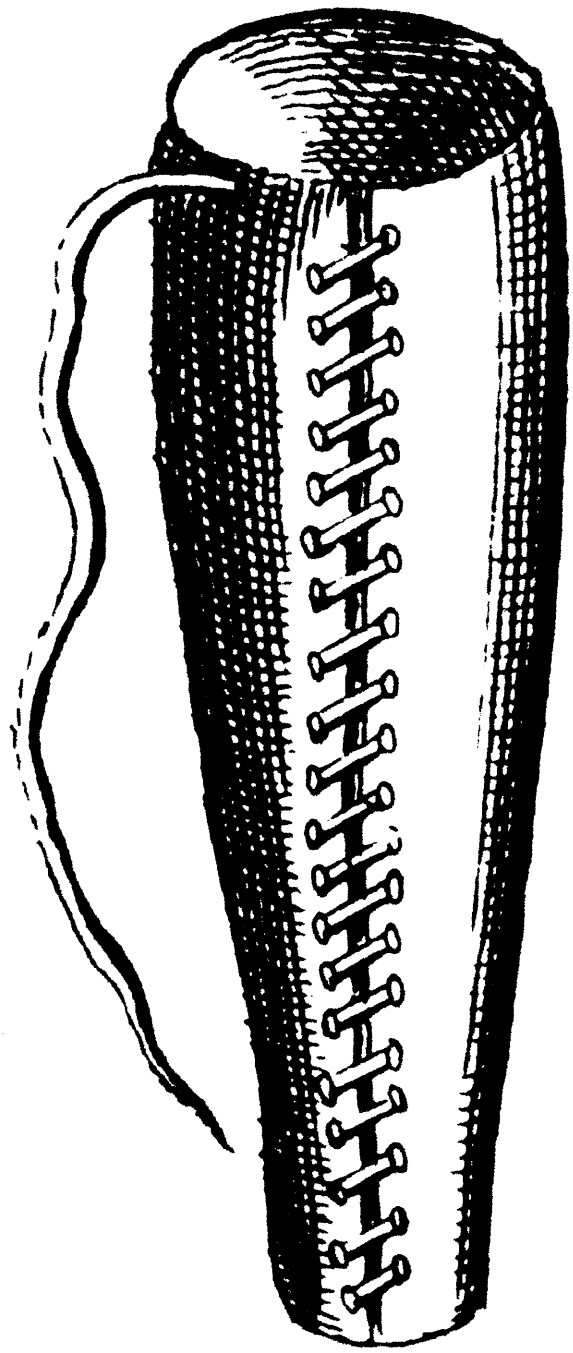
when there is no repairable venous valve present. The technique has been investigated in dogs (popliteal vein) and shown to improve AVP to almost normal values when combined with a distal AV fistula to maintain patency (Dalsing *et al.* 1994).

Several techniques of constructing venous valves are possible. The Psthakis sling technique involves slinging the popliteal vein with a silastic loop which is sutured to the gastrocnemius muscle. As the patient walks the popliteal vein is permitted to open and shut just as a valve would do. McMullin *et al.* (McMullin *et al.* 1990) have reviewed the technique used on 12 patients with deep venous incompetence. One patient died of a pulmonary embolus, eight cases had a clinical improvement and six cases achieved complete healing of venous ulcers. In all surviving cases the popliteal vein remained patent.

The possibility of constructing venous valves from peritoneum is being investigated by Van den Broek *et al.* (Van-den-Broek *et al.* 1991). So far encouraging results on piglets and rats have been published.

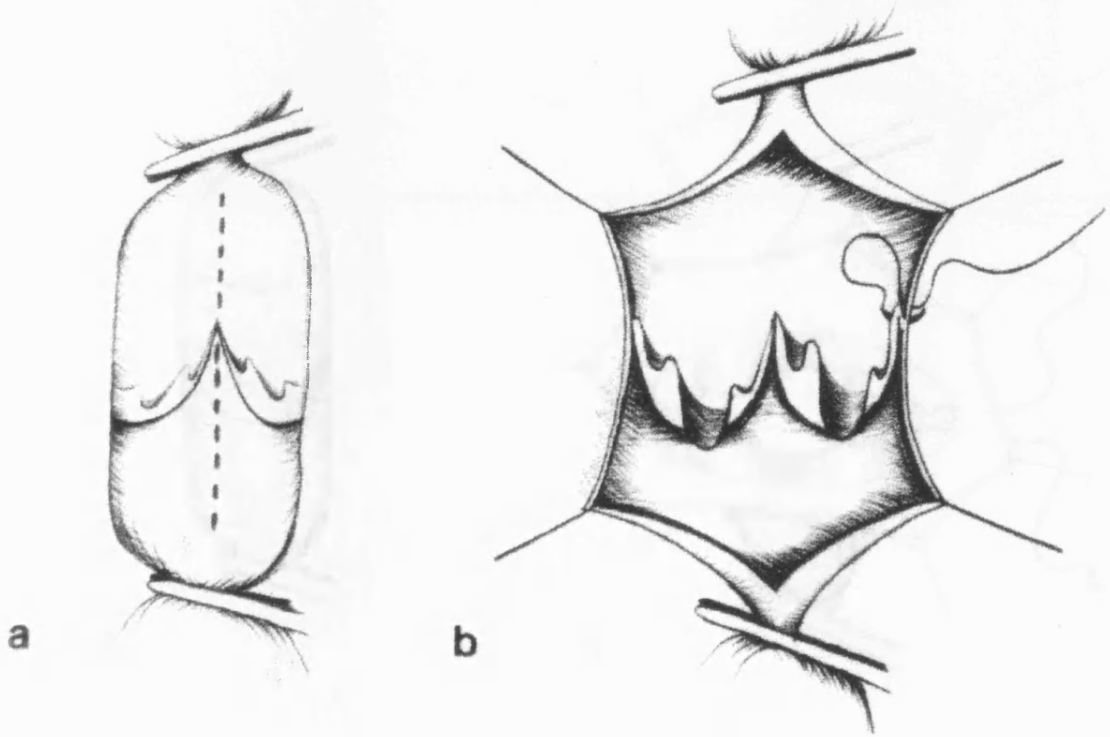
An innovative technique of forming a venous valve by intussuscepting the popliteal vein has been developed by Wilson et al. (Wilson *et al.* 1990) at St Thomas's Hospital. Encouraging results have so far been shown using dogs and human studies are awaited.

Figure 4.1 Wiseman's leather laced compression stocking



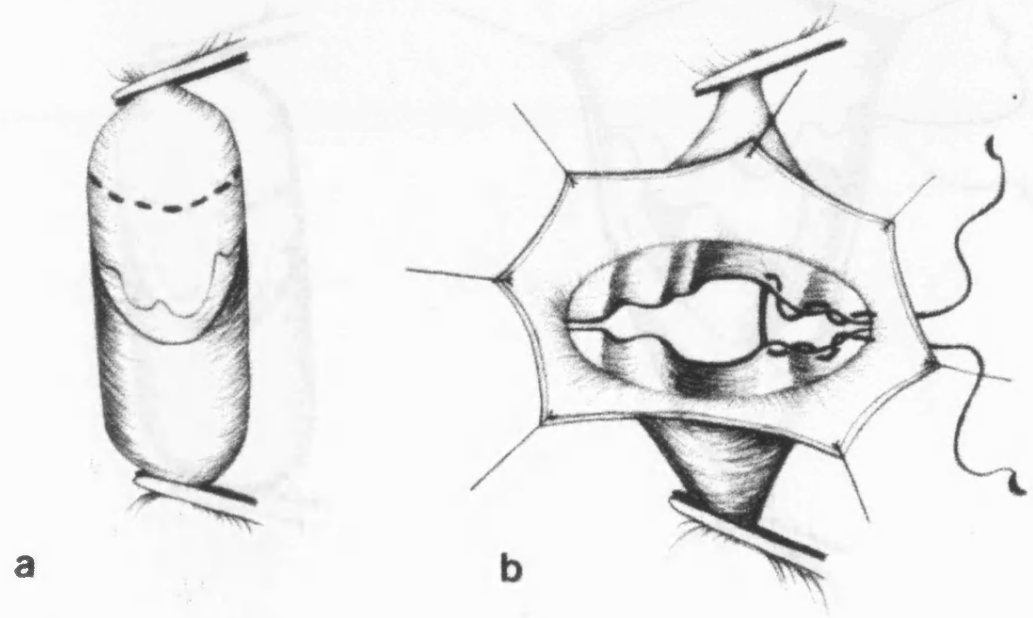
The forerunner of todays graduated elastic compression stocking

Figure 4.2 Deep venous valve repair 1



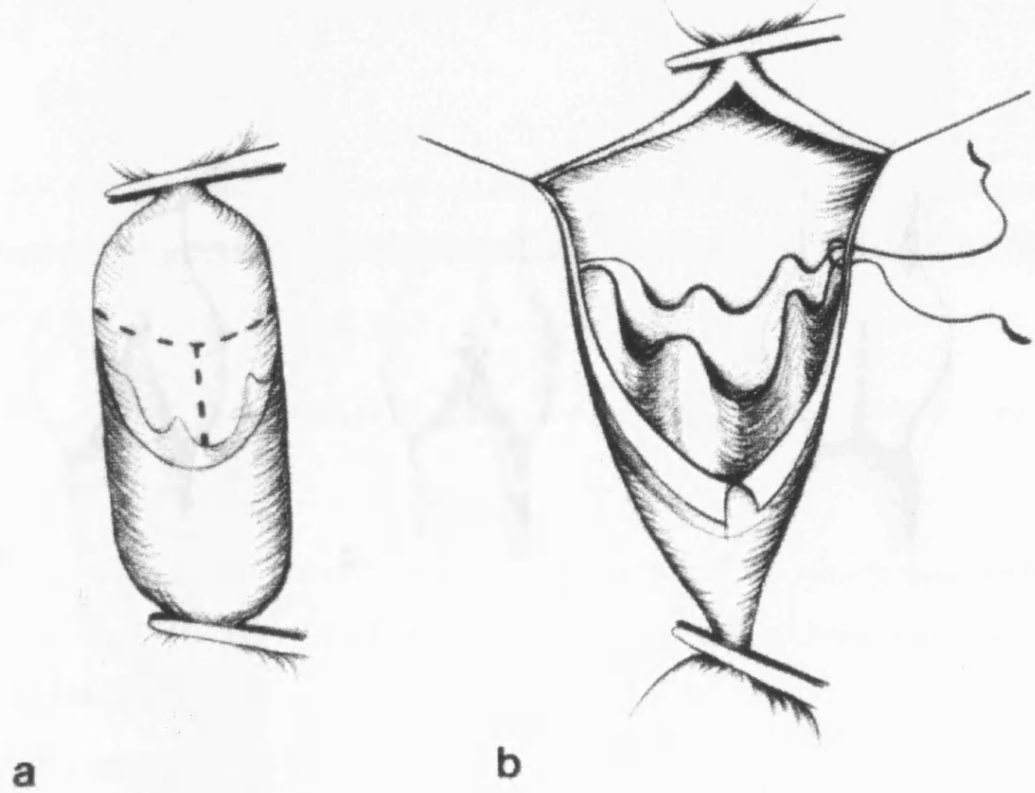
Internal valvuloplasty (Kistner's method)

Figure 4.3 Deep venous valve repair 2



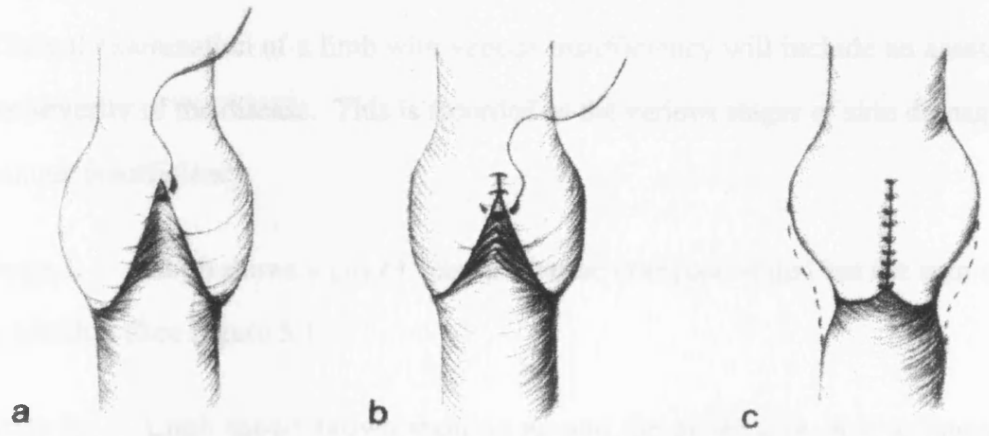
Internal valvuloplasty (Raju's method)

Figure 4.4 Deep venous valve repair 3



Internal valvuloplasty (Sottiurrai's method)

Figure 4.5 Deep venous valve repair 4



External valvuloplasty (Kistner's method)

CHAPTER FIVE

CALF MUSCLE PUMP; METHODS OF INVESTIGATION

As discussed above, venous function in the lower limb is reliant on the pumping mechanism of the venous calf muscle pump, failure of which results in the familiar sequelae of venous disease. The methods used to quantify the severity of venous disease (i.e. efficiency of the calf muscle pump) are discussed.

5.1 Clinical Assessment

Clinical examination of a limb with venous insufficiency will include an assessment of the severity of the disease. This is recorded as the various stages of skin damage seen in venous insufficiency.

Stage 1: Limb shows signs of venous disease (varicose veins) but the skin of the leg is healthy. (See Figure 5.1)

Stage 2: Limb shows brown staining around the gaiter area, due to haemosiderin pigment deposition. (see figure) The skin may also be dry and flaky; this is venous eczema (see Figure 5.2)

Stage 3: Due to deposition of fibrin within the subcutaneous fatty tissues, the skin of the gaiter area becomes hard, shiny and indurated. This is lipodermatosclerosis. This tissue cannot be distended by oedema, so an oedematous leg will take on the "inverted champagne bottle appearance" of chronic venous insufficiency.

Stage 4: The final pathological stage of chronic venous insufficiency is ulceration, the mechanism of which is discussed in the text (see Figure 5.3).

Figure 5.1 Varicose veins with no evidence of skin damage

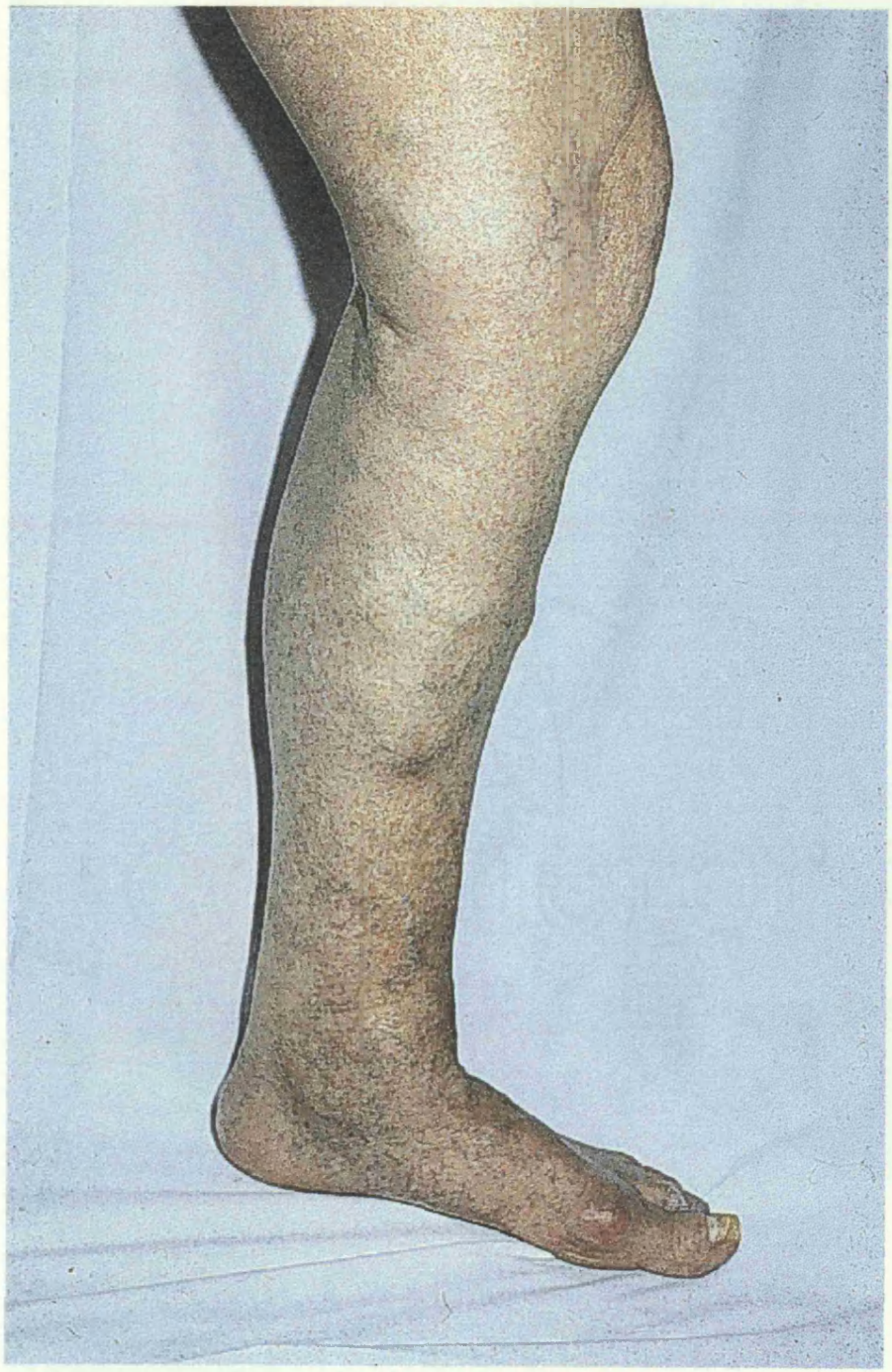


Figure 5.2 Venous eczema and pigmentation around the ankle (first stage of venous skin damage)

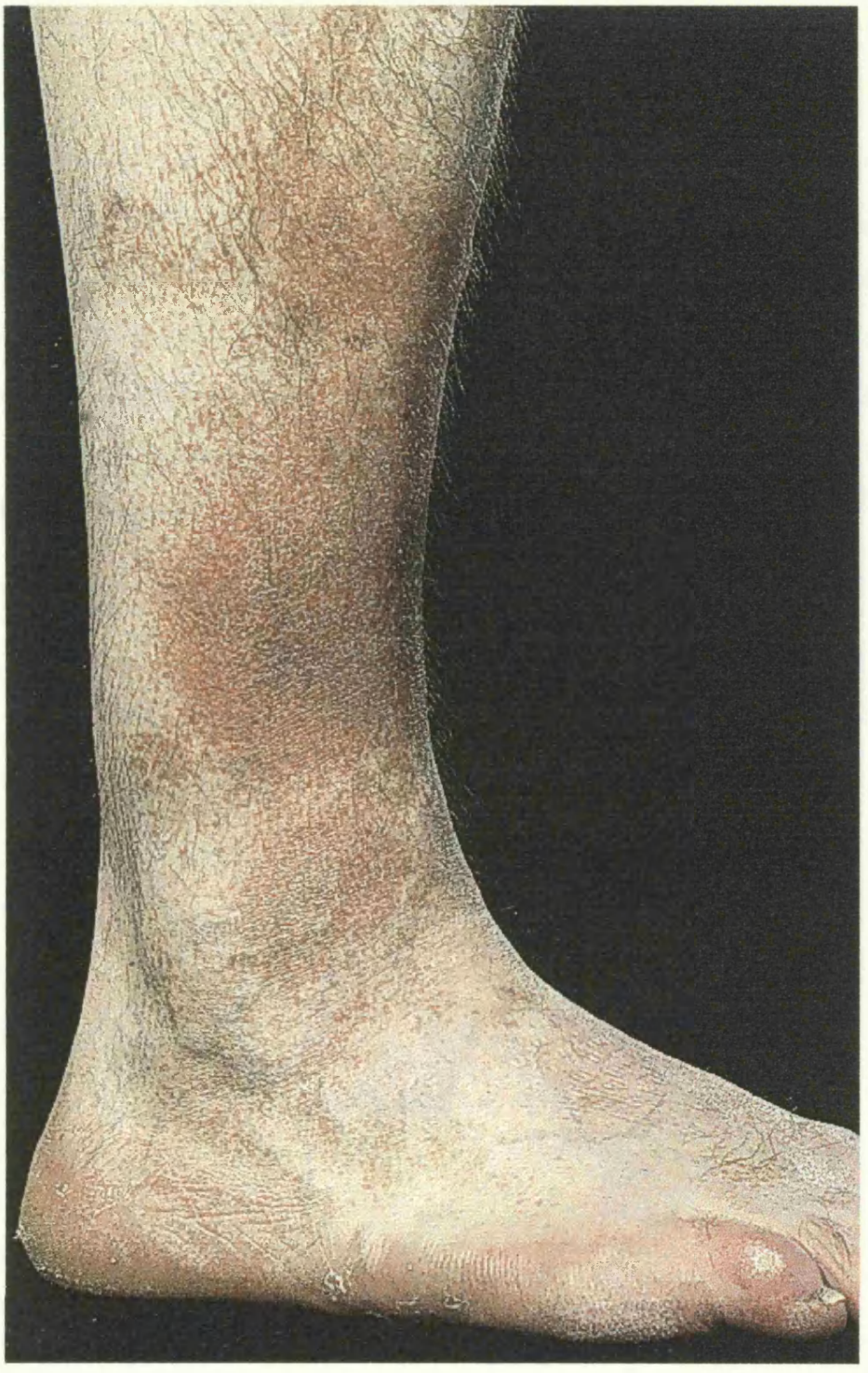
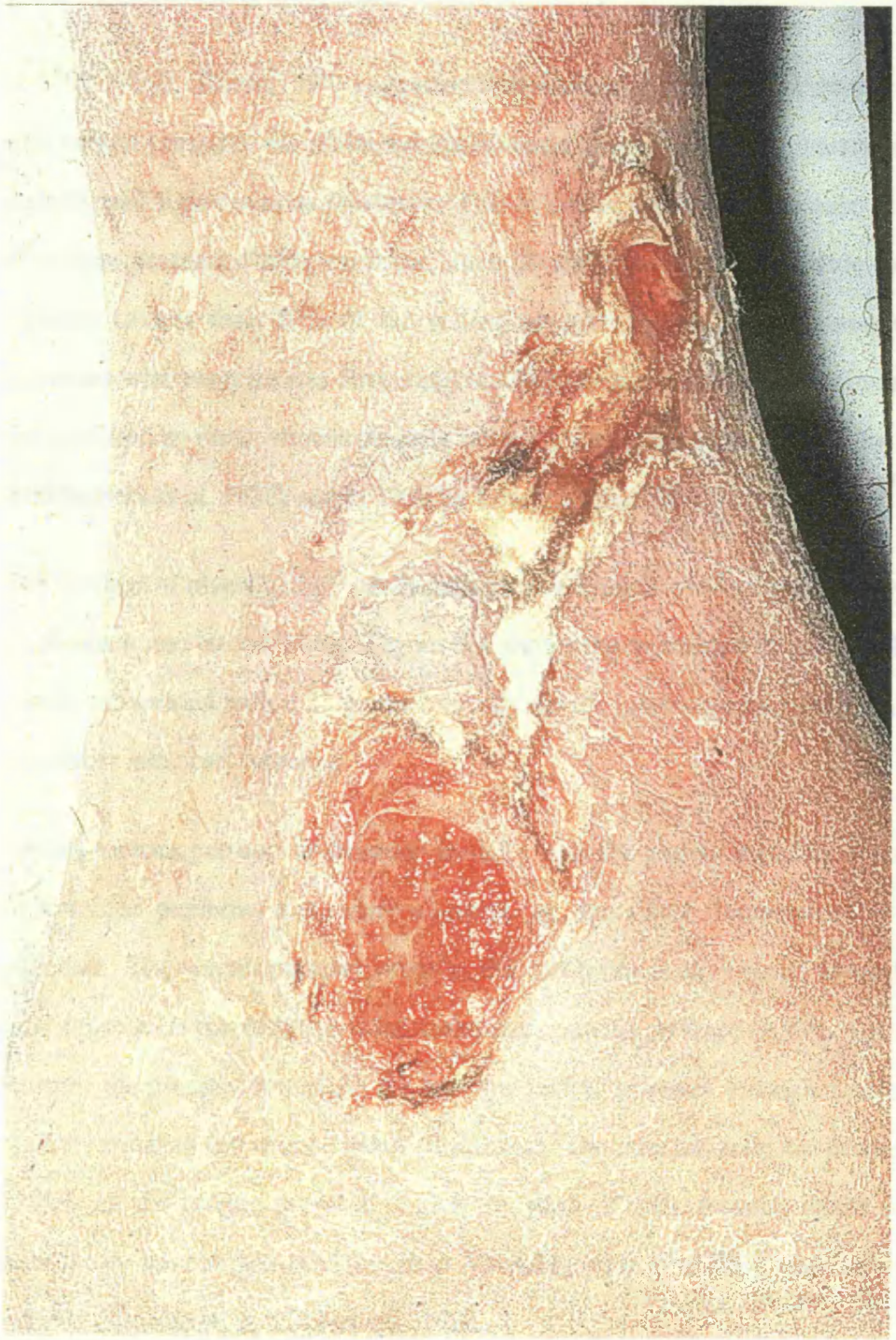


Figure 5.3 Varicose ulcer with surrounding lipodermatosclerosis and eczema.



5.2 Ambulatory venous pressure.

Venous pressure at rest is related to the distance between the right atrium and the point at which measurement is being made.

In 1797 Home (Home,1797) suggested that venous ulceration was due to abnormally high venous pressure. He attributed this however to the patients height, stating that taller patients had higher venous pressures. This is true of the venous pressure at rest but not of venous pressure during exercise, since the calf muscle pump is able to reduce the pressure to less than 20% of the resting pressure. The fact that venous pressure decreases with exercise was first noted in 1911(Hooker,1911) using an indirect method and qualified by direct venous pressure measurement at the ankle in 1932 by McPheeters (McPheeters *et al.* 1932) and in 1936 by Smirk (Smirk,1936).

This method of investigation was introduced into clinical use in the 1940's by Pollack et al. (Pollack and Wood 1949) Figure 5.4 shows the technique in use. A dorsal pedal vein is cannulated with a 21 gauge butterfly needle connected to a Statham™ pressure transducer and chart recorder.

Resting venous pressure is recorded initially with the patient standing erect (RP) The patient then performs a standard exercise, eg. ten tiptoe manoeuvres at the rate of 1/second. The venous pressure drops as the calf pump returns blood towards the heart, until a plateau is reached; this is the ambulatory venous pressure (AVP). On cessation of exercise the pressure returns to the baseline resting pressure through a combination of capillary refilling and venous reflux (if present). The time taken for the pressure to return to 90% of the resting pressure is also recorded (RT90). Normal limbs should have ambulatory venous pressure less than 30mmHg with a refilling time in excess of 20 seconds (Nicolaides and Zukowski 1986).

Failure of the calf muscle pump will result in increased AVP and will reduce RT90. Arnoldi has demonstrated close agreement between the pressure recordings obtained by

superficial venous cannulation and the pressure changes taking place in the deep veins of the calf (Arnoldi,1966; Arnoldi and Linderholm 1966).

Björdal has studied a large number of patients by simultaneously measuring venous pressure and blood flow (Björdal,1971). In cases with sapheno-femoral incompetence there is retrograde flow in the long saphenous vein. Exercise does not reduce the venous pressure effectively (ie. AVP is increased) and on cessation the pressure rapidly returns to pre-exercise values (ie. RT90 is shortened). By occluding the long saphenous vein with a tourniquet the AVP and RT90 are normalised. In cases with long saphenous and perforator incompetence, occlusion of the long saphenous vein results in pressure normalisation even though some retrograde flow is still present in the perforating veins.

A number of workers have examined the association between ambulatory venous pressure and the risk of venous ulceration (Warren *et al.* 1949; Tyson and Goodlett 1945). Figure 5.5 shows this association graphically (Pollack *et al.* 1949).

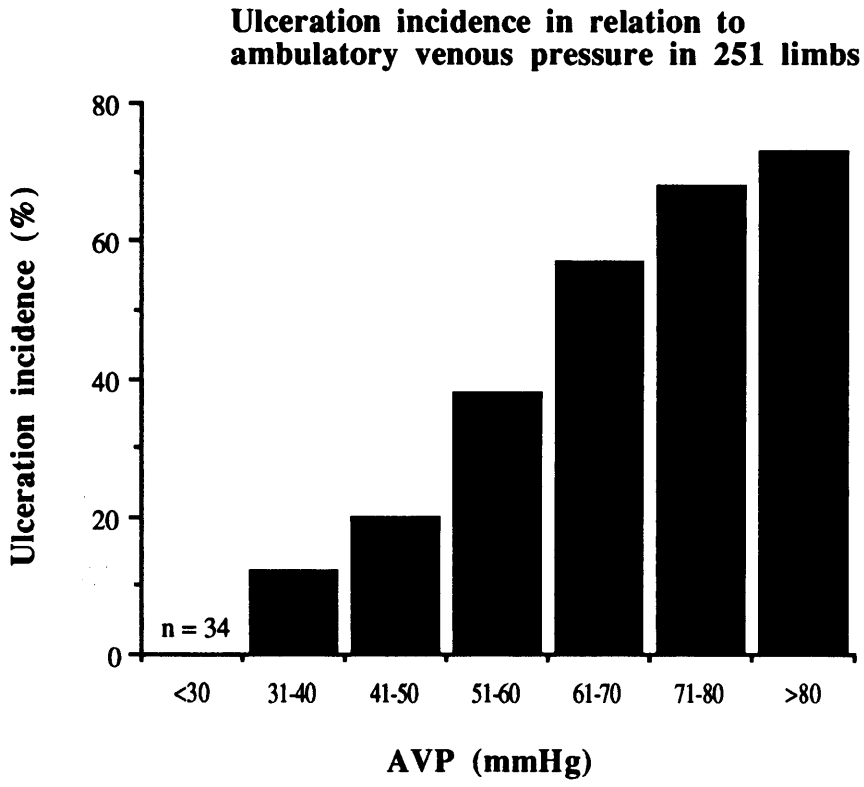
There seems to be a clear relationship between venous pressure after exercise (AVP) and venous ulceration. It is likely that this is a central factor in the pathogenesis of venous ulceration.

As Björdal has shown, the contribution that superficial reflux makes to venous hypertension may be determined by the application of narrow tourniquets which will abolish reflux within the superficial veins. This principle may be used when assessing patients prior to venous surgery. Tourniquets may be placed at any level but commonly one is placed around the ankle, one just below the knee, one just above the knee and one at the upper thigh level sequentially. By taking into account at what tourniquet level the ambulatory venous pressure is improved it is possible to determine at what level surgery should be directed. For example limbs with sapheno-femoral reflux should benefit from sapheno-femoral disconnection and will have an improvement in AVP when a thigh tourniquet is applied. Limbs with significant deep venous reflux will not show an improvement in AVP when a tourniquet is applied and would not be expected to benefit

from superficial venous surgery. The effect of long saphenous stripping on ambulatory venous pressure has been studied by Darke. He studied a group of patients with long saphenous reflux and venous ulceration. An improvement in ambulatory venous pressure with a tourniquet was associated with a post operative improvement in ambulatory venous pressure, together with clinical improvement (Sethia and Darke 1984).

Figure 5.5 Ambulatory venous pressure and venous ulceration

From Pollack *et al.* 1949.



Raju et al. have recently examined the relationship between ambulatory venous pressure and ulceration. Although there was a trend towards ulceration in limbs with high ambulatory venous pressure the correlation was much better if Valsalva induced pressure measurements were also included in the assessment of venous function. A reflux index was produced by multiplying ambulatory venous pressure by Valsalva induced venous

pressure (Raju and Fredericks 1991). Ambulatory venous pressure seems to be central to the pathogenesis of venous ulceration but other factors may also play a part.

5.3 Air-plethysmography.

Since ambulatory venous pressure measurement is an invasive procedure investigators have long sought a non-invasive method of venous assessment which is just as reliable as the AVP method. Air-plethysmography has recently been introduced as a method which fulfils these criteria. The device comprises a 35 cm long PVC air-chamber which surrounds the lower leg and is connected to a pressure transducer and chart recorder. After inflation and a period of equilibration at room temperature (22 - 24°C), the device is calibrated by recording pressure changes as $100cm^3$ of air is injected and then removed. The following volume changes are then recorded (cm3) by reading from the pressure recorder. The leg is elevated to empty the veins as much as possible; the subject then stands erect with their weight on the opposite limb until the veins are full. This volume change represents the functional venous volume (VV) and the time taken to 90% of VV is the 90% filling time (VFT90). The venous filling index (VFI) is derived from; VFI = 90 per cent VV/VFT90. The subject then performs one heel raise manoeuvre and the volume displaced during this manoeuvre recorded as the ejection volume (EV), ejection fraction (EF) is EV/VV. Ten heel raise manoeuvres at the rate of one/second are then performed in order to reach a residual volume (RV) plateau, the residual volume fraction (RVF) is RV/VV. Figure 5.6 shows the device in use. The volume changes are depicted in Figure 5.7.

VFT90 is greater than 70 seconds in normal limbs. In limbs with deep venous reflux it ranges from 8 to 82 seconds (90% confidence limits).

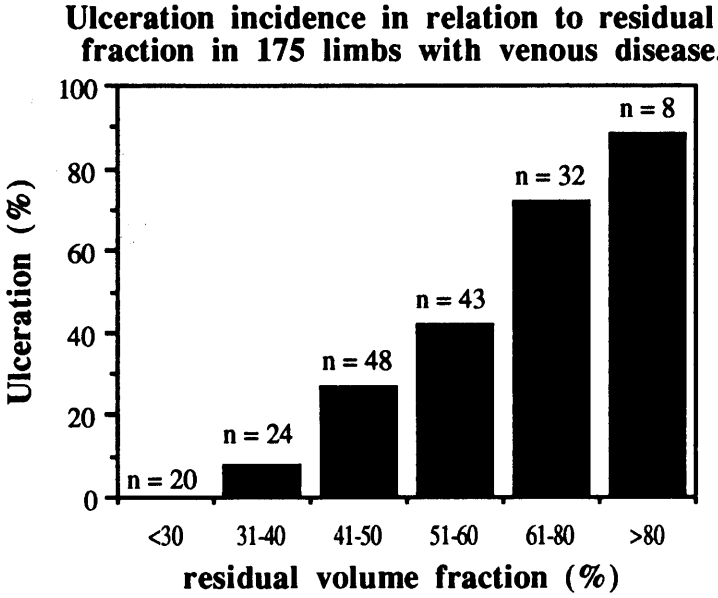
Venous filling index is normally less than 1.7 mls/sec. In limbs with varicose veins (uncomplicated) the range is 2 - 9.5 mls/sec and in limbs with skin complications of

superficial reflux the range is 3 - 30 mls/sec. In limbs with popliteal reflux the range is 7 - 28 mls/sec (Christopoulos and Nicolaides 1988).

The ejection fraction is normally 60 - 80% of venous volume. In limbs with varicose veins this is reduced to 30 - 60 % and in limbs with deep venous insufficiency the range is 10 -50%. The presence of a good ejection fraction in limbs with reflux appears to prevent ulceration (Christopoulos *et al.* 1988).

Residual volume fraction is less than 30% in normal limbs. Limbs with varicose veins have a range from 30 -70% and in limbs with deep venous reflux the range is from 40 - 80%. Figure 5.8 shows the relationship between residual volume fraction and the incidence of ulceration (Christopoulos *et al.* 1989). The residual volume fraction has been found to correlate well with the ambulatory venous pressure (R = 0.83) (Christopoulos *et al.* 1987).

Figure 5.8 Residual volume fraction and venous ulceration



Air-plethysmography thus shows good correlation with the clinical severity of disease and with the ambulatory venous pressure. The rate of reflux may be quantified (VFI) in mls/second. The efficacy of the calf muscle pump is expressed as ejection fraction (%),

and a combination of these two parameters of venous function is the residual volume fraction which appears to demonstrate a close correlation both with clinical severity and ambulatory venous pressure.

If these encouraging results stand the test of time then this method of air-plethysmography may become the "gold standard" test of venous function, replacing ambulatory venous pressure which is invasive (and not always possible to perform if a suitable vein cannot be found). Independent corroboration of these findings is needed.

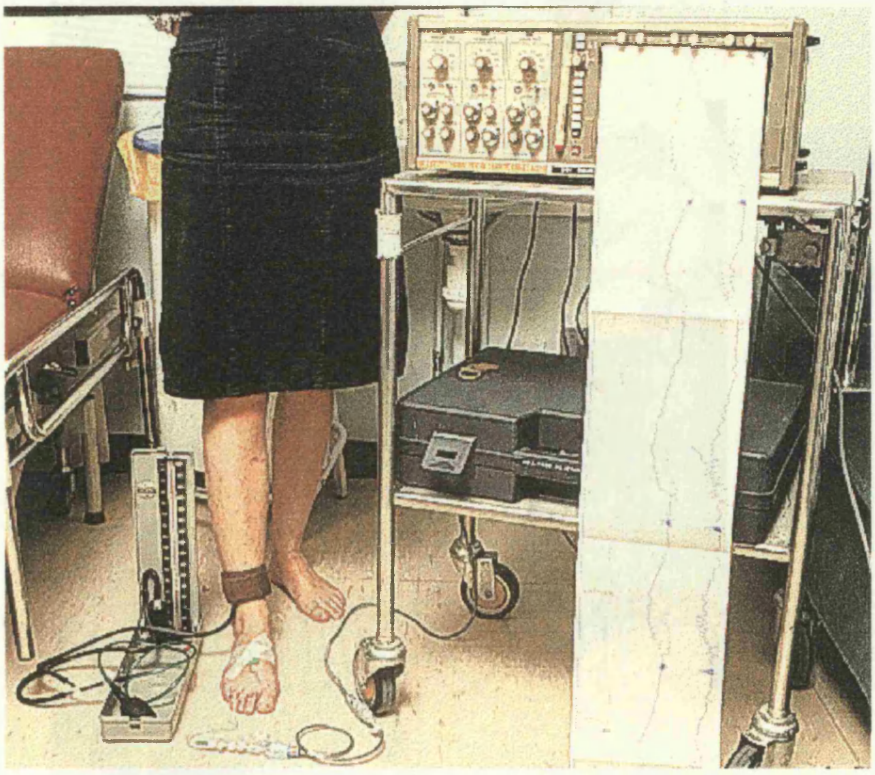
Disadvantages of air-plethysmography are that it is more time consuming than ambulatory venous pressure assessment (about 30 minutes per limb compared to approximately 20 minutes for a bilateral examination) and that tourniquets cannot be placed below the knee since the device occupies the calf.

5.4 Strain gauge plethysmography.

Strain gauge plethysmography was developed by Whitney (Whitney,1953) in Oxford. This method is an indirect means of measuring increases in the circumference of a limb using a thin column of mercury in a rubber tube, the principle upon which it relies is that changes in the electrical resistance of a mercury in silastic tube are related in a linear fashion to the proportional change in length.

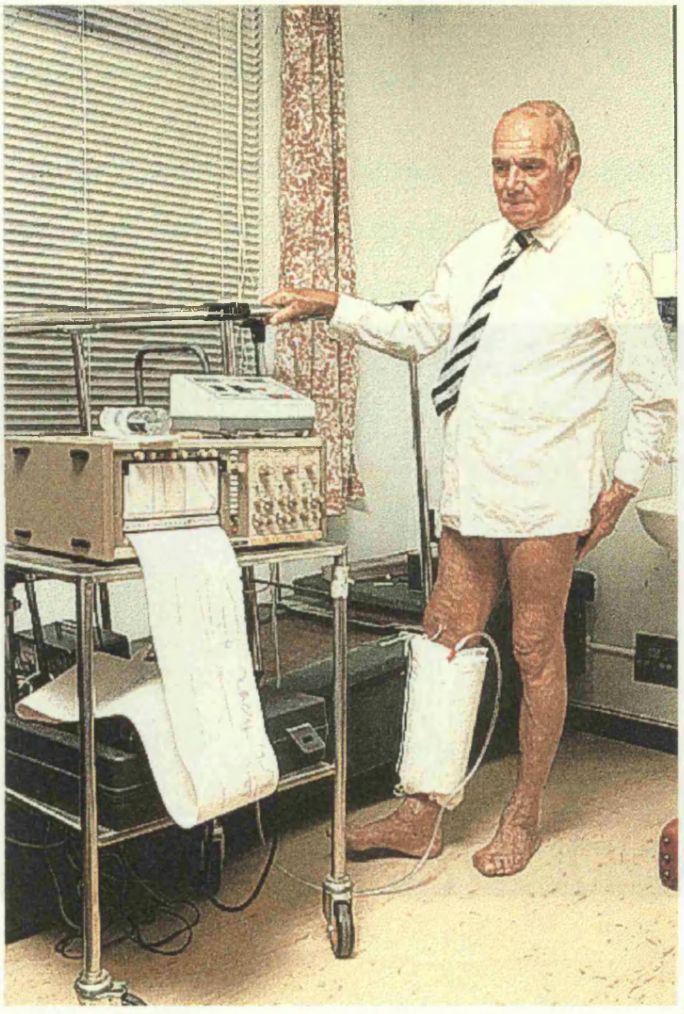
The mercury in silastic tube forms one arm of a Wheatstone Bridge (Figure 5.9). This apparatus will measure changes in the electrical resistance of the mercury in silastic coluumn. If it is balanced at an initial length of the strain gauge then the galvanometer will effectively register proportional increases in the length of the strain gauge.

Figure 5.4 Method of measuring ambulatory venous pressure



Ambulatory venous pressure measured by cannulating a pedal vein with a 21 gauge needle connected to a pressure transducer and chart recorder. The illustration also shows a narrow tourniquet used to obstruct the superficial veins.

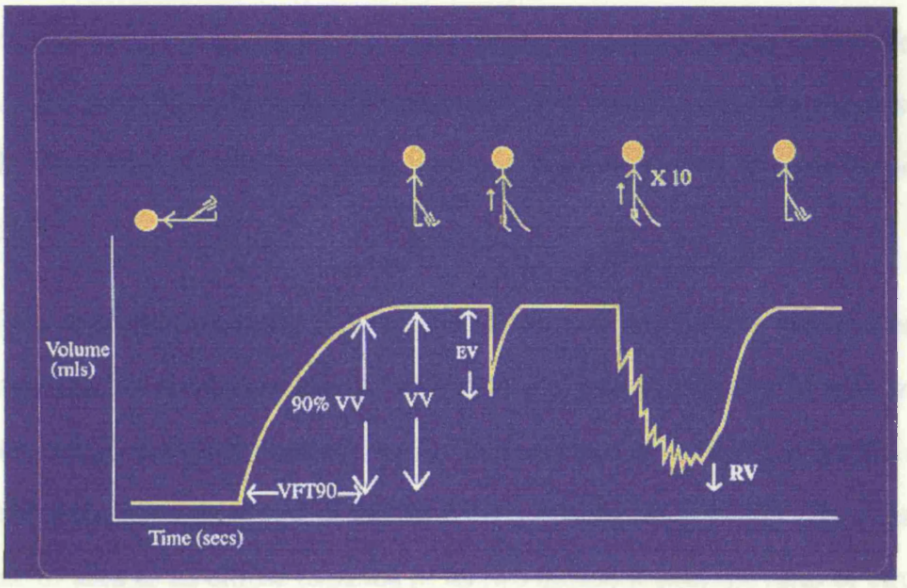
Figure 5.6 Air-plethysmograph in use



The air-plethysmograph in use. The air filled jacket around the calf can be seen connected to the pump and calibration equipment. The device is then connected to the chart recorder, from which readout the venous volumes are calculated.

Figure 5.7 Measuring venous volumes using the air-plethysmograph

(Redrawn after Christopoulos *et al. 1988)*



Since the silastic is extremely elastic this narrow tube may be placed around a limb in order to record changes in circumference (from which volume changes may be calculated, see below).

There are a few considerations which need to be addressed however when using this method of assessing limb volume changes.

1. The mercury in silastic strain gauge measures increase in circumference at one point on the length of the limb. It is assumed that the increase in volume is uniform along the length of the limb and that there is no increase in the length of the limb. The second assumption clearly is reasonable thus all swelling takes place in the transverse axis of the limb. The first depends upon the measuring device not restraining the tissues as they swell. Therefore increase in volume is proportional to increase in cross sectional area of the limb.

2. If the cross section of the limb is circular and remains so as it swells then it may be assumed that for small increases of volume the percentage change in area will be twice the percentage change in circumference. There are no data to substantiate the assumption that the cross sectional shape of the limb does not alter as it swells. By considering the change of area as an ellipse expands in its two different axes the ratio of circumference change to area change ranges from 1.44 to 3.27 (Whitney,1953). However, even in the region of joints it is unlikely to vary much since most swelling occurs in the skin and soft tissues, therefore such a large error is unlikely to occur.

The technique overcame many of the disadvantages that other plethysmographic methods had. The apparatus is portable and lightweight, so it could be worn by a patient for a long period of time if necessary. It is not filled with water so it could be used in any position, the subject does not need to be immobilised during recording. The apparatus does not enclose the limb and therefore cannot lead to any vasomotor changes which may affect the limb volume.

Fernandes *et al.* (Fernandes *et al.* 1979) found the strain gauge method was useful in measuring venous volume changes during ambulation. They produced a good correlation between the decrease in venous volume (ml / 100 ml tissue) with ambulation and the decrease in venous pressure with the same exercise.

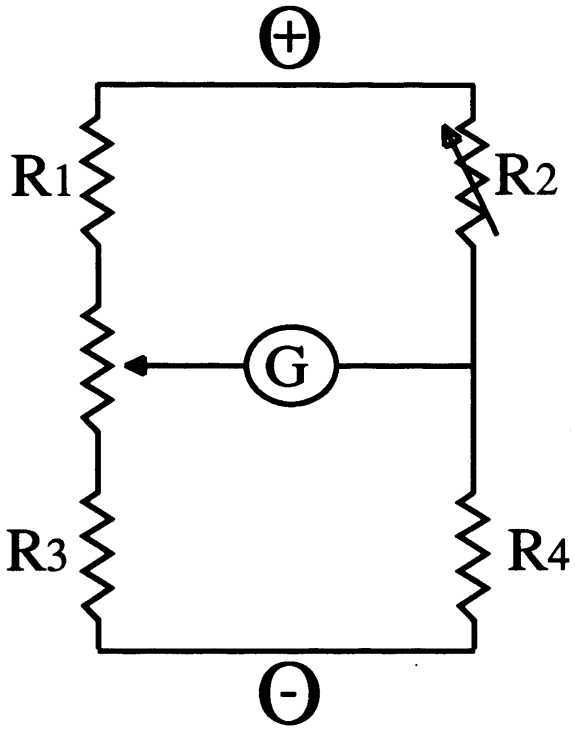
Perhoniemi *et al.* (Perhoniemi *et al.* 1990) have also employed this method using the Witney strain gauge plethysmograph to assess venous reflux flow and volume after subfascial ligation of incompetent perforating veins (Linton's procedure). They showed that the strain gauge was able to document the improvement in venous haemodynamics very well.

Using the strain gauge to record venous volume and pressure measurement simultaneously Struckman and Mathiesen (Struckmann and Mathiesen 1985) examined the relationship between the two measurements, finding a good correlation between refilling times (R = 0.91) but a poor correlation between venous volumes and venous pressure changes (R = 0.4).

5.5 Duplex scanning

The success of duplex scanning has resulted in an explosion of the sale of these machines. Very few hospitals in the United Kingdom lack duplex facilities, many owning several scanners. For the vascular Surgeon this is the greatest advance in diagnostic techniques since angiography was introduced. Angiograms have been hailed as "the eyes of the vascular surgeon (..without them, he at once becomes a mole)" in a speech read before Edwin J Wylie at a dinner given in his honour. Continuing in this vein Nicolaides has termed duplex scanning "The second sight of the Vascular Surgeon" (Nicolaides and Renton 1990).

Figure 5.9 The Wheatstone Bridge



Wheatstone Bridge:

This comprises 4 resistances wired as shown on this diagram. When a current is passed across the bridge then provided that R1.R4 = R2.R3 is satisfied then the galvanometer (G) will register no current; ie. the bridge is 'balanced'. In a strain gauge plethysmograph R1 is substituted for a mercury in silastic tube which varies it's resistance with length, R2 is a variable resistor (potentiometer). Once the mercury in silastic tube has been set to it's initial length the variable resistance is altered until the bridge is balanced. The galvanometer will then register percentage changes of length in the mercury / silastic tube. In order to correct for temperature changes some strain gauges have R4 situated next to R1. R4 is not subject to any change in length, only temperature, thus any change in resistance due to temperature change is automatically balanced.

This modality is a marriage of B-mode ultrasound imaging and pulsed Doppler signal analysis. The ultrasound image enables one to identify a vessel, the doppler beam is then directed using a cursor which appears superimposed on the ultrasound image. Directional doppler signal analysis is usually graphically represented on the other half of the screen. The frequency shift of the reflected signal may be used to calculate the velocity of blood flow according to the Doppler formula:

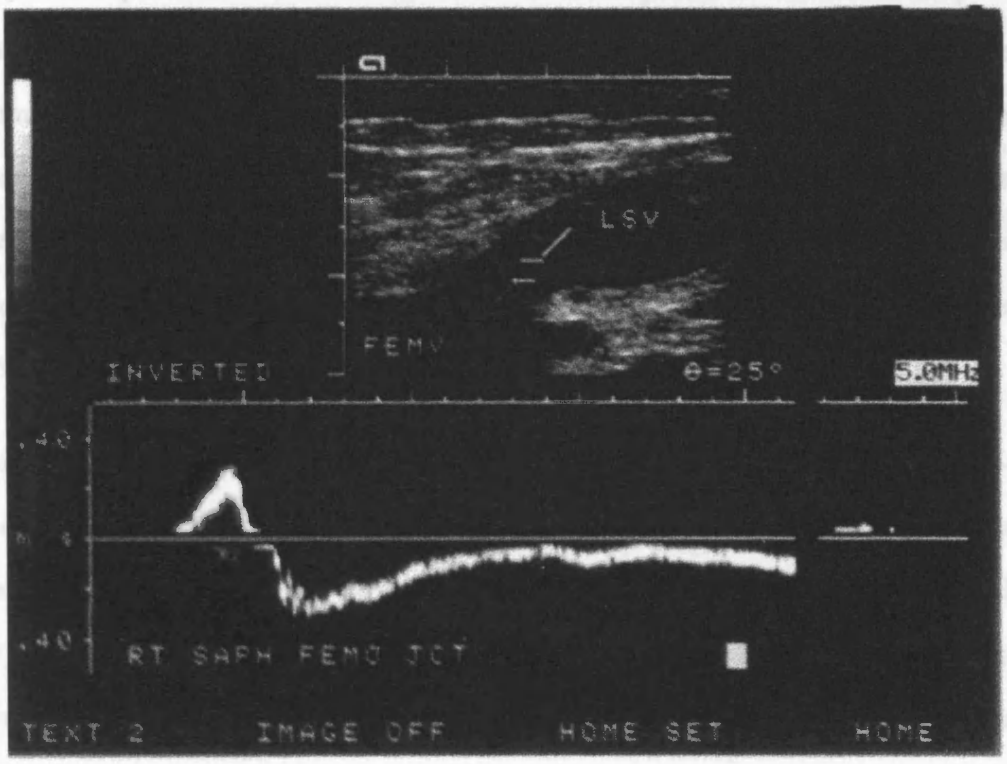
$$\Delta F = \frac{2f_0 . v . \cos a}{C}$$

ΔF = frequency shift, $2f_0$ = frequency of transmitted signal, v = velocity of the objects, a = angle of the incidence beam with the object path, C = velocity of sound in the medium being studied

Colour scanners have now become available (sometimes referred to as Triplex) which show the Doppler signal analysis superimposed on the ultrasound image in a colour scale (usually blue - red). The use of colour mapping enables more rapid identification of the veins since an area of interest may be scanned with the colour facility, then once a vein has been identified the pulsed Doppler may be accurately focussed in the vein lumen and flow represented graphically. Thus duration of reflux may be measured together with peak velocity of reflux. The technique has become the "gold standard" test of venous reflux.

To detect venous reflux either Valsalva manoeuvre may be used or release of distal compression. The Valsalva method requires that all proximal valves to the one examined are incompetent and thus it is less useful than the release of compression method. Most workers examine patients standing or sitting in order that gravity may assist in the detection of reflux. Figure 5.10 shows a duplex scan of the sapheno-femoral junction which demonstrates sapheno-femoral reflux on release of calf compression.

Figure 5.10 Duplex scan of sapheno-femoral junction



The scan shows the saphenofemoral junction (femoral vein and long saphenous vein labelled). The lower graph shows the flow interrogation at the junction (cursor). Initial forward flow is produced by a calf squeeze and is followed by prolonged reflux on release of compression.

Van-Bemellan *et al.* (Van-Bemmelen *et al.* 1989) have shown that a duration of venous reflux of < 0.5s may be found in normal veins with functioning venous valves, therefore this figure has been used as a cut-off point when evaluating venous reflux with duplex. This figure has been corroborated more recently, using release of manual calf compression to generate reflux (Sarin *et al.* 1994).

Hanrahan has evaluated patients with venous ulcers using duplex scanning. He found that venous reflux was usually present in multiple systems in patients with ulceration, ie. one of the superficial or perforating veins was incompetent in addition to deep venous reflux (Hanrahan *et al.* 1991). Szendro *et al.* used the technique to diagnose deep venous incompetence. They found close agreement between this method and ambulatory venous pressure assessment (Szendro *et al.* 1986). Duplex scanning has been used to assess the distribution of reflux in limbs with varicose veins. Primary varicose veins demonstrate reflux in the long saphenous vein in 95 % of cases, additionally in the short saphenous vein in 15% and perforating veins in 45% (Almgren and Eriksson 1990).

Localising the sapheno-popliteal junction is often difficult, many surgeons using on-table venography. With duplex scanning however the sapheno-popliteal junction may be localised with confidence and marked prior to operation (Engel *et al.* 1991). Vasdekis *et al.* (Vasdekis *et al.* 1989) and Gongolo *et al.* (Gongolo *et al.* 1990) compared duplex scanning with venography prior to sapheno-popliteal disconnection. They found the duplex to be almost as accurate as the venogram. Sugrue *et al.* (Sugrue *et al.* 1988) however, found duplex scanning to be lacking in accuracy when compared to venography. Duplex has also been used to identify and localise reflux in cases of recurrent saphenofemoral incompetence, varicography being recommended for cases where the anatomy is still unclear on the scan (Bradbury *et al.* 1994). Overall, this technique is accepted today as a useful method of diagnosing venous incompetence and localising it. It is therefore more useful than other tests of venous function when planning appropriate surgery (Goren and Yellin 1990; Hanrahan *et al.* 1991; Hanrahan *et al.* 1991; Leu,1990).

CHAPTER SIX

THE ELASTIC PROPERTIES OF THE VEIN WALL

6.1 Young's modulus of elasticity

The venous system functions in part as a reservoir, able to accommodate large changes in the circulating blood volume with comparatively small changes in pressure. This capacitance functions as a buffer against the insult that changes in circulating volume would impose upon the heart. Attinger (Attinger,1969) has demonstrated that veins are much more compliant than arteries at low pressure, but that at high pressure the veins are less compliant. The elastic properties of the vein wall, in particular with reference to the aetiology of varicose veins are discussed below.

Defining stress, strain and elastic modulus.

Strain. When a solid is deformed by an increase in length as a result of the application of a force F the ratio of the increase in length to the initial length is known as longitudinal strain.

Stress. In order to restore the solid to it's original shape , it opposes the deforming force by an equal and opposite force. This restoring force is called the stress.

Elasticity is the relationship between stress and strain and is expressed in a perfectly elastic body by the equation.

Elasticity = Stress/Strain.

This is known as Young's modulus of elasticity and is an expression of the stiffness or resistance to deformation of the material.

In order that this may be applied to a cylindrical structure Laplace's law may be used (Hildebrandt,1970). This states Tt = P.ri, where T = tangential tension in the cylinder

wall, ri is the internal radius and P is the pressure within the cylinder. Consider a cylinder of length L, outside circumference C. When pressure inside the cylinder is increased by ΔP, the circumference increases by ΔC. Strain therefore is ΔC/C or the ratio of the change in outside radius ΔR/R. If we consider pressure multiplied by radius to represent stress, then the elasticity equation becomes;

$$Elasticity = \Delta P.R/\Delta R.ri/\delta$$

where ri/δ is the ratio between the internal radius and wall thickness.

It is often difficult to measure wall thickness and consequently internal radius in blood vessels. Therefore ri/δ is often ignored when measuring blood vessel elasticity. This approximation is regarded as adequate and furthermore does not impose upon the calculation data that would contain severe experimental error (Gow and Taylor 1968).

Young's modulus however is only constant in a perfectly elastic substance. The vein wall is far from perfectly elastic and therefore the measurement of elasticity must be expressed as an incremental modulus which represents the stress / strain ratio at a given stress or given strain which must be stated.

The effect of elliptical cross section.

Since veins do not always have a circular cross section (particularly at low pressure) the volume compliance of the tube must also be taken into account. Veins collapse into an elliptical cross section at low pressure. As the pressure increases a circular cross section is obtained. The cross sectional area and thus the volume of the tube is increased as the circular cross section is approached without any stress (change in length) of the vein wall. Thus during the elliptical stage relatively small increases in pressure lead to large changes in volume, even though the elastic modulus of the vein wall may be high. The volume compliance of the tube is represented by the equation;

$$Volume\ compliance = (\Delta V/V).(1/\Delta P)$$

If the vein wall is assumed to always be circular in cross section then compliance = 1/elasticity. Most studies of venous elasticity or compliance use this volume modulus or bulk modulus as the method of measurement.

Bulk modulus of elasticity = Δ Pressure/(Δ Volume/initial volume)

In practice we are able to measure volume and pressure changes accurately and therefore this measurement lends itself to the study of venous elasticity, provided that the elliptical effect is borne in mind. Moreno *et al.* (Moreno *et al.* 1970) have shown that the maximum compliance occurs at a pressure of 4mmHg and is due to the "bending" rather than distension of the vein wall. Above 10mmHg the pressure/volume curve flattens out as the cross section of the vein assumes a circular configuration. The point at which the pressure/volume curve flattens out is determined by the degree of smooth muscle tone in the vein wall (Lange *et al.* 1971; Alexander,1963). Contraction of the smooth muscle reduces the circumference of the vein; thus the volume at which the vein wall starts to stretch rather than just bend is decreased. This is the physiological mechanism which occurs during blood loss and is mediated by the sympathetic nerves. Thus venous elasticity comprises both active and passive components (Ludbrook,1966; Folkow,1949; Folkow,1953; Bayliss,1902).

Studies on venous compliance at low pressures must be controlled as much as possible to allow for the effects of sympathetic tone on the resting venous volume. Therapeutic maneouvres may have an effect on either the active or passive components of venous elasticity and therefore it is helpful to record venous elasticity at different points on the distension curve.

6.2 Measurement of venous elasticity

Volume measurement in-vitro is relatively straightforward. It is important to fix the length of the vein under study in order that change in volume may be ascribed to increase

in cross sectional area (therefore circumferential elasticity and not longitudinal elasticity is measured). When a section of vein is distended in order to measure it's elasticity or compliance a known volume of physiological salt solution may be infused into the lumen of the vein at a known rate. In order to ensure that there is no leakage Evans blue dye is added to the salt solution (Bocking and Roach 1974; Zsotér *et al.* 1967).

In vivo measurement of volume becomes more difficult. In order to achieve a pressure-volume curve venous outflow is usually occluded by a proximal occlusion cuff (Eiriksson and Dahn 1968; Goodrich and Wood 1964; Kidd and Lyons 1958; Litter and Wood 1954). Other methods include using a tilt table to alter the hydrostatic pressure in the veins (Barendsen and Van-den-Berg 1976; Ludbrook and Loughlin 1964), Norgren and Thulesius (Norgren and Thulesius 1975) used exercise to empty the veins and studied the volume as the veins refilled.

Plethysmographic methods have been used to measure the volume changes. These methods measure the volume of all components of the limb (ie. they also measure the extravascular volume and the arterial blood volume) (Landowne and Katz 1942). Water bath plethysmography and strain gauge plethysmography are the most commonly used methods. Recently air-plethysmography has been reintroduced into clinical use using a new, easy to use device.

In order to deduce volume changes from changes in circumference it is necessary to clarify two assumptions. Firstly there is no increase in length of a limb as the volume increases. Provided that there is no restraining force applied by the plethysmograph this assumption is self evidently correct. The second assumption is that as the volume increases the cross sectional shape of the limb remains essentially the same. This is true for sections of the limb that are circular in cross section, such as the calf. In areas such as the ankle however, it is possible with large increases in volume to change the cross sectional shape, thus changing the relationship between circumference and volume. Experiments on venous volume changes involve small volume changes which are not subject to these errors.

In order to justify the use of the strain gauge plethysmograph Whitney compared the values obtained using strain gauge plethysmography with water bath plethysmography, obtaining regression coefficients of the order of 0.80 to 0.95 which were highly statistically significant.

The phenomenon of stress relaxation has been noted in veins (Attinger,1969). A constant feature of all studies of venous distensibility is to allow time for stress relaxation to occur after each change in venous pressure.

Many studies of venous distensibility use venous occlusion cuffs to increase the venous pressure whilst monitoring volume changes. The cuff pressures however do not always equate with venous pressure (especially at low pressures) and therefore results obtained using this method should be interpreted with caution.

If an occlusion cuff is inflated to high pressure for a long period, particularly if the ambient temperature is high then the recorded volume will continue to creep up in spite of a constant venous volume. This is due to oedema formation (Kitchin,1963; Krogh *et al.* 1932; Drury and Jones 1927). During these studies this is not usually significant, however it should be borne in mind. Appreciable oedema formation will of course be apparent when the occlusion is released, since the volume recorded will not return to it's pre-occlusion value.

Using these plethysmographic methods in-vivo several groups have shown that varicose veins are more distensible than controls (Woodyer *et al.* 1981; Pupita *et al.* 1981; Eiriksson and Dahn 1968; Zsotér and Cronin 1966; McCausland *et al.* 1961). In an interesting further study Eiriksson (Eiriksson,1968) repeated the measurements of venous distensibility after radical removal of all visible superficial varicose veins, finding that the results were not markedly changed. This suggests that the abnormality affects all the veins of the leg and not just those which become visible as varicose veins.

A flaw in all these studies is that the initial volume of neither the limbs nor the veins was used in the calculation of venous elasticity (hence use of the term distensibility, although

really that also should be similarly corrected). Each limb will have a different resting venous volume at 0 mmHg and a different overall volume; thus an increase in volume of 50cm3 over a given change in pressure in a large limb would represent an entirely different distensibility or elasticity to the same volume change in a smaller limb.

Whilst this may not matter in studies which examined distensibility in the same limb under 2 different circumstances (eg. Eiriksson's perceptive study of venous distensibility before and after varicose vein extirpation), it is clearly relevent when comparing two groups of limbs (eg. one set of limbs with varicose veins with another control set).

A more recent study by Clarke (Clarke *et al.* 1989) claims to address this issue. Direct pressure measurements rather than indirect cuff pressure measurements were used to record venous pressure changes, and the strain gauge plethysmograph was used to monitor limb volume changes. The pressure / volume curve was examined at it's flattest section, where the veins are thought to have fully assumed their circular configuration, in order to avoid the area of the curve which is most susceptible to influence from the surrounding tissues, the configuration of the vein and dynamic factors such as smooth muscle tone. The flat part of the curve was then extrapolated back to the ordinate where the strain gauge measurements were recorded and the intercept taken as an initial volume, into which the volume change may be divided to calculate elasticity according to the equation above. The problem with this is that a strain gauge plethysmograph records percentage volume change relative to the initial volume which is set by "zeroing" the machine at the start of each measurement, and therefore the initial volume is still not known and cannot be calculated from the available data.

This paper, despite the limitations discussed above, reported an interesting finding; that limbs thought to be at high risk of developing varicose veins have a modulus of elasticity similar to those which are already affected by varicose veins or deep venous insufficiency. This suggests that vein wall weakness (i.e. loss of elasticity) precedes the development of visible varicose veins. This reinforces the concept of vein wall weakness (due to whatever cause) being the underlying defect responsible for varicose

veins and venous insufficiency. I have some reservations though since the group of limbs decrees to be at risk of developing varicose veins were selected partly on basis of having abnormal venous function tests or reflux on duplex examination. The presence of valvular incompetence fulfills the definition of varicose veins used in some epidemiological studies, particularly if corroborated by symptoms associated with varicose veins which was another of the selection criteria. What is needed is a prospective study of subjects with normal venous function tests and no visible varicose veins but abnormal venous elasticity, this would of course be very difficult to do.

The same method has been used by this group to examine the changes produced by compression hosiery on venous elasticity (Leon *et al.* 1993). They demonstrated that some limbs had a deterioration in venous elasticity whilst others had an improvement. They found that those limbs which had been affected by varicose veins for 10 years or more did not show an improvement in venous elasticity. I have similar reservations regarding this paper since the elastic stockings might be expected to reduce the initial limb volume (by reducing oedema) and therefore this should affect the calculation of elasticity.

SECTION II

EXPERIMENTAL WORK

CHAPTER SEVEN

THE CLINICAL SIGNIFICANCE OF CALF PUMP FAILURE

7.1 Ambulatory venous pressure and skin condition

Introduction

Ambulatory venous pressure (AVP), as previously mentioned has been the "gold standard" test of venous function in the lower limb since it's introduction into clinical practice in the 1940's (Arnoldi,1966; Warren *et al.* 1949; Ludbrook,1966; Tyson and Goodlett 1945; Nicolaides and Zukowski 1986; Pollack *et al.* 1949). The function of the venous calf muscle pump is to pump blood with each muscle contraction from the calf proximally towards the heart, with venous valves preventing it's reflux prior to the next pump systole. This pumping mechanism therefore reduces venous pressure, measurement of which provides an index of efficacy of the calf muscle pump. A high venous pressure remaining after a standardised exercise is associated with a high risk of venous ulceration, and is thought to be central to the pathogenesis of ulceration.

No previous study has examined the spectrum of skin changes from normal through to ulceration with respect to ambulatory venous pressure. The aim of this study was to establish, in our referral population with venous disease, the relationship between AVP and the clinical severity of their venous disease assessed on a four point score from normal skin through to ulceration.

Patients and methods

Two hundred and twelve patients attending the vascular clinic of a University teaching hospital with a diagnosis of either varicose veins or chronic venous insufficiency were studied. Twenty eight limbs had previous deep venous thrombosis proven on phlebography. Three-hundred and sixty limbs were assessed, patients who were diabetic or had coexistent arterial disease were excluded from the study. Clinical examination was performed in order to divide them into four groups;

Group 1 Varicose veins but healthy skin.

Group 2 Mild skin changes (eczema or pigmentation).

Group 3 Severe skin changes (lipodermatosclerosis).

Group 4 Ulceration (either active at the time of examination or a history of recurrent ulceration).

Eczema, pigmentation and lipodermatosclerosis were classified as defined by Browse & Burnand (Browse and Burnand 1988). Pigmentation; the brown haemosiderin staining of the skin of the gaiter area. Eczema; or dermatitis, inflammation of the skin which may be dry and scaly or vesicular, ulcerated and weeping. Lipodermatosclerosis; the progressive fibrosis of the skin and subcutaneous tissues associated with venous hypertension (Browse, 1983).

All clinical assessments were performed by the same observer (myself) prior to measuring the venous pressure. Ambulatory venous pressure was recorded as described in the introduction. Briefly, a pedal vein was cannulated with a 21 gauge needle, connected to a pressure transducer, amplifier and chart recorder. The ambulatory venous pressure was recorded after a short, standardised exercise regimen (ten tiptoe exercises performed at the rate of one/second). The time taken for the pressure to return to 90% of the initial resting pressure on cessation of exercise was also recorded (RT90). The lowest of three repeated measurements of AVP was recorded.

One-hundred and forty-three patients had both limbs assessed. In many cases it was not possible to cannulate a vein on both feet, therefore in 74 cases only one limb entered the study.

Statistical analysis.

Data were analysed using non-parametric methods. Comparisons between groups were made using the Mann-Whitney U test for unpaired data (two tailed analysis). Confidence limits were calculated as 95% confidence limits using the one sample Wilcoxon test.

In those limbs with unilateral ulceration the median AVP was 68mmHg (95% confidence interval; 57 - 80 mmHg) in the ulcerated limb compared to 56.5mmHg (95% confidence interval; 42.5 - 68.5mmHg) in the non-ulcerated limb. This difference is statistically significant at $p < 0.05$ using the paired Wilcoxon test. I therefore analysed these data by limb rather than by patient.

Results

One-hundred and thirty-three limbs had varicose veins and healthy skin with no evidence of eczema, pigmentation, lipodermatosclerosis or ulceration. Seventy-one limbs had evidence of eczema or pigmentation but no lipodermatosclerosis. Fifty-eight limbs had lipodermatosclerosis but no ulceration and 98 limbs had either active ulceration or a history of recurrent ulceration.

The median ambulatory venous pressure in the group with healthy skin was 47.5 mmHg (95% CI; 43.5 - 51 mmHg), compared to 62 mmHg (95% CI; 57.5 - 64 mmHg) in the eczema/pigmentation group, 65 mmHg (95% CI; 61 - 68 mmHg) in the lipodermatosclerosis group and 69 mmHg (95% CI; 65 - 73 mmHg) in the ulcerated group. Figure 7.1 shows this graphically, with 95% confidence intervals (Wilcoxon) for each group. Significant differences in ambulatory venous pressure were obtained between the group with healthy skin and the group with mild skin changes ($p < 0.0001$, Mann-Whitney U test) and between the group with mild skin changes and the ulcerated group ($p < 0.01$, Mann-Whitney U test). The differences obtained between the group with mild skin changes and those with more severe skin changes and between those with severe skin changes and those with ulceration were not statistically significant.

The AVP data were also analysed by grouping limbs according to their ambulatory venous pressure recording (in bands of 10 mmHg) and looking at their clinical classification. Figure 7.2 shows this analysis graphically giving the proportion of limbs with each clinical classification in these groups.

The median venous refilling time (RT90) in the limbs with healthy skin was 12 seconds, compared with 5.25 seconds in the group with eczema or pigmentation, 4.9 seconds in the group with lipodermatosclerosis and 5 seconds in the ulcerated group (see Figure 7.3). The difference obtained between the group with healthy skin and those with skin changes was statistically significant ($p < 0.0001$, Mann-Whitney U test). Other differences between groups were not significant.

Discussion

These data show a clear association between the clinical severity of venous disease and ambulatory venous pressure in a large sample of limbs with a wide spectrum of venous disease. Previous studies have assessed fewer patients and have only examined the incidence of ulceration. Those limbs with skin complications of venous disease have a shorter venous refilling time and a higher venous pressure after exercise (AVP) than those with uncomplicated varicose veins. This suggests that it is not varicose veins per se which cause skin complications but the effect that the varicose process has on the venous calf muscle pump.

The measurement of ambulatory venous pressure was more sensitive than the measurement of venous refilling time in detecting differences between the clinical groups. There was a significant deterioration in AVP between limbs with mild skin changes and those with ulceration, which was not seen in the refilling time measurements. This is not surprising since it is thought that it is the prolonged exposure to elevated venous pressure which causes venous ulceration. Ambulatory venous pressure measures overall calf pump function, refilling time measures just the rate of the venous reflux.

Figure 7.1 Ambulatory venous pressure in limbs grouped by clinical condition (medians & 95% confidence intervals)

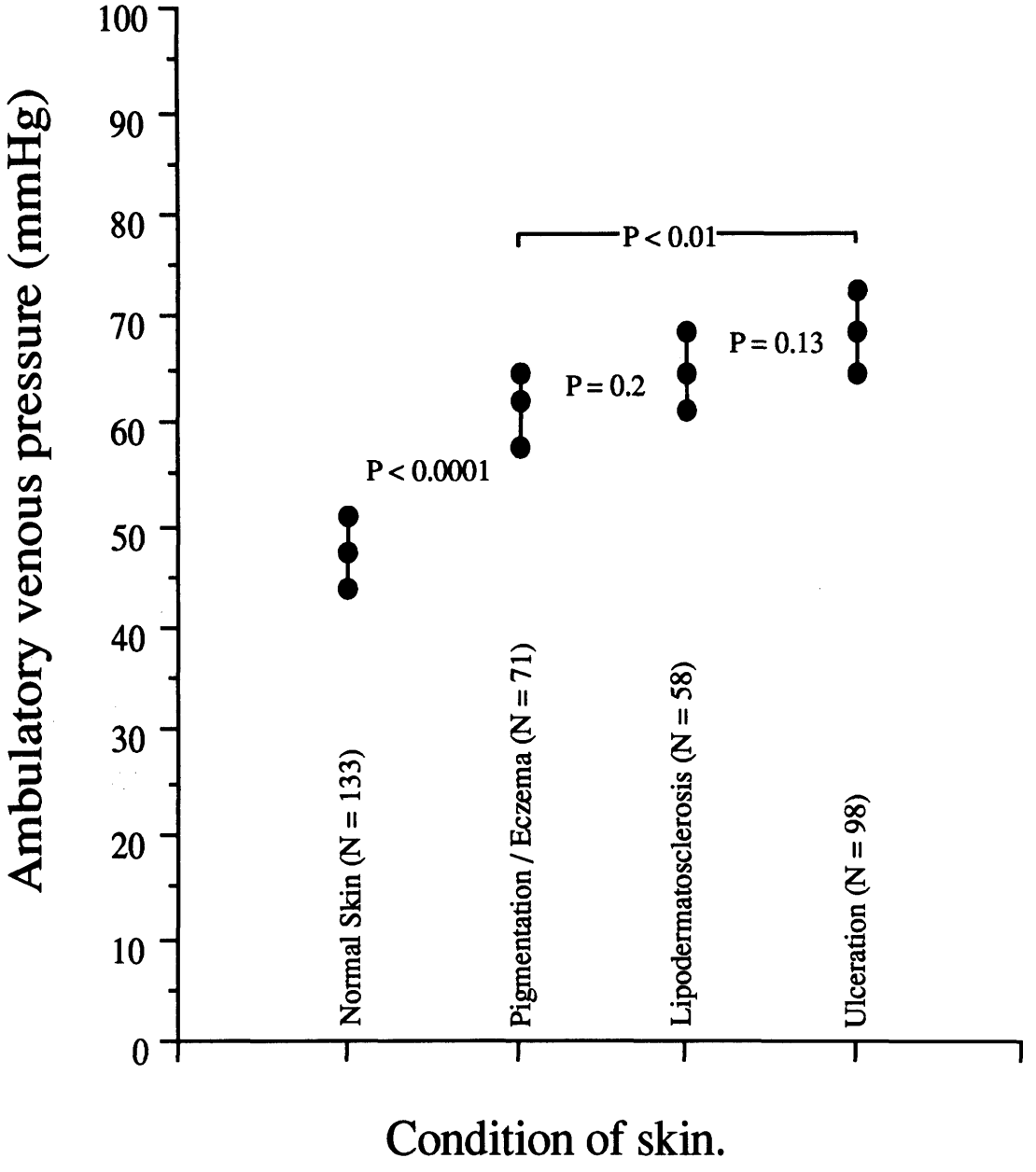


Figure 7.2 Clinical condition of limbs grouped by ambulatory venous pressure

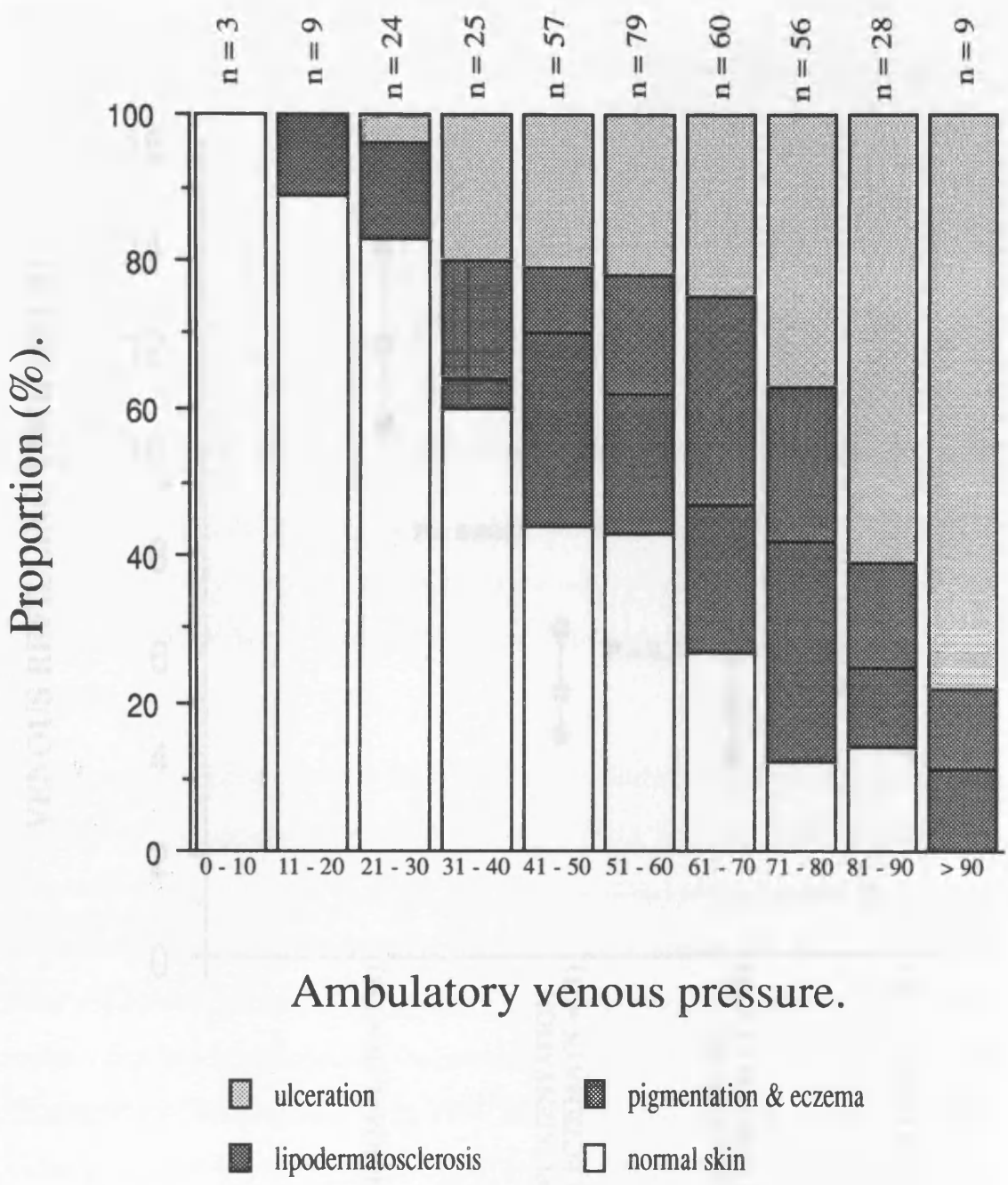


Figure 7.3 Venous refilling time in limbs grouped by clinical condition (medians & 95% confidence intervals)

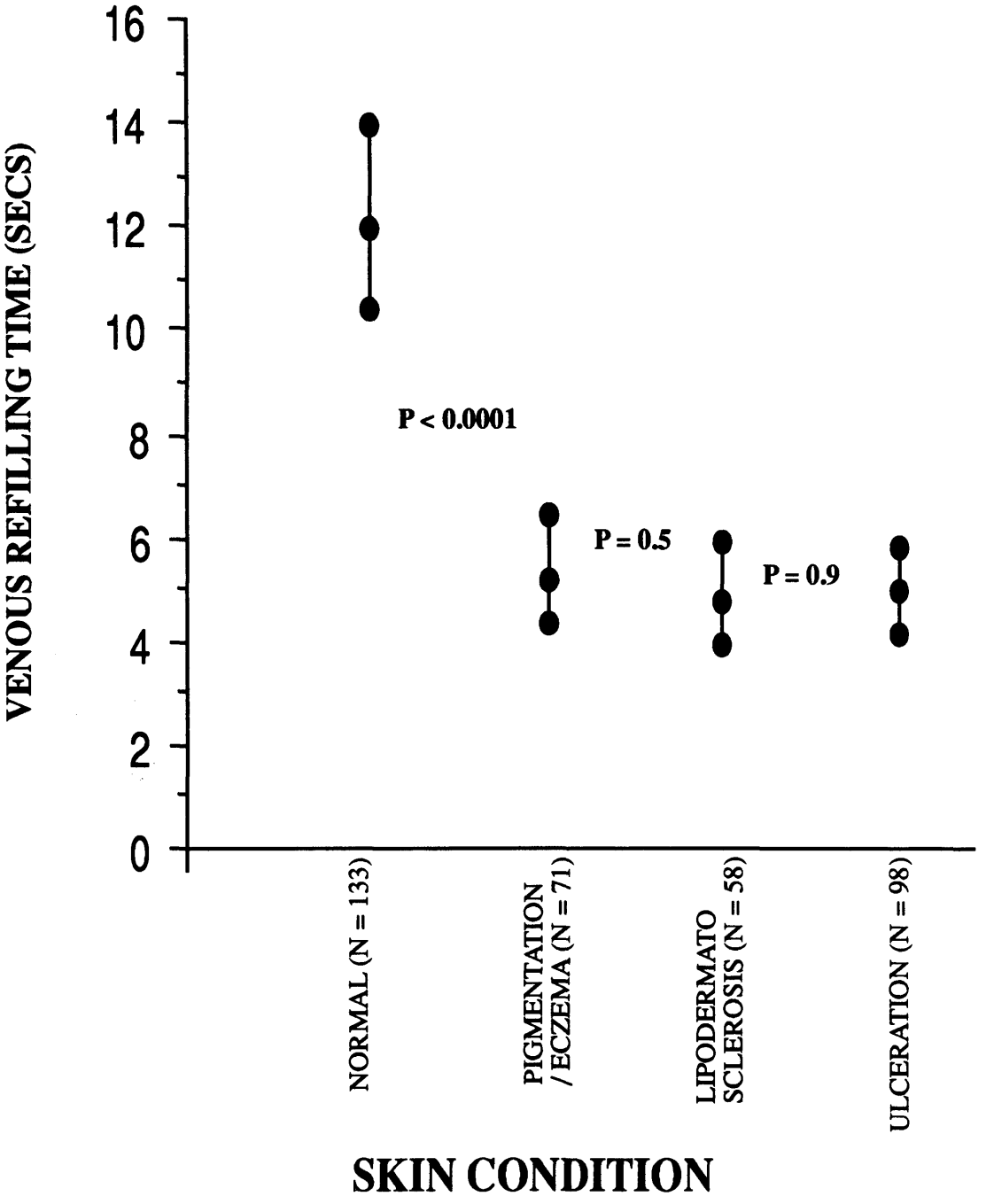


Figure 7.2 shows that the likelihood of venous ulceration and skin damage increase in a linear fashion with increasing AVP. There is, however some overlap between AVP measurements in limbs grouped by their clinical condition as shown in Figure 7.1. There are a number of explanations why this may be so.

Some limbs reach their AVP within one or two tiptoe movements whilst others continue to reduce their venous pressure over the ten tiptoe movements. In order to reach common agreement on what constitutes AVP the standard exercise regimen is generally accepted, however since most of the day's activity is confined to very brief shuffles from one foot to the other it is clear that the group which reach AVP rapidly will spend a greater proportion of the day with a lower venous pressure in spite of having a similar AVP to those which reach AVP towards the end of the ten tiptoe movements.

In addition to this, the level of activity (and therefore the time spent at AVP) during a 24 hour period will vary between subjects. An immobile subject may have a low AVP but will spend most of the day with a high venous pressure since the calf muscle pump is not working.

Difference in lymphatic function may play a role in determining which patients develop ulceration in the presence of an elevated AVP (Franzeck *et al.* 1993) however this study does not address this issue. Similarly and perhaps related to this, several studies have examined the role of the leukocyte in the pathology of venous disease. It is likely that local and systemic factors affecting neutrophil function and fibrinolysis may determine which limbs develop ulceration in the presence of an elevated AVP (Whiston *et al.* 1994; Bradbury *et al.* 1993; Browse *et al.* 1977; Hach *et al.* 1986; Leach and Browse 1986; Falanga *et al.* 1991).

This study therefore demonstrates that ambulatory venous pressure correlates well with the clinical condition of the skin in patients with venous disease. Limbs affected by the skin changes of eczema / pigmentation or lipodermatosclerosis are associated with calf

muscle pump failure as measured by AVP. Ulceration is associated with further deterioration of calf pump function.

7.2 Which refluxing veins are the most important clinically?

Introduction.

The venous calf muscle pumping mechanism of the leg relies on the competence of the venous valves. The sequelae of chronic venous insufficiency (skin damage such as lipodermatosclerosis, pigmentation, eczema and ulceration) are usually the result of venous valvular incompetence. The overall function of the valves in the leg may be assessed using ambulatory venous pressure (AVP) measurement, but in planning surgery it is more helpful to have an indication of the relative contribution of each vein in the pathological process. Duplex scanning may be used to assess individual veins for valvular incompetence but, to date, there has been no comprehensive analysis of the relative contribution made by each vessel. The present study addresses this issue.

Patients and methods.

One hundred and sixty-one patients attending the vascular clinic of a university teaching hospital with a clinical diagnosis of either varicose veins or the skin changes associated with chronic venous insufficiency were studied. Diabetics and patients with coexisting arterial disease were excluded. Twenty-eight limbs previously had a deep venous thrombosis shown by phlebography that had recanalised. No limb with residual venous occlusion as detected by duplex was included in the study.

Clinical examination was carried out by one observer (myself) in order to divide the limbs into three groups of increasing clinical severity of disease: (1) Limbs with varicose veins but healthy skin; (2) limbs with varicose veins and associated skin changes, i.e. varicose eczema, pigmentation due to haemosiderin deposition or

thickening of the subcutaneous tissue due to fibrin deposition (lipodermatosclerosis); and (3) limbs with venous ulceration (either active or healed ulcers; but those which remained healed as a result of previous surgery were excluded).

Duplex scanning was carried out in 274 limbs using an Hitachi® duplex scanner with an 8.5MHz probe and pulsed Doppler signal analysis. Patients were studied seated on the edge of a couch with a foam back rest so that their legs were dependent and completely relaxed during the examination. The common femoral, superficial femoral, profunda femoris, long and short saphenous and popliteal veins (just below the sapheno-popliteal junction) were interrogated using duplex. As each vein was identified by ultrasonography the subject performed a Valsalva manoeuvre as hard as possible in order to produce retrograde venous flow which was detected by the Doppler signal. If a Valsalva manoeuvre failed to produce venous reflux, the calf was manually compressed and released. If either Valsalva or release of calf compression produced venous reflux of duration greater than 0.5 s, the vein was classified as incompetent (Van-Bemmelen *et al.* 1989). Perforating veins were not examined as it is difficult to be certain whether all perforators in a limb have been interrogated and because it is not clear yet what constitutes normal flow in these vessels (McMullin *et al.* 1991). The agreement between Duplex and venography in diagnosing incompetent perforators has also been shown to be poor (Phillips *et al.* 1995).

Ambulatory venous pressure was also recorded as previously described in 197 of these limbs. The lowest of three repeated measurements were recorded.

Statistical analysis.

The clinical condition of the skin was classified as described above into three categories; 'normal', 'skin changes' and 'ulcerated' in order of increasing severity. Duplex data for each vessel was recorded as; 'normal', 'reflux' or 'absent'. The 'absent' category was included so that limbs which had previously undergone long or short saphenous disconnection could be included in the analysis. For technical reasons, it was not always

possible to be certain whether the profunda femoris vein was competent and in such circumstances this was recorded as 'absent'. Six short saphenous veins could not be identified despite the absence of previous surgery and were recorded as 'absent'.

Analysis of the association between the skin condition (dependent variable) and the presence of reflux in the six veins (predictor variables) was by ordered polytomous regression using PROC LOGISTIC in the SAS statistical package (SAS Institute, Cary, North Carolina, USA). As the dependent variable had 3 levels, the models fitted had 2 intercept terms, one corresponding to the comparison of normal skin *versus* skin changes plus ulcer, and the second to normal plus skin changes *versus* ulceration. This technique is *similar* to logistic regression but allows for the dependent variable to be ordinal rather than binary. All six predictor variables were included in the first model. Each predictor variable was then tested by dropping it from the analysis. If, by dropping a given predictor variable the deviance of the model was increased, it was returned to the analysis. If the variable did not appear significantly to influence the deviance of the model it was left out. Predictor variables were dropped in the order of least effect on the deviance of the model.

Results.

A total of 274 limbs were studied, of which 116 had normal skin, 82 skin changes and 76 either active or healed venous ulceration. The distribution of the duplex findings for the six veins (predictor variables) with the clinical condition of the limb is shown in Table 7.1.

The profunda femoris, superficial femoral and short saphenous vein variables were dropped from the analysis since they produced no increase in the deviance of the statistical model. The final model contained the variables common femoral, popliteal and long saphenous veins. Each of these contributing significantly to the fit of the final model. Table 7.2 shows the relative risks of different skin conditions from the duplex

result as derived from the final logistic model. The final statistical model was then used to produce an indication of the likely skin condition for any combination of venous duplex results. Table 7.3 shows the fitted probabilities (with 95% confidence limits) of either skin ulceration or normal skin for different combinations of duplex data. In order to test that this model was statistically robust, the data were randomly split into two and the same analysis performed on each half of the data. In this analysis the popliteal and long saphenous veins were found to significantly influence the fit of the model, with similar weighting. The common femoral vein showed the greatest weighting of the other veins, however this fell below the level of statistical significance.

One-hundred and ninety-seven of these limbs also had AVP measurements performed at the same visit. Table 7.4 shows the relationship between the median AVP recordings and the clinical state of the limb. Analysis of variance with the natural logarithm of AVP as the dependent variable showed that the mean AVP was significantly different between the levels of skin condition ($F = 26.65$, 2185 d.f, $p = 0.0001$). Pairwise comparisons of the levels of skin condition by means of Bonferroni *t* tests gave significant differences in median AVP between normal and skin changes but not between skin changes and ulceration. The median difference in AVP between normal and skin damaged limbs was 18mmHg whilst that between skin damage and ulceration was 4mmHg (see Table 7.4).

Table 7.1 Distribution of Duplex results by skin condition

VEIN	SKIN CONDITION					
	Normal		Skin changes		Ulcerated	
Common femoral						
Normal	103	(89)	56	(68)	36	(47)
Reflux	13	(11)	26	(32)	40	(53)
Superficial femoral						
Normal	107	(92)	63	(77)	46	(61)
Reflux	9	(8)	19	(23)	30	(39)
Profunda femoris						
Normal	99	(85)	55	(67)	41	(54)
Reflux	2	(2)	5	(6)	14	(18)
Absent	15	(13)	22	(27)	21	(28)
Long saphenous						
Normal	39	(34)	12	(15)	10	(13)
Reflux	60	(52)	65	(79)	53	(70)
Absent	17	(15)	5	(6)	13	(17)
Popliteal						
Normal	106	(91)	56	(68)	35	(46)
Reflux	10	(9)	26	(32)	41	(54)
Short saphenous						
Normal	74	(64)	44	(54)	36	(47)
Reflux	33	(28)	32	(39)	34	(45)
Absent	9	(8)	6	(7)	6	(8)

Values in parentheses are percentages

Table 7.2 Relative risk of different skin conditions for the three-category logistic model

		Relative risk	(95% c.i.)	*P* *
Common femoral	(refluxversus normal)	3.16	(1.76 - 5.66)	0.0001
Popliteal	(refluxversus normal)	5.17	(2.80 - 9.54)	0.0001
Long saphenous	(refluxversus normal)	4.81	(2.43 - 9.52)	0.0001
Long saphenous	(absentversus normal)	3.67	(1.50 - 8.97)	0.0043

**P* value of Wald χ^2 to test slope parameter of 0. 95% c.i.= 95% confidence interval

Table 7.3 Patterns of reflux and skin condition: calculated probabilities

Fitted probabilities of normal skin and ulceration from the final statistical model

Duplex scan result CFV	LSV	POP	Probability (95% c.i.) Normal skin	Ulceration	No.of limbs
N	N	N	0.82 (0.71-0.90)	0.04 (0.02-0.07)	38
R	N	N	0.60 (0.41-0.77)	0.11 (0.05-0.21)	2
N	A	N	0.56 (0.39-0.72)	0.12 (0.06-0.22)	19
N	R	N	0.49 (0.41-0.58)	0.15 (0.11-0.22)	111
N	N	R	0.48 (0.30-0.66)	0.16 (0.08-0.29)	6
R	A	N	0.29 (0.15-0.49)	0.30 (0.16-0.51)	6
R	R	N	0.24 (0.15-0.36)	0.36 (0.24-0.51)	24
R	N	R	0.22 (0.12-0.37)	0.38 (0.23-0.55)	16
N	A	R	0.20 (0.10-0.37)	0.42 (0.24-0.62)	7
N	R	R	0.16 (0.09-0.27)	0.48 (0.33-0.64)	17
R	A	R	0.07 (0.03-0.16)	0.69 (0.50-0.84)	3
R	R	R	0.06 (0.03-0.11)	0.75 (0.62-0.84)	25

CFV = Common femoral vein. LSV = Long saphenous vein. POP = Popliteal vein.

N = normal, no evidence of reflux. R = venous reflux. A = absent, as described above.

95% c.i. = 95% Confidence interval

Table 7.4 Ambulatory venous pressure and skin condition

Skin condition	Ambulatory venous pressure (mmHg)	
Normal	48	(30 - 59)
Skin changes	66	(50 - 74)
Ulcerated	70	(56 - 80)

Values are medians (interquartile range)

Discussion.

Venous calf muscle pump function relies on the integrity of the venous valves, incompetence of which results in reflux of blood, with consequent pump failure. The skin changes and ulceration found in limbs with chronic venous insufficiency are the result of calf muscle pump failure (Browse and Burnand 1988), caused in most cases by valvular incompetence (McEnroe *et al.* 1988). The calf muscle pump is normally able to reduce the venous pressure from between 80 and 100 mmHg at rest, to between 0 and 20 mmHg after exercise. The pressure after exercise, the AVP, is a measure of calf pump efficiency. An increase in AVP correlates well with the risk of venous ulceration, and is thought to be central to the pathogenesis of ulceration (Arnoldi,1966; Ludbrook,1966; Nicolaides and Zukowski 1986; Pollack *et al.* 1949; Tyson, and Goodlett 1945; Warren *et al.* 1949). If the condition of the skin is to be improved then surgery should be aimed at correcting sites of venous incompetence, to improve the pumping mechanism and so reduce AVP.

I have been unable to find any study which examines in a comprehensive way the contribution that reflux in different veins make to the clinical condition of the limb.

O' Donnell has reviewed several studies which looked at the relative roles of deep and superficial reflux, concluding that the limbs with venous ulceration were more likely to have deep venous incompetence than those without ulceration (O'Donnell, 1991). Lees and Lambert (Lees and Lambert 1993) came to the same conclusion reviewing 300 limbs, 98 of which had skin changes. Sethia and Darke (Sethia and Darke 1984) have drawn attention to the role of long saphenous reflux in venous ulceration. They describe excellent clinical results from long saphenous stripping in patients with ulceration and long saphenous incompetence.

AVP measurement gives a global indication of calf muscle pump function. The addition of narrow tourniquets to obstruct superficial reflux has been used to determine the contribution that deep venous incompetence alone makes to calf pump function. Stripping the long saphenous vein has been shown to have a similar effect to that of a tourniquet placed just above the knee (Sethia and Darke 1984). Using this method therefore the relative contributions made by deep and superficial reflux may be analysed. I have examined in the next section the role of tourniquet testing in predicting the results of superficial venous surgery and in differentiating deep from superficial incompetence.

Duplex scanning has been used to study the pattern of venous incompetence found in different clinical states. Hanrahan *et al.* (Hanrahan *et al.* 1991) examined 54 limbs with varicose veins and found that 28 per cent had long saphenous incompetence and 41 per cent had deep vein incompetence. He also examined 95 limbs with venous ulceration (Hanrahan *et al.* 1991) and found that the majority (66 per cent) had deep and superficial reflux, or deep and perforator incompetence, or superficial and perforator incompetence. He concluded that venous incompetence is a heterogenous disorder, and full evaluation using duplex scanning was recommended.

This study used duplex scanning to evaluate the relative contribution made by each vein to the overall clinical condition of the limb. Eliminating the results for superficial femoral, profunda femoris and short saphenous veins there was no significant increase in the deviance from the statistical model. This suggests that these veins have little clinical and haemodynamic significance with respect to skin change; operating on them would seem unlikely to improve the condition of the skin. The other 3 veins are significant in this context, and should be worth treating surgically.

The final statistical model, which relates skin condition to the duplex scan results from the common femoral, popliteal and long saphenous veins was used to construct Table 7.2. This table may be used to infer whether a limb is likely to develop skin changes or ulceration, based on the duplex findings.

The analysis emphasizes the importance of the popliteal and long saphenous veins since these have the highest relative risk values (Table 7.2) of 5.17 and 4.81 respectively. By virtue of their location perhaps these veins (with their valves) may be regarded as the "gatekeepers" of the venous calf muscle pump. Bradbury *et al.* (Bradbury,1993) showed in a small follow up study of patients undergoing thorough superficial venous surgery including perforator ligation for recurrent ulceration that popliteal reflux was very strongly associated with recurrent ulceration, adding weight to the hypothesis that the function of the popliteal vein is central to the function of the venous calf muscle pump and the maintenance of healthy skin.

Since the statistical model predicts the severity of disease from the duplex scan data it is not surprising to find a correlation between the duplex scan derived probability of ulceration and AVP ($r_S = 0.27$, $p = 0.0001$)

This statistically derived model now needs to be tested prospectively to determine it's predictive value. Reference to the model (summarised in Table 7.3) may allow an improvement in decision making in venous surgery, both in deciding whether to operate and also in deciding upon which veins to operate.

CHAPTER EIGHT

TOURNIQUETS AND VENOUS ASSESSMENT

8.1 The predictive value of the ambulatory venous pressure/tourniquet test

Introduction.

Routinely stripping the long saphenous vein (LSV) in patients with varicose veins is a contentious issue. Many surgeons routinely strip the LSV arguing that the more extensively an incompetent venous system is removed the lower is the recurrence rate (Munn *et al.* 1981; Myers,1957; Jakobsen,1979). Others however have demonstrated that adding routine stripping to the technique of sapheno-femoral disconnection and avulsions does little to improve surgical results (Large,1985). Hammarsten *et al.* (Hammarsten *et al.* 1990) have recently shown after 5 years follow-up that sapheno-femoral disconnection, combined with selective perforator ligation gives similar clinical and haemodynamic results when compared with long saphenous stripping.

Advantages of routine stripping therefore, are that there may be a reduced recurrence rate and that any incompetent thigh perforators are dealt with effectively. Advantages of sapheno-femoral disconnection are that the vein may be preserved for potential use as an arterial conduit (Hammarsten *et al.* 1990), there is less risk of damage to the saphenous nerve (Holme *et al.* 1988) and the procedure is more suitable for day case surgery (Jakobsen,1979).

If one considers the advantages sufficient to justify a selective approach to long saphenous stripping then it is important to have a means of deciding in which patients would sapheno-femoral disconnection suffice. McMullin *et al.* (McMullin *et al.* 1991) recently demonstrated that high ligation fails to control functionally significant reflux in a

high proportion of cases selected on clinical criteria alone. This selection may be aided by considering the haemodynamic principles of venous incompetence.

As discussed above the severity of venous calf muscle pump failure is accurately measured by the ambulatory venous pressure and is strongly correlated with the clinical condition of the leg, therefore effective venous surgery should aim to lower the ambulatory venous pressure. By inflating narrow tourniquets around the leg it is said to be possible to obstruct superficial venous flow without affecting deep venous flow (Nicolaides *et al.* 1971). Since sapheno-femoral disconnection just controls reflux at the sapheno-femoral junction a tourniquet placed high on the thigh should mimic this effect. Long saphenous vein stripping to just below the knee should control all deep to superficial reflux above that level. A tourniquet placed just below the knee should mimic this effect. Limbs with reflux distal to this or deep venous reflux would not be expected to benefit either from tourniquet application or from long saphenous surgery. Thus a thigh tourniquet should predict the result of sapheno-femoral ligation and a knee tourniquet the result of long saphenous stripping.
This study examines the use of tourniquets to predict post-operative AVP after sapheno-femoral disconnection and long saphenous vein stripping.

Patients and Methods

Forty-eight limbs of 41 patients with symptomatic varicose veins in the distribution of the long saphenous vein were studied. Prior to surgery the ambulatory venous pressure was measured as described above. AVP was recorded initially with no tourniquet, and then with a 2.5 cm wide tourniquet inflated just below the knee to 140 mmHg and lastly with a 2.5 cm wide tourniquet inflated to 180 mmHg around the upper thigh.

Sapheno-femoral disconnection was carried out in 22 limbs and in 26 limbs in addition the long saphenous vein was stripped from the groin to a point just below the knee (both procedures were carried out blind to the results of haemodynamic tests according to the individual surgeon's preference, under general anaesthesia and were supplemented by

avulsion of visible superficial varices). After surgery, when the patients were ambulant and all wounds had healed the AVP was recorded with no tourniquet in order to detect any improvement due to the surgery.

Results

The age of patients in the two groups was not significantly different. In the group which underwent sapheno-femoral disconnection the median age was 58 years (95% confidence interval; 52 - 65), compared with 62 years (95% confidence interval; 57 - 67) in the LSV stripping group. P = 0.3, *Mann-Whitney U* .

All patients reported a subjective improvement in their symptoms and there had been no ulcer recurrence in the post-operative period in the small group with previous ulceration. The distribution of limbs in the two groups classified by the clinical condition of the limb is shown in Table 8.1

Table 8.1 Distribution of limbs classified by clinical condition

	Condition of skin		
	Healthy	Skin damage	Ulceration
Saphenofemoral disconnection	9	8	5
Long saphenous strip	2	15	9

Healthy = *varicose veins with healthy skin*

Skin damage = *eczema, pigmentation or lipodermatosclerosis*

Ulceration = *active or healed venous ulceration*

Sapheno-femoral disconnection

The median preoperative AVP in this group was 60 mmHg (95% confidence interval 53 - 68) and median return time was 6 secs (95% confidence interval 3.5 - 10). These values were improved by the operation to a median AVP of 44 mmHg (95% confidence interval 34 - 53) and a median return time of 13 secs (95% confidence interval 10 - 16)

Long saphenous stripping

The median preoperative AVP in this group was 59 mmHg (95% confidence interval 52 - 68) and median return time was 6 secs (95% confidence interval 5 - 9). These values were improved by the operation to a median AVP of 49 mmHg (95% confidence interval 43 - 54) and a median return time of 13 secs (95% confidence interval 10 - 18)

There was no significant difference between the improvement of AVP produced by the two operations ($P > 0.05$, Mann-Whitney U test).

In order to examine the predictive value of the AVP and RT measurements I have calculated the Spearman rank correlation between pre-operative predicted measurements and the true post-operative results. I have also calculated the positive and negative predictive values, the sensitivity and specificity and the overall accuracy of these pre-operative predictive measurements.

Figure 8.1 shows the relationship between the predicted AVP (ie. the AVP with the tourniquet inflated at the appropriate position) and the post-operative findings. A statistically significant correlation was found ($rho = 0.504$, $p = 0.0005$).

From these data the sensitivity, specificity, positive and negative predictive values and accuracy of the predictions with tourniquets have been calculated and are shown in Table 8.2.

Table 8.2. Predictive value of the tourniquet / AVP test

Overall accuracy	77%
Positive predictive value	81%
Negative predictive value	69%
Sensitivity	84%
Specificity	65%

Figure 8.2 shows the relationship between the predicted RT (ie. the RT with the tourniquet inflated at the appropriate position) and the post-operative findings. A statistically significant correlation was found (rho = 0.305, p = 0.04).

From these data the sensitivity, specificity, positive and negative predictive values and accuracy of the predictions with tourniquets have been calculated and are shown in Table 8.3.

Table 8.3 Predictive value of the tourniquet / RT test

Overall accuracy	75%
Positive predictive value	91%
Negative predictive value	40%
Sensitivity	77%
Specificity	33%

Figure 8.1 Predicted AVP (ie. the AVP with the tourniquet inflated at the appropriate position) and post-operative AVP

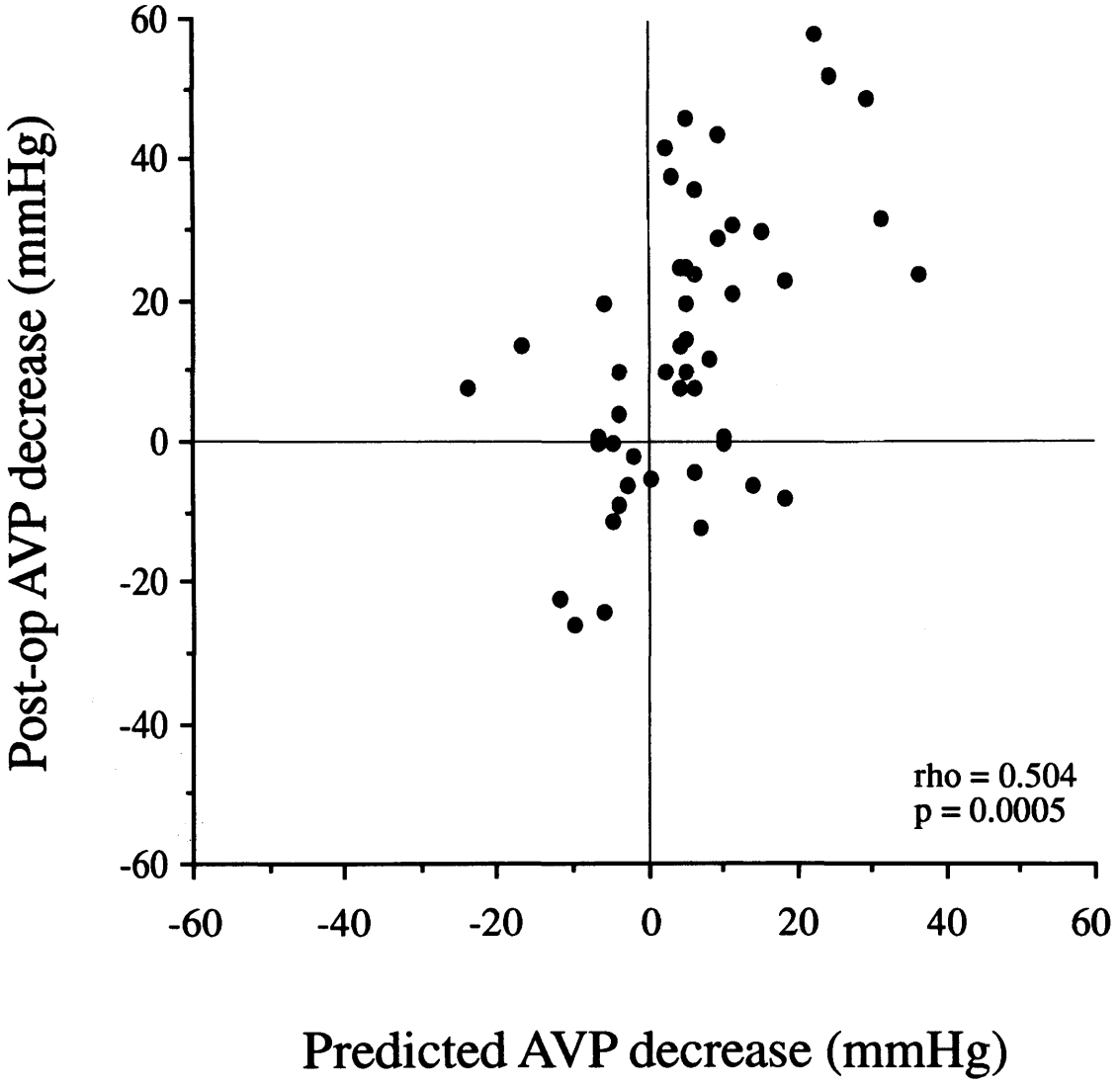
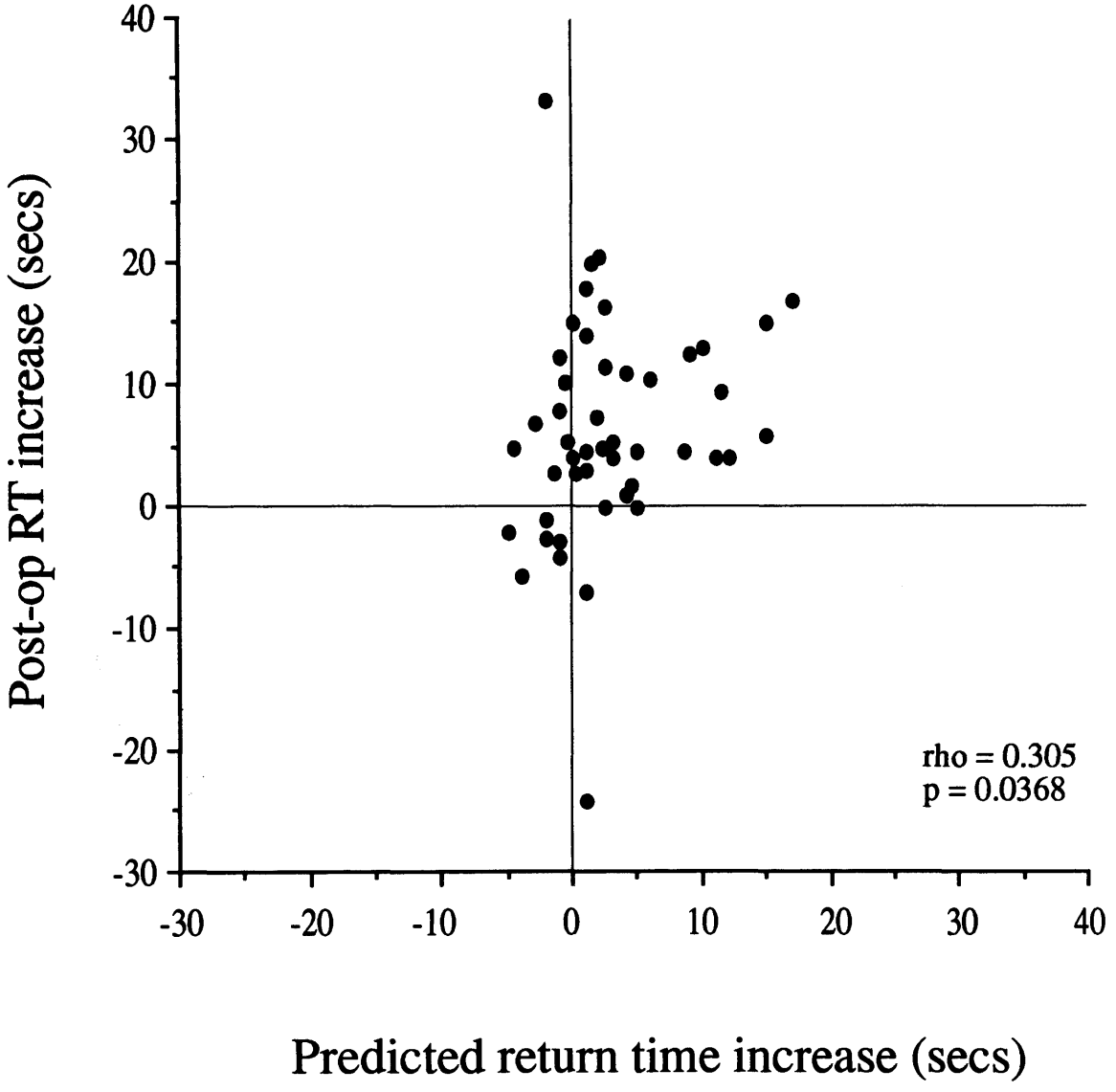


Figure 8.2 Predicted Refilling time (ie. the RT with the tourniquet inflated at the appropriate position) and post-operative RT



Discussion

By using a narrow tourniquet to obliterate long saphenous reflux the measurement of AVP has been used to predict those patients who will benefit from long saphenous stripping. Sethia and Darke (Sethia and Darke 1984) showed in 12 patients with venous ulceration that the improvement in AVP which a tourniquet produced was similar to that produced by stripping the long saphenous vein in the thigh. Kiely (Kiely,1990) corroborated this finding on a larger series of patients.

This study demonstrates a relationship between the venous haemodynamic effects of a narrow tourniquet inflated around the upper thigh and sapheno-femoral disconnection. Similarly between a narrow tourniquet inflated just below the knee and long saphenous stripping to that level.

The correlation between these "predictive measurements" (i.e. with the appropriate tourniquet in place) and the post-operative result is not good however. (Rho = 0.504 for AVP prediction and 0.305 for RT prediction). By examining the two graphs (Figs 8.1 & 8.2) it can be seen that the majority of limbs were improved (i.e. had a reduction in AVP and an increase in RT) by the surgery. This improvement overall was greater than that predicted by the tourniquets.

This is also borne out when the predictive values are examined. Both the AVP and the RT predictions have high positive predictive values and sensitivities but low negative predictive values and specificities.

The use of the tourniquet tests in predicting the haemodynamic effect of venous surgery cannot therefore be relied upon when making a clinical decision for an individual patient (or limb).

There are a number of possible explanations for these discrepencies.

1. Most of these procedures were supplemented by avulsion of visible varicosities in addition to the primary operation. These varicosities are (almost always) dilatations of

the tributaries of the long saphenous vein rather than the main trunk (Browse and Burnand 1988). Removal of these varicosities is not expected to have any haemodynamic benefit but is included in the surgical procedure since many patients are disappointed with their operation when visible varicosities remain. It is possible, but unlikely, that avulsion of these varicose tributaries causes a reduction in AVP and prolongation of RT which would account for the results obtained.

2. The operations were routinely accompanied by the use of thigh length compression stockings for the first two weeks after operation. It is possible that the use of these compression stockings confers some haemodynamic benefit. All patients when studied had been free of compression stockings for a least 2 weeks and therefore any effect due to the stockings was not likely to still be apparent. The effect of compression stockings on venous function is discussed later.

3. The overload of the venous calf muscle pump caused by superficial venous incompetence may take time to improve (much as the function of the heart improves after diuresis in congestive heart failure). Thus the short term action of a tourniquet would not reveal the full benefit of superficial venous surgery in improving calf muscle pump function.

4. These narrow tourniquets may not adequately obstruct superficial venous flow whilst leaving deep venous flow unaffected.

The use of tourniquets to distinguish between deep and superficial venous reflux is discussed in the next section.

8.2 The tourniquet/AVP test in differentiating deep from superficial venous incompetence

Introduction

In the previous section I showed that the tourniquet / AVP test gave an indication of the likely result of venous surgery but was not sufficiently accurate for any reliance to be placed upon it when considering individual patients. One possible reason for this would be if the AVP / tourniquet test failed to distinguish between deep and superficial venous reflux. This study compares the AVP / tourniquet test in differentiating deep from superficial reflux with Duplex scanning as a reference standard.

Patients and methods

Two-hundred and thirty four limbs of 141 patients attending the vascular clinic of a university teaching hospital were studied. All patients were referred with a diagnosis of either varicose veins or chronic venous insufficiency. Diabetics and patients with coexistent arterial disease were excluded. Twenty-two limbs had previously been shown to have a deep venous thrombosis on ascending phlebography.

Each limb was assessed clinically by one observer (myself) in order to determine the presence of lipodermatosclerosis, active ulceration or a history of recurrent ulceration. Ambulatory venous pressure was measured as previously described after ten tiptoe exercises performed at the rate of one/second, taking the lowest of three recordings. AVP and RT90 were recorded again with a narrow (2.5cm) tourniquet inflated just below the knee to a pressure of 140 mmHg (Nicolaides and Zukowski 1986). This has been shown previously to occlude superficial veins but not deep veins on phlebographic examination.

Each limb was assessed by duplex scanning in order to detect the presence of venous reflux in the popliteal and short saphenous veins and also in the long saphenous vein at

knee level. The duplex scan was carried out using a Hitachi scanner with an 8.5 MHz probe with pulsed Doppler signal analysis. Each patient sat with legs dependent over the side of a couch. Significant reflux was defined as reverse flow on release of manual calf compression with a duration greater than 0.5 secs. These three assessments were all performed at the same visit.

Results

Each limb was classified on the basis of the duplex scan as demonstrating either deep or superficial venous incompetence; a combination of both, or neither. One hundred and thirty four limbs demonstrated superficial venous reflux, 23 deep reflux, 39 had reflux in none of these veins examined and 38 had venous incompetence in both superficial and deep systems.

Table 8.4 shows the distribution of venous ulceration in these four groups based on the pattern of venous incompetence. It can be seen that the group with no venous incompetence at this level had the lowest incidence of ulceration (8%) and the group with incompetence in both superficial and deep systems had the highest incidence (53%). The limbs with deep incompetence alone also had a higher incidence of ulceration than did those with superficial incompetence alone (39% compared with 20%). The chi-squared test has been used to demonstrate the statistical significance of these differences.

A history of deep venous thrombosis proven on phlebography was found in 22 limbs (10%). Eight limbs with superficial incompetence had a previous DVT (6%), 5 with deep venous incompetence (22%), 1 with neither deep nor superficial incompetence (3%) and 8 with both deep and superficial incompetence. The presence of previous DVT was associated with deep venous reflux ($p < 0.001$, Chi-squared test) but not with superficial venous reflux ($p > 0.1$, Chi-squared test).

Table 8.5 shows the median ambulatory venous pressure (and 95% confidence limits) in each of these four groups. This shows that limbs with venous reflux in superficial

system have a higher ambulatory venous pressure than those without reflux ($p < 0.01$, Mann-Whitney U test). The median AVP in limbs with superficial reflux alone was 61 mmHg (58 - 64) compared with 60 mmHg (49 - 70) in those with deep reflux alone. Limbs with both deep and superficial reflux had a median AVP of 66 mmHg (60 - 72) compared with 60 mHg (49 - 70) in those with deep reflux alone. Thus the AVP alone is higher in the presence of venous incompetence but does not indicate whether that incompetence is in the superficial veins or the deep.

The same situation is found when the refilling times are examined:

Table 8.6 shows the median venous refilling times (RT90) with 95% confidence limits in each of the four groups. This shows a clear difference in RT90 between limbs with either deep or superficial reflux and those without reflux at this level ($p < 0.01$, Mann-Whitney U test). The median refilling time in limbs with superficial reflux alone at this level was 7 seconds (6 - 8) compared with 5 seconds (3 - 6) in those with both deep and superficial reflux. The limbs with deep reflux alone had a median refilling time of 8 seconds (6 - 10) compared with 5 seconds (3 - 6) in those with reflux in both the deep and superficial systems. Thus venous refilling time is shorter in the presence of venous incompetence but gives no indication of the location of that incompetence.

The effect of the tourniquet placed below the knee on AVP was calculated thus: Effect of tourniquet = AVP without tourniquet - AVP with tourniquet. Similarly for refilling times the effect of the tourniquet was calculated in the same way. Tables 8.7 and 8.8 show the median improvements in these parameters (with 95% confidence intervals) in the four groups with different patterns of reflux.

As can be seen from the Tables the tourniquet produced an improvement in both haemodynamic parameters in all groups instead of the "expected" improvement in just those limbs with superficial incompetence. In addition there is wide overlap between the haemodynamic improvements in all these groups demonstrating that the use of the

tourniquet does not differentiate significantly between reflux in the deep and superficial systems.

Table 8.4 Distribution of venous incompetence and skin ulceration

		Ulceration	
No reflux	(n = 39)	3	(8%) Δ§
Superficial reflux	(n = 134)	27	(20%) Δ¶
Deep reflux	(n = 23)	9	(39%) §¶#
Superficial & deep	(n = 38)	20	(53%) #

Chi squared: # ; p = 0.7 Δ ; p = 0.19 § ; p = 0.04 ¶ ; p = 0.2

Table 8.5 Distribution of venous incompetence and ambulatory venous pressure

		Median Ambulatory venous pressure (95% confidence limits)	
No reflux	(n = 39)	47 mmHg	(42 - 52)*
Superficial reflux	(n = 134)	61 mmHg	(58 - 64)*
Deep reflux	(n = 23)	60 mmHg	(49 - 70)
Superficial & deep	(n = 38)	66 mmHg	(60 - 72)

* $p < 0.01$, Mann - Whitney.

Table 8.6 Distribution of venous incompetence and venous refilling times (without tourniquet)

		Median Venous refilling time 90% (RT90) (95% confidence limits)		
No reflux	(n = 39)	14 secs	(11 - 19)	*§#
Superficial reflux	(n = 134)	7 secs	(6 - 8) *†	
Deep reflux	(n = 23)	8 secs	(6 - 10)	§†
Superficial & deep	(n = 38)	5 secs	(4 - 6) #	

*§; $p < 0.01$ †; $p > 0.05$ #; $p < 0.01$ Mann - Whitney.

Table 8.7 Distribution of venous incompetence and reduction of AVP with below-knee tourniquet

Duplex scan at knee level		Median Reduction in AVP with tourniquet. (95% confidence limits)	
No reflux	(n = 39)	1 mmHg	(-2 - 6)
Superficial reflux	(n = 134)	2 mmHg	(1 - 4)
Deep reflux	(n = 23)	3 mmHg	(0 - 7)
Superficial & deep	(n = 38)	3 mmHg	(0 - 5)

Table 8.8 Distribution of venous incompetence and increase in venous refilling time with below-knee tourniquet

Duplex scan at knee level		Median refilling time increase with tourniquet (95% confidence limits)	
No reflux	(n = 39)	1 secs	(0 - 3)
Superficial reflux	(n = 134)	1 secs	(0 - 1)
Deep reflux	(n = 23)	1 secs	(1 - 2)
Superficial & deep	(n = 38)	0 secs	(0 - 1)

Discussion.

The measurement of ambulatory venous pressure has been shown by this study to be unhelpful in determining whether venous reflux is present in the deep or the superficial veins at knee level (as assessed by duplex scanning). There was no greater reduction in AVP with the application of a tourniquet in the patients with superficial reflux, compared either with those who had deep venous reflux or those who had no reflux. Similarly, there was no greater increase in RT90 in the patients with superficial reflux compared with the others. This might be because the tourniquet fails to obstruct the superficial veins or compresses the popliteal vein (reducing flow or even restoring an incompetent valve to competence). A similar problem with using tourniquets has been noted by McMullin (McMullin *et al.* 1991). Another explanation would be that reflux through the perforating veins below the tourniquet influences the AVP to such an extent that the effect of the tourniquets is irrelevent. This seems unlikely, however the study has not addressed perforating vein incompetence. It has also been postulated that superficial reflux may overwhelm the venous calf muscle pump to such an extent that deep reflux is generated. In such a case obliterating the reflux circuit through the superficial veins also restores competence to the deep veins (Walsh *et al.* 1994).

The study also demonstrates that the highest incidence of ulceration is in limbs with both deep and superficial venous reflux, and that deep venous reflux is associated with a higher incidence of ulceration than superficial reflux (although not statistically significant) and that the lowest incidence of ulceration is in limbs with no reflux in the three veins examined at knee level. These findings are in accordance with all other analyses of the distribution of venous incompetence and skin ulceration. Ambulatory venous pressure and venous refilling time also follow this trend (Tables 8.5 & 8.6) although the limbs with deep venous reflux had a median AVP slightly lower and RT90 slightly longer than those with superficial reflux alone.

The tourniquet test in combination with AVP measurement is not helpful in determining whether superficial venous reflux is present, and therefore cannot be used as a means of selecting patients for superficial venous surgery. The following section addresses one aspect of why this is so.

8.3 The effect of narrow tourniquets on venous flow

Introduction.

The previous section has shown that the use of tourniquets in combination with ambulatory venous pressure measurement is unhelpful in distinguishing between deep and superficial venous reflux. In addition a recent study has highlighted that the use of tourniquets introduces a source of error into venous evaluation (McMullin *et al.* 1991). They demonstrated that the pressure in a 2.5 cm wide cuff required to occlude the long saphenous vein in the thigh ranged from 40 to 300 mmHg! Thus there is no guarantee that superficial veins are occluded by using a tourniquet. It is also possible that narrow tourniquets produce a reduction in venous diameter in the deep veins. This might conceivably restore valvular competence to an incompetent deep venous system and improve AVP. This study investigates the effect of narrow tourniquets on the deep and superficial veins using Duplex scanning to record venous flow and to measure venous diameter.

Methods & subjects

Ten limbs of 5 healthy volunteers were studied. Each limb was assessed using an Hitachi™ duplex scanner with 8.5 MHz probe and pulsed doppler signal analysis, with a 2.5 cm wide tourniquet placed just below the knee. The long saphenous, short saphenous and popliteal veins were identified just above the cuff using the duplex scanner while the subject sat with legs dependent over the edge of a couch. Antegrade venous blood flow was produce both by flexion/extension of the great toe and by calf compression (antegrade flow was used in order that the venous valves would have no effect on blood flow , whether competent or not).

The depth of each vein from the skin surface was recorded. In addition, flow in the superficial veins was sought both with the cuff deflated and then inflated to a pressure of

140 mmHg. The popliteal venous diameter was also measured three times with the cuff deflated and three times with the cuff inflated.

Results

The inflation of the tourniquet obliterated flow in the long saphenous vein in 5 cases of 10 patent veins. The same tourniquet obliterated flow in 5 of 6 short saphenous veins examined. The median diameter of the popliteal vein with the cuff deflated was 8.4 mm (95% confidence limits 7.7 - 8.9) compared with 8.3 mm (7.8 - 8.9) when the cuff was inflated. This difference was not statistically significant ($p > 0.05$, Wilcoxon test for paired data).

Figure 8.3 shows the depth of veins from the skin surface and the effect of the venous tourniquet on blood flow in these veins. It demonstrates that the more superficial veins are effectively controlled by the tourniquet, but that those veins lying deeper than about 4.5 mm from the skin surface are not effectively controlled.

The median circumference of the limbs where the tourniquet effectively controlled superficial venous flow was 34.3 cm (95% confidence limits; 31.5 - 37.3) compared to a median circumference of 35.4 cm (30.5 - 38cm) in the group where venous flow was not effectively controlled. There was no significant difference between these two groups ($P > 0.05$, Mann-Whitney U test).

Discussion

These data show that the use of a superficial venous tourniquet 2.5 cm wide, inflated to 140 mmHg is not effective in controlling superficial venous blood flow reliably. Six of 16 veins examined (37.5%) were still patent with venous flow demonstrable on duplex scanning with the tourniquet inflated. It appears that the short saphenous vein was more effectively controlled than the long saphenous vein (only one short saphenous vein of the 6 examined was not occluded by the tourniquet), however the median depth of the short

saphenous veins was 3.9 mm (95% confidence limits; 2.8 - 4.5) compared with 4.5 mm (2.6 - 6.4) for the long saphenous veins. Figure 8.3 shows a clear difference in the depth of veins which were occluded by the tourniquet compared to those which were not occluded.

The use of a 2.5 cm tourniquet inflated to 140 mmHg therefore controls venous flow effectively to a level of 4.4 mm, however the long and short saphenous veins often lie deeper than this level and therefore the tourniquet cannot be used to differentiate popliteal from long or short saphenous reflux.

There was no significant difference in the diameter of the popliteal vein as the tourniquet was inflated, suggesting that the tourniquet has little effect on deep venous blood flow. Although an effort was made to examine the popliteal vein underneath the tourniquet by angling the ultraound probe, this method cannot reliably exclude any reduction in diameter of this vein as the tourniquet is inflated. It would be possible to answer this question by using a water filled tourniquet, through which the popliteal vein may be imaged.

In summary, a major source of error has been identified which would explain why the use of the AVP/tourniquet test is unreliable in distinguishing between deep and superficial venous reflux. In order to design an effective study using tourniquets it would be necessary to measure the depth of the veins from the skin surface prior to application of the tourniquet. It would also be necessary to produce a profile of the depths that the tourniquet is able to occlude venous flow at different pressures. This clearly makes this test impractical for routine clinical use.

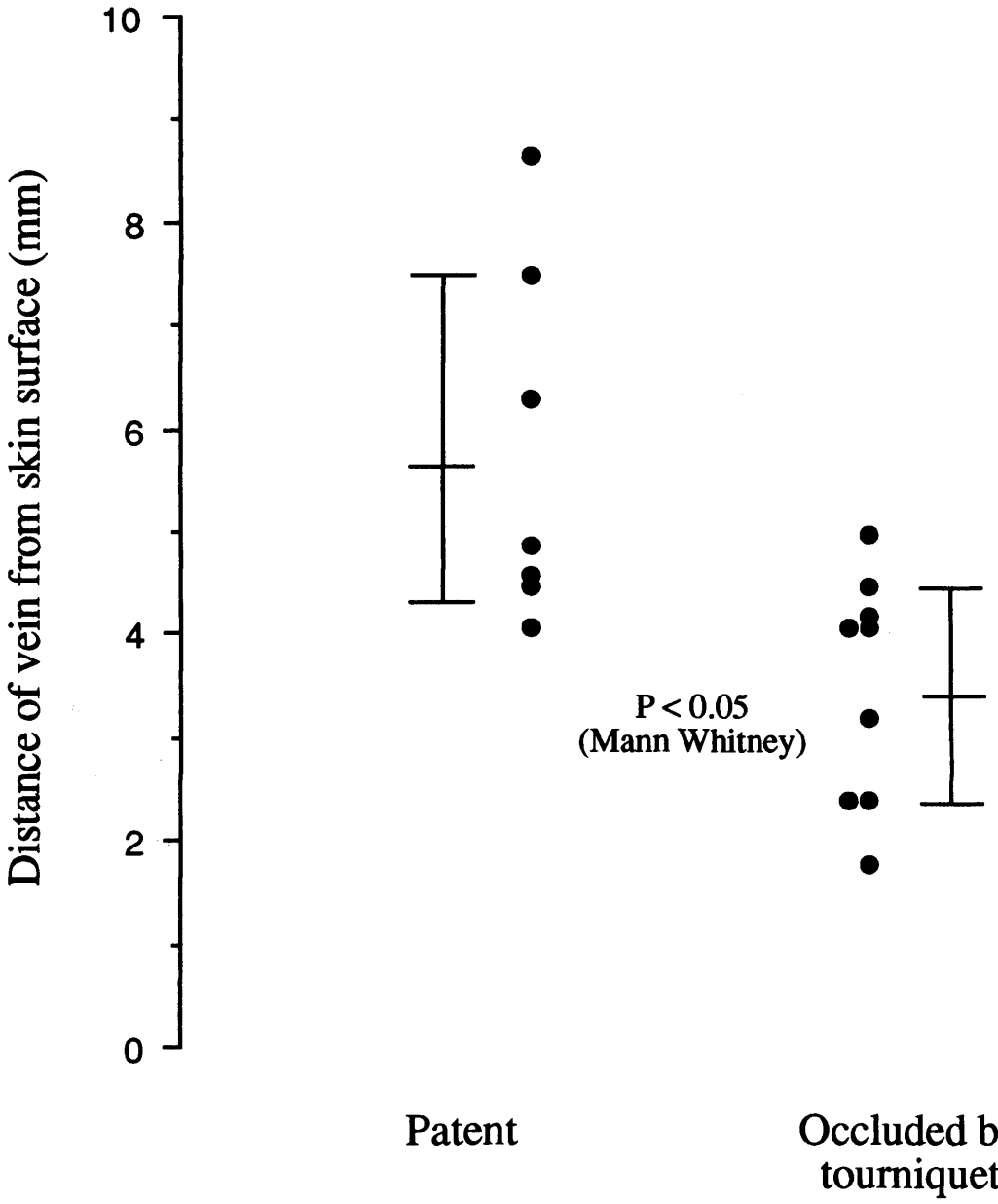
From these four studies it may be concluded that:

1. Overall efficacy of the venous calf muscle pump may be effectively measured using ambulatory venous pressure assessment.
2. The skin sequelae of chronic venous insufficiency are linked closely to this measurement of calf muscle pump efficacy.

3. It is not possible to determine with accuracy whether reflux is present in the superficial or deep systems using this method of AVP/tourniquet testing. Nor is it possible to accurately predict the result of superficial venous surgery.

4. One reason why tourniquets are unable to distinguish between deep and superficial venous reflux is that the (superficial) veins lie at a wide range of depths below the skin, and therefore it is difficult to select a pressure within the tourniquet which will reliably occlude superficial veins but leave deep venous flow unaffected.

Figure 8.3 Depth of veins beneath skin surface and effect of inflating a narrow tourniquet designed to occlude superficial veins.



CHAPTER NINE

AIR PLETHYSMOGRAPHY AND VENOUS ASSESSMENT

9.1 Venous assessment using air-plethysmography; a comparison with clinical examination, ambulatory venous pressure and duplex assessment.

Introduction

Ambulatory venous pressure measurement, as already stated, has been used since the 1940's to assess venous disorders and is accepted as being the "gold standard" test of venous function. The test is invasive however, requiring cannulation of a pedal vein. Therefore investigators have long sought a non-invasive method which is equally reliable in assessing venous disorders. Air-plethysmography has recently been reintroduced using a novel design air-plethysmograph which is portable and simple to use. The technique is claimed to quantify venous insufficiency, and it's results said to correlate well with ambulatory venous pressure measurement, making it a possible non-invasive equivalent. Independent confirmation of it's value however is lacking, therefore this study re-examines some of the claims for the use of air-plethysmography in venous assessment.

Patients and methods

One hundred and three limbs of fifty-five patients attending the vascular clinic of a university teaching hospital were studied. All patients had been referred with either varicose veins or chronic venous insufficiency. Fourteen limbs had previously been shown to have a deep venous thrombosis on venography. In addition a control group of 10 limbs in 10 subjects without varicose veins and no family history of varicose veins were studied. Limbs with coexisting arterial disease were excluded.

Each limb was assessed clinically by one observer (myself) in order to divide them into three groups.

1. Normal controls. These subjects had no history of varicose veins, venous insufficiency or deep venous thrombosis. In addition they had no family history of varicose veins *(n = 10).*

2. Limbs with varicose veins but no ulceration. These limbs had varicose veins with or without skin changes but no history of ulceration*(n = 66).*

3. These limbs had either active or healed venous ulcers. Limbs which had remained healed as a result of previous venous surgery were excluded*(n = 37).*

Measurements of air-plethysmography, ambulatory venous pressure and duplex scanning were carried out on the same day for each limb.

The technique of air-plethysmography has been described already (Christopoulos *et al.* 1988). Briefly, the device comprises a 35 cm long PVC air-chamber which surrounds the lower leg and is connected to a pressure transducer and chart recorder. After inflation and a period of equilibration at room temperature (22 - 24°C), the device was calibrated by recording pressure changes as $100cm^3$ of air was injected and then removed. This calibration was repeated 5 times on 22 occasions in order to measure the coefficient of variation on repeated inflations and deflations. In addition the calibration was measured both before and after the clinical measurements on 11 occasions in order to measure the drift during the procedure.

The following volume changes were then recorded (cm3) by reading from the pressure recorder. The leg was elevated to empty the veins as much as possible; the subject then stood erect with weight on the opposite limb until the veins were full. This volume change represented the functional venous volume (VV) and the time taken to fill 90 per cent of VV recorded as the 90 per cent filling time (VFT_{90}). The venous filling index (VFI) was derived from;

$$VFI = 90 \text{ per cent } VV/VFT_{90}.$$

Each subject then performed one heel raise manoeuvre and the volume displaced during this manoeuvre recorded as the ejection volume (EV). Ejection fraction (EF) was calculated as the ejection volume divided by the venous volume. Ten heel raise manoeuvres were then performed in order to reach a residual volume (RV) plateau. The residual volume fraction (RVF) was calculated as residual volume divided by venous volume.

Ambulatory venous pressure was measured as described above by cannulating a pedal vein with a 21 gauge needle. The normal control group were not subjected to ambulatory venous pressure assessment.

Duplex scanning was performed using a scanner with an 8.5 MHz probe and pulsed Doppler signal (Hitachi, Bedford, UK). Subjects sat on the edge of a couch with legs dependent and relaxed; a foam wedge was used as a back rest to help them relax. Each subject performed the best Valsalva manoeuvre they could manage. If this failed to produce retrograde flow in the vein being interrogated then calf compression was applied and then released. If either manoeuvre produced reflux with a duration greater than 0.5 second then the vein was classified as incompetent (Van-Bemmelen *et al.* 1989). All major veins in the leg were examined in the control group. In patients with venous disease the popliteal vein alone was assessed in order to classify limbs into those with and those without deep venous incompetence at this level.

Results

1. Reproducibility

The coefficient of variation on repeated inflation/deflation was 5.8 per cent and the calibration drift during the procedure was 0.54 per cent.

2. Air plethysmography and AVP measurement

The two measurements of RT90 and AVP by venous cannulation were compared with their counterparts VFT90 and RVF as measured by air-plethysmography. Figures 9.1 & 9.2 demonstrate poor correlation between RT90 and VFT90 ($r_s = 0.58$) and between AVP and RVF ($r_s = 0.04$).

3. Air-plethysmography and Clinical examination

There was evidence of active or healed ulceration in 37 limbs, 66 had no ulceration. The median VFT90 was 96 seconds in control limbs (95% confidence limits, 64 - 132), 31 seconds (27 - 36) in those with varicose veins and 21 seconds (15 - 25) in those with ulcers (Figure 9.3). The median VFI was 0.9 mls/sec in control limbs (95% confidence limits, 0.6 - 1.6), 3.7 mls/sec (2.9 - 4.8) in those with varicose veins and 8.5 mls/sec (6.7 - 10.4) in those with ulcers (Figure 9.4). Corresponding values for median RVF were 26 per cent (14 - 35), 40 per cent (36 - 44) and 44 per cent (39 - 49) respectively (Figure 9.5).

4. Air-plethysmography and Duplex scanning

All limbs examined had a patent popliteal vein, 30 limbs had popliteal reflux and in the remainder the popliteal vein was competent. The control group had no evidence of venous reflux in any of the major veins on duplex scanning. The median VFT_{90} in limbs with popliteal reflux detected on duplex was 17 seconds (95% confidence limits, 13 - 24) compared with 30 (26 - 34) seconds in those without popliteal reflux (Figure 9.6). The median VFI in limbs with popliteal reflux was 9 ml s^{-1}(7 - 12) compared with 4 ml s^{-1}(3 - 6) in those without (Figure 9.7). The ejection fraction was measured in 30 limbs with popliteal reflux . The median EF in 15 limbs with venous ulceration was 47 per cent (37 - 56) compared with 51 per cent (39 - 61) in 15 limbs without .

The median RVF in limbs with popliteal reflux was 47 per cent (40 - 54) compared with 40 per cent (36 - 44) in those with a competent popliteal vein (Figure 9.8).

Discussion

All measurements using air-plethysmography in this study show a wide scatter of data, with overlap between the different groups. There is a trend in the data, however, towards a higher VFI and shorter VFT_{90} in more severely affected limbs as determined by clinical examination. Increased venous reflux, as measured by VFI, is associated with a deterioration in the clinical severity of venous disease (normal, varicose or ulcerated). In addition, the presence of popliteal reflux, thought to play a central role in the pathogenesis of chronic venous insufficiency, was associated with an increase in the rate of reflux as measured by VFI.

The measurements performed during tiptoe manoeuvres, however, did not contribute much to the assessment of these limbs. The ejection fraction has been claimed to measure the efficacy of the the calf muscle pump. Christopoulos *et al.* (Christopoulos *et al.* 1989). studied the ejection fraction in limbs with deep venous reflux and demonstrated that a good ejection fraction was able to prevent ulceration despite deep venous incompetence. In this study I identified 30 limbs with popliteal reflux of which 15 had venous ulcers. There was no difference in ejection fraction between those limbs with ulcers and those without. The RVF, previously claimed to correlate well with the incidence of ulceration (Christopoulos *et al.* 1989), showed substantial overlap of data between the clinical groups. This parameter has also been claimed to correlate with AVP (Christopoulos *et al.* 1989), the accepted reference measurement of venous insufficiency. No correlation was found between these two measurements in this study ($r_S = 0.04$).

Parameters that measure the rate of venous reflux (VFI, VFT_{90}) using air-plethysmography may show useful trends in quantifying venous disease, but the relationship between volume measurements using air-plethysmography and direct pressure measurement is less clear cut. Substantial overlap was found in the measurements of RVF between the groups of limbs examined and, in addition the correlation between RVF and AVP was extremely poor.

The pressure - volume curve as a vein is distended is far from linear; initially the volume increases with minimal rise in pressure, then at higher pressures the volume increase is minimal for a large rise in pressure (Thulesius, 1989). Limbs with less severe venous disease (i.e. low AVP) are examined at one place on the pressure-volume curve while those with more severe disease are examined at a point on the curve with a different gradient and thus a different pressure - volume relationship. This may be one reason why AVP and RVF do not correlate. Struckman has previously noted a lack of correlation between venous pressure measurements and volume measurements (using the strain gauge plethysmograph) (Struckmann and Methiesen 1985).

The RVF is not useful in assessing clinical severity of disease and this measurement does not correlate well with AVP, the accepted reference standard of venous investigation. The rate of venous refilling is more quickly and simply measured using photoplethysmography (Carrel *et al.* 1989). It is concluded that air-plethysmography does not fulfil some of the claims of previous reports. Assessment of RVF by air-plethymography did not correlate with AVP measurement and so should not be used as a direct substitute.

Figure 9.1 Comparison between venous refilling time measured by direct pressure measurement and air-plethysmography

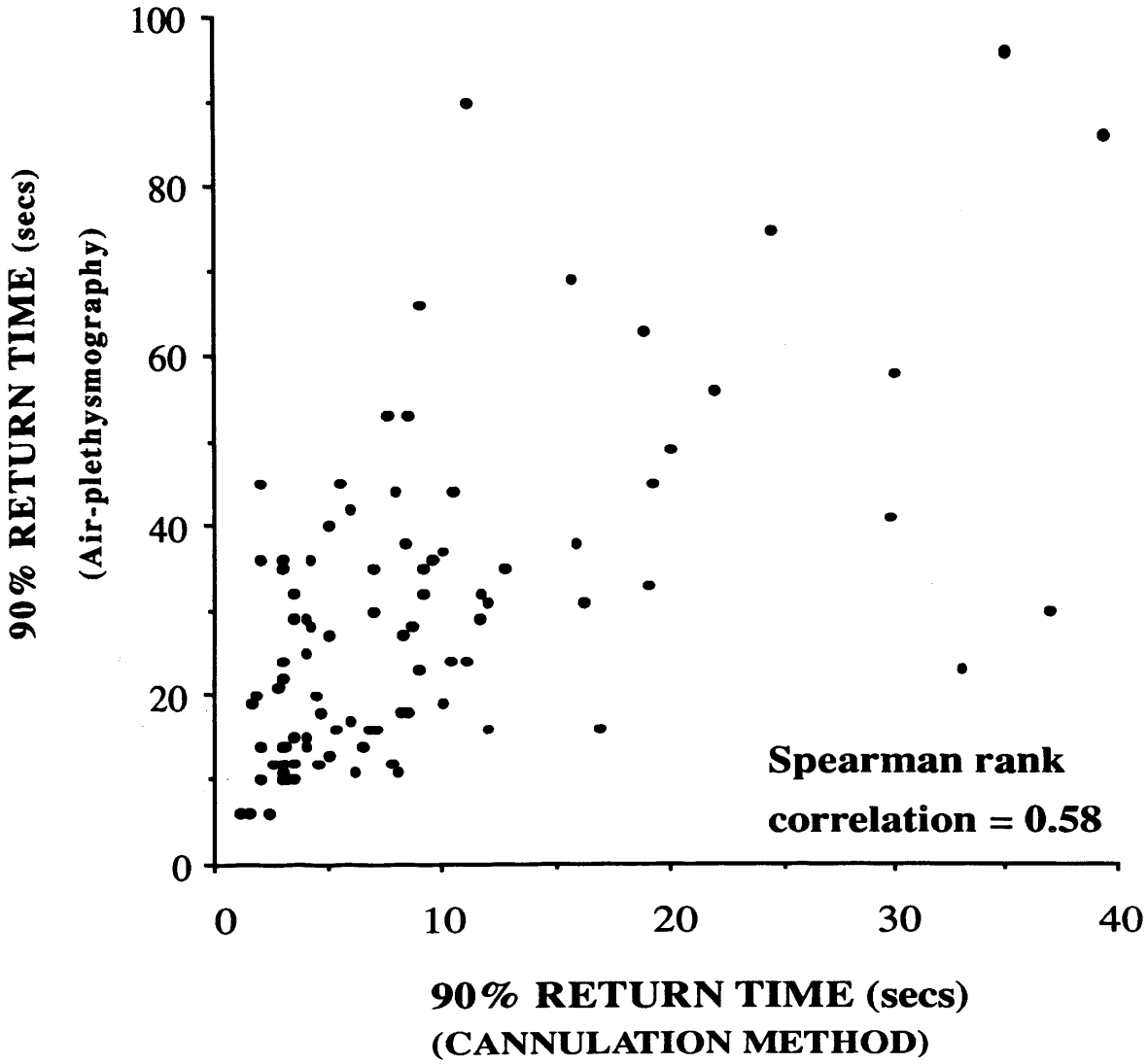


Figure 9.2 Residual volume fraction and ambulatory venous pressure compared

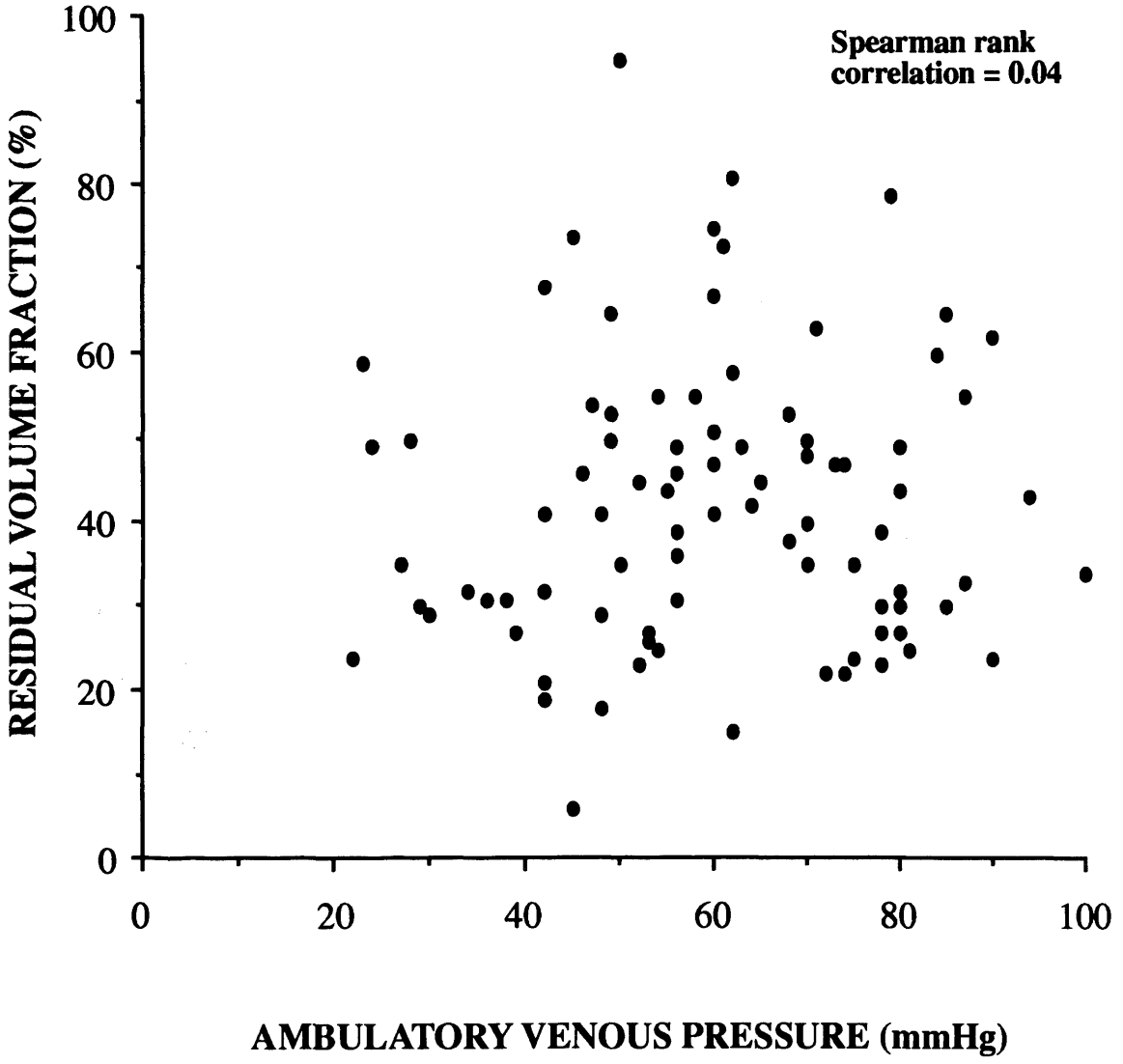


Figure 9.3 Venous filling time in limbs grouped by clinical condition (medians & 95% confidence intervals)

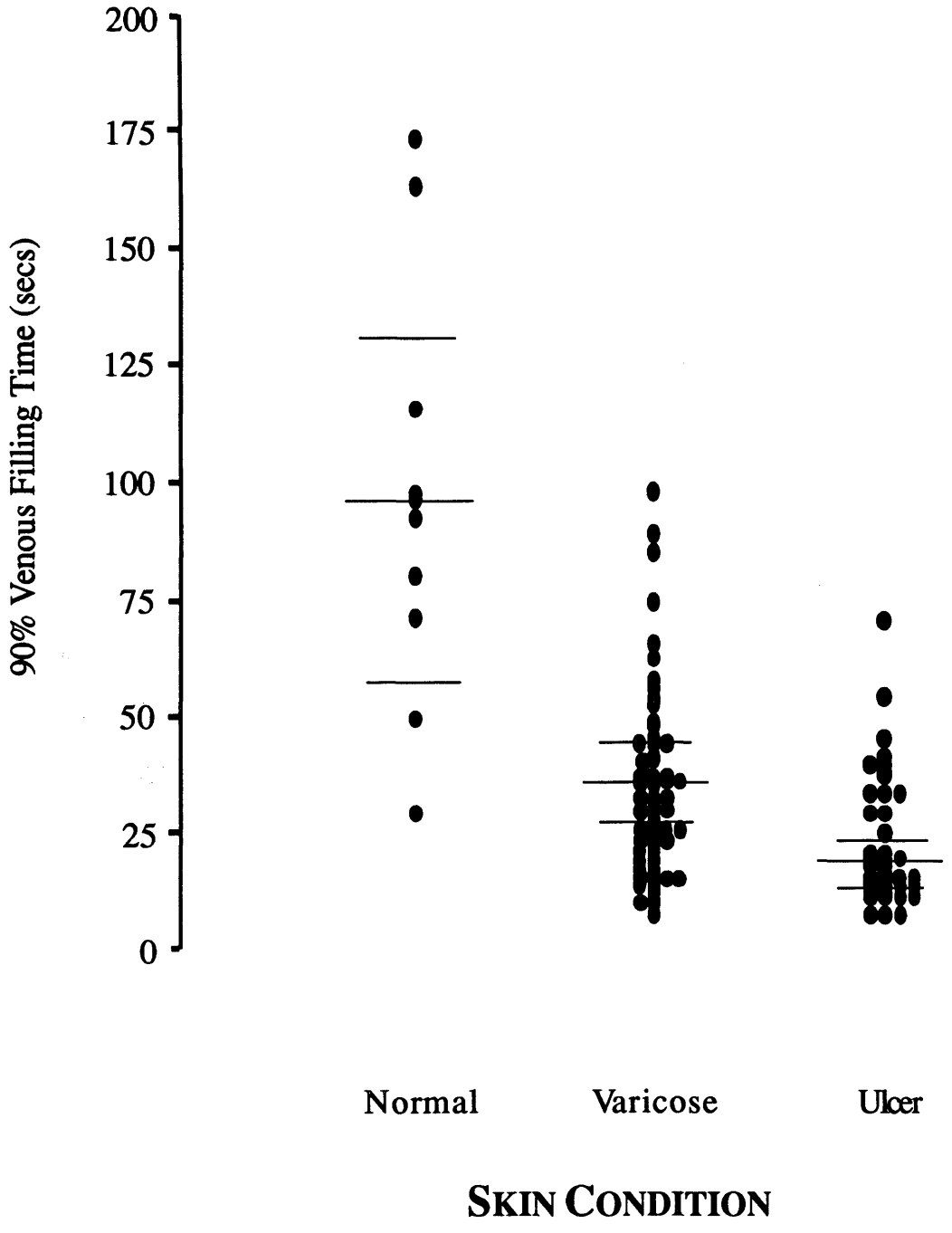


Figure 9.4 Venous filling index in limbs grouped by clinical condition (medians & 95% confidence intervals)

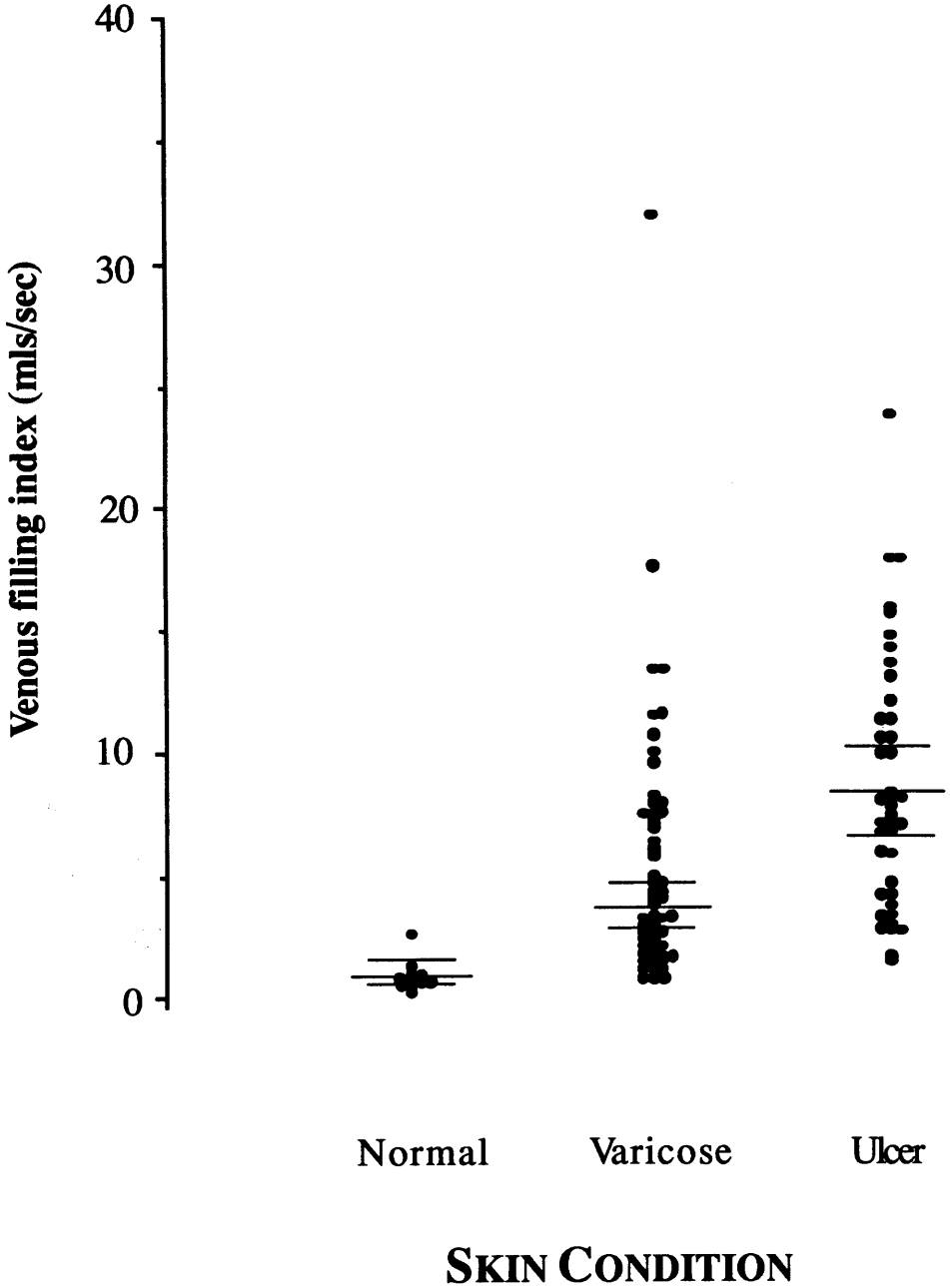


Figure 9.5 Residual volume fraction in limbs grouped by clinical condition (medians & 95% confidence intervals)

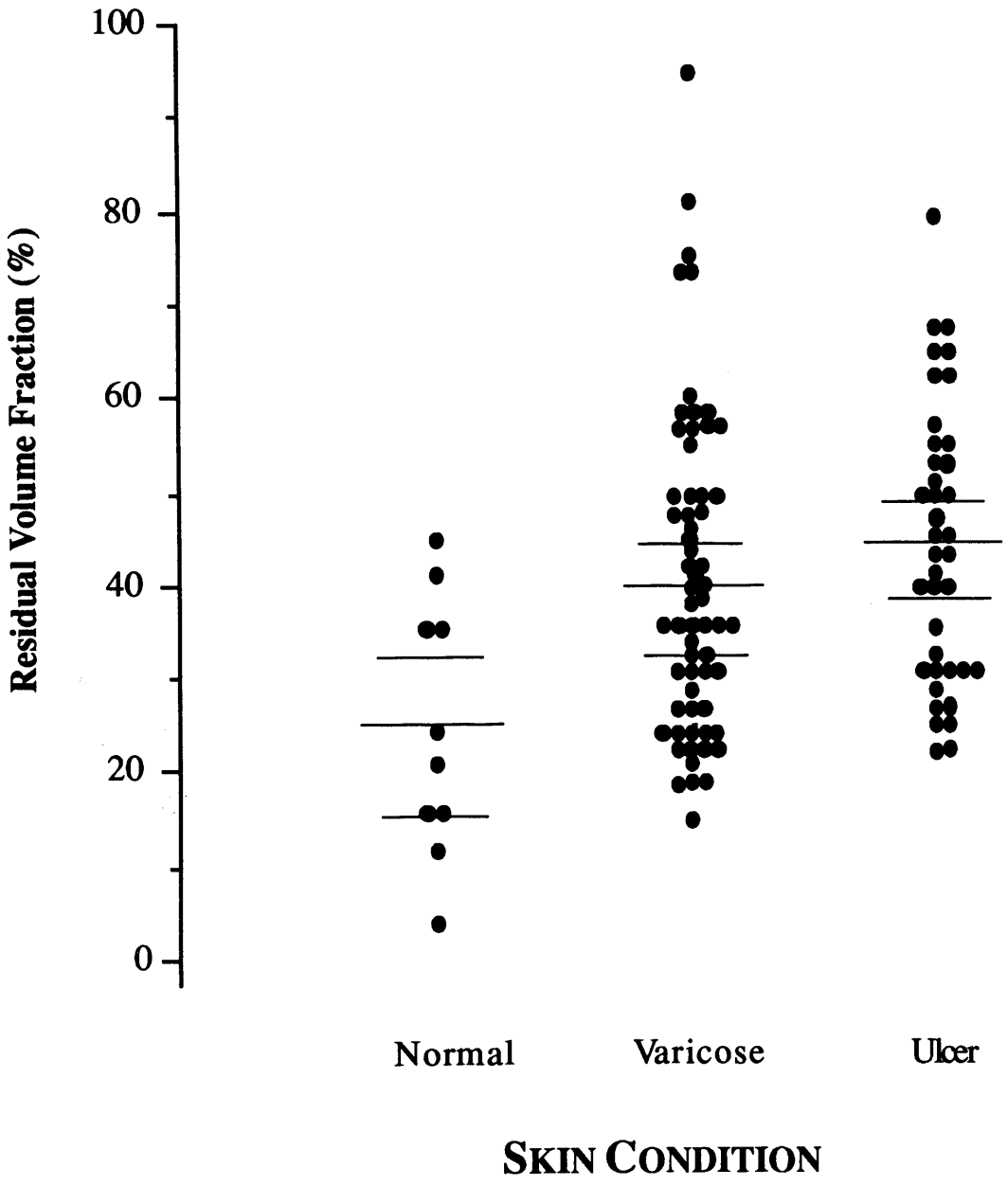


Figure 9.6 Effect of popliteal reflux on venous refilling time (medians & 95% confidence intervals)

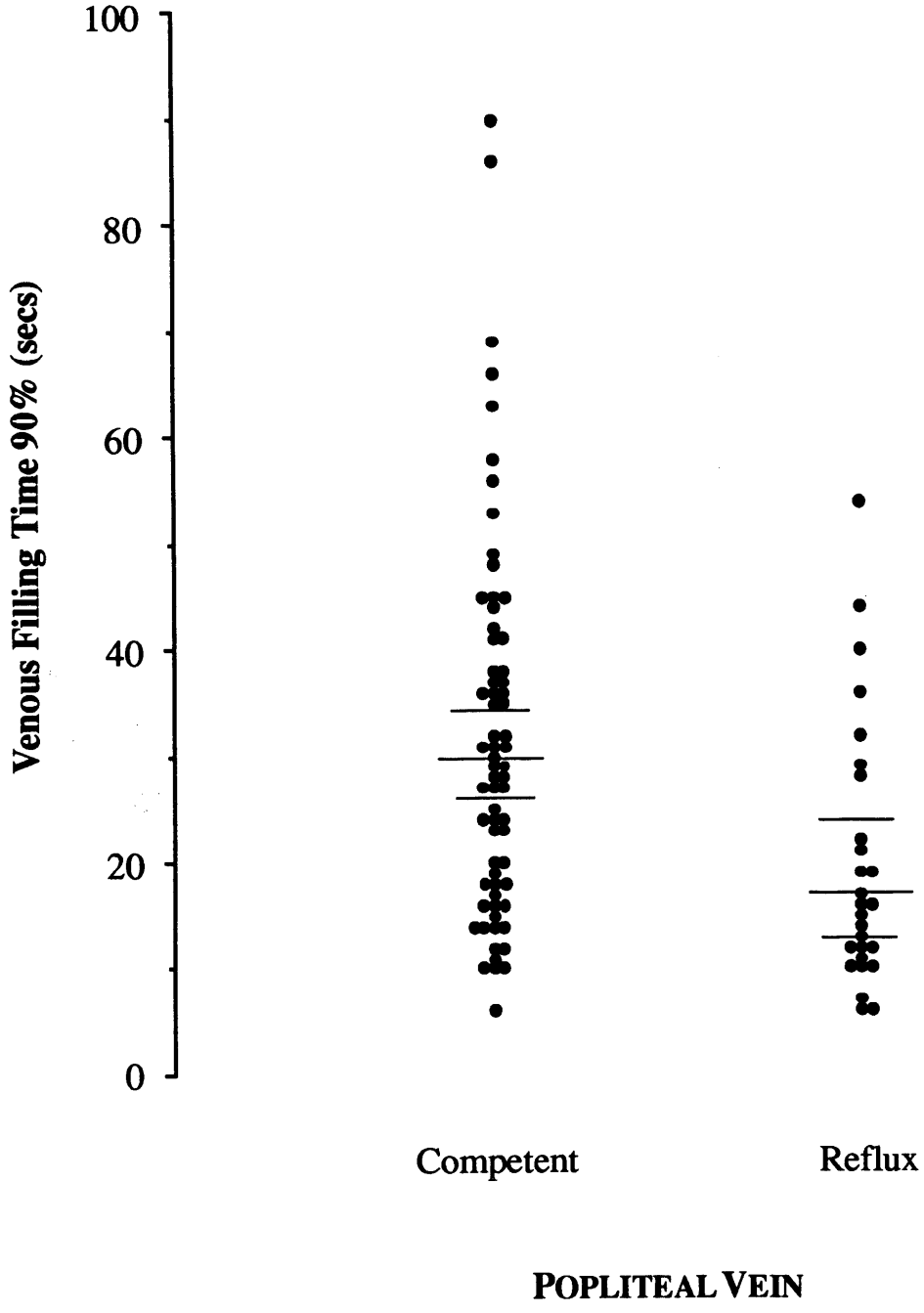


Figure 9.7 Effect of popliteal reflux on venous filling index (medians & 95% confidence intervals)

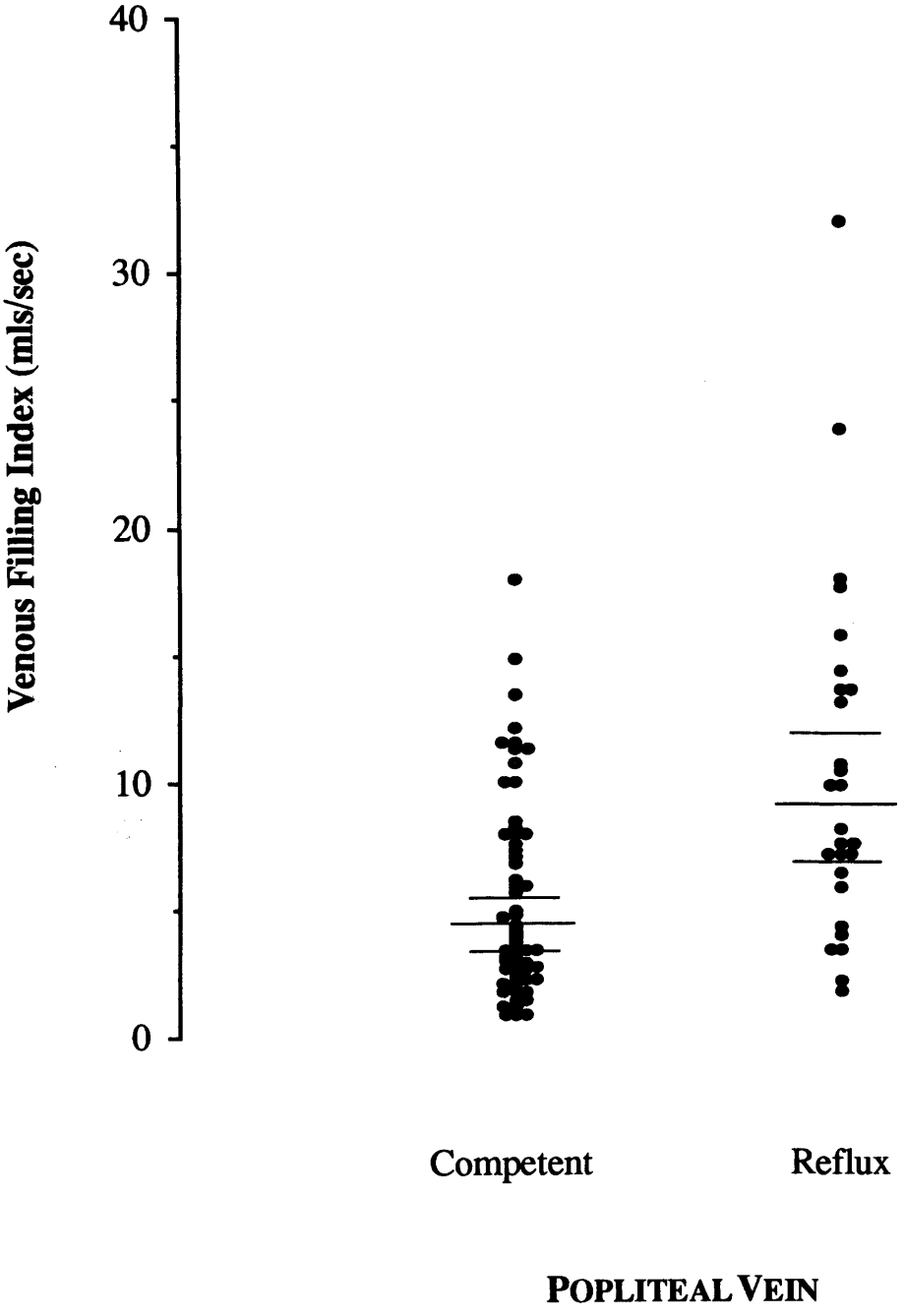
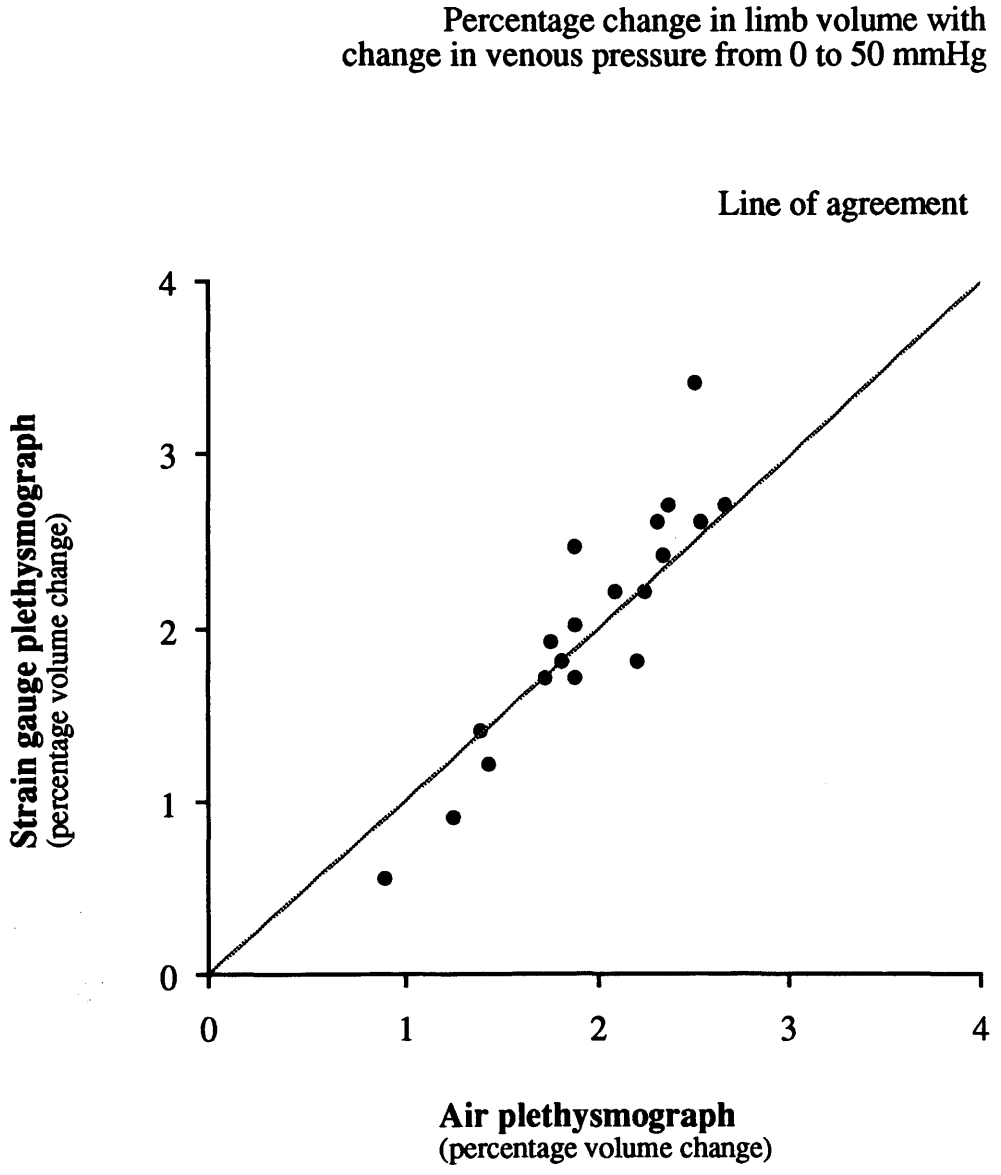


Figure 9.8 Effect of popliteal reflux on residual volume fraction (medians & 95% confidence intervals)



CHAPTER TEN

VENOUS ELASTICITY MEASUREMENT

Introduction

The methods for measuring venous function previously described above may also be used to investigate venous compliance or elasticity. As explained in the introduction, the process of venous insufficiency commences with a loss of venous elasticity (an increase in compliance) which causes the veins to become more "baggy". These dilated veins therefore are unable to coapt the cusps of the venous valves adequately and thus venous reflux with consequent venous hypertension results.

As explained above, venous elasticity is measured for practical purposes as a bulk modulus. Elasticity is the relationship between stress and strain; for these purposes stress is measured as an increase in pressure (mmHg) of blood within the veins and strain is measured as the volume increase which results from this increase of pressure. Elasticity over a specified pressure range may therefore be calculated if pressure changes and volume changes can be measured simultaneously.

The formula for the bulk modulus of elasticity which I have used is shown here:

$$Elasticity\ [P_1\text{-}P_2] = {}^{(P_2\text{-}P_1)}\!/_{V2\text{-}V1/V1}$$

Where P1-P2 is the venous pressure range specified, V1 is the volume of the limb when venous pressure is P1 and V2 is limb volume when venous pressure is P2.

I have used limb volume rather than venous volume here because it is impossible to measure the initial venous volume before distension, but it is possible to measure the initial limb volume. The assumption is made that other components of limb volume such as the intra-arterial volume and the quantity of intra and extracellular fluid are not altered significantly during this distension. Bearing in mind the mean arterial pressure it is unlikely that arterial volume will be altered. If the quantity of intra and extracellular fliud is significantly altered then the limb volume on release of the tourniquet will not return to zero and will thus become apparent.

Previous studies of venous elasticity have relied mostly on strain-gauge plethysmography to measure limb volume changes. The reintroduction of air-plethysmography, using a convenient portable unit however gives the opportunity for assessing volume changes over a greater length of the leg, rather than just one cross section at the point where the strain gauge is applied. In addition, the air-plethysmograph provides a measurement of true volume changes instead of a proportional increase, after setting the zero, which the strain gauge provides. Indeed the paper by Clarke *et al.* (Clarke *et al.* 1989) which demonstrated that limbs thought to be prone to varicose veins have abnormal venous elasticity measurements which are similar to those found in limbs with varicose changes, used the strain gauge to measure limb volume changes. The change in elasticity as the veins distend with increasing venous pressure was noted, and in order to produce a single measurement for each limb the flattest part of the distension curve was extrapolated back to the ordinate which represented the strain gauge readings. The gradient of the line was then divided by the strain gauge reading where the extrapolation intersected the ordinate, which was said to represent the limb volume at pressure = zero, if elasticity were constant. This is flawed, since the point where the line intersects the ordinate *merely records a proportionate increase in limb volume*, compared with an initial volume. The initial volume was not known.

For these reasons I chose to use the air-plethysmograph to measure volume changes in the study of venous elasticity. Before employing the air-plethysmograph a preliminary

study was undertaken to check the agreement between these two methods of measuring venous volume changes.

10.1 Comparison between strain gauge and air-plethysmography

Strain gauge plethysmography measures the change in electrical resistance of a fine mercury in silastic tube. As discussed above the chart recorder displays the proportional increase in volume of the limb enclosed within the mercury in silastic tube (i.e. increase in cross sectional area).

i.e.: chart recorder 1 unit = increase of volume / initial volume

The calibration of the strain gauge and chart recorder was checked by measuring the strain gauge to a length of 20 cm and then increasing the length by increments of 2cm (10%). The relationship between the two was linear with no demonstrable disagreement.

In order to measure limb volume changes with the strain gauge plethysmograph, the subjects were studied lying supine on an examination couch with the head elevated 10°. The heel of the limb being measured was rested on a foam block in order to prevent the calf touching the couch whilst maintaining muscle relaxation. The mercury in silastic strain gauge was then wrapped around the calf where the circumference was greatest, and taped in position. A 15 cm pneumatic cuff was used to occlude the venous outflow in the thigh. The long saphenous vein was cannulated with a 21 gauge butterfly needle connected to a Statham pressure transducer and the chart recorder in order to simultaneously record venous pressure. Pressure within the thigh cuff was gradually increased in increments of 10 mmHg, producing simultaneous curves of increasing pressure and limb volume on the chart recorder.

To compare the measurement produced by the strain gauge plethysmograph with the air-plethysmograph the same procedure was adopted, however before cannulating the vein the dimensions of the limb enclosed by the air-plethysmograph were measured (limb

circumference at the tibial tubercle, 35 cm below this and half way between the two). By substituting the circumference measurements into the equations relating radius, diameter, circumference and cross sectional area and multiplying by 35 the initial resting volume of each limb was calculated:

$$\textit{Limb volume} = \textit{cross sectional area} \times \textit{length}$$

$$\textit{Area at tibial tubercle} = A1, \textit{Area 17.5 cm below this} = A2,$$

$$\textit{Area 35 cm below this} = A3.$$

$$\textit{Mean area} = (A1 + A2 + A3)/3$$

$$Circ = 2\pi R$$

$$R = C/2\pi$$

$$A = \pi.C^2/4\pi^2$$

$$\textit{Volume} = 35.(C_1^2 + C_2^2 + C_3^2)/_{(4 \times 3)\pi}$$

The air-plethysmograph was then applied to the calf over the strain gauge and allowed to equilibrate. Calibration was carried out exactly as described above when the air-plethysmograph was used alone.

The chart recorder thus produced simultaneous measurements of venous pressure, strain gauge measured volume changes and air-plethysmograph measured volume changes. In order to compare these two methods of measurement of venous volume I recorded the volume change in 20 limbs over an increase in venous pressure from 0 - 50 mmHg by both methods simultaneously and then used the method of Bland & Altman (Bland and Altman 1986) to compare differences in methods of measurement. This method plots the differences between the two measurements against the mean measurement for each subject / reading. The graph demonstrates the range of differences which might be expected together with any relationship between mean measurement and difference between the methods. From the data the mean difference, the standard deviation of the

differences and the limits of agreement (mean difference +- 2SD of differences) may be calculated.

Table 10.1 shows the measurements obtained in these 20 limbs: C_{1-3} represent the measurements of calf circumference, vol. is the calf volume calculated from these measurements. APG is the increase in calf volume with an increase of venous pressure of 50 mmHg as measured with the air-plethysmograph, SGP is the measurement recorded on the chart recorder as the % increase in calf volume as measured with the strain gauge plethysmograph. By dividing the volume increase into the initial volume of the calf both measurements may be expressed in the next two columns as percentage increases of calf volume. The remaining columns show the differences between the two methods of measurement, and the mean measurement on each occasion.

In order to compare the two methods of measurement they are shown below plotted against each other (Figure 10.1). The line is not the regression line between the two sets of data but is the line of complete accordance between the two methods of measurement.

The data appear to show reasonable agreement. In order to demonstrate that the differences between the methods are not dependent upon the magnitude of the measurement these are plotted against each other.

The median difference is 0.052 with 95% confidence intervals of -0.09 to 0.19 The median difference is not significantly different from 0 and the confidence limits are narrow. The mean difference is 0.016 with Standard deviation of 0.22; these are shown in the graph below (Figure 10.2).

I have therefore accepted that the two methods show a reasonable level of coherance, and have used the air-plethysmograph in the following studies.

Table 10.1 Comparison between strain-gauge and air-plethysmography in assessing venous volume changes

C1	C2	C3	Vol.	APG	APG (%)	SGP (%)	Diffs	Means
36	36	26	3039	42	1.38	1.42	0.04	1.4
36	35	25	2926	26	0.89	0.57	-0.32	0.73
33	33	22	2476	62	2.50	3.42	0.92	2.96
31	33	22	2357	44	1.87	2.47	0.60	2.17
31	33	23	2398	42	1.75	1.92	0.17	1.84
33	31	21	2317	52	2.24	2.22	-0.02	2.23
33	32	21	2375	60	2.53	2.62	0.10	2.57
32	33	21	2375	56	2.36	2.72	0.36	2.54
35	36	24	2880	36	1.25	0.92	-0.33	1.09
35	34	25	2796	48	1.72	1.72	0.00	1.72
33	33	24	2561	56	2.19	1.82	-0.36	2
35	37	25	2994	56	1.87	1.72	-0.15	1.8
31	35	24	2569	48	1.87	2.02	0.15	1.95
35	35	24	2814	40	1.42	1.22	-0.20	1.32
34	33	22	2538	36	1.42	1.22	-0.20	1.32
32	32	23	2397	56	2.34	2.42	0.09	2.38
31	34	24	2504	52	2.08	2.22	0.15	2.15
32	31	20	2218	40	1.80	1.82	0.02	1.81
35	37	24	2948	68	2.31	2.62	0.32	2.46
34	36	28	3009	80	2.66	2.72	0.06	2.69

C1 = Circumference of leg at tibial tubercle (cm), C2 = Circumference of leg 17.5 cm below tibial tubercle, C3 = Circumference of leg 35 cm below tibial tubercle, Vol. = calculated volume of section of leg within air-plethysmograph

Figure 10.1 Measurement of limb volume changes: correlation between air and strain-gauge plethysmography

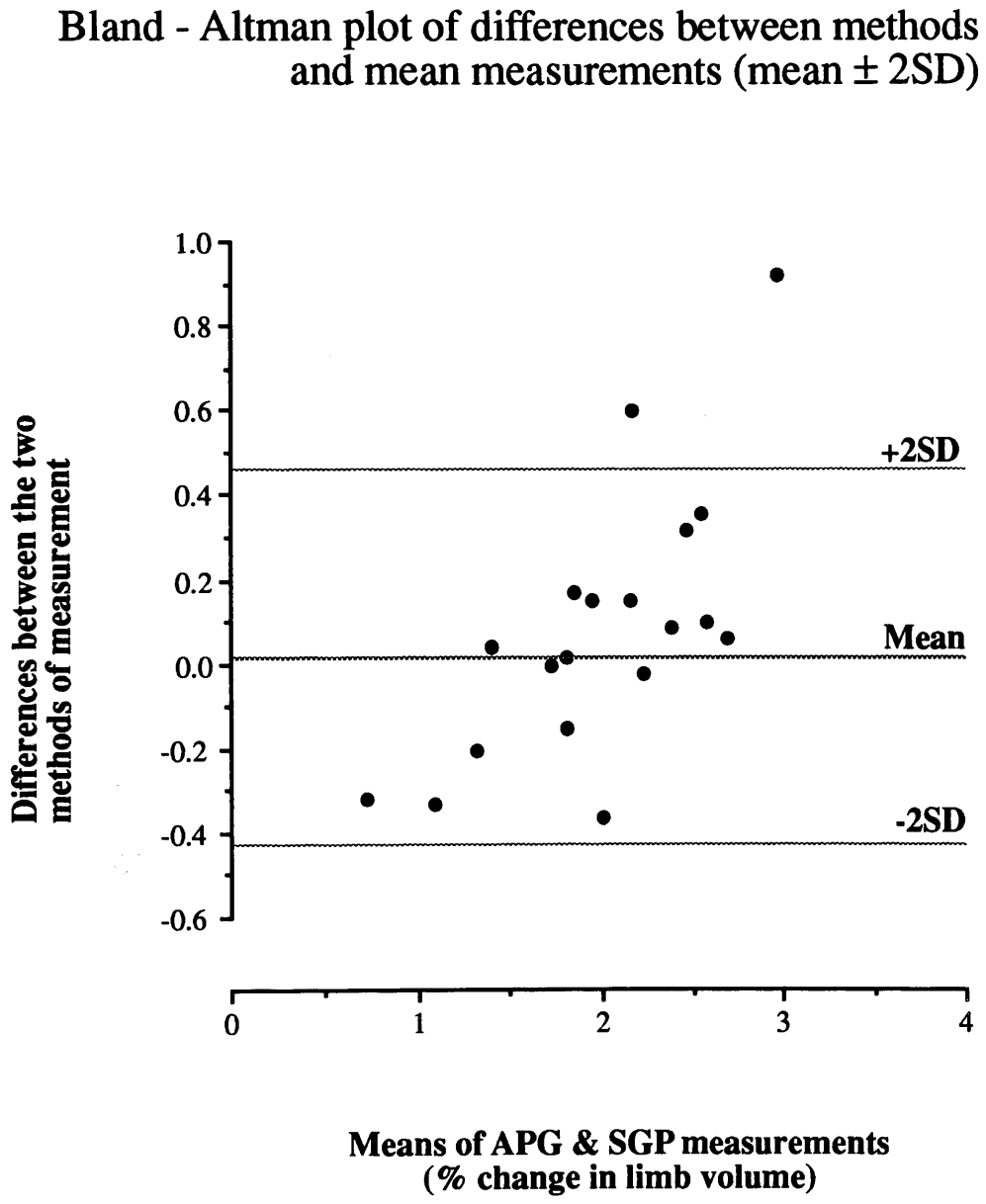
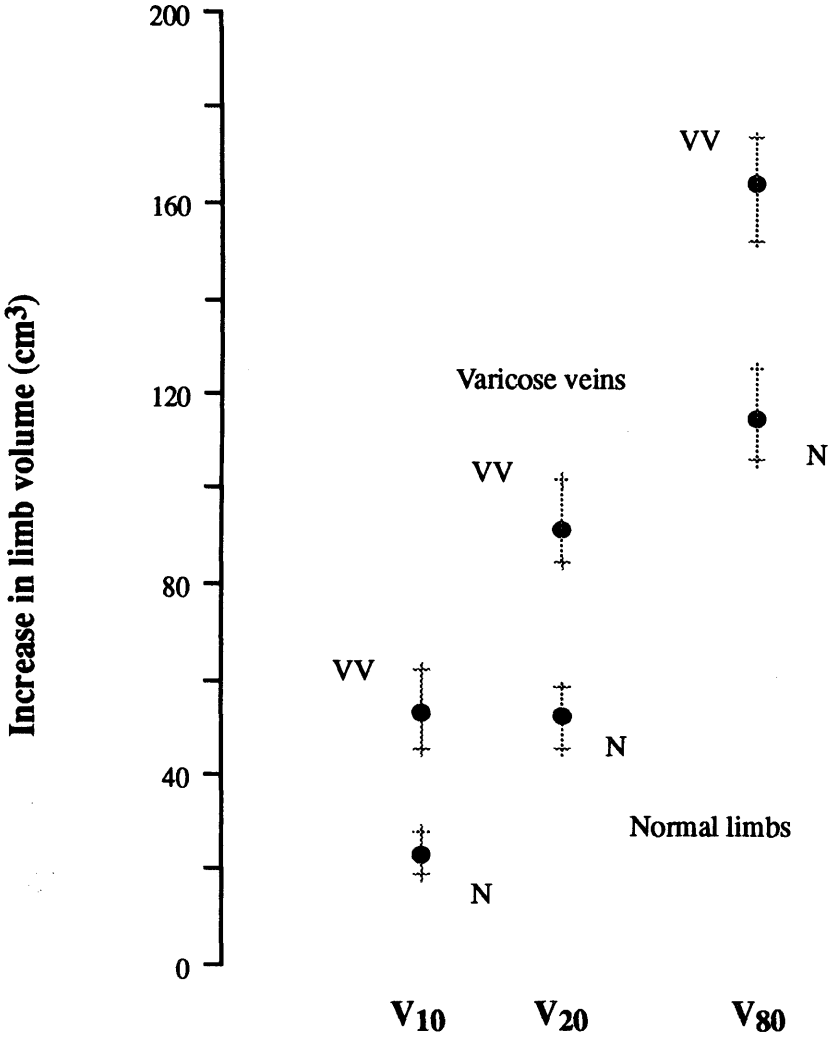


Figure 10.2 Measurement of limb volume changes: differences between air and strain-gauge plethysmography



Increase in limb volume with venous pressure from initial volume when pressure is zero

(V_{10}; volume at 10 mmHg, etc. Median values, error bars are 95% ci.)

10.2 Reproducibility of elasticity measurement using air-plethysmography

In order to study the reproducibility of these measurements obtained using air-plethysmography and direct venous cannulation, I have measured the coefficient of variation of repeated measurements taken from 30 limbs.

As described above each limb was fitted with the air-plethysmograph and the long saphenous vein cannulated at the ankle. A pneumatic cuff provided venous occlusion in the thigh. For each limb the occlusion cuff was inflated gradually in increments of 10 mmHg. The venous pressure and the volume changes were recorded simultaneously on the chart recorder. Once a pressure of 80 mmHg was achieved and the volume had ceased to increase, the proximal cuff was released, the pressure returned to zero in order to empty the veins and the procedure repeated.

Three volume measurements were noted using the air-plethysmograph: the increase in limb volume from 0 to 10 mmHg, the increase in volume from 0 to 20 mmHg and the increase in volume from 0 to 80 mmHg. The repeated measurements were compared in a pairwise manner, subtracting one from the other to obtain the differences in measurement. The coefficient of variation was then calculated using the sum of squares of the differences [(standard deviation of the error)^2 = (sum of differences)^2/2n].

Table 10.2 shows the measurements recorded in these 30 limbs. These data show an acceptable coefficient of variation, ranging from 4.5% to 10%. The first distension did not produce a detectable degree of oedema which might be expected if the cuff had been inflated for a longer period of time.

In addition a further 8 subjects were assessed one month later; Table 10.3 shows the data obtained one month later compared with those obtained initially. Since the numbers are smaller the overall coefficient of variation has been calculated in the same way (8%).

The reproducibility of this method of volume measurement is therefore acceptable.

Table 10.2 Immediate reproducibility of air-plethysmography

$V_{10}a$	$V_{10}b$	Diff V_{10}	Diff V_{10}^2	$V_{20}a$	$V_{20}b$	Diff V_{20}	Diff V_{20}^2	$V_{80}a$	$V_{80}b$	Diff V_{80}	Diff V_{80}^2
60	60	0	0	90	92	-2	4	156	160	-4	16
38	38	0	0	86	90	-4	16	160	160	0	0
80	76	4	16	140	140	0	0	192	196	-4	16
72	72	0	0	144	116	28	784	184	184	0	0
40	40	0	0	80	80	0	0	168	168	0	0
52	36	16	256	84	76	8	644	168	156	12	144
96	96	0	0	148	144	4	16	248	256	-8	64
24	24	0	0	36	28	8	64	108	114	-6	36
48	48	0	0	68	60	8	64	188	180	8	64
20	20	0	0	44	60	-16	256	120	136	-16	256
70	76	-6	36	100	104	-4	16	164	160	4	16
56	48	8	64	88	92	-4	16	180	200	-20	400
64	54	10	100	92	84	8	64	156	160	-4	16
76	80	-4	16	104	116	-12	144	220	228	-8	64
80	76	4	16	94	90	4	16	140	134	6	36
12	16	-4	16	32	32	0	0	80	80	0	0
16	12	4	16	50	40	10	100	92	92	0	0
66	64	2	4	108	120	-12	144	184	200	-16	256
14	14	0	0	44	48	-4	16	92	92	0	0
108	112	-4	16	128	128	0	0	188	200	-12	144
104	112	-8	64	134	176	-42	1764	196	224	-28	784
80	84	-4	16	110	112	-2	4	188	200	-12	144
60	60	0	0	108	104	4	16	200	216	-16	256
40	40	0	0	64	62	2	4	108	104	4	16
32	32	0	0	40	40	0	0	120	108	12	144
40	40	0	0	116	112	4	16	220	216	4	16
74	86	-12	144	116	136	-20	400	196	208	-12	144
40	40	0	0	132	120	12	144	204	208	-4	16
52	52	0	0	104	88	16	256	188	180	8	64
36	32	4	16	56	44	12	144	124	112	12	144
1650	1640		796	2740	2734		5112	4932	5032		3256
Tot.	3290			Tot.	5474			Total	9964		
Mean	54	Sum/2n	13.27	Mean	91	Sum/2n	85.20	Mean	166	Sum/2n	54.27
		SD err	3.64			SD err	9.23			SD err	7.37
		Co. vn	**6.64%**			**Co. vn**	**10.1%**			**Co. vn**	**4.44%**

$V_{10}a$ = volume change from pressure = 0 to 10 mmHg, first measurement.

$V_{10}b$= volume change from pressure = 0 to 10 mmHg, second measurement.

Diff V_{10} = first measurement - second measurement.

Diff V_{10}^2= difference between measurements squared.

SD err = standard deviation of the differences.

Co. vn = coefficient of variation (standard error of the differences / mean measurement)

Table 10.3 Reproducibility of air-plethysmography after 1 month

$V_{10}a$	$V_{10}b$	Diff V_{10}	Diff V_{10}^2	$V_{20}a$	$V_{20}b$	Diff V_{20}	Diff V_{20}^2	$V_{80}a$	$V_{80}b$	Diff V_{80}	Diff V_{80}^2
34	34	0	0	68	82	-14	196	132	140	-8	64
56	56	0	0	108	108	0	0	200	188	12	144
80	72	8	64	96	100	-4	16	184	184	0	0
36	36	0	0	68	68	0	0	130	140	-10	100
16	12	4	16	32	40	-8	64	96	96	0	0
12	16	-4	16	40	44	-4	16	96	108	-12	144
68	40	28	784	116	104	12	144	200	192	8	64
24	32	-8	64	64	84	-20	400	116	112	4	16
Tot.	624	28	944		1222	-38	836		2314	-6	532

SD err 6.94

Co.vn 8%

10.3 Comparison between limbs with varicose veins and normals

Introduction

This study compares the measurement of elasticity during venous distension in limbs with venous disease with normal controls.

Patients and methods

A total of 58 subjects with varicose veins or chronic venous insufficiency attending the vascular clinic were studied. These were compared with 45 subjects who had no history of varicose veins or venous disease (including deep venous thrombosis). These subjects had no first degree family history of varicose veins (2 subjects cited a 1st degree relative with probable venous thrombosis). As before, patients with coexistent arterial disease were excluded.

Each of the control subjects underwent duplex scanning as described above in order to exclude venous reflux in the major veins of the leg.

Limb volume measurements were recorded during venous distension as described above. Briefly, the long saphenous vein was cannulated to record venous pressure, an air-plethysmograph was used to record volume changes in the calf and a 15 cm pneumatic cuff was inflated around the thigh to provide venous occlusion. Subjects were studied in the vascular laboratory under controlled conditions (temp range 22 - 24°C). Initial limb volume was calculated from measurements at three points around the calf as described above and using the chart recorder the limb volumes at 10, 20 and 80 mmHg venous pressure were recorded.

Results

The median age of the control subjects was 56 yrs (95% CI: 47.5 - 64) and the subjects with venous disease 51.5 yrs (95% CI: 47.5 - 56.5).

The median initial limb volume (95% ci.) in varicose limbs was 2679 cm3 (2535 - 2805) compared with 2445 cm3 (2322 - 2574) in normal limbs *($p = 0.01$ Mann-Whitney)*. The median increase (95% CI) in venous volume from 0 to 10 mmHg venous pressure was 54 cm3 (46 - 62) in limbs with venous disease compared with 24 cm3 (20 - 28) in limbs of control subjects. The median increase from 0 to 20 mmHg was 92 cm3 (83 - 102) in limbs with venous disease compared with 53 cm3 (47 - 60), and from 0 to 80 mmHg was 162 cm3 (150 - 174) in limbs with venous disease compared with 117 cm3 (108 - 127). These differences are shown in Figure 10.3.

Elasticity was calculated according to the formula of the bulk modulus of elasticity above for the ranges 0 - 10 mmHg, 10 - 20 mmHg and 20 - 80 mmHg. The median modulus of elasticity for the range 0 - 10 mmHg was 568 (483 - 690) in limbs with venous disease compared with 1242 (1034 - 1550); for the range 10 - 20 mmHg the median modulus was 786 (697 - 917) in limbs with venous disease compared with 909 (792 - 1084) and for the range 20 - 80 mmHg the median modulus was 2585 (2357 - 2818) in

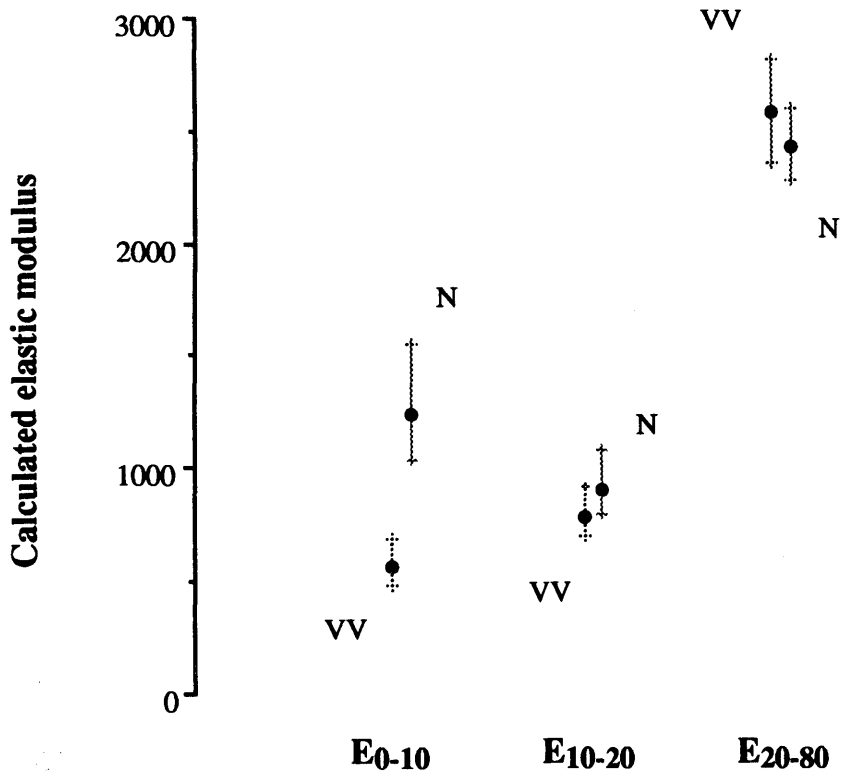
limbs with venous disease compared with 2432 (2276 - 2595) in control limbs. These are illustrated in Figure 10.4. It is plain to see that the modulus of elasticity from 0 to 10 is significantly greater in control limbs than limbs with venous disease (ie. the varicose veins are more distensible at these low pressures), the other measurements are not significantly different from each other.

Discussion

These data show that limbs with varicose veins undergo a greater increase in their volume than normal limbs during venous occlusion plethysmography. This is to be expected since the varicose process produces veins which are dilated and tortuous. The difference between varicose limbs and normals occurs mostly during low pressure distension; the difference between the median volume measurements was 30 cm3 at 0 - 10 mmHg, compared with 39 cm3 and 45 cm3 for 0 - 20 mmHg and 0 - 80 mmHg respectively.

During low pressure distension veins are not circular in cross section and therefore volume changes are due to a combination of factors, including the elasticity of the surrounding tissue and elasticity of the vein wall (involving both flexion of the wall to change shape and stretching of the vein wall). At higher pressures the veins are circular in cross section and therefore no change in shape is involved. It seems likely that bulk elasticity at low pressure is influenced more by dynamic factors (such as smooth muscle tone) than at higher pressure.

Figure 10.3 **Limb volumes during venous occlusion plethysmography; varicose and normal limbs compared. (medians & 95% confidence intervals)**

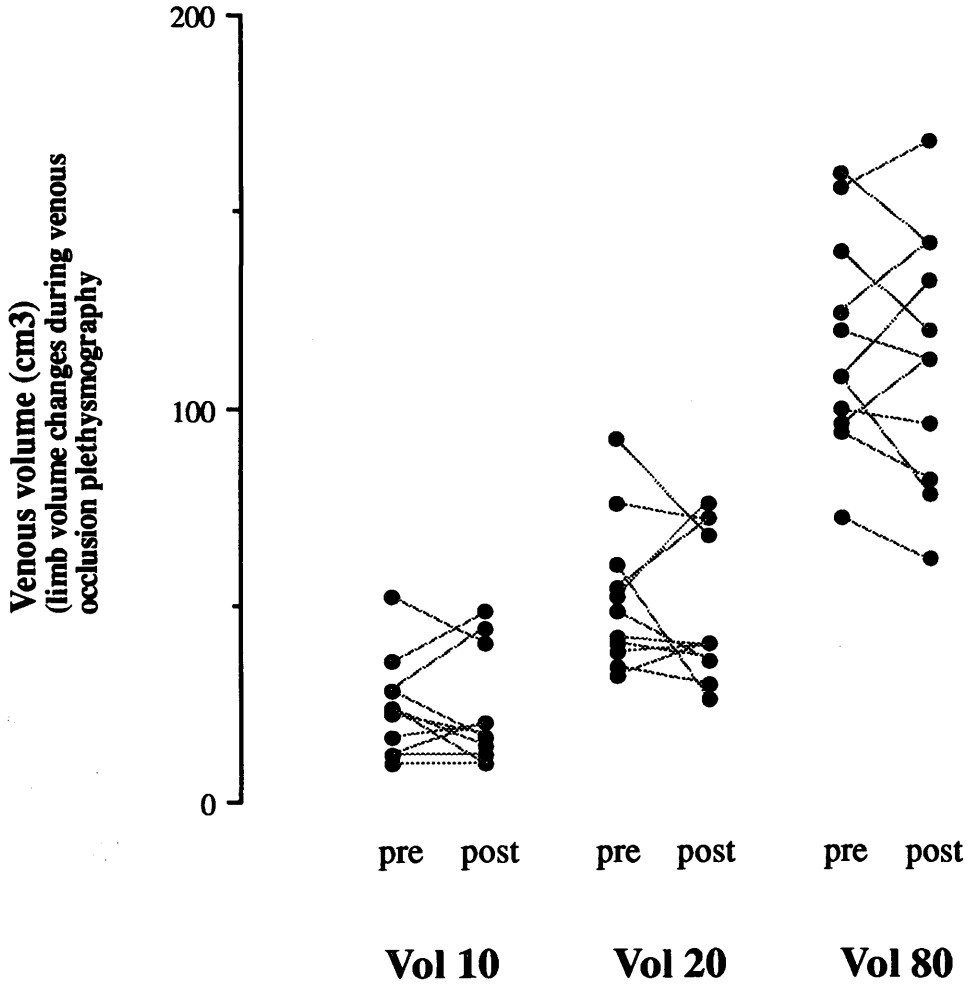


Calculated bulk elastic modulus (see text)

$E_{0\text{-}10}$; modulus from 0 to 10 mmHg, etc.

Median values, error bars are 95% ci.

Figure 10.4 **Calculated bulk modulus of elasticity during venous occlusion plethysmography; varicose and normal limbs compared.**



The calculation of elasticity shows a clear difference between the normal and the varicose limbs at low pressure. The normal limbs are more resistant to distension at these low pressures (have a higher modulus of elasticity) than the varicose limbs. This difference was also shown by Clarke et al., although they studied venous elasticity at higher pressures, choosing to ignore the changes at low pressure. These data above show that at higher pressure (20 - 80 mmHg) the modulus of elasticity in varicose limbs is not significantly different from normals. The distension data show that at these pressures the varicose limbs distend to a greater degree than normal limbs. These limbs were initially larger however, and in addition they were more distensible at the lower pressures; thus the volume change between 20 and 80 mmHg must be divided by a larger figure to calculate elastic modulus.

Clarke also noted that limbs said to be at high risk of developing varicose veins had a similar modulus of elasticity to those which already had venous disease, however the criteria for inclusion on the high risk group were; a standing occupation, a family history of varicose veins, symptoms and signs associated with varicose veins, venous reflux on duplex scanning or abnormal ambulatory venous pressure and refilling time.

It seems likely that limbs which cause symptoms and have signs associated with varicose veins especially if they have venous reflux demonstrated either by duplex scanning or ambulatory venous pressure measurement *already* have veins which are dilated and have incompetent valves, even if surface varices are not visible. Therefore it is not surprising that the measured venous elasticity is similar. The age of these subjects is not quoted, however an age matched cohort (to the subjects who already have varicose veins) would be of such an age that if they were going to develop varicose veins they would have already done so.

The finding that most of the difference in venous elasticity between varicose veins and normals is at low venous pressures is interesting: As has been mentioned, dynamic factors such as smooth muscle tone influence venous elasticity at these pressure,

therefore it may be that a modification in smooth muscle tone would reduce distension at low pressures and perhaps even bring about valvular competence to dilated, incompetent venous valves.

10.4 The effect of major abdominal surgery on venous elasticity

Venodilatation during surgery under general anaesthesia has been suggested to influence the pathogenesis of postoperative deep venous thrombosis. The proposed pathological pathway is that excessive venodilatation causes endothelial damage with exposure of subendothelial collagen. This then acts as an initiation site of deep venous thrombosis.

Coleridge-Smith *et al.* (Coleridge-Smith *et al.* 1990) have noted that venous distension takes place in the deep veins of the calf during surgery under general anaesthesia. They have also shown (Coleridge-Smith *et al.* 1991) that a standard TED stocking prevents this venodilatation and even reduces venous diameter slightly. Comerota *et al.* (Comerota *et al.* 1989) have shown in a group of 21 patients undergoing total hip replacement that per-operative dilatation of the cephalic vein correlates with a greater incidence of post-operative deep venous thrombosis.

If the deep veins of the leg are excessively dilated during surgery it is possible that this will cause a reduction in venous elasticity and therefore further impair venous function during the post-operative period. This study examines the bulk modulus of elasticity during venous occlusion plethysmography before and after abdominal surgery.

Method

A total of 11 subjects (8 men) were studied. Patients were included in the study if they had no evidence of varicose veins and no history of venous thrombosis and were about

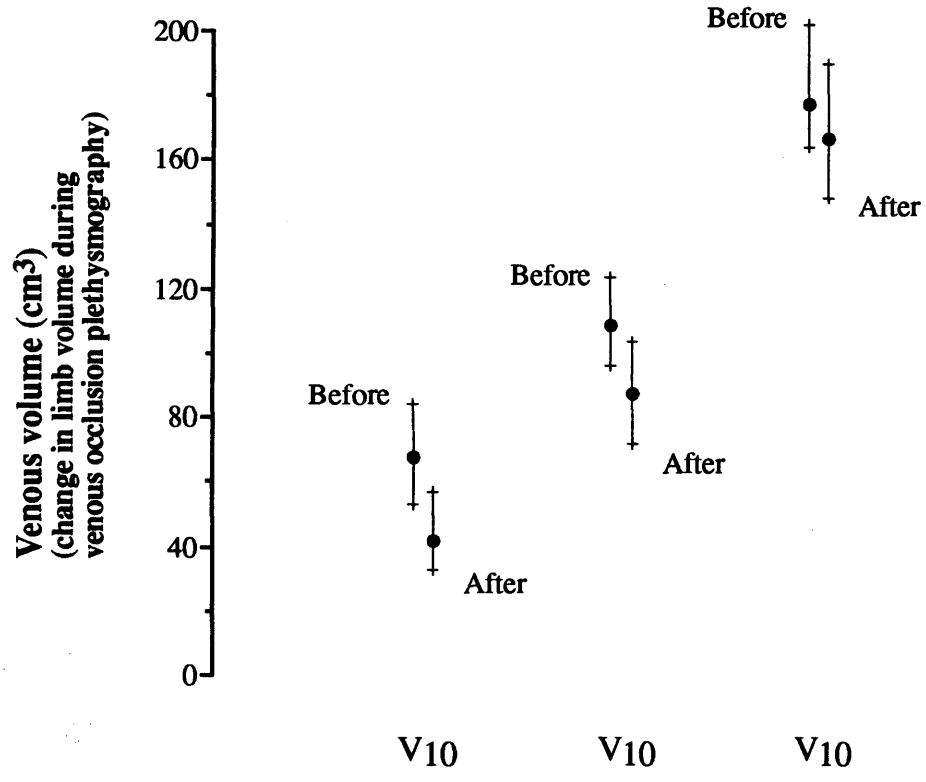
to undergo abdominal surgery (5 gastric procedures, 2 colectomies, 4 hepatobiliary procedures) which was likely to involve an hour or more of general anaesthesia.

Before surgery each patient had one limb measured as described above (circumference measured at three points and volume measurements during venous occlusion using the air-plethysmograph). Standard deep venous thrombosis prophylaxis in the dept. of surgery was to use subcutaneous heparin, TED stockings and intermittent pneumatic compression during surgery. Following ethical committee approval these patients did not have a TED stocking on the limb being studied and did not have the intermittent pneumatic compression device fitted per-operatively. On the fifth day after surgery when patients were comfortable enough to be tested again in the vascular studies unit, the measurements were repeated.

Results

No patient during this study developed signs or symptoms suggestive of deep venous thrombosis. The median age of the subjects was 46.5 years (range 32 - 71). Figure 10.5 shows the effect of the surgery on venous volume measurements during occlusion plethysmography; it is clear from this that there is no overall trend produced by the surgery. This is confirmed by a median (95% ci.) reduction of venous volume when the limbs are distended between 0 - 10 mmHg of 1 (-6 - 10) cm^3. The reduction in the range 0 - 20 mmHg is 3 (-10 - 14) cm^3, and 3 (-10 - 16) for the range 0 - 80 mmHg. Thus using the Wilcoxon test for paired data there is no statistically significant change in these volume measurements. The *resting* volume at 0 mmHg however, does show a median (95% ci) reduction of 71 (13 - 136) cm3 which is significant. As a result the calculated elastic moduli show a change: The median (95% ci.) reduction for the range 0 - 10 mmHg was 1003 (541 - 1564) and for the range 10 - 20 mmHg was 1436 (1137 - 1761). The change for the range 20 - 80 was not significant, the median reduction being 198 (-578 - 866).

Figure 10.5 **The effect of major abdominal surgery on venous distension changes during occlusion plethysmography**



Vol 10 = change in limb volume from 0 to 10 mmHg venous pressure
Vol 20 = change in limb volume from 0 to 20 mmHg venous pressure
Vol 80 = change in limb volume from 0 to 80 mmHg venous pressure

Discussion

These data demonstrate no significant difference in the limb distension profiles after major abdominal surgery. It is apparent from the data points that this is not due to a "type 2" error; larger numbers in the study are not likely to produce a significant result. The limb volumes at 0 mmHg venous distension pressure were, however reduced compared with the pre-operative values and this produced some changes in the calculated bulk elastic moduli as noted above. Thus when the overall limb volume is taken into account the limbs have a lower bulk modulus of elasticity (are more distensible) between 0 and 20 mmHg venous pressure than before surgery. Possible explanations for the reduction in initial limb volume after surgery include a reduction in intravascular fluid volume (it is unlikely that veins are truly empty at 0 mmHg) and a reduction in extravascular fluid. If the first is true then there is a true reduction in venous elasticity as a result of major abdominal surgery, if the latter then that may not be the case. Unfortunately there is not a straightforward method of measuring the intravenous volume of a limb, therefore this cannot be easily answered. A reduction in venous elasticity after undergoing major abdominal surgery would certainly accord with the conclusions of the previous cited papers, and could conceivably be the result of venous overdistension as described.

The previous studies showed a tendency for deep venous thrombosis in patients with a greater degree of venous distension during surgery. No measurement of venous pressure was made however and therefore the greater distension may be a consequence of greater venous pressure in veins of similar elasticity, or of similar venous pressure in veins of differing elasticity. The conclusion regarding the influence on venous thrombosis would be very different depending which is the case: If the veins are of similar elasticity and some were "over distended" then the concept that this causes endothelial damage, initiating the coagulation pathway is the likely explanation. If, however the veins were of differing elasticity and the venous distension pressures were broadly similar (which seems the more likely to me) then it is less likely that the veins were over distended. Rather these "baggy" veins have impaired venous drainage during surgery, thus venous stasis is the favoured explanation.

CHAPTER ELEVEN

THE EFFECT OF COMPRESSION STOCKINGS

11.1 The effect of compression stockings on venous elasticity

Introduction

Compression stockings, as mentioned above have been shown to improve various aspects of venous function and also to help alleviate the symptoms of venous insufficiency. It is not clear how these affects are mediated. The following study was performed to demonstrate the effect of wearing compression stockings on limb distension and the calculated modulus of elasticity during venous occlusion plethysmography.

Methods

A total of 20 subjects were studied over a 4 week period. In addition 9 of these subjects were studied for a further week. All subjects, with the exception of 2 healthy volunteers from the hospital staff, had been referred to the vascular clinic with a diagnosis of varicose veins or chronic venous insufficiency.

At the initial visit the measurements described in the previous section were performed: calf circumference at three points and the simultaneous measurement of venous pressure and venous volume using the air-plethysmograph. The volume changes from 0 - 10, 20 and 80 mmHg were noted as before. Each subject was then fitted with an appropriately sized grade 2 compression stocking (Medi-Plus™) to wear during the day for four weeks. These stockings produce a compression of 30 - 40 mmHg at the ankle decreasing towards the knee. They are one of the most common stockings to be prescribed for venous insufficiency and varicose veins. After 4 weeks of using the compression stockings each subject was then studied again immediately upon removing

the stockings and the same measurements repeated. Nine of the subjects agreed to return for a further set of measurements after a further week, during which time they did not wear the stockings; the purpose of this was to determine whether any of the changes noted would persist. All measurements were carried out at the same time of day for each subject in order to minimise any variation due to the diurnal variation in vascular tone. The temperature of the vascular studies unit was kept between 22° and 24° Celsius.

Results

The median age of the subjects was 50.5 yrs (95% ci; 45 - 57). Before compression the median (95% ci.) resting limb volumes were 2734 (2558 - 2964) and after 1 month compression therapy were 2632 (2456 - 2837). The median (95%ci.) decrease in resting volume was 108.5 cm3 (54.5 - 153) This was statistically significant using the Wilcoxon test for paired data ($p = o.oo4$). The median (95% ci.) change in resting limb volume between the initial visit and week 5 was 0 cm3 (-50 - 86) [No significant difference].

The median (95% ci.) changes in limb volume during occlusion plethysmography between 0 - 10 mmHg, 0 - 20 mmHg and 0 - 80 mmHg respectively were 68 cm3 (53 - 84), 109 cm3 (96 - 124) and 178 cm3 (164 - 202) before compression and 42 cm3 (32 - 57), 88 cm3 (72 - 104) and 167 cm3 (148 - 190) after compression. These are illustrated in Figure 11.1. At week 5 they were 47 cm3 (28 - 74), 92 cm3 (60 - 128) and 162 cm3 (132 - 200). These effects are illustrated in Figure 11.2 for individual limbs.

The changes in these volumes during plethysmography produced by the compression stockings are illustrated in figure 11.3. The median (95% ci.) reduction in limb volumes when distended from 0 - 10 mmHg was 23 cm3 (15 - 30) after 4 weeks of compression. The median (95% ci.) reduction in the range 0 - 20 mmHg was 21 cm3 (10 - 32) and in the range 0 - 80 mmHg was 7 cm3 (0 - 28). Comparing week 0 and 5 the reductions were -2 cm3 (-15 - 24), 2 cm3 (-24 - 22) and 2 cm3 (-13 - 20). The stockings thus produced a significant ($p < 0.05$, Wilcoxon paired test) reduction in the distension

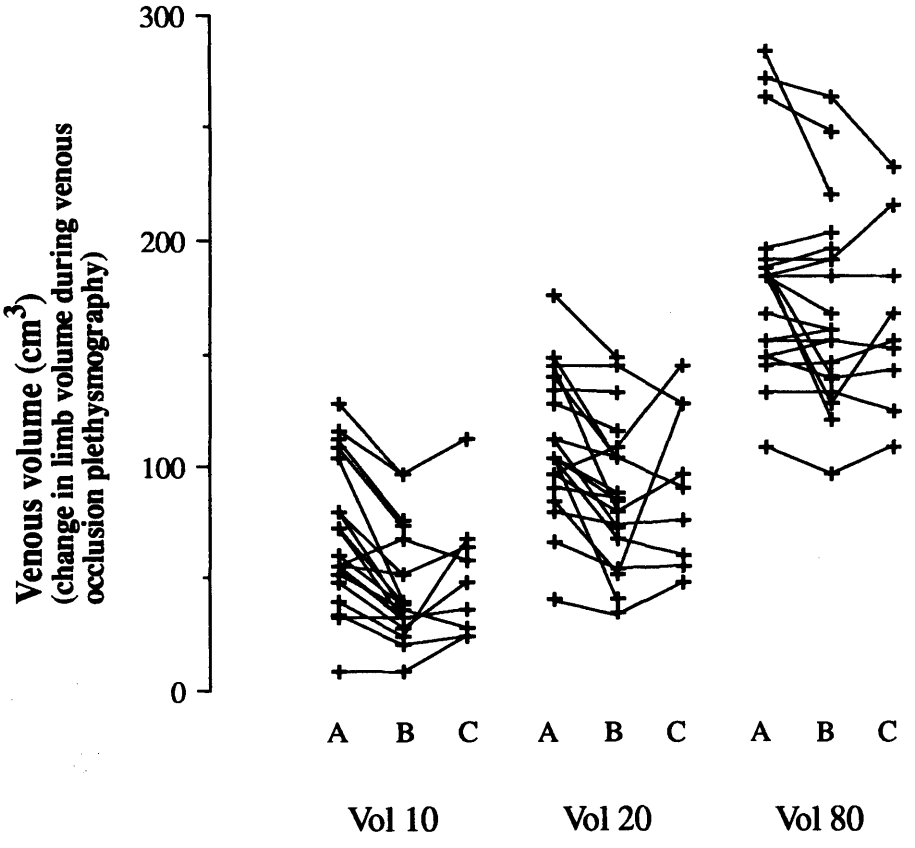
volume profiles in the ranges 0 - 10 mmHg and 0 - 20 mmHg but not in the range 0 - 80 mmHg. The differences between weeks 0 and 5 were not significant.

The median (95% ci.) elastic moduli before compression were 451 (358 - 550), 701 (606 - 846) and 2515 (2093 - 3004). After compression these were 686 (546 - 837), 664 (567 - 762) and 2028 (1873 - 2224). These are illustrated in Figure 11.4. At week 5 they were 623 (406 - 827), 681 (519 - 1434) and 2201 (1912 - 3126). Thus the median (95% ci.) changes in elasticity after 4 weeks were an increase of 214 (99 - 301) from 0 - 10 mmHg ($p < 0.05$, Wilcoxon paired test), a decrease of 55 (-121 - 245) ($p > 0.05$, Wilcoxon) between 10 - 20 mmHg and a decrease of 426 (118 - 881) ($p < 0.05$, Wilcoxon) between 20 - 80 mmHg. These are illustrated in Figure 11.5. At week 5 these figures were 26 (-257 - 937), -30 (-493 - 198) and 0 (-1191 - 962) respectively (not significant).

Discussion

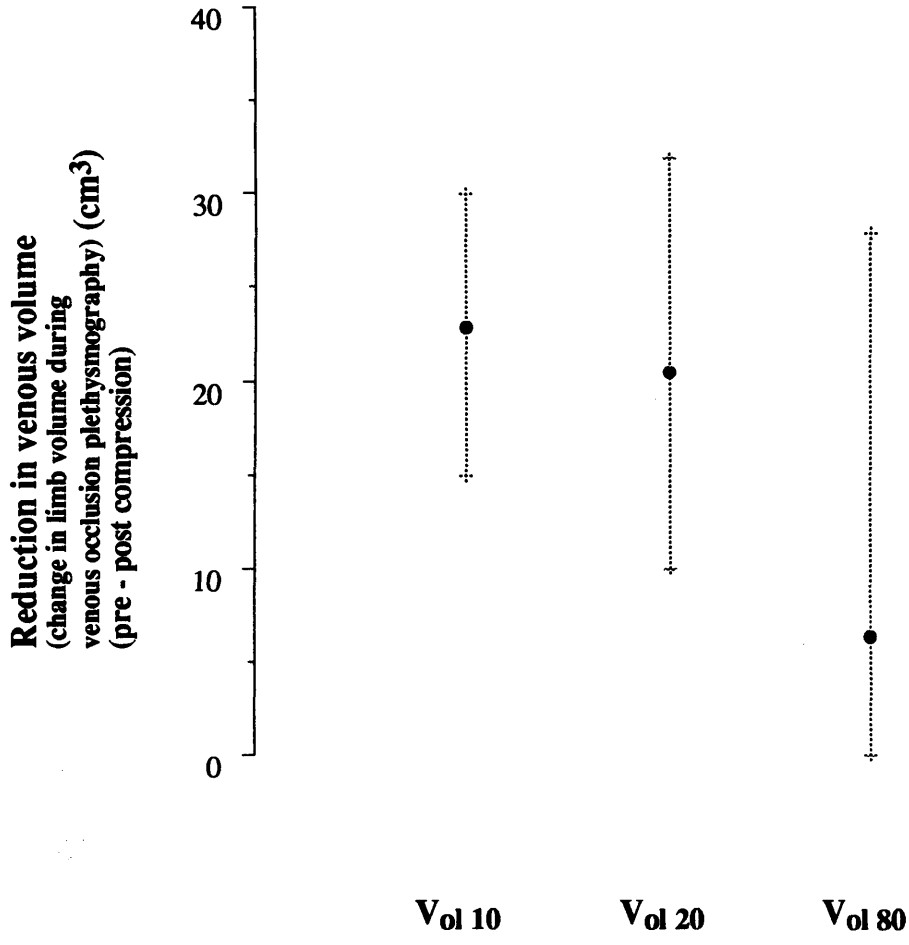
The effect of the compression stockings was therefore twofold: firstly the resting volume of the calf was reduced after 4 weeks of wearing the compression stocking. It is likely that this effect is due to a reduction in extra vascular fluid in the limb. If the veins are not completely empty at 0 mmHg venous pressure (which is probable) there may also be a reduction in the intravascular volume at 0 mmHg after compression therapy.

Figure 11.1 **Limb volume changes during venous occlusion, before and after compression therapy (medians & 95% c.i.)**



Vol 10 = change in limb volume from 0 to 10 mmHg venous pressure
Vol 20 = change in limb volume from 0 to 20 mmHg venous pressure
Vol 80 = change in limb volume from 0 to 80 mmHg venous pressure

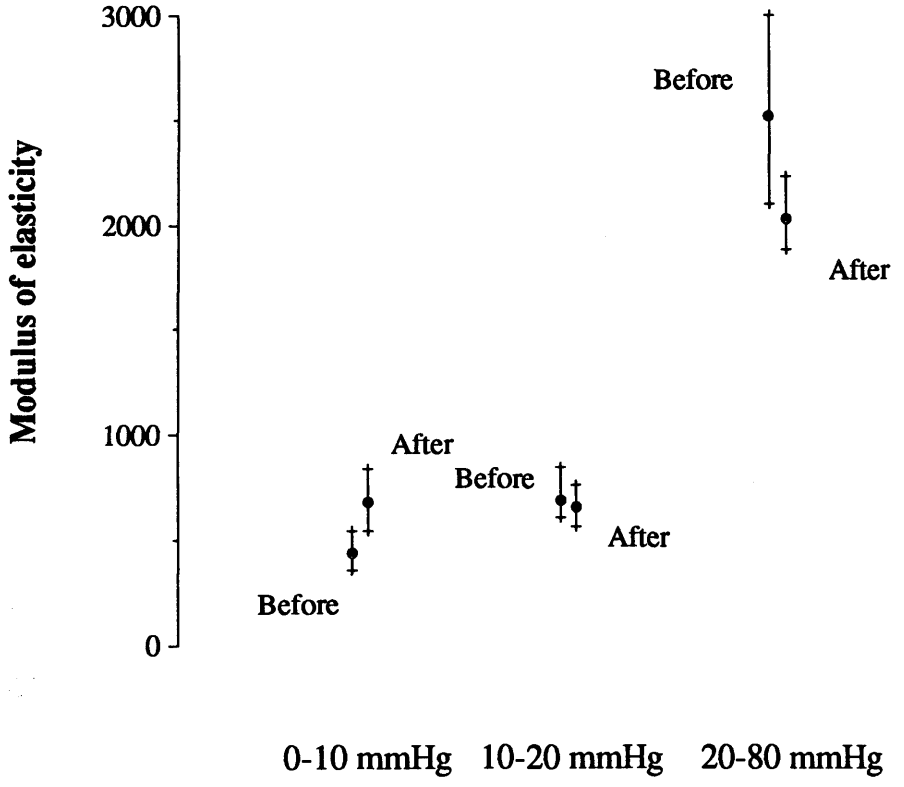
Figure 11.2 **The effect of elastic compression on venous volumes during occlusion plethysmography**



A = Volume prior to compression therapy
B = Volume after four weeks of compression therapy
C = Volume one weeks after removing compression stockings

Vol 10 = change in limb volume from 0 to 10 mmHg venous pressure
Vol 20 = change in limb volume from 0 to 20 mmHg venous pressure
Vol 80 = change in limb volume from 0 to 80 mmHg venous pressure

Figure 11.3 **Decrease in venous distension profiles after 4 weeks of compression therapy**



Vol 10 = change in limb volume from 0 to 10 mmHg venous pressure
Vol 20 = change in limb volume from 0 to 20 mmHg venous pressure
Vol 80 = change in limb volume from 0 to 80 mmHg venous pressure

Figure 11.4 **Calculated bulk modulus of elasticity: the effect of compression therapy (medians & 95% confidence intervals)**

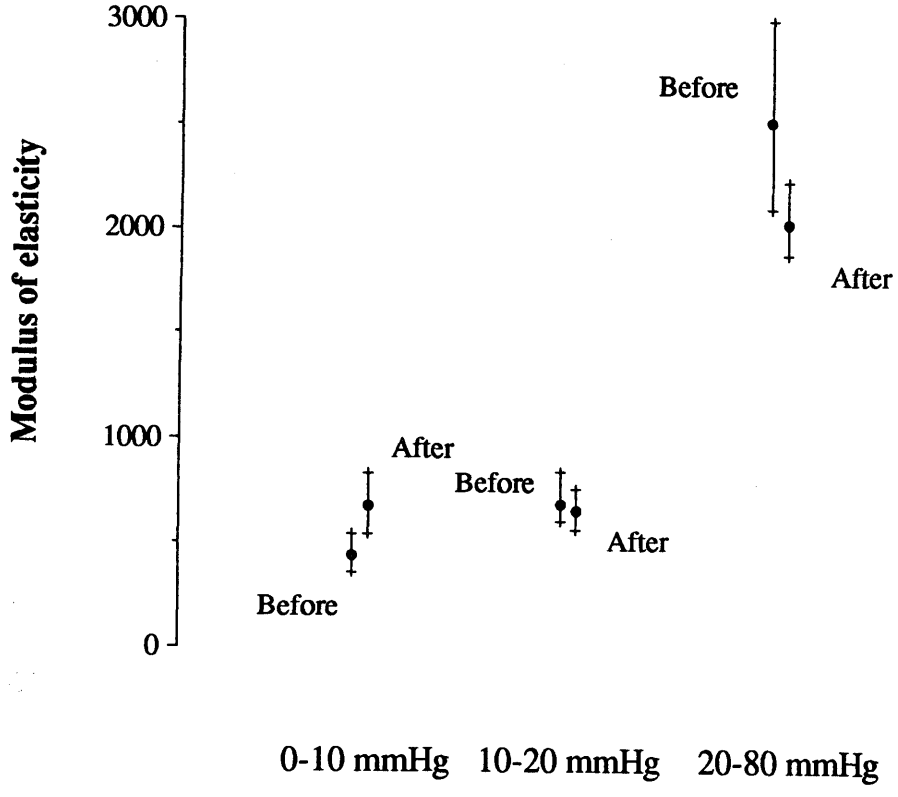
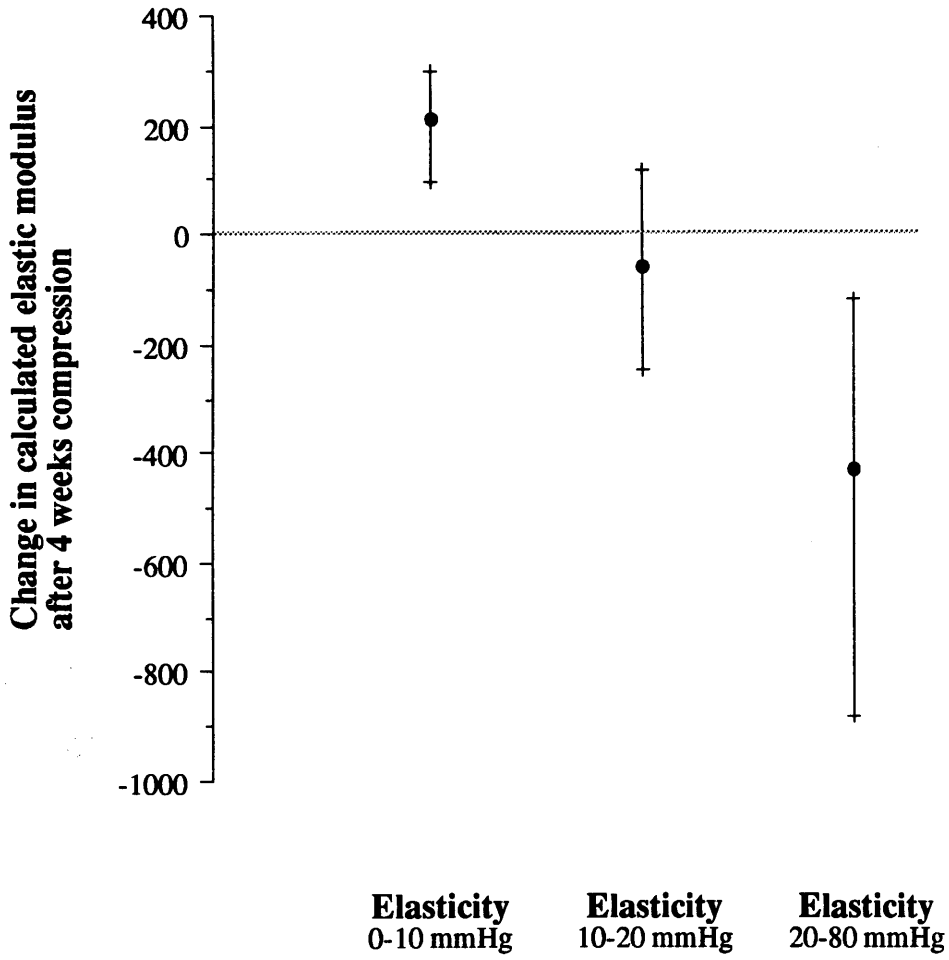


Figure 11.5 **Changes in calculated incremental bulk modulus of elasticity after four weeks of compression therapy**



The compression stockings also reduced the limb volume changes during venous occlusion. These changes were especially marked at the lower distension pressures. As mentioned in the previous section, changes at these distension pressure are more likely to occur as a result of alterations in the dynamic aspects of venous elasticity (smooth muscle tone). The result of these alterations in the venous distension profiles and change in resting limb volume on the calculated bulk modulus of elasticity are that from 0 - 10 mmHg there is an increase in elasticity and from 20 - 80 mmHg there is a decrease in elasticity. The reduction in the distension profile between 0 and 80 mmHg was not statistically significant, therefore it appears that the change in the calculated bulk modulus of venous elasticity was due to the decrease in initial limb volume produced by the stockings. As mentioned above this is probably due to a reduction in extravascular fluid, therefore the change in distension profiles of the limbs are probably more relevant to venous function than the calculated bulk modulus of elasticity.

11.2 The reproducibility of duplex measurements of venous diameter.

The next section requires the measurement of venous diameter using duplex ultrasonography. I have therefore assessed the reproducibility of this method by repeated measurements on eighteen limbs.

The superficial veins of eighteen healthy subjects were examined using a duplex scanner with an 8.5 MHz probe (Hitachi, Bedford, UK). An ultrasonic "landmark" was sought in order that the same point on the vein could be found again. The diameter of the vein at this point was recorded (Diameter 1). After an interval of thirty minutes each subject was scanned again and the measurement repeated (Diameter 2).

Using the formula:

$$s^2 = \Sigma \text{ differences}^2/2n$$

s = standard deviation of the error, n = number of limbs examined (18)

S was calculated at 0.13 mm

Using the formula:

Coefficient of variation = s/mean observed diameter x 100

The coefficient of variation was calculated at 3.5 per cent

The measurements of venous diameter are shown in Table 11.1

Table 11.1

Repeated measurements of venous diameter

Diameter 1 (mm)	Diameter 2 (mm)	Difference	Difference^2
2.9	3.2	0.3	0.09
3.4	3.3	0.1	0.01
3.5	3.3	0.2	0.04
3.7	3.3	0.4	0.16
3.5	3.5	0.0	0.00
3.8	3.7	0.1	0.01
3.6	3.8	0.2	0.04
3.8	3.8	0.0	0.00
3.8	3.8	0.0	0.00
3.8	3.8	0.0	0.00
3.5	3.8	0.3	0.09
4.0	3.9	0.1	0.01
3.8	4.0	0.2	0.04
3.9	4.0	0.1	0.01
4.1	3.9	0.2	0.04
4.1	4.0	0.1	0.01
4.0	4.2	0.2	0.04
4.2	4.2	0.0	0.00
			0.59

Sum of differences^2 = 0.59

Mean Diameter = 3.75 mm

Standard deviation of the error = 0.13

Coefficient of variation = 3.5 per cent

The median difference was 0.05mm (95% confidence limits: -0.05mm - 0.1mm), which was not significantly different from a difference of zero (p = 0.6, Wilcoxon).

I have therefore accepted this method as reproducible, and have used duplex ultrasonography to measure venous diameter in the next section.

11.3 The effect of compression stockings on valvular function.

Introduction

The complications of venous insufficiency such as venous ulceration are thought to be the result of venous hypertension. In order to reduce venous pressure during exercise the venous calf muscle pump relies on the integrity of venous valves to prevent reflux of blood. The incidence of venous ulceration has been shown to increase in a linear fashion with increasing ambulatory venous pressure (the superficial venous pressure at the conclusion of a standard exercise regimen). Although there has been some disagreement in the past it is widely accepted that the varicose process involves the loss of venous elasticity with pathological dilatation of the venous valve ring. As a result of this dilatation the valve cusps are unable to coapt and the valve is thus rendered incompetent, with consequent failure of the venous calf muscle pump resulting in venous hypertension.

Compression stockings are commonly prescribed for the treatment of venous insufficiency states. Fitted graduated compression stockings have been shown to improve the symptoms of venous insufficiency and improve skin condition. It has also been shown that compression stockings are able to reduce ambulatory venous pressure. It is possible that the mechanism of action of compression stockings is that dilated, incompetent venous valves are rendered competent by bringing the valve cusps into

apposition. A recent study has shown that it is possible to restore venous competence to a proportion of veins at knee level by applying a compression tourniquet with a pressure of 40mmHg (Sarin *et al.* 1992).

This study examines the effect of grade 2 compression stockings on venous valvular competence using duplex ultrasonography.

Patients and methods

Twenty seven patients (27 limbs) attending the vascular clinic of a university teaching hospital with a clinical diagnosis of varicose veins or chronic venous insufficiency were studied. One limb had a (currently) healed venous ulcer, seven limbs had either eczema, pigmentation or lipodermatosclerosis and the remainder had healthy skin. The median age of the sample was 41 years (95% confidence limits 35.5 - 47). 12 males and 15 females were studied.

In order to exclude post-phlebitic veins whose valve cusps may be destroyed no subject was included who had previously suffered from deep venous thrombosis or had ultrasonic evidence suggestive of previous thrombosis.

Duplex evaluation was carried out with the subject seated on the edge of a couch, supported by a 45° foam wedge with legs dependent and relaxed. Venous reflux was sought in each vein on release of manual calf compression, reflux which lasted for longer than 0.5 sec was regarded as significant.

Those limbs which exhibited venous reflux in either the popliteal, long or short saphenous veins and in which an identifiable ultrasonic landmark (such as a venous tributary) could be identified were studied further. The maximal velocity of venous reflux which was obtained by release of calf compression was recorded, together with the venous diameter at this point. A compression stocking (knee length "Medi-Plus") designed to apply 30 mmHg compression at the ankle, decreasing towards the knee was

then applied. The same section of vein was then imaged on the duplex (hence the ultrasonic landmark) and the maximal reflux velocity and venous diameter recorded whilst scanning through the compression stocking.

By using the equation: flow = velocity x $(diam/2)^2 \times \pi$. the maximum reflux flow was also calculated. Results were compared by using the Wilcoxon test for paired data, $p < 0.05$ was taken as representing a statistically significant result.

Results.

Data were obtained for 31 veins in these 27 limbs; 5 long saphenous, 5 popliteal and 21 short saphenous veins.

The coefficient of variation for measuring maximal reflux velocity was 13% on 20 repeated measurements.

The median venous diameter without compression was 6.6 mm (95% confidence interval: 5.8 - 7.45) and the median peak reflux velocity was 39 cm/sec (95% confidence interval: 31.5 - 48.5). These figures give a median peak reflux flow of 1199 cm3/sec (95% confidence interval: 898 - 1873).

Scanning through the compression stocking the median venous diameter was 5.6 mm (95% confidence interval: 4.9 - 6.5) and the median peak reflux velocity was 24.5 cm/sec (95% confidence interval: 20 - 29.5). These figures give a median peak reflux flow with compression stockings of 611 cm3/sec (95% confidence interval: 447 - 815). Figure 11.6 shows graphically the venous diameter of each vein both with and without compression. Figure 11.7 shows the peak reflux velocity with and without compression. In one case there was no reflux demonstrable with the compression stocking in place (reflux velocity became zero) and in one other case the duration of venous reflux fell below 0.5 seconds and therefore should be classified as within normal limits, the maximal reflux velocity for this vein though is represented on the graph. Figure 11.8 shows the peak reflux flow calculated from the diameter and velocity data.

All parameters were reduced by the compression stockings, the difference reaching statistical significance using the Wilcoxon test for paired data ($p < 0.01$, all parameters).

Discussion

The concept that compression stockings reduce venous diameter to such a degree that dilated, incompetent venous valves are rendered competent is attractive. In the previous section it has been shown that compression stockings reduce venous distensibility, which may account for their effect on venous function. The effect however is short lived. This is in agreement with the findings of Somerville (Somerville *et al.* 1974) who found that the beneficial effect of compression stockings on ambulatory venous pressure is short lived.

If compression stockings do act by restoring valvular competence to dilated, incompetent venous valves then we would expect to find that reflux, as detected by the duplex scanner is abolished in the majority of veins underneath the compression stocking. As can be seen from the data above only one vein was restored to a state of venous valvular competence. In addition one vein, although still exhibiting retrograde venous flow on release of calf compression should be classified as competent since the duration of reflux was less than 0.5 second. Thus only 2 of 31 veins (6.5% of our sample) were restored to valvular competence by the use of grade 2 compression stockings.

Figure 11.6 **Venous diameter and the effect of compression stockings (bars show medians & 95% confidence intervals)**

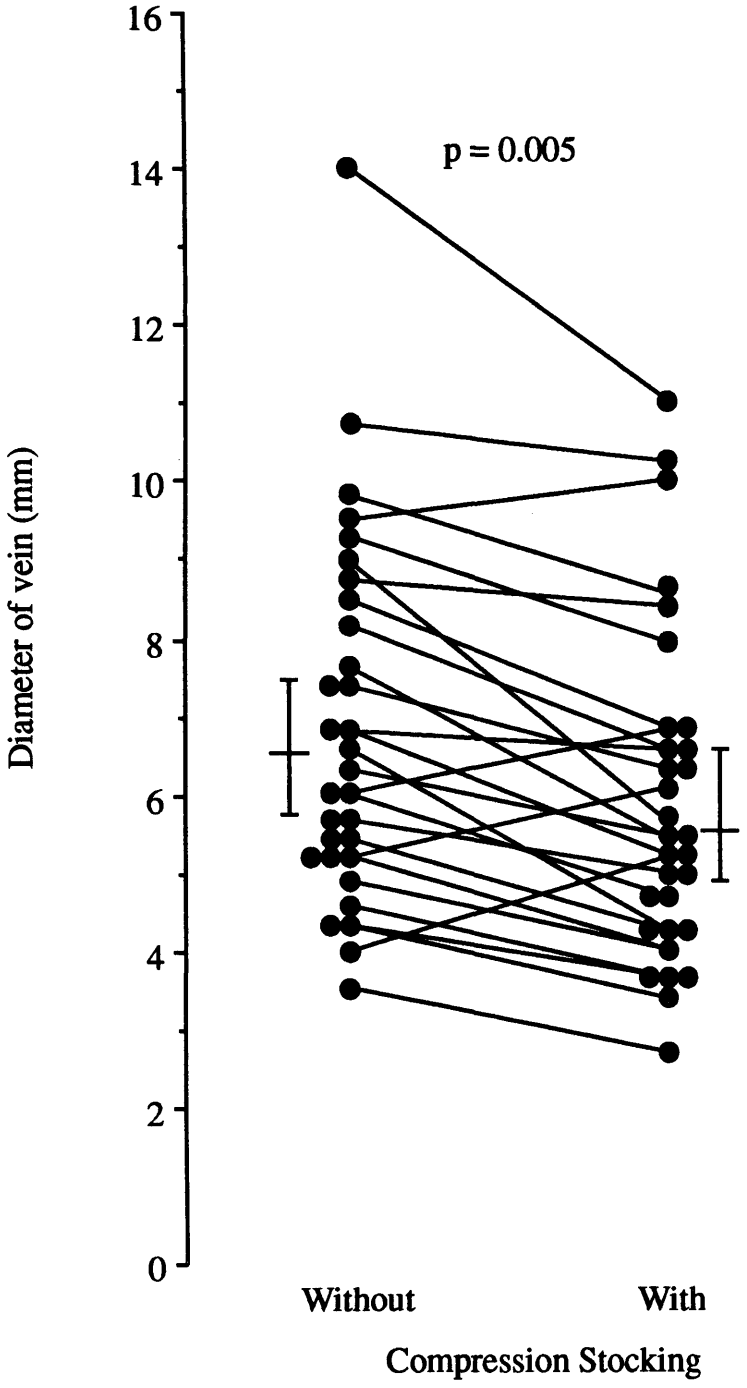


Figure 11.7 **Peak venous reflux velocity on compression release; effect of compression stockings (bars show medians and 95% confidence intervals)**

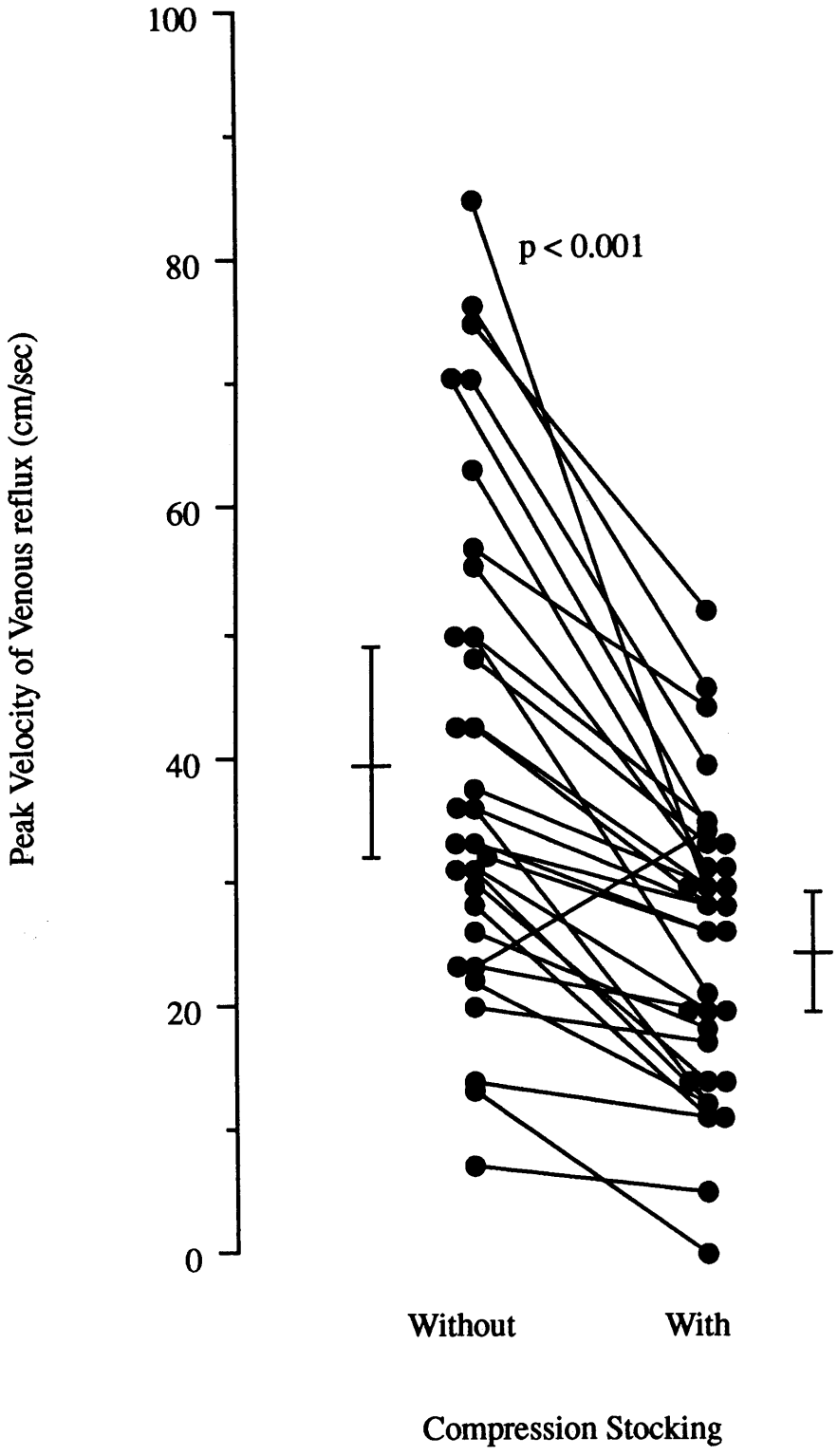
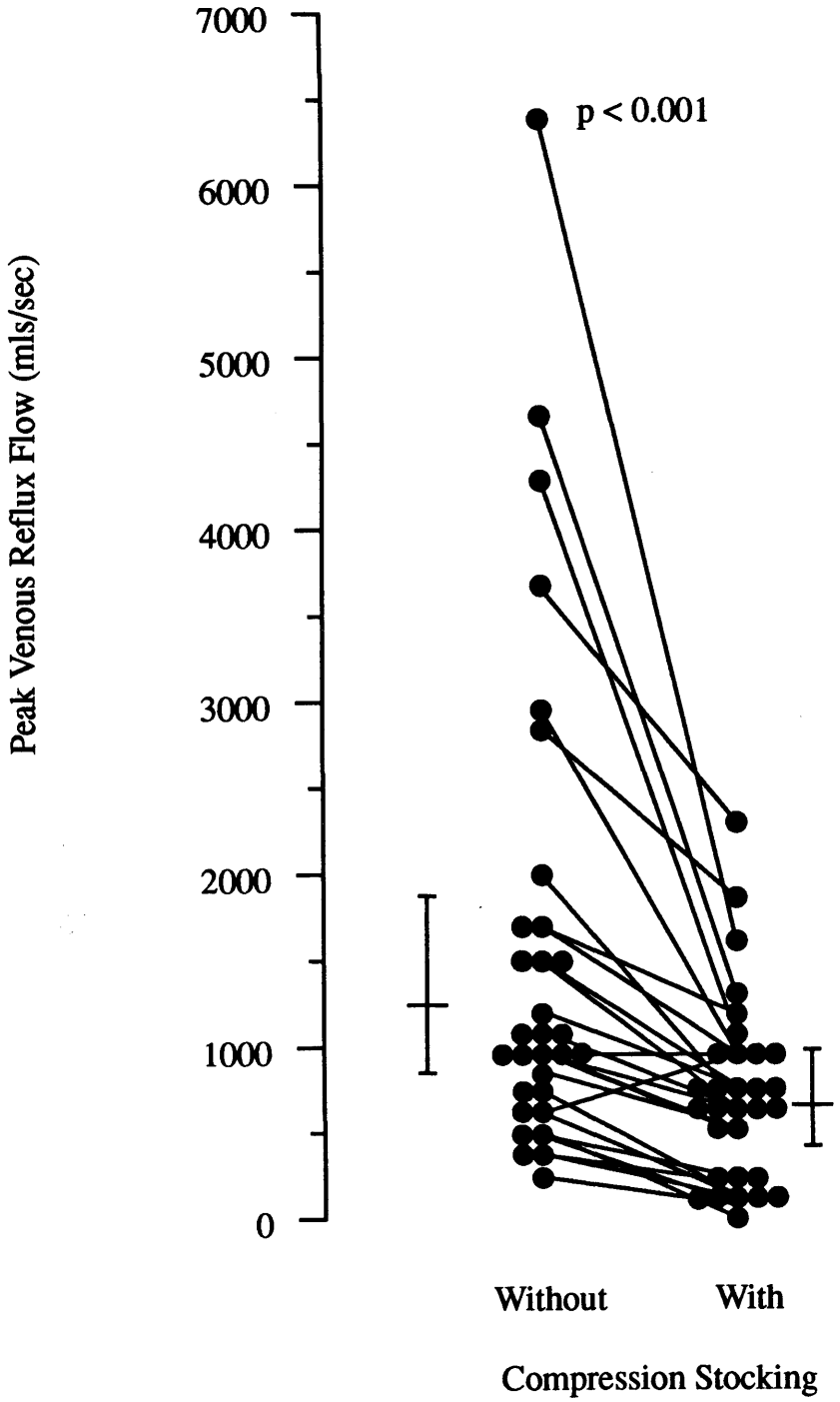


Figure 11.8 **Peak venous reflux flow on compression release; effect of compression stockings (bars show medians and 95% confidence intervals)**



The venous haemodynamics were altered significantly however; there was a significant reduction in reflux velocity from 39 cm/sec to 24.5 cm/sec. This does not appear to be mediated by restoring valvular competence but may be due to the reduction in venous diameter, thus reducing the venous volume of the calf. A reduction in venous volume would lead to an improvement in pump activity; resting venous volumes would be reduced, therefore with each step it is likely that a greater proportion of the venous volume will be "pumped" proximally toward the heart. In addition I have demonstrated that the rate of venous refilling is slower when the compression stockings are worn, which is in agreement with the findings of Evander (Evander *et al.* 1984) and Christopoulos (Christopoulos *et al.* 1987).

Although compression stockings clearly improve venous haemodynamics, it has been demonstrated by this study that in most cases they do not act by restoring valvular competence to dilated, incompetent venous valves. Their beneficial effect may be due to the reduction in venous volume of the calf that they produce. There is also some evidence that compression stockings have a beneficial effect on the microcirculation (Belcaro *et al.* 1988), although this may be a secondary effect (since it is thought that the microcirculatory changes in venous disease are secondary to chronic venous hypertension). These two effects could be the result of reducing the transmural pressure across the vein and capillary wall, thus allowing the microcirculation to function more effectively.

CHAPTER TWELVE

DISCUSSION AND SUGGESTIONS FOR FURTHER WORK

As always with research, the depth of knowledge advances abreast an increasing appreciation of our ignorance. The work in this thesis has thrown up many questions which I would like to try and answer given unlimited time. In this section I have discussed how I would like to develop the themes touched upon in the thesis.

This thesis has emphasized the importance of ambulatory venous pressure measurement in assessing the efficiency of the venous calf muscle pump, by examining the correlation between ambulatory venous pressure and the clinical condition of limbs affected by venous disease. The agreement however is not complete and I have suggested several explanations why this may be so. Differences in lymphatic and leukocyte function may also influence the severity of venous skin damage in limbs with a similar ambulatory venous pressure (i.e. calf muscle pumps which are equally efficient). The mechanisms of leukocyte trapping and activation are being unravelled apace. Antibodies to study selectin expression, which is thought to be responsible for the initial adhesion of leukocytes and also integrins, which are thought to be responsible for leukocyte activation and migration, are now available. Some selectins may be assayed in peripheral blood samples and expression of these factors changes within 15 or 20 minutes, therefore the response to changes in venous pressure may be studied in healthy individuals and patients with venous disease. The integrins may be assayed from small punch biopsies from the gaiter area. Further study should be carried out in a spectrum of patients with differing severity of venous disease, including the measurement of ambulatory venous pressure. If a group of patients with more severe skin damage than would be expected, given their ambulatory venous pressure, are discovered to show increased expression of one or more of the cellular adhesion molecules then therapy might be worth targeting towards that link.

Another variable however (and one which I think is important to study) is the *use* of the calf muscle pump: One subject may be able to generate a low ambulatory venous pressure in the laboratory situation, proving that he has an efficient calf muscle pumping mechanism, but it does not necessarily follow that he will be active during the day. Thus although ambulatory venous pressure measures calf muscle pump function it does not measure the mean venous pressure throughout the day. There is a real need for a comprehensive study addressing the issue of venous pressure and the skin damage associated with venous hypertension.

One suggestion is that subjects be studied by continuous ambulatory venous pressure recording with an indwelling cannula in the long saphenous vein. Whilst it may be possible to maintain a cannula in this vein for 24 hours in spite of "unrestricted" ambulation I cannot believe that this would represent a subjects normal level of activity and therefore such a measurement would be of limited value.

Unfortunately there is not a non-invasive equivalent of the ambulatory venous pressure, as I have demonstrated. If volume changes were a direct substitute then a portable strain gauge plethysmograph might throw further light on the average venous function over 24 hours in the home environment. What is needed is a non-invasive device which is calibrated to record venous pressure and does not interfer with normal activity.

I have recently used a modified Psion™ computer, connected to two position sensors and an accelerometer to record in real time over 24 hour time periods all position changes (lying, sitting, standing) and all steps taken, together with a measure of the vigour of step in patients with peripheral vascular disease (Payne *et al.* 1997). Such a monitor is worn in a waistband and interfers very little with daily activity (the only exception is that the device is not waterproof and therefore patients may not bathe or shower with the device on). By simultaneously recording venous pressure in the standing, sitting and lying positions and then recording venous pressure and recovery time after 1 step, 2 steps, 3 steps...etc..10 steps, it would be possible to derive the basic data from which to

analyse a period of 24 hours activity recorded with the monitor in terms of venous pressure changes. This would then be a matter of entering these data into the analysis program used to produce summaries of given time intervals. From this, the mean venous pressure over the observed time interval could also be calculated. I suggest that by analysing 200 limbs in this fashion it would be possible to examine the relationship between

1. Ambulatory venous pressure and severity of venous disease, including venous pressure after 1 step, 2 steps etc up to 10 steps. It may be that a measure of calf pump function after less than 10 tiptoe exercises is more representative of the daily use of the venous calf muscle pump.
2. Daily activity (time spent standing, number of steps taken, vigour of steps taken and total energy expended (number x vigour of steps)) and severity of venous disease.
3. Calculated mean venous pressure and severity of venous disease.

If most of the overlap between the groups classified by ambulatory venous pressure in the above study (7.1) was due to differences in daily activity between subjects then I would expect the latter to show a much better agreement.

The question of which veins should be dealt with surgically, given different patterns of venous reflux is an important issue and one which is still not resolved. I have shown that reflux in the popliteal vein seems to have the most influence over the clinical condition of the leg. I believe that this is partly due to it's position as the "gatekeeper" of the calf muscle pump and partly because it is a large vein, through which a great quantity of blood may reflux in a short space of time. The above study may be flawed in that the calf compression and release was not standardised. Various methods of mechanical calf compression and release were tried but I could not make one perform reliably. Sarin et al. (Sarin *et al.* 1994) demonstrated that manual calf compression was sufficiently reproducible. In spite of this I still believe that when comparing limbs in this fashion a standard test of valve function should be used if possible. One solution might be to quantitate the initial flow of blood proximally, just prior to compression release. thus a

standard quantity of blood may be displaced before relaxation when the valve is tested. In order to dissect the contribution of each vein to the clinical condition of the limb and the venous calf muscle pump I would duplex each vein during a standardised calf compression / release recording venous diameter, peak velocity of flow and duration of flow. The clinical condition of the limb would be recorded as before on a 4 point scale, in addition the venous calf muscle pump function would be measured by recording ambulatory venous pressure. The analysis could then be performed as before (7.2) but with weighting of each vein relative to the degree of reflux measured (since unlike multivariate regression analysis, the variable may be ordinal rather than binary for this analysis). By performing the analysis in this way an indication of whether the site of reflux rather than just quantity is important.

In attempting to gauge the predictive value of the tourniquet / AVP test in determining the likely outcome of superficial venous surgery, I made the mistake of assuming that the recommended method of performing the test was valid. Therefore when assessing why the test did not predict the results of surgery accurately I had to trace back to why the test did not work. It may still be that a modification of the tourniquet test is a useful way of determining which patients will benefit from superficial venous surgery. I would approach the problem now by inflating the narrow tourniquet under duplex control until flow in the superficial veins is occluded but flow in the deep veins is unaffected and then record the ambulatory venous pressure. By examining the effect of this on AVP and RT90 with the tourniquets in the appropriate positions it will be possible to decide whether this test is able to predict which limbs are likely to benefit from superficial venous surgery.

A number of limbs were identified in the duplex study which had reflux in both the superficial and the deep veins. There are many surgeons who would not offer such patients superficial venous surgery, however there is no evidence that patients with deep venous reflux in addition to superficial venous reflux do not benefit from long saphenous stripping. A valuable study would be to take such a group and examine the effect of long

saphenous stripping (verified by Duplex scanning pre and post-operatively) on both symptomatology, including venous ulceration and also ambulatory venous pressure.

The study of the statistical weighting given to each vein when the clinical condition of the limb is examined gives a number of different probabilities for finding venous ulceration with different combinations of venous reflux. Many of these limbs have since been operated upon (mostly long saphenous stripping). Those limbs which have undergone venous surgery should be duplex scanned to ensure that the stated procedure has been performed adequately. Their new pattern of reflux should then be fitted to the statistical model and compared with the clinical result. This type of analysis will give an indication of the value of this statistical model in determining which veins should be operated upon. If venous elasticity is the first element of venous function to deteriorate in patients with varicose veins, I would expect it to deteriorate over time in patients with minor varicose veins. Since most patients spend a period of about one year on the waiting list for varicose veins surgery, this provides the opportunity to study whether venous elasticity does deteriorate over time, in line with other parameters of venous function. Such a study would examine a cohort of patients with varicose veins awaiting surgery. Limbs would be classified clinically (symptomatology and skin condition), by ambulatory venous pressure measurement in order to document overall calf pump efficacy, and by duplex scanning to document the function of each vein segment. Venous elasticity would be measured whilst the pedal vein is cannulated for AVP measurement as above (7.1).

In order that the natural history is examined, it should be specified that compression stockings are not worn during the period awaiting surgery. On the day prior to surgery, these same parameters would again be recorded.

Such a study would elucidate whether the presumed pathological pathway which states that venous elasticity deteriorates, thus causing secondary valvular incompetence, is correct. I believe that the venous distension profiles are more relevent to venous function when examining changes in the same limbs over time or after a specific intervention. Of

course when comparing different limbs the comparison cannot be made since each limb will have a different initial size, the difference only partly being due to different venous volumes.

It is often noted that pregnancy causes varicose veins. These generally appear at an early stage of the pregnancy, before the uterus has enlarged appreciably (and before the expectant mother has attended the hospital), and often resolve albeit to a variable degree after parturition. Thus if mothers could be identified prior to conception, this would provide an opportunity to study the development of varicose veins over a shortened time interval. Unfortunately identifying mothers prior to conception is very difficult. One possibility would be to recruit hopeful mothers from a fertility clinic, but even this is likely to require a large number of investigations in order to produce enough subjects completing such a study.

Women often state that the symptoms of their varicose veins fluctuate with their menstrual cycle. The alterations in oestrogen / progestogen with consequent change in smooth muscle tone may be responsible for this. Using the method of measuring venous distension profiles this change could be observed and correlated with changes in these hormones. A similar study may be helpful in patients considering starting hormone replacement therapy, since the question of whether HRT causes venous function to deteriorate has not been answered and is commonly asked of general practitioners.

We know that a significant proportion of patients who have deep venous thrombosis will go on to develop venous incompetence. It is likely that these veins are less distensible than primary varicose veins. By performing venous distension profiles on limb with post-phlebitic legs and comparing them with primary varicose veins this question could be answered. This has clinical relevence, since the results of venous surgery in post-phlebitic limbs is much poorer than in primary varicose veins (Burnand *et al.* 1976).

I have shown that compression stockings help improve the elastic response of varicose veins. It has been shown previously that compression stockings help improve

ambulatory venous pressure (Somerville *et al.* 1974) and that greater compression has a more marked effect (Jones *et al.* 1980). It has also been noted that graduated compression produces a greater effect than non-graduated compression (Horner *et al.* 1980). The optimum compression / gradient of compression however has never been studied (and this may vary between limbs of different dimensions).

Such a study would be possible to perform using the sequential compression device manufactured by Huntleigh Health Care™. This is often used to treat venous ulcers, in combination with bed rest. It consists of a plastic jacket, divided into several compartments which fits around the lower leg. These are inflated sequentially to different pressures by a pump mechanism. In order to investigate the optimum compression for a given leg I would modify such a device, such that the compression chambers could be inflated individually to set pressures. This device would then be fitted to the leg of subjects during ambulatory venous pressure measurement. The effect of applying different pressures and gradients could then be compared, and thus the optimum compression required to improve the venous calf muscle pump mechanism determined.

Presentations of this work

Do compression stockings restore venous valvular competence?

Surgical Research Society of Australasia, Sydney, August 94

Association of International Vascular Surgeons, Austria Feb 93

Which veins are most important when considering a case of venous insufficiency?

Eurosurgery 93, London Sept 93

The clinical significance of venous reflux detected by duplex scanning

International Non-invasive Vascular Course, St Mary's Hospital. (Invited lecture) October 92

The relevance of short saphenous vein incompetence

Association of Surgeons of Great Britain and Ireland, Dublin, Sept 92

The role of Air-plethysmography in venous assessment

Royal Society of Medicine; Venous Forum, May 1992

Predicting the haemodynamic effect of superficial venous surgery

Association of International Vascular Surgeons, France, March 1991

The clinical significance of venous reflux detected by duplex scanning

Oxford Region Surgeons Meeting, Sept 92

The mechanism of action of compression therapy

Surgical Grand Round, John Radcliffe Hospital, October 92

The role of short saphenous reflux in venous ulceration

Midlands Vascular Society, April 1992

Leicester University Postgraduate Clinical Research Prize, March 1992

Publications of this work

Payne SPK, London NJM, Newland CJ, Thrush AJ, Barrie WW & Bell PRF Ambulatory venous pressure: Correlation with Skin Condition and Role in Identifying Surgically Correctible Disease *Eur J Vasc & Endovasc Surg* 1996: 11; 2; 195 - 200

Payne SPK, London NJM, Jagger C, Newland CJ, Barrie WW and Bell PRF. The Clinical Significance of Venous Reflux detected by Duplex Scanning *Brit. J Surg* 1994; 81; 39 - 41

Payne SPK, London NJM, Jagger C, Newland CJ, Barrie WW and Bell PRF. The Clinical Significance of Venous Reflux detected by Duplex Scanning *Phlebology Digest* (Invited paper, In press)

Payne SPK, London NJM, Thrush AJ, Barrie WW & Bell PRF. Venous assessment using air-plethysmography; a comparison with clinical examination, ambulatory venous pressure and duplex assessment *Brit. J Surg* 1993; 80; 967 - 970

Payne SPK, Newland CJ, London NJM, Barrie WW and Bell PRF. The investigation and significance of short saphenous vein incompetence. *Annals of the Royal College of Surgeons of England* 1993; 75; 354 - 357

Payne SPK, London NJM and Barrie WW The relevance of short saphenous vein incompetence (letter) *Eur J Vasc Surg* 1992: 6; 4; 449 - 450

References cited

Abramson JH, Hopp C and Epstein LM (1981). The epidemiology of varicose veins. A survey in western Jerusalem. *J Epid Comm Health* 35:213-217

Abu-Own A, Scurr J and Coleridge-Smith P (1994). Effect of leg elevation on the skin microcirculation in chronic venous insufficiency. *J Vasc Surg* 20(5):705-710

Abu-Own A, Scurr J and Coleridge-Smith P (1994). Saphenous vein reflux without incompetence at the saphenofemoral junction. *Brit J Surg* 81:1452-54

Ackroyd JS, Lea TM and Browse NL (1986). Deep vein reflux: an assessment by descending phlebography. *Brit J Surg* 73(1):31-3

Åkesson H, Brudin L, Cwikiel W, Ohlin P and Plate G (1990). Does the correction of insufficient superficial and perforating veins improve venous function inpatients with deep venous insufficiency? *Phlebology* 5:113 - 123

Alexander R (1963). The peripheral venous system In: *Handbook of Physiology* Ed, Hamilton W and Dow P Americal Physiological Soc, Washington DC pp 1075-1098

Almen T (1969). Contrast agent design: some aspects of the synthesis of water soluble contrast agents of low osmolality. *J Theo Biol* 24:216

Almgren B and Eriksson I (1990). Valvular incompetence in superficial, deep and perforator veins of limbs with varicose veins. *Acta Chir Scand* 156(1):69-74

American Venous Forum (1994). Classification and grading of chronic venous disease in the lower limbs. A Consensus Statement. *Report of the International Ad Hoc Committee of the Sixth Annual Meeting of the American Venous Forum.* Maui, Hawaii, Feb 22-26, 1994.

Andreotti L, Cammelli D, Sampognaro S, et al (1985). Biochemical analysis of dermal connective tissue in subjects affected by primary uncomplicated varicose veins. *Angiology* 36(5):265-70

Arnoldi CC (1957). The aetiology of primary varicose veins. *Dan Med Bull* 4:102-107

Arnoldi C (1964). The venous return from the lower leg: a synthesis. *Acta Orthop Scand* 64:1 - 75

Arnoldi CC (1966). Venous pressure in patients with valvular incompetence of the veins of the lower limb. *Acta Chir Scand* 132:628-645

Arnoldi CC and Linderholm H (1966). Intravenous pressure of the calcaneus and venous pressure in the calf of healthy human subjects in the erect position. *Acta Chir Scand* 132:646

Arnoldi CC (1989).Physiology and pathophysiology of the venous pump of the calf In: *Controversies in the management of venous disorders* Ed, Eklöf B, Gjöres JE, Thulesius O and Bergqvist D. Butterworths, London pp 6-23

Arpaia MR, Ferrone R, Amitrano M, Nappo C, Leonardo G, del GR (1990). Effects of Centella asiatica extract on mucopolysaccharide metabolism in subjects with varicose veins. *Int J Clin Pharmacol Res* 10(4):229-33

Attinger E (1969). Wall properties of veins. *IEEE Trans Biomed Eng BME* 16:253

Babcock W (1907). A new operation for the extirpation of varicose veins of the leg. *N Y Med J* 86:153-156

Baker S, Stacey M, Jopp-McKay A, Hoskin S and Thompson P (1991). Epidemiology of chronic venous ulceration. *Br J Surg* 78:864-867

Barendsen G and Van-den-Berg J (1976). Venous pressure-volume relation and calf blood flow determined by changes in posture. *Cardiovasc Res* 10:206-13

Barker A (1964). Varicose veins. *Lancet* ii:970-971

Baron HC and Cassaro S (1986). The role of arteriovenous shunts in the pathogenesis of varicose veins. *J Vasc Surg* 4(2):124-8

Bayliss W (1902). On the local reactions of the arterial wall to changes of internal pressure. *J Physiol* 28:220 - 31

Beaglehole R, Salmond CE and Prior IAM (1976). Varicose veins in New Zealand: Prevalence and severity. *NZ Med J* 84:396-399

Belcaro G, Grigg M, Vasdekis S, Rulo A, Christopoulos D and Nicolaides A (1988). Evaluation of the effects of elastic compression in patients with postphlebitic limbs by laser-doppler flowmetry. *Phlébology* 41(4):797 - 802

Belcaro G (1989). Plication of the sapheno-femoral junction. An alternative to ligation and stripping? *Vasa* 18(4):296-300.

Bergan J (1991).Surgical procedures for varicose veins In: Bergan J and Yao J ed. *Venous disorders*. WB Saunders, Philadelphia. pp 201-216

Bergan J (1985). Conrad Jobst and the Development of pressure Gradient Therapy for Venous Disease In: Bergan J and Yao J ed. *Surgery of the Veins*. Grune & Stratton, Orlando pp 529-540.

Bergan JJ (1996) New technology and recurrent varicose veins *Lancet* 348; 210-11

Bergan JJ (1996) Saphenous vein stripping and quality of outcome *Brit J Surg* 83; 1025-27

Berridge D, Westby J, Makin G and Hopkinson B (1989). Do compression stockings potentiate the fibrinolytic capacity of the lower limbs? *Phlebology* 4:161-166

Bier A, Braun H and Kummel H (1917). Chirurgische Operations Lehre. *Leipzig J A Barth* 5:334 (German)

Bisgaard H (1948). In: *Ulcers and Eczema of the Leg Sequels of Phlebitis*. Munksgaard, Copenhagen

Björdal R (1971). Pressure patterns in the saphenous system in patients with venous leg ulcers. *Acta Chir Scand* 137:495-501

Blair SD, Wright DD, Backhouse CM, Riddle E and McCollum CN (1988). Sustained compression and healing of chronic venous ulcers [published erratum in BMJ 1988 Dec 10;297(6662):1500]. *Br MedJ* 297(6657):1159-61

Blalock A (1929). Oxygen content of blood in patients with varices. *Arch Surg* 19:898-905

Bland J and Altman D (1986). Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*; i:307 - 310

Blumoff R and Johnson G (1977). Saphenous vein PpO2 in patients with varicose veins. *J Surg res* 23:35-6

Bobek K, Cajzl L, Cepelak V, Slaisova V, Opatzny K and Barcal R (1966). Etude de la frequence des maladies phlebologiques et de l'influence de quelques facteurs etiologiques. *Phlebologie* 19:217-230 (French)

Bocking K and Roach M (1974). The elastic properties of the human great saphenous vein in relation to primary varicose veins. *Can J Physiol Pharmacol* 52:153-7

Boka SA (1985). Individual variability in the structure of the walls of the principal trunks of the subcutaneous veins of the lower extremities of the human fetus. *Arkh Anat Gistol Embriol* 88(6):44-8

Bollinger A (1971). Klappenagnesie und dysplasie der Beinvenen. *Schweiz med Wschr* 101:1348 (German)

Bosanquet N (1992). Costs of venous ulcers: From maintenance therapy to investment programmes. *Phlebology* 1((Suppl)):44-6

Bradbury A, Murie J and Ruckley C (1993). Role of the leucocyte in the pathogenesis of vascular disease. *Brit J Surg* 80 (12):1503 - 12

Bradbury AW, Stonebridge PA, Ruckley CV and Beggs I (1993). Recurrent varicose veins: correlation between preoperative clinical and hand-held Doppler ultrasonographic examination, and anatomical findings at surgery. *Brit J Surg* 80(7):849-51

Bradbury AW and Ruckley CV (1993). Foot volumetry can predict recurrent ulceration after subfascial ligation of perforators and saphenous ligation. *J Vasc Surg* 18(5):789-95

Bradbury AW, Stonebridge PA, Callam MJ, Ruckley CV and Allan PL (1993). Foot volumetry and duplex ultrasonography after saphenous and subfascial perforating vein ligation for recurrent venous ulceration. *Brit J Surg* 80(7):845-8

Bradbury A, Stonebridge P, Callam M, et al (1994). Recurrent varicose veins: assessment of the saphenofemoral junction. *Brit J Surg* 81:373-75

Brand FN, Dannenberg AL, Abbott RD and Kannel WB (1988). The epidemiology of varicose veins: the Framingham Study. *Am J Prev Med* 4(2):96-101

Brodie B (1846). *Lectures on Pathology and Surgery*

Browse N, Gray L, Jarrett P and Morland M (1977). Blood and vein-wall fibrinolytic activity in health and vascular disease. *Br Med J* 1:478-481

Browse N and Burnand K (1982). The cause of venous ulceration. *Lancet* 2:243-245

Browse NL (1983) Venous ulceration *Br Med J* 286;1920

Browse N and Burnand K (1988).Physiology and functional anatomy In: Browse NL Burnand KG and Thomas ML eds. *Diseases of the veins*. Arnold, London. pp 53-69

Browse N and Burnand K (1988).Varicose veins: diagnosis In: Browse NL Burnand KG and Thomas ML eds. *Diseases of the veins*. Arnold, London. p 170.

Browse N and Burnand K (1988).The calf pump failure syndrome: diagnosis and treatment In: Browse NL Burnand KG and Thomas ML eds. *Diseases of the veins*. Arnold, London. pp 339-340

Browse N and Burnand K (1988).Venous ulceration: natural history and treatment In: Browse NL Burnand KG and Thomas ML eds. *Diseases of the veins*. Arnold, London p 433

Browse N and Burnand K (1988). In: Browse NL Burnand KG and Thomas ML eds *Diseases of the veins*. Arnold, London pp 326 - 7.

Buchan W (1822). *Domestic Medicine; or a Treatise on the Prevention and Cure of Diseases* . Lewis, London

Burkitt DP (1972). Varicose veins, deep vein thrombosis and haemorrhoids: Epidemiology and suggested aetiology. *Br Med J* ii:556-561.

Burnand KG, Lea Thomas M, O'Donnell T, Browse NL (1976) Relationship between post-phlebitic changes in the deep veins and results of surgical treatment of venous ulcers *Lancet* 2; 936

Burnand K, Clemenson G, Morland M, Jarrett P and Browse N (1980). Venous lipodermatosclerosis: treatment by fibrinolytic enhancement and elastic compression. *Br Med J* 280:7-11.

Callam M, Ruckley C, Harper D and Dale J (1985). Chronic ulceration of the leg: extent of the problem and provision of care. *Br Med J* 290:1855-6.

Callam M, Harper D, Dale J and Ruckley C (1987). Chronic ulcer of the leg: clinical history. *Br Med J* 294:1389-91.

Callam M (1994). Epidemiology of varicose veins. *Br J Surg* 81:167-173

Carrel A and Guthrie CC (1906). Uniterminal and biterminal venous transplantation. *Surg Gynec Obstet* 2:266

Carrel T, Bar W, Stirnemann P and Nachbur B (1989). Use of quantitative photoplethysmography for estimating ambulatory venous pressure and venous filling time: initial results in healthy subjects and in patients with varicose veins and chronic venous insufficiency. *Vasa* (suppl) 27:146 - 8

Celsus A (1756). *Of Medicine in Eight Books* . Wilson, London

Chant AD, Magnussen P and Kershaw C (1985). Support hose and varicose veins. *Br Med J Clin Res* 290(6463)

Chassaignac E (1855) Nouvelle Méthode Pour le Traitement des Tumeurs Haemorrhoidalis. Baillière, Paris

Christopoulos DG, Nicolaides AN, Szendro G, Irvine AT, Bull ML and Eastcott HH (1987). Air-plethysmography and the effect of elastic compression on venous hemodynamics of the leg. *J Vasc Surg* 5(1):148-59

Christopoulos D, Nicolaides AN, Galloway JM and Wilkinson A (1988). Objective noninvasive evaluation of venous surgical results. *J Vasc Surg* 8(6):683-7

Christopoulos D, Nicolaides AN and Szendro G (1988). Venous reflux: quantification and correlation with the clinical severity of chronic venous disease. *Brit J Surg* 75(4):352-6

Christopoulos D and Nicolaides AN (1988). Noninvasive diagnosis and quantitation of popliteal reflux in the swollen and ulcerated leg.*J Cardiovasc Surg Torino* 29(5):535-9

Christopoulos D, Nicolaides AN, Cook A, Irvine A, Galloway JM and Wilkinson A (1989). Pathogenesis of venous ulceration in relation to the calf muscle pump function. *Surgery* 106(5):829-35

Christopoulos D, Nicolaides A and Belcaro G (1991). The long term effect of elastic compression on the venosu haemodynamics of the leg. *Phlebology* 6:85-93

Clarke H, Smith SR, Vasdekis SN, Hobbs JT and Nicolaides AN (1989). Role of venous elasticity in the development of varicose veins. *Brit J Surg* 76(6):577-80

Clough A (1859). In: *Dryden's Translation "Plutarch's Lives..* Sampson Low,London p 53

Clyne CA, Ramsden WH, Chant AD and Webster JH (1985). Oxygen tension on the skin of the gaiter area of limbs with venous disease. *Br J Surg* 72(8):644-7

Cockett FB and Jones DE (1953). The ankle blow-out syndrome. A new approach of the varicose ulcer problem. *Lancet* ;1:17

Cockett F (1955). The pathology and treatment of venous ulcers of the leg. *Brit J Surg* 43:260-78

Cockett FB (1991). Venous valves: history up to the present day. *Phlebology* 6:63-73

Coleridge-Smith P, Thomas P, Scurr J and Dormandy J (1988). Causes of venous ulceration: a new hypothesis. *Br Med J Clin Res* 296(6638):1726-7

Coleridge-Smith P, Hasty J and Scurr J (1990). Venous stasis and lumen changes during surgery. *Brit J Surg* 77:1055-9

Coleridge-Smith P, Hasty J and Scurr J (1991). Deep vein thrombosis: effect of graduated compression stockings on distension of the deep veins of the calf. *Br J Surg* 78:724 - 726

Coleridge-Smith PD and Scurr JH (1991). In: Bergan and Yao eds. *Venous disorders*.. WB Saunders, Philadelphia. Current views on the pathogenesis of venous ulceration pp 36-51

Coles RW (1974). Varicose veins in tropical Africa. *Lancet* ii:474-475

Colgan MP, Dormandy JA, Jones PW, Schraibman IG, Shanik DG and Young RA (1990). Oxpentifylline treatment of venous ulcers of the leg. *Brit Med J* 300(6730):972-5

Comerota A, Stewart G, Alburger P, Smalley K and White J (1989). Operative venodilation: A previously unsuspected factor in the cause of postoperative deep vein thrombosis. *Surgery* 106(2):301 - 309

Coon WW, Willis PW and Keller JB (1973). Venous thromboembolism and other venous disease in the Tecumseh Community Health Study. *Circulation* 48:839 - 846

Cooper A (1824). *The Lectures of Sir Astley Cooper Bart. on the Principles and Practice of Surgery* . Thomas, London

Corcos L, Peruzzi G, Romeo V and Procacci T (1989). Preliminary results of external valvuloplasty in saphenofemoral junction insufficiency. *Phlebology* 4:197 - 202

Corcos L, Peruzzi G, Romeo V, Procacci T and Dini S (1992). In: Raymond-Martimbeau P Prescott R and Zummo M eds. *Phlebologie 92*. John Libbey Eurotext, Paris. Indications and exclusion criteria for external valvuloplasty of sapheno-femoral junction. pp1258 - 1260

Cornu TA, Maraval M, Boivin P and Parpex P(1986). Left predominance of varices: myth or reality? *Phlebologie* 39(2):465-71

Cornwall J, Dore C and Lewis J (1986). Leg ulcers: epidemiology and aetiology. *Br J Surg* 73:693-6

Dale JJ, Callam MJ, Ruckley CV, Harper DR and Berrey PN (1983). Chronic Ulcers of the Leg: A Study of prevalence in a Scottish Community. *Health Bull (Edin)* 41:310-314

Dalrymple J and Crofts T (1975). Varicose veins in developing countries. *Lancet* i:808-809

Dalsing M, Lalka S, Zukowski A, Unthank J, Sawchuk A and Cikrit D (1994). Valve transplantation to the canine popliteal vein: The utility of a distal arteriovenous fistula and the haemodynamic result of a single functional valve. *J Vasc Surg* 20(5):736-43

Darke SG (1992). The morphology of recurrent varicose veins. *Eur J Vasc Surg* 6(5):512-7

Darke SG and Penfold C (1992). Venous ulceration and saphenous ligation. *Eur J Vasc Surg* 6(1):4-9

Daynes G and Beighton P (1973). Prevalence of varicose veins in Africa. *Br Med J* iii:354

De Toma G, Gabriele R, Campli M, Sgarzini G, Pompa G and Mazzocconi G (1989). Varicose veins of the lower limbs caused by incompetence of the saphenous-femoral ostium: standard or complete stripping? *G Chir* 10(11):637-40

Dickson-Wright A (1930). Treatment of varicose ulcers. *Br Med J* 2:996

Dickson-Wright A (1931). The treatment of the indolent ulcer of the leg. *Lancet* i:457-460

Dodd H, Calo A, Mistry M and Rushford A (1957). Ligation of ankle communicating veins in the treatment of the venous -ulcer syndrome of the leg. *Lancet* 2:1249 - 1252

Dodd H, Gaylarde P and Sarkany I (1985). Skin oxygen tension in venous insufficiency of the lower leg. *J R Soc Med* 78:373-376

Drury A and Jones N (1927). Observations upon the rate at which oedema forms when the veins of the human leg are congested. *Heart* 14:55-70

Drury M (1965). Varicose veins in pregnancy. *Br Med J* ii:304

Eberth-Willerhausen W and Marshall M (1984). Prevalenz, riskofaktoren und komplkationen peripherer venenerkrankungen in der Munchner bevolkerung. *Hautarzt* 35:68-77 (German)

Edwards J and Edwards E (1940). The saphenous valves in varicose veins. *Am Heart J* 19:338

Eiriksson E and Dahn I (1968). Plethysmographic studies of venous distensibility in patients with varicose veins. *Acta Chir Scand* (Suppl) 398:19.

Eiriksson E (1968). Venous distensibility in the legs after surgical removal of varicose veins. *Acta Chir Scand* (suppl) ;398:27.

Engel A, Davies G and Keeman J (1991) Preoperative Localisation of the Saphenopopliteal Junction with Duplex Scanning *Eur J Vasc Surg* 5:507-509

Eriksson I and Almgren B (1986). Influence of the profunda femoris vein on venous hemodynamics of the limb. Experience from thirty-one deep vein valve reconstructions. *J Vasc Surg* 4(4):390-5.

Ettmulleri M (1688) In: *Opera Omnia* Zunneri, Frankfurt (German)

Evander E, Evander A, Scigala E, *et al.* (1984). Use of photoplethysmography to evaluate the effectiveness of elastic support stockings *Bruit* 8:75-8

Fabricius H (1986) Anatomica patavini de venarum ostiolois - valves of veins. In: Laufman H ed. *Silvergirl's Surgery.* Silvergirl Inc, Austin, Texas pp14-16.

Falanga V, McKenzie A and Eaglstein WH (1991) Heterogeneity in oxygen diffusion around venous ulcers. *J Dermatol Surg Oncol* 17(4):336-9

Falanga V, Kruskal J and Franks JJ (1991) Fibrin- and fibrinogen-related antigens in patients with venous disease and venous ulceration. *Arch Dermatol* 127(1):75-8

Falanga V KR Katz MH, Gould E, Eaglstein WH and McFalls S (1992) Pericapillary fibrin cuffs in venous ulceration *J Dermatol Surg Oncol* 18:409-14

Fegan WG (1967) Varicose Veins, Compression Sclerotherapy. London, Heinemann.

Fegan W and Kline A (1972) The cause of varicosity in superficial veins of the lower limb *Brit J Surg* 59:798

Fernandes E, Fernandes J, Horner J, Needham T and Nicolaides A (1979) Ambulatory calf volume plethysmography in the assessment of venous insufficiency *Brit J Surg* 66:327 - 30

Ferris E and Kistner R (1986) Femoral vein reconstruction in the management of chronic venous insufficiency *Arch Surg* 117:1571-1579

Fischer H (1981) In:*Venenleiden-Eine reprasentative Untersuchung in der Bundesrepublik Deutschland* Urban und Schwarzenberg, München (German)

Fischer R, Sattler G and Vanderpuye R (1993) Endoscopic treatment of perforating veins--current data *Phlebologie* 46(4):701-7 (French)

Fischer R, Sattler G and Vanderpuye R (1993) Endoscopic perforant vein revision. Current status *Vasa* 22(1):3-7 (German)

Fischer R (1994) Prognosis in endoscopic perforans vein excision in postphlebitic syndrome *Wiener Medizinische Wochenschrift* 144(10-11):258-60

Fligelstone LJ, Salaman RA, Oshodi TO, et al (1995) Flush saphenofemoral ligation and multiple stab phlebectomy preserve a useful greater saphenous vein four years after surgery *JVasc Surg* 22(5):588-92

Folkow B (1949) Intravascular pressures as a factor regulating the tone of the small vessels *Acta Physiol Scand* 17:289 - 310

Folkow B (1953) A study of the factors influencing the tone of denervated blood vessels perfused at various pressures *Acta Physiol Scand* 27:99 117

Folse R (1970) The influence of femoral vein dynamics on the development of varicose veins *Surgery* 68:974

Fontaine R (1957) Remarks concerning venous thrombosis and it's sequelae. John Homans memorial lecture *Surgery* 41:6-24

Franzeck U, Hasselbach P, Speiser D and Bollinger A (1993) Microangiopathy of cutaneous blood and lymphatic capillaries in chronic venous insufficiency *Yale J Bio Med* 66(1):37-46

Galen C (1562) In: *Ad scripti libri.* Vincentium Valgrisium, Venice p34

Giorgetti PL, Bortolani EM, Morbidelli A, et al.(1990) Use of a new anti-inflammatory drug in the treatment of varicophlebitis of the lower limbs *Minerva Chir* 45(12):883-6

Gjores J and Thulesius O (1977) Compression treatment in venous insufficiency evaluated with foot volumetry *Vasa* 6(4):364-368

Gongolo A, Spreafico G, Buttazzoni L, Giraldi E, Ravasini R and Pinzani A (1990) Duplex sonography in the preoperative evaluation of the small saphenous vein *Radiol Med Torino* 80(3):234-8

Goodrich S and Wood J (1964) Peripheral venous distensibility and velocity of venous blood flow during pregnancy or during oral contraceptive therapy *Am J Obstet Gynecol* 90:740-44

Goren G and Yellin AE (1990) Primary varicose veins: topographic and hemodynamic correlations *J Cardiovasc Surg Torino* 31(5):672-7

Gow B and Taylor M (1968) Measurement of viscoelastic properties of arteries in a living dog *Circ Res* 23:111

Gray WA, de Burgh Mm, Lippey E and Palme A (1985) Ascending cinevenography in chronic venous insufficiency: a comparison with ambulatory venous pressure measurements *Aust N Z J Surg* 55(6):565-9

Guillot B, Dandurand M and Guilhou JJ (1988) Skin perfusion pressure in leg ulcers assessed by photoplethysmography. *Int Angiol* 7 (2 suppl): 33-4

Haardt B (1986) Histochemical comparison of the enzyme profiles of healthy veins and varicose veins *Phlebologie* 39(4):921-31

Hach V, Fink M, Blees N and Scharrer I (1986) Tissue fibrinolytic activity in different types of varicose veins *Angiology* 37(10):718-24

Haimovici H, Steinman C and Caplan L (1966) Role of arteriovenous anastomosis in vascular diseases of the lower extremity *Ann Surg* 164:990-1002

Haimovici H (1976) Abnormal arteriovenous shunts associated with chronic venous insufficiency *J Cardiovasc Surg* 17:473

Haimovici H (1985) Arteriovenous shunting in varicose veins. Its diagnosis by Doppler ultrasound flow detector *J Vasc Surg* 2(5):684-91

Hallbook T (1988) Leg Ulcer Epidemiology *Acta Chir Scand* (Suppl) 544:12-16

Hammarsten J, Pedersen P, Cederlund CG and Campanello M (1990) Long saphenous vein saving surgery for varicose veins. A long-term follow-up *Eur J Vasc Surg* 4(4):361-4

Hanrahan LM, Araki CT, Fisher JB, et al (1991) Evaluation of the perforating veins of the lower extremity using high resolution duplex imaging *J Cardiovasc Surg Torino* 32(1):87-97

Hanrahan LM, Araki CT, Rodriguez AA, Kechejian GJ, LaMorte WW and Menzoian JO (1991) Distribution of valvular incompetence in patients with venous stasis ulceration *J Vasc Surg* 13(6):805-11

Hanrahan L, Kechejian G, Cordts P, Rodriguez A, Araki C and LaMorte W (1991) Patterns of venous insufficiency in patients with varicose veins. *Arch Surg* 126(6):687-90.

Harding K (1991) Wound management in General Practice In:*Royal College of General Practitioners members reference book* Ball et al eds Sabre-Crown, London pp313-316

Harman R (1974) Haemorrhage from varicose veins *Lancet* 1:363

Harvey W (1628) In: *Exercitatio anatomica de motu cordis et sanguini in animalibus* W. Fitzer, Frankfurt

Hauer G (1985) Die endoscopische subfasciale Diszision der Perforansvenen-vorlaufige mitteilung *Vasa* 14; 59-61 (German)

Hauer G and Gaitzsch A (1988) Endoscopic dissection of perforating veins *Langenbecks Arch Chir* 2(157):157-60

Hildebrandt J (1970) Extension of small-strain theory to finite deformation of cylindrical vessels by internal over-pressure *Angiologica* 7:257

Hippocrates (1886) In:*The Genuine Works of Hippocrates* . Wm Wood & Co, New York

Hoare MC NA Miles CR, Shull K, Jury RP, Needham T and Dudley HAF (1982) The role of primary varicose veins in venous ulceration. *Surgery* 92:450-453

Hobbs J (1974) Surgery and sclerotherapy in the treatment of varicose veins *Arch Surg* 109:793-796

Hohn L, Chiarenza S, Schmied E and Bounameaux H (1990) Age-related rather than ulcer-related impairment of venous function tests in patients with venous ulceration *Dermatologica* 180(2):73-5

Holling H, Beecher H and Linton R (1938) Study of the tendency to oedema formation associated with incompetence of the valves of the communicating veins of the leg. Oxygen tension of the blood contained in varicose veins *J Clin Invest* 17:555

Holme J, Holme K and Sorensen L (1988) The anatomic relationship between the long saphenous vein and the saphenous nerve *Acta Chir. Scand.* 154:631 - 633

Holme J, Skajaa K, Holme K (1990) Incidence of lesions of the saphenous nerve after partial or complete stripping of the long saphenous vein. Acta Chir Scand 156:145 - 8

Homans J (1917) The aetiology and treatment of varicose ulcers of the leg *Surg Gynec Obstet* 24:300

Homans J (1917) The operative treament of varicose veins and ulcers *Surg Gynecol Obstet* 22:143-158

Home E (1797) *Practical Observations on the Treatment of Ulcers on the Legs Considered as a Branch of Military Surgery* . Nichol, London

Hooker DR (1911) The effect of exercise upon the venous blood pressure. *Am J Physiol* 28:235

Horner J, Fernandes e Fernandes J and Nicolaides A (1980) Value of graduated compression stockings in deep venous insufficinecy *Brit Med J* 1:820

Hoshino S, Satakawa H, Iwaya F, Igari T, Ono T and Takase S (1993) External valvuloplasty under preoperative angioscopic control *Phlebologie* 46(3):521-9 (French)

Hunt T (1859) In: *A Guide to the Treatment of Diseases of the Skin: with Suggestions for their Prevention* (4th ed) Richards, London

Jakobsen B (1979) The value of different form of treatment for varicose veins. *Brit J Surg* 66:182-184

Jamieson WG, DeRose G and Harris KA (1990) Management of venous stasis ulcer: long-term follow-up*Can J Surg* 33(3):222-3

Jessup G and Lane R (1988) Repair of incompetent venous valves: A new technique *J Vasc Surg* 8:569-575

Johnson N, Queral L, Flinn WR et al. (1981) Late objective assessment of venous valve surgery *Arch Surg* 116:1461-1466

Jones NAG, Webb PJ, Rees RI and Kakkar VV (1980) A physiological study of elastic compression stockings in venous disorders of the leg *Br. J. Surg.* 67:569-572

Jugenheimer M and Junginger T (1992) Endoscopic subfascial sectioning of incompetent perforating veins in treatment of primary varicosis *World Journal of Surgery* 16(5):971-5

Jugenheimer M (1992) Endoscopic sub-fascial perforant vein dissection in the treatment concept of primary varicose veins *Medizinische Klinik* 87(6):289-92 (German)

Kamber V, Widmer L and Madar G (1991) Haufigkeit von anamnestischen Angaben und Befunden. In: Widmer LK Stahelin HB Nissen C and da Silva A eds *Venen-, Arterien-Krankheiten, koronaree Herzkrankheit bei Berufstatigen.* Hans Huber, Bern pp 83-94

Kanter A, Thibault P (1996) Saphenofemoral incompetence treated by ultrasound-guided sclerotherapy *Dermatologic Surgery* 22 (7): 648-52

Katsamouris AN, Kardoulas DG and Gourtsoyiannis N (1994) The nature of lower extremity venous insufficiency in patients with primary varicose veins *Eur J Vasc Surg* 8(4):464-71

Keller (1905) A new method of extirpating the internal saphenous and similar veins in varicose conditions *New York Med J* 82:385-386

Khaira HS, Crowson MC, Parnell A (1996) Colour flow duplex in the assessment of recurrent varicose veins *Ann R Coll Surg Engl* 78: 139-41

Kidd B and Lyons S (1958) The distensibility of the blood vessels of the human calf determined by graded venous congestion *J Physiol* 140:122-8

Kiely PE (1990) Evaluation of tourniquet ambulatory venous pressure as a selective test of superficial and deep venous function *Brit J Surg* 78:3:371

Kistner R (1978) Transvenous repair of the incompetent femoral vein valve. In: Bergan J and Yao J, eds *Venous problems.* Year Book Medical Publishers, Chicago pp 493-509.

Kistner R (1991) Valve repair and segment transposition in primary valvular insufficiency. In: Bergan J and Yao J, eds *Venous disorders.* WB Saunders, Philadelphia pp 261-272

Kistner R (1996) Definitive diagnosis and definitive treatment in chronic venous disease: A concept whose time has come *J Vasc Surg* 24; 5; 703-10

Kistner RL, Eklof B, Masuda EM (1996) Diagnosis of chronic venous disease of the lower extremities: the CEAP classification. *Mayo Clinic Proc* 71; 338-45

Kitchin A (1963) Peripheral blood flow and capillary filtration rates *Br Med Bull* 19(2):155-60

Kok KYY, Goh P, Tan WTL (1997) Simple technique for endoscopic subfascial dissection of perforating veins *Brit J Surg* 84;333

Krogh A, Landis E and Turner A (1932) The movement of fluid through the human capillary wall in relation to venous pressure and to the colloid osmotic pressure of the blood *J Clin Inv* 11:63-95

Lake M, Pratt GH and Wright IS (1942) Arteriosclerosis and varicose veins: occupational activities and other factors *J Am Med Assoc* 119:696-701

Landowne M and Katz L (1942) A critique of the plethysmographic method of measuring blood flow in the extremities of man *Am Heart J* 23:644-75

Lang W, Bockler D, Meister R and Schweiger H (1995) Endoscopic dissection of perforating veins. *Chirurg* 66(2):131-4 (German)

Lange L, Echt M, Kirsch K and Thron H (1971) Studies on the distensibility characteristics of capacitance and resistance vessels of the isolated rabbit ear *Pflüegers Arch* 330:111

Large J. (1985) Surgical treatment of saphenous varices, with preservation of the main great saphenous trunk *J Vasc Surg* 2(6):886-91

Leach R (1984) Venous ulceration, fibrinogen and fibrinolysis *Ann R Coll Surg Eng* 66:258-263

Leach RD and Browse NL (1986) The clearance of 125I-labelled fibrin from the subcutaneous tissue of limbs with lipodermatosclerosis *Br J Surg* 73(6):465-8

Lees T and Lambert D (1993) Patterns of venous reflux in limbs with skin changes associated with chronic venous insufficiency *Brit J Surg* 80:725 - 728

Leon M, Volteas N, Labropoulos N, Kalodiki E and Nicolaides A (1993) Effect of elastic stockings on the elasticity of the veins *Phlebology* 8(1):42.

Leu H, Vogt M and Pfrundes H (1979) Morphological alterations of non-varicose and varicose veins. A morphological contribution to the discussion on pathogenesis of varicose veins *Basic Res Cardiol* 74:435

Leu HJ (1990) Chronic venous insufficiency today (a status determination) *Vasa* 19(3):195-202

Lewis J, Parsons D, Needham T, et al. (1973) The use of venous pressure measurements and directional doppler recording in distinguishing between superficial and deep valvular incompetence in patients with venous insufficiency *Br J Surg* 60:312

Lindemayr W, Löfferer O, Mostbeck A and Partsch H (1972) Arteriovenous shunts in primary varicosis? A critical essay *Vasc Surg* 6:9

Lindval N and Lodin A (1961) Congenital absence of valves in the deep veins of the leg *Acta Dermato-Venerologica Scand* 41(Suppl):45

Linton R (1938) The communicating veins of the lower leg and the operative technique for their ligation *Ann Surg* 107:582

Litter J and Wood J (1954) The venous pressure volume curve of the human leg measured in vivo *J Clin Inv* 33:953

Lofgren EP (1984) Leg ulcers. Symptom of an underlying disorder *Postgrad Med* 76(4):51-4

Lonie I (1973) The paradoxical text "On the Heart" *Medical History* 17(II):137

Loveday EJ and Thomas ML (1991) The distribution of recurrent varicose veins: a phlebographic study *Clin Radiol* 43(1):47-51

Löfferer O, Mostbeck A and Partsch H (1969) Arteriovenöse Kurzseblüsse der Extremitäten nuclearmedizinische untersuchungen mit besonderer Berücksichtigung des postthrombotischen Unterschenkelgeschwüs *Zbl Phlebol* 8:2 (German)

Ludbrook J and Beale G (1962) Femoral venous valves in relation to varicose veins *Lancet* 1:79

Ludbrook J (1963) Valvular defects in varicose veins, cause or effect? *Lancet* 2:1289

Ludbrook J and Loughlin J (1964) Regulation of volume in post-arteriolar vessels of the lower limb *Am Heart J* 67:493-507

Ludbrook J (1966) In: *Aspects of venous function in the lower limbs* Charles C Thomas, Springfield, Illinois p90

Maffei FHA, Magaldi C, Pinho SZ, et al. (1986) Varicose veins and chronic venous insufficiency in Brazil: Prevalence among 1755 inhabitants of a country town *Int J Epid* 15:210-217

Majno G (1975) In: *The Healing Hand.* Harvard University Press, Cambridge p153

Majno G (1975) In: *The Healing Hand.* Harvard University Press, Cambridge p328

Major R (1954) In: *A History of Medicine* . Blackwell, Oxford

Martin HA (1878) The india-rubber bandage for ulcers and other diseases of the legs *Brit Med J* 2:624

Mashiah A, Rose SS and Hod I (1991) The scanning electron microscope in the pathology of varicose veins *Isr J Med Sci* 27(4):202-6

Maurel E, Azema C, Deloly J and Bouissou H (1990) Collagen of the normal and the varicose human saphenous vein: a biochemical study *Clin Chim Acta* 193(1-2):27-37

Mayberry JC, Moneta GL, Taylor LJ and Porter JM (1991) Fifteen-year results of ambulatory compression therapy for chronic venous ulcers *Surgery* 109(5):575-81

Mayberry J, Moneta G, DeFrang R and Porter J (1991) The influence of elastic compression stockings on deep venous hemodynamics *J Vasc Surg* 13(1):91-9

Mayo CH (1906) Treatment of varicose veins *Surg Gynecol Obstet* 2:385-388

McCausland AM, Hyman C, Winsor T and Trotter AD (1961) Venous distensibility during pregnancy *Am J Obstet Gynecol* 81:472-9

McEnroe C, O'Donnell T and Mackey W (1988) Correlation of clinical findings with venous haemodynamics in 386 patients with chronic venous insufficiency *Am J Surg* 156:145-152

McMullin G, Coleridge-Smith P and Scurr J (1990) Evaluation of Psathakis' silastic sling procedure for deep vein reflux: a preliminary report *Phlebology* 5:95-106

McMullin GM, Coleridge-Smith PD and Scurr JH (1991) Objective assessment of high ligation without stripping the long saphenous vein *Br J Surg* 78:1139-1142

McMullin G, Coleridge-Smith P and Scurr J (1991) Which way does blood flow in the perforating veins of the leg? *Phlebology* 6(2):127-132

McMullin G, Coleridge-Smith P and Scurr J (1991) A study of tourniquets in the investigation of venous insufficiency *Phlebology* 6:133-139

McPheeters H, Merkert C and Lundblad R (1932) The mechanism of reverse flow of blood in various veins as proved by blood pressure readings *Surg Gynecol Obstet* 55:298

Mekky S, Schilling RSF and Walford J (1969) Varicose veins in women cotton workers. An epidemiological study in England and Egypt *Br Med J* ii:591-595.

Michel C (1990) Oxygen diffusion in oedematous tissue and through pericapillary cuffs *Phlebology* 5:223-230

Milne AA, Stonebridge P, Bradbury AW and Ruckley CV (1994) Venous function and clinical outcome following deep venous thrombosis *Br J Surg* 81:847-49

Mitchell D and Darke S (1987) The assessment of primary varicose veins by doppler ultrasound - the role of sapheno-popliteal incompetence and the short saphenous system in calf varicosities *Eur J Vasc Surg* 1:113-115

Moreno A, Katz A, Gold L and Reddy R (1970) Mechanics of distension of dog veins and other very thin walled tubular structures *Circ Res* 27:1069

Moyses C, Cedholm-Williams S and Michel C (1987) Haemoconcentration and the accumulation of white cells in the feet during venous stasis *Int J Microcirc Clin Exp* 5:311-320

Munn SR, Morton JB, Macbeth WAAG, McLeish AR (1981) To strip or not to strip the long saphenous vein? A varicose veins trial *Brit J Surg* 68:426-428

Myers TT (1957) Results and technique of stripping operation for varicose veins *J A M A* 163:87-92

Myers KA, Ziegenbein RW, Zeng GH and Matthews PG (1995) Duplex ultrasonography scanning for chronic venous disease: patterns of venous reflux *Journal of Vascular Surgery* 21(4):605-12

Nelzen O, Bergqvist D and Lindhagen A (1994) Venous and non-venous leg ulcers: clinical history and appearance in a population study *Br J Surg* 81:182-7

Nemeth AJ, Eaglstein WH and Falanga V (1989) Clinical parameters and transcutaneous oxygen measurements for the prognosis of venous ulcers *J Am Acad Dermatol* 20 (2 Pt 1):186-90

Nicolaides A, Kakkar V, Field E and Renney J (1971) The origin of deep venous thrombosis: A venographic study *Br J Radiol* 44:653

Nicolaides AN and Zukowski AJ (1986) The value of Dynamic Venous Pressure Measurements *World J Surg* 10:919-924

Nicolaides A and Renton S (1990) Duplex Scanning: The Second Sight of the Vascular Surgeon *Eur J Vasc Surg* 4:445-447

Nicolaides A, Hussein M, Szendro G, Christopoulos D, Vasdekis S and Clarke H (1993) The relation of venous ulceration with ambulatory venous pressure measurements *J Vasc Surg* 17(2):414-9

Norgren L and Thulesius O (1975) Pressure-volume characteristics of foot veins in normal cases and patients with venous insufficiency. *Blood Vessels* 12:1-12

O'Donnell T (1991) Popliteal vein valve transplantation for deep venous valvular reflux: Rationale, Method, and Long-Term Clinical, Hemodynamic, and Anatomic Results. In: Bergan J and Yao J ed. *Venous Disorders*. WB Saunders, Philadelphia pp 273-295

Palma EC, Risi F and De Campo F (1958) Tratamiento de los trastornos postflebiticos mediante anastomosis venosa safeno-femoral conro-lateral *Bull Soc Surg Uruguay* 29:135 (Spanish)

Paraskeva PA, Cheshire N, Stansby G, Darzi AW Endoscopic subfascial division of incompetent perforating calf veins *Brit J Surg* 83;1105-1106

Parona (1894) Poloclinico *Chirugie* 8:9

Partsch H (1984) Do we need firm compression stockings exerting high pressure? *Vasa* 13(1):52-57

Payne SPK, Waldron MW, Dugdill S, Heslop P, Walker D and Jones NAG NUMACT: comprehensive ambulatory mobility recording in the home environment *Brit J Surg* (abstract in press)

Perhoniemi V, Salo J, Haapiainen R and Salo H (1990) Strain gauge plethysmography in the assessment of venous reflux and subfascial closure of perforating veins: A prospective study of twenty patients *J Vasc Surg* 12:43-7

Perthes G (1895) Uber die Operation der Unterschenkel-varicen nach Trendelenberg. *Dtsch med Wechr* 21:253 (German)

Petruzzellis V, Florio T, Quaranta D, Troccoli T and Serra MA (1990) Epidemiologic observations on the subject of phlebopathy of the legs and its dermatologic complications *Minerva Med* 81(9):611-6

Phillips ARJ and Fleischl JM (1996) Videoscopic subfascial incompetent perforator vein ablation *Brit J Surg* 83; 1552

Phillips GW, Paige J and Molan MP (1995) A comparison of colour duplex ultrasound with venography and varicography in the assessment of varicose veins *Clinical Radiology* 50(1):20-5

Pierik EG, Wittens CH, van Urk H (1995) Subfascial endoscopic ligation in the treatment of incompetent perforating veins *Eur J Vasc Endovasc Surg* 9(1):38-41

Pigeaux A (1843) In: *Traite Pratique des Maladies des Vaisseaux Conterant des Recherches Historiques Speciales* Labe et Raivier, Paris (French)

Piulachs P and Vidal-Barraquer F (1953) Pathogenic study of varicose veins *Angiology* 4:59-100

Plate G, Brudin L, Eklöf B, Jensen R and Ohlin P (1983) Physiologic and therapeutic aspects in congenital valve aplasia of the lower limb *Ann Surg* 198:229

Pollack AA and Wood EH (1949) Venous pressure in the saphenous vein at the ankle in man during exercise and changes in posture *J Appl Physiol* 1:649

Pollack AA, Taylor BE, Myers TT and Wood EH (1949) The effect of exercise and body position on the venous pressure at the ankle in patients having venous valvular defects *J Clin Invest* 28:559

Psaila J and Melhuish J (1989) Viscoelastic properties and collagen content of the long saphenous vein in normal and varicose veins *Brit J Surg* 76:37-40

Pupita F, Rotatori D and Frausini G (1981) The study of venous distensibility as an index of varicose diathesis. In: AHM Jageneau ed. *Noninvasive methods on cardiovascular haemodynamics* Biomedical press, Elsevier pp 139-42

Quaba AA, McDowall RA and Hackett ME (1987) Layered shaving of venous leg ulcers *Br J Plast Surg* 40(1):68-72

Queral L, Whitehouse WJ, Flinn W, et al. (1980) Surgical correction of chronic deep venous insufficiency by valvular transposition *Surgery* 86:688-695

Queral LA, Criado FJ, Lilly MP and Rudolphi D (1990) The role of sclerotherapy as an adjunct to Unna's boot for treating venous ulcers: a prospective study *J Vasc Surg* 11(4):572-5

Quigley FG, Raptis S, Cashman M and Faris IB (1992) Duplex ultrasound mapping of sites of deep to superficial incompetence in primary varicose veins. *Aust NZ J Surg* 62(4):276-8

Raju S (1985) Valvuloplasty and valve transfer *Int Angiol* 4:419-424

Raju S and Fredericks R (1991) Hemodynamic basis of stasis ulceration - a hypothesis *J Vasc Surg* 13(4):491-5

Randhawa G, Dhillon J, Kistner R and Ferris E (1984) Assessment of chronic venous insufficiency using dynamic venous pressure studies *Am J Surg* 148:203-209

Reagan B and Folse R (1971) Lower limb venous dynamics in normal persons and children of patients with varicose veins *Surg Gynec Obstet* 132:15

Rose SS and Ahmed A (1986) Some thoughts on the aetiology of varicose veins. *J Cardiovasc Surg Torino* 27(5):534-43

Rougement A (1974) Varicose veins in Tropical Africa. *Lancet* i:870

Rutgers PH and Kitslaar PJ (1994) Randomized trial of stripping versus high ligation combined with sclerotherapy in the treatment of the incompetent greater saphenous vein *Am J Surg* 168(4):311-5

Ryan T and Copeman P (1970) Microvascular patterns and blood stasis in skin diseases *Br J Dermatol* 8:563

Ryan T (1983) In: *The management of leg ulcers* Oxford medical publications, Oxford

Sarin S, Scurr J and Coleridge-Smith P (1992) Mechanism of action of external compression on venous function *Brit J Surg* 79:499-502

Sarin S, Scurr J and Coleridge-Smith P (1994) Stripping of the long saphenous vein in the treatment of primary varicose veins *Brit J Surg* 81:1455-58

Sarin S, Sommerville K, Farrah J, Scurr J and Coleridge-Smith P (1994) Duplex ultrasonography for assessment of venous valvular function of the lower limb *Brit J Surg* 81:1591-5

Schalin L (1989) Role of arteriovenous shunting in the development of varicose veins. In: Eklöf B, Gjöres J, Thulesius O, Bergqvist D eds. *Controversies in the management of venous disorders* Butterworths, London pp 182-194

Schanzer H and Skladany M (1994) Varicose vein surgery with preservation of the saphenous vein: A comparison between high ligation-avulsion versus saphenofemoral banding valvuloplasty-avulsion *J Vasc Surg* 20(5):684-687

Schmeller W, Roszinski S, Tronnier M and Gmelin E (1992) Combined morphological and physiological examinations in lipodermatosclerosis. In: Raymond-Martimbeau P, Prescott R and Zummo M eds. *Phlebologie 92* John Libbey, Montrouge pp 172-4

Scott H, Cheatle T, McMullin G, Coleridge-Smith P and Scurr J (1990) Reappraisal of the oxygenation of blood in varicose veins *Brit J Surg* 77:934-936

Scott HJ, Coleridge SP and Scurr JH (1991) Histological study of white blood cells and their association with lipodermatosclerosis and venous ulceration *Brit J Surg* 78(2):210-1

Sethia K and Darke S (1984) Long saphenous incompetence as a cause of venous ulceration. *Brit J Surg* 71:754-755

Shields D, Andaz S, Sarin S, Scurr J and Coleridge-Smith P (1994) Plasma elastase in venous disease *Brit J Surg* 81:1496-99

Shields D, Andaz S, Timothy-Antoine C, Porter J, Scurr J and Coleridge-Smith P (1994) CDIIb/CD18 and neutrophil activation in venous hypertension *J Dermat Surg Oncol* 20:72

Shull K, Nicolaides A, Fernandes E, et al. (1979) Significance of popliteal reflux in relation to ambulatory venous pressure and ulceration *Arch Surg* 114:1304

Smirk F (1936) Observations on the causes of oedema in congestive heart failure *Clin Sci* 2:317-335

Somerville J, Brow G, Byrne P, Quill R and Fegan W (1974) The effect of elastic stockings on superficial venous pressures in patients with venous insufficiency *Brit J Surg* 61:979

Sottiurai V (1988) Technique in direct venous valvuloplasty *J Vasc Surg* 8:646-648

Sparrow R, Hardy J and Fentem P (1995) Effect of 'antiembolism' compression hosiery on leg blood volume *Brit J Surg* 82:53-59

Stacey M, Burnand K, Layer G and Pattison M (1987) Transcutaneous oxygen tensions as a prognostic indicator and measure of treatment of recurrent ulceration *Brit J Surg* 74:545

Stacey MC, Burnand KG, Layer GT, Pattison M (1988) Calf pump function in patients with healed venous ulcers is not improved by surgery to the communicating veins or by elastic stocking *Brit J Surg* 75; 436-9

Stemmer R, Marescaux J and Furderer C (1980) Compression treatment of the lower extremities particularly with compression stockings *The Dermatologist* 31:355

Stonebridge P, Chalmers N, Beggs I, Bradbury A and Ruckley CV (1995) Recurrent varicose veins: a varicographic analysis leading to a new practical classification. *Brit J Surg* 82:60-62

Struckmann J and Methiesen F (1985) A noninvasive plethysmographic method for evaluation of the musculovenous pump in the lower extremities *Acta Chir Scand* 151:235-40

Sugrue M, Stanley S, Grouden M, Feeley M, Moore D and Shanik D (1988) Can pre-operative duplex scanning replace pre-operative short saphenous venography as an aid to localising the sapheno-popliteal junction? *Phlebologie* 41(4):722-5

Sun JM (1990) Epidemiologic study on peripheral vascular diseases in Shanghai *Chung Hua Wai Ko Tsa Chih* 28(8):480-3

Szendro G, Nicolaides AN, Zukowski AJ, et al. (1986) Duplex scanning in the assessment of deep venous incompetence *J Vasc Surg* 4(3):237-42

Thibault P, Bray A, Wlodarczyk J and Lewis W (1990) Consmetic leg veins: evaluation using duplex venous imaging *J Dermat Surg Oncol* 16(7):612-8

Thomas P, Nash G and Dormandy J (1988) White cell accumulation in the dependent legs of patients with venous hypertension: A possible mechanism for trophic changes in the skin *Br Med J* 296:1693-1695

Thomas PR, Nash GB, Dormandy JA (1991) Increased white cell trapping in the dependent legs of patients with chronic venous insufficiency *J Mal Vasc* 16(1):35-7

Thulesius O, Gjöres J, Eriksson O and Berlin E (1984) Mechanical and biochemical factors in chronic venous insufficiency *Vasa* 13:195

Thulesius O (1989) Pathophysiology of venous insufficiency. In: Eklöf B, Gjores J, Thulesius O and Bergqvist D eds *Controversies in the management of venous disorders* Butterworths, London pp 1-5

Trendelenberg F (1891) Über die Unterbindung der Vena Saphena magna bei Unterschenkel varicen *Beitrag Klin Chir* 7:195-210 (German)

Turner-Warwick W (1931) In: *The Rational Treatment of Varicose Veins and Varicocoele* Faber, London

Tyson MD and Goodlett WC (1945) Venous pressures in disorders of the venous system of the lower extremities *Surgery* 18:669-672

Unna PG (1854) Veber Paraplaste eine neue form medikaneutoser Pflaster *Wien Med Wochenschr 1896* 46 (German)

van Rij A, Solomon C and Christie R (1994) Anatomic and physiologic characteristics of venous ulceration *J Vasc Surg* 20(5):759-64

Van der Molen H (1982) The choice of compressive methods in phlebology *Phlebologie* 35:73

Van-Bemmelen P, Bedford G, Beach K and Strandness D (1989) Quantitative segmental evaluation of venous valvular reflux with duplex ultrasound scanning *J Vasc Surg* 10:425-431

Van-den-Broek TA, Rauwerda J and Kuijper C (1991) Construction of Peritoneal Venous Valves: An Experimental Study in Rats and Piglets *J Surg Res* 50:279-283

Vasdekis S, Clarke G, Hobbs J and Nicolaides A (1989) Evaluation of non invasive and invasive methods in the assessment of short saphenous vein termination *Brit J Surg* 76:929-932

Vogler E (1954) Angiographische Beiträge zur Eusterhung von Gefässerkrankungen unter besonderer Berücksichtigung der terminalen Strombahn *Fortschr Roentgenstr* 81:479 (German)

Walsh J (1934) Galen's writings and influences inspiring them *Ann Med Hist* 1:14

Walsh JC, Bergan JJ, Beeman S and Comer TP (1994) Femoral venous reflux abolished by greater saphenous vein stripping *Annals of Vascular Surgery* 8(6):566-70

Warren R, White EA and Belcher CD (1949) Venous pressures in the saphenous system in normal, varicose and postphlebitic extremities *Surgery* 26:435-445

Warren R and Thayer T (1954) Transplantation of the saphenous vein for postphlebitic stasis *Surgery* 35:867

Weddell JM (1969) Varicose veins pilot survey 1966. *Brit J Prev Soc Med* 23:179-186

Weiss RA (1995) Video-guided CHIVA treatment *Dermatologic Surgery* 21(7)

Whiston R, Hallett M, Davies E, Harding K and Lane I (1994) Inappropriate neutrophil activation in venous disease *Brit J Surg* 81(5):695-8

Whitney R (1953) The measurement of volume changes in human limbs *J Physiol* 121:1-27

Widmer LK (1978) *Peripheral Venous disease: Prevalence and Sociomedical Importance* Hans Huber, Bern

Williams EH (1974) Varicose veins in Tropical Africa *Lancet* i:1291

Wilson NM, Rutt DL and Browse NL (1990) Venous valve construction: a new technique *Brit J Surg* 77; 701-2

Wiseman R (1676) *Severall Chirurgicall Treatises* Royston and Took, London

Wittens CH, Bollen EC, Kool DR, van Urk H, Mul T and van Houtte H (1993) Good results of subfascial endoscopy as treatment of communicating vein insufficiency *Nederlands Tijdschrift voor Geneeskunde* 137(24):1200-4 (Dutch)

Woodyer A, Batch A, Berent A and Dormandy J (1981) The correlation of periflow and direct manometric results in venous disorders. In: Jageneau AHM ed. *Noninvasive methods on cardiovascular haemodynamics*. Biomedical press, Elsevier pp 105-12

Worsfold JT (1974) Varicose veins in Tropical Africa *Lancet* ii:1322-1323

Yang ZH, Gu XP and Zhang JW (1994) Study on correlation of valvular function of deep vein and clinical symptoms *Chung Hua Wai Ko Tsa Chih (Chinese Journal of Surgery)* 32(3):140-2.(Chinese)

Zamboni P and Liboni A (1991) External valvuloplasty of the sapheno-femoral junction using perforated prosthesis *Phlebology* 6:141-147

Zamboni P, Feo C, Marcellino MG, Manfredini R, Vettorello GF, De Anna D (1995) Angiovideo-assisted hemodynamic correction of varicose veins *International Angiology* 14(2):202-8

Zamboni P, Marcellino MG, Feo C, Berta R, Vasquez G and Pansini GC (1995) When CHIVA treatment could be video guided *Dermatologic Surgery* 21(7):621-5

Zamboni P, Marcellino MG, Murgia AP, Fabi P, Ortolani M and Mari C (1995) Clinical and hemodynamic effects of external valvuloplasty of the sapheno-femoral junction *Minerva Chirurgica* 50(5):463-8.(Italian)

Zsotér T and Cronin R (1966) Venous distensibility in patients with varicose veins *Can Med Assoc J* 94:1293

Zsotér T, Moore S and Keon W (1967) Venous distensibility in patients with varicosities in vitro studies *J Appl Physiol* 22:505-8