VENOUS HYPERTENSIVE MICROANGIOPATHY:
EVALUATION WITH LASER DOPPLER FLOWMETRY

by

Giovanni V. Belcaro MD

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Irvine Laboratory for Cardiovascular Investigation and Research,
Academic Surgical Unit, St Mary's Hospital Medical School,
Imperial College of Science and Medicine

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ABSTRACT

The skin microcirculation was evaluated in subjects with venous microangiopathy using laser Doppler flowmetry (LDF) and other noninvasive microcirculatory methods. Resting skin flux (RF) and the venoarteriolar response (VAR) were the main measurements studied. RF was found to be increased with a variable decrease in VAR. A linear correlation (r=0.712) between RF and the ambulatory venous pressure was found. Combined LDF and transcutaneous PO2-PCO2 measurements indicated that RF is not linearly related to PO2-PCO2 changes. PO2 did not appear to be related to venous hypertension while PCO2 was related to the flux increase. Capillary filtration measurements indicated a correlation between RF and filtration increase (r> 0.7). This indicated an association between the increased skin flux and oedema in chronic venous insufficiency. LDF findings were also associated with histology changes (an apparent increase in the number of capillary loops, glomerular-like aspect of the capillaries, increased capillary size and wall thickening).

The effects of compression (elastic stockings, intermittent sequential compression) on venous microangiopathy were also prospectively evaluated. They produced a decrease in RF and an improvement in the VAR. Two oral compounds (a flavonoid and a fraction of Centella Asiatica, TTFCA), venous surgery and sclerotherapy produced a decrease in RF. A 12-month study comparing sclerotherapy and surgery showed that both treatments reduce RF and that their effects may persist months after treatment.

The final study indicated that RF and VAR, combined in a microangiopathy score, are effective in predicting the healing potential of venous ulcerations.

In conclusion the evaluation of venous microangiopathy with LDF can be useful to define the degree of microangiopathy and to assess treatment. Although LDF is not diagnostic in individuals because of a high variability it may be effectively used to quantify venous microangiopathy, to evaluate treatment and to predict the healing of venous ulcerations.

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CHAPTER 1

INTRODUCTION AND REVIEW OF LITERATURE

1.1 HISTORICAL INTRODUCTION

The papyrus of Ebers (c. 1550 BC) probably contains the first written record of varicose veins. Hippocrates (460-377 BC) thought leg ulcers were associated with enlarged leg veins and dependency (Adams, 1949). A tablet from the Asklepieion in Athens illustrates a man holding a huge leg with a varicose vein. Hippocrates reported that the Scythians developed leg ulcers as a result of leg dependency while horse-riding. He recommended that patients with ulcers should avoid standing or hanging their feet and abandon riding. He introduced "puncturing and bandaging" for the treatment of ulcers and the associated varicose veins.

Herophilus of Chalcedon, working in Alexandria in the third century BC, differentiated veins from arteries. He established that arteries had vigorous pulsation, whereas veins pulsated little, if at all.

In Roman times, treatment of bandaging with linen as advised by Aurelius Cornelius Celsus (25 BC-50 AD) and applying wine to the ulcer was recommended by Galen (130-200 AD) (Scott, 1992).

Haly Abbas (died 994 AD) believed that varices were full of black bile, having been pushed out of the main veins by the weight of stagnant blood. They occurred in those who worked hard and stood for long periods. Bandaging was thought to push back these humours into the main venous vessels and cause madness (Scott, 1992).

In 1363 G. de Chauliac (E. Nicaise, 1890) suggested that humours descended to the legs as a result of standing, and were responsible for ulcer development. In 1555, Sanctus of Barletta (Sanctus M. of Barletta, 1555) thought that varicose veins were a result of child bearing and too much standing thereby combining humoral and mechanical theories. The theory that "faeculant humours" situated within the accompanying varicose veins resulting in ulcers was proposed by Falloppio in 1530 (Maffei, 1620). In Frankfurt Jean Fernel (1506-1588) considered that varices were caused by a thickening of the blood (Fernel, 1604). Ambrose Paré (1510-1590), in keeping with the humoral theory, attributed varicose veins to a high melancholy temper in men, and pregnancy in women (Paré, 1649). He suggested that "varices grow in men of melancholic temper and which feed on gross meats". Fernel (1604) combined both mechanical and humoral theories, believing that "excessive effort, hard work, and much travelling" caused a collection of corrupt humours in the leg, which eventually led to ulceration. He observed that varicose veins were caused from "plethora as in most pregnant women" and "thickening of the blood following a blow or contusion".

Avicenna (980-1037) did not believe that it was possible to heal ulcers in old people (Underwood, 1783).

Vicray in 1636 noted that leg ulcers were very difficult to heal and when injured would leak great quantities of the humours (Vicray, 1636). Le Dran (1731) in France and Heister (1768) in Germany took a similar view, and both thought that the function of the ulcer was to act as a drain for the humours, which if retained would cause madness (Scott, 1992).

In 1758, Sharp wrote that a cure in old people is often dangerous but some years later Benjamin Bell stated that with a small degree of caution, a cure of every ulcer should be attempted (Sharp, 1758; Bell, 1789). In 1801, Home wrote that if a patient of a "gouty habit" had an ulcer on the leg, any attempt to heal it was imprudent. In 1822, Buchanan wrote that ulcers should not be healed if the patient was not ill. If a fever or lethargic state developed, attempted healing should be encouraged (Buchanan, 1822). Hunt (1859) believed that the ulcer was salutary, and that a general illness followed its healing.

Barbette (1675), applying the humoral theory of menstrual ulcers, supposed that the menstrual blood collected in the legs during pregnancy. It became stagnant, and in order to escape caused ulceration. Suppression of the menstruals caused a fall into melancholy madness. Pigeaux (1843) much later also felt that the female reproductive system was related to ulceration and reported that suppression of ulcer exudation was responsible for a cook having several abortions. Ettmüller (1688) supported the idea that menstrual blood was "gross" and collected in the legs during pregnancy, causing varicose veins and ulcers. In 1761, Astruc was the first to record and clearly state that the menstrual loss was not a collection of bad humours (Astruc, 1761). Critchett (1849) and Astley Cooper (1824) both wrote in terms of the humoral theory with amenorrhoea being related to menstrual ulcers. Cooper agreed with Home and felt it was wrong to heal these ulcers. The belief that ulcers should not be healed, as they were a necessary escape for the evil humours, continued throughout the eighteenth century and into part of the nineteenth century (Nunn, 1852).

Wiseman sergeant-chirurgeon to Charles II of England realised in 1676 that valvular incompetence results from venous dilatation (Wiseman, 1676). He concluded that ulcers might be a direct result of stagnation secondary to a circulatory defect and used the term "varicose ulcer". He used stockings and laced bandages to repress the humours impacted in the leg. He also said that sometimes it was necessary to achieve a cure if plethora was present, and that a body might have to be purged and a vein opened. He also stated that varices were not dangerous in themselves as they freed the patient from imminent diseases, especially that of melancholy. "If varices are suppressed, madness, pleurisy, couching of blood, pain in the kidneys, and apoplexies do follow. Varices ought not to be cured, for they preserve health". In 1676 Wiseman gave the original description of post-partum thrombosis responsible for many intractable ulcers.

Hunter in 1775 (Scott, 1992) described the association of thrombosis and phlebitis in man after venesection. Many of his eighteenth century contemporaries writing on leg ulcers made no reference to varicose veins as a cause of ulceration (Underwood, 1783; Bell, 1789; Baynton, 1799; Whateley, 1799). Whateley said " that ulcers of the legs are more difficult than those in any other part of the body, it is a circumstance that is attributed either to their dependent situation, or to the greater languor of the circulation in them as extreme parts" and recommended emollient poultices to be applied twice daily.

Home (1801) believed ulcers were more difficult to heal if varicose veins were present, and Hodgson (1851) wrote of ulcers near the ankle being intractable. "They appear to depend upon the varicose condition of the veins, for when the latter is relieved, the ulcers are as readily cured as ulcers in general". He also believed that it was the obliteration of a vein that made the surrounding ones varicose as the circulation continued through them.

It has been known for long time that ulceration of the lower limb is a serious and often intractable consequence of venous disease (Anning, 1954). However it was observed that many patients with venous disease did not develop ulcers and the precise cause of the ulceration remained unclear.

1.11 <u>Modern theories on pathophysiology</u>

The importance of varicose veins became recognised in the nineteenth century (Home, 1801; Hodgson, 1851) but it was the work of Gay and Spender, writing independently in 1868, which showed that venous thrombosis played a major role, and discarded the theory of varicose ulceration (Gay, 1867; Spender, 1868). This was a few years after Virchow had described the triad of aetiological factors responsible for the formation of venous thrombosis: stasis, endothelial damage, and changes in blood coagulability (Scott, 1992). Gay observed that "ulceration is not a direct consequence of varicosity but of other conditions of the venous system with which varicosity is not infrequently a complication, but without which neither one of the allied skin affections, induration and bronzing, is met with, conditions which involve obstruction of the trunk veins, deep and superficial, either from impediments on the venous side, or incompetency on the arterial, or from both causes combined". Gay also described the ankle perforating veins, thrombus formation and recanalisation, and he was the first to use the term "venous ulcer". Although it was recognised that ulceration of the lower limb and superficial varicosities did not necessarily coexist, there was little understanding of the relationship between venous thrombosis and the postphlebitic syndrome.

More recently Homans in 1916, found that incompetence of the perforating veins of the calf and ankle occurred in the post-phlebitic limb and introduced the term "post-phlebitic syndrome" to describe the effects of deep vein thrombosis (Homans, 1916). In 1938 he described two types of ulcers: varicose ulcers, associated with superficial varicose veins which were easily cured by the removal of the veins, and venous ulcers, which were often intractable and generally not curable by the removal of varicose veins alone (Homans, 1938). He observed that venous ulcers generally occupied the same position, the medial aspect of the perimalleolar region. Homans emphasised the importance of valve incompetence in the perforating veins as a consequence of thrombosis and subsequent recanalisation (Homans, 1916).

Cockett in 1953 described three constant perforating veins on the medial side of the lower third of the calf and suggested that the most important cause of post-thrombotic ulceration was due to valvular incompetence in these veins (Cockett and Jones, 1953). Such incompetence results in high-pressure venous "leaks" from the calf pump, with the high exercising pressure transmitted directly to the superficial tissues. Croft in 1981 found in his series a great reduction in calf muscle efficiency in the majority of ulcerated limbs (Croft, 1981). He suggested that the situation is worsened by poor arteriolar supply in the perimalleolar region where most venous ulcers are localised (Cockett and Jones, 1953). Perforator incompetence can exist without complete incompetence of the deep veins of the leg (Dodd and Cockett, 1976), but perforating vein incompetence alone seems less likely to cause ulceration than when it is associated with deep vein incompetence (Halliday, 1967). Recently it has been suggested that perforator incompetence may be secondary to primary or secondary venous incompetence (Burnand et al, 1977). Other authors found that no venous ulcers were observed without reflux in perforating veins (Dodd, 1964; Haeger, 1977). Other reports have disputed this and in a number of cases ulceration could be attributed to pure long saphenous insufficiency (Wright et al, 1988). Incompetent perforating veins have also been described as irrelevant (Recek, 1971). Bjordal (1972) demonstrated that the main cause of raised venous pressure in patients with venous insufficiency was due to reflux of blood within the major venous channels. He demonstrated that the incompetent perforating veins contribute little to this increase in pressure. In recent times more scientific explanations for the development of skin alterations and venous ulcerations have been proposed. However, the mechanism by which venous disease results in ulceration of the leg is still unresolved. Homans in 1917 thought that stagnant blood in tortuous and dilated veins close to the skin resulted in tissue hypoxia and cell death (Homans, 1917). De Takats (1929) found a lower oxygen tension in varicose veins than in the normal antecubital vein. However, Blalock, in the same year, showed that oxygen tension was higher in the venous blood of legs with venous ulcers than that in normal legs (Blalock, 1929). His work was confirmed by Holling in 1938 and Fontaine in 1957 (Holling et al, 1938; Fontaine, 1957). However Blalock's work was not confirmed in a study by Reikerås and Sorlie (1983) which reported a raised oxygen tension in the normal saphenous veins.

Piulachs and Vidal Barraquer in 1953 suggested that the high O_2 saturation within the venous blood of patients with chronic venous insufficiency could be explained by "pathological shunting" through arteriovenous fistulae (Piulachs and Vidal-Barraquer, 1953). The shunting of blood was thought to be responsible for the development of venous ulcers by a process of anaemic anoxia. This theory was supported by some other studies that relied on the indirect evidence of increased O_2 saturation in the venous blood or reduced transit time of dye injected intra-arterially as proof of shunting (Fontaine, 1957; Haimovici et al, 1966a; 1966b). However, despite this work, the concept of anoxia caused by stasis producing "gravitational ulcers" (Dickson-Wright, 1931) is still considered possible (Schanzer and Peirce, 1982). Even the term "stasis" associated with venous ulceration is debatable (Burton, 1989).

Pratt (1949) and Brewer (1950) suggested that arteriovenous anastomoses under the skin produced cell death by anaemic anoxia in venous ulceration. Suquet had recognised such anastomoses in 1860, and other workers (Grant, 1930, Clark and Clark, 1930; Clara, 1956; Scott, 1992) had observed them in the rabbit's ears and bird's foot. Thermography has been used to claim the existence of arteriovenous communications, but the evidence is generally poor and cannot be generalised to all types of venous insufficiency (Haeger, 1963; Haeger and Bergman, 1963; Schalin, 1989; Eger and Casper, 1943). The radiological work of Piulachs and Vidal-Barraquer, Haimovici and Vogler provides some evidence of arteriovenous communications and some links between arteriovenous shunts and varicose veins and ulceration (Piulachs and Vidal-Barraquer, 1953; Vogler, 1953; Haimovici et al, 1966; 1966a; Haimovici, 1976; Haimovici and Sprayregeb, 1986; Haimovici, 1987). The interpretation of reported operative findings of visible vessels joining arteries and veins is probably subjective (Haeger, 1963; Haimovici et al, 1966a; Gius, 1960).

The doubt concerning arteriovenous communications as the major cause of varicosity and venous insufficiency was summarised by Browse in the commentary to the work of Shalin (1989), where it was argued that a clear demonstration of a fistula requires physiological techniques. It has been pointed out that even radiological results are open to subjective interpretation (Scott, 1992).

Direct evidence of arteriovenous fistulae developing within the limbs with venous disease comes from Gius (1960), who described the existence of arteriovenous anastomoses, observed at operation with a dissecting microscope (Haimovici et al, 1966a). Histology of these vessels showed a uniformly hypertrophied muscle coat. This work had not been confirmed by others and Gius admitted that he was unable to differentiate the fistulae from the normal venules. The presence of an increased number of arteriovenous fistulae within the skin of the gaiter region of the leg cannot be predicted from anatomical distribution studies (Grant and Bland, 1931). Ryan and Copeman (1969) have observed that smaller anastomoses are common in other areas of the skin. These anastomoses are reported to be of capillary calibre and are thought to open in response to temperature or pressure alterations. Ryan (1970) claimed that they play a significant role in the development of the skin change with chronic venous insufficiency (Ryan, 1970).

Dynamic studies with venous occlusion plethysmography (Abramson and Fiest, 1962), studies with tagged albumin (Lindemayr et al, 1972) or technetium-labelled microspheres (Hehne et al, 1974) have failed to show increased arteriovenous shunting in limbs of patients with chronic venous insufficiency in comparison with normal controls.

However, Blumoff and Johnson in 1977 confirmed that there is an elevated partial pressure of oxygen within the blood taken from varicosities and saphenous veins of patients with varicose veins (Blumoff and Johnson, 1977) under anaesthetic. These results were obtained in awake individuals and if the concept of increased shunting is rejected, these findings can only be explained on the basis of decreased tissue use of oxygen or an alteration in the total blood flow through the limb (Baron and Cassaro, 1986).

More recently with the development of vital videomicroscopy (Steiser and Bollinger, 1991), the final pathophysiological changes in legs with venous ulcerations have been observed in the microcirculation. Bollinger (1982a) using Na-fluorescein and Fagrell (1979) using dynamic video-capillaroscopy have been able to show the microcirculatory changes which occur as the consequence of chronic venous hypertension. Franzeck in 1984 was able, using combined capillaroscopic and transcutaneous PO_2 measurements, to show that microcirculatory changes (such as a decreased number of capillaries per unit area) are associated with abnormalities in PO_2 in the affected skin (i.e. in areas of white atrophy PO_2 was extremely low, in the proximity of 0 mmHg).

In 1989 the complex microcirculatory dynamic and organic alterations observed in the perimalleolar region as a consequence of chronic venous hypertension were defined as "venous hypertensive microangiopathy" (Belcaro and Christopoulos, 1989). The attempt to classify by objective measurements some of the microcirculatory changes leading to ulcerations and the degree of venous microangiopathy became possible when laser Doppler flowmetry became available (Belcaro et al, 1989; 1991).

This review of the historical literature on venous disease indicates that a large number of old theories were based sometimes on science but more often on conjecture.

Much was understood about venous ulceration even in ancient times, despite the lack of knowledge of the fundamental mechanisms of the physiology and pathology. There were of course, many misconceptions, some of which persist even today. The next section reviews the current theories on the aetiology and predisposing factors of chronic venous disease.

1.2 AETIOLOGY AND FACTORS PREDISPOSING TO CHRONIC VENOUS DISEASE

1.21 Primary Varicose Veins

Attempts to understand the aetiology of varicose veins have led to two major theories. The first assumes that primary valvular insufficiency precedes venous distension (theory of valvular incompetence), the second that primary distension of the venous wall leads to valvular incompetence (theory of venous distensibility).

According to the first theory absence or functional failure of the iliofemoral valves produces a chronic increase in venous pressure onto the next lower valve, which in turn, causes more distal dilatation and valvular failure. Sequentially all the valves in the long saphena and its branches may become incompetent (Ludbrook, 1963, 1966a; Leu, 1974). This theory was supported by the studies of Ludbrook and Beale (1962) which by measuring the pressure in the femoral vein of normal volunteers and in patients with varicose veins, using direct cannulation, showed a correlation between iliofemoral insufficiency and primary varicose veins. Post-mortem studies have shown congenital absence of the iliofemoral valves in 21-25% of the population. However, in studies with Doppler ultrasound it was found that the incidence of iliofemoral incompetence was 100% in limbs with long saphenous incompetence, 64% in the asymptomatic limbs of patients with unilateral primary varicose veins and only 16% in normal volunteers.

The theory of increased venous wall distensibility is based on the observation of Zsoter and Cronin (1966) who demonstrated that even the arm veins of patients with primary varicose veins were more distensible than the veins of normal subjects when subjected to the same pressures. These findings have been confirmed with plethysmography (Hallbook et al, 1970, 1971). In addition, a decreased amount of collagen has been found in the wall of varicose veins, as well as a decrease in the number of elastic and collagen fibres, which appeared disorganised in comparison to the orderly arrangement seen in normal veins (Zsoter et al, 1967).

Fegan (1970) suggested that primary varicose veins were often the result of incompetence of calf perforating veins following recanalisation of localised traumatic thrombophlebitis after minor leg injury. He assumed that ejection of venous blood through the perforators, as a result of calf muscle contraction, was responsible for the dilatation of the superficial veins and the formation of the varices. This "perforator" theory was in disagreement with the observations of Ludbrook (1966b), and Lea Thomas (1976; 1982) who noticed that many patients with primary varicose veins did not have incompetent perforators. In addition, the perforator theory was not confirmed by the experimental work of Bjordal (1971a, b), who measured the flow in such incompetent perforating veins, using an electromagnetic flowmeter and simultaneously the pressure in the incompetent long saphenous vein, during exercise. Bjordal observed a fall in pressure in the long saphenous vein after proximal occlusion of this vein, despite the increased outflow through the calf perforating veins.

Traumatic, congenital or iatrogenic (i.e., for dialysis) arteriovenous fistulae may produce secondary varicose veins. However, there is evidence that arterio-venous communications may exist in limbs with primary varicose veins. The oxygen tension in the blood of varicose veins was found to be greater than in other veins (Blalock, 1929) and the arterial blood flow was found to be 130% greater in limbs with varicose veins than normal limbs. Haimovici (1966a,b; 1986) found radiological evidence of arteriovenous shunting and Shalin (1982) demonstrated in limbs with recurrent varicose veins the existence of minute arteriovenous fistulae with operative microscopy as well as the existence of increased arterial inflow by strain gauge plethysmography. Furthermore, Sumner (1975) using Doppler ultrasound over incompetent perforating veins, observed that the blood flow was increased and sometimes almost pulsatile (Sumner, 1975). However, these observations were not confirmed on measuring the arterial inflow in legs with primary varicose veins using venous occlusion plethysmography (Abramson and Fierst, 1946; Eirikson and Dahn, 1968). This suggests that arteriovenous communications may exist only in a particular group of patients or may be a consequence and not a cause of varicose veins (Christopoulos et al, 1990).

Experimental venous hypertension produced by ligating the iliac vein of dogs, resulted in the formation of dilated capillaries in the skin of the limb. These capillaries were surrounded by fibrotic tissue and acted as arteriovenous communications (Browse et al, 1982). Similar capillaries have been observed in histological sections of the skin that surrounded venous ulcers in humans (Burnand et al, 1981). At this stage further research is needed to clarify the correlation between microscopic arteriovenous shunts and varicose veins.

1.22 Predisposing Factors

The finding of a positive family history in 62% of patients with primary varicose veins may support the existence of some hereditary predisposing factors (Myers, 1962). Gunderson and Hauge (1969) observed that when both parents had varicose veins, the probability of the offspring developing varicosities was twice as high as when only one parent was affected. In addition, they found that if only the father had varicosities, the propensity of the person of developing them was greater than when only the mother was affected. It has also been observed that women have varicose veins five times more often than men. It seems that a polygenic mechanism is responsible for the hereditary tendency to varicose veins and that men require more genetic material than women for the manifestation of the disease which also depends on external factors (Gunderson and Hauge, 1969).

Although primary varicose veins exist in 10-17% of the population of Europe and North America, the incidence of the disease in Africa and Asia is only 0.12% (Boeshberg, 1967; Callam, 1992). This great difference is unlikely to be linked to only hereditary factors because the African-American population have the same incidence of varicose veins as the white American population (Burkitt, 1972). This observation as well as the geographical distribution of primary varicose vein disease - similar to the distribution of haemorrhoids and comparable to the distribution of populations feeding on low-residue diet - led Burkitt (1972) to postulate the hypothesis that chronic constipation and straining may produce high pressure in the pelvis which predisposes to varicose veins. However, an increased incidence of varicose veins was also found in persons who tend to stand or sit in a chair for prolonged periods, or use constricting clothing (Alexander, 1972). Obesity also appears to predispose to varicosities and it has been suggested that it is partially caused by the greater external pressure to the vena cava and pelvic veins. In patients with varicose veins studied by Myers (1962), men were on average 8 and women 17 kilograms heavier than average weight for their age (Strandness, 1978).

Compression of the iliac veins from the uterus, increased pelvic blood flow and hormonal factors are mainly responsible for the enlargement of normal veins and the development of varicose veins during and after pregnancy. Doppler ultrasound examination has shown that blood flow in the femoral veins stops in the standing position of 40% of women after the first trimester of pregnancy, in 70% after the second trimester and in 86% in the third. However, less than 10% of those women in the first trimester and less than 25% of those in the third trimester were obstructed in the supine position (Kerr, 1964; 1965, Ikard et al, 1971). The distensibility of the veins was also found to be greater during pregnancy, probably because of hormonal factors (Goodrich and Wool, 1964).

In conclusion, heredity, sex, pregnancy, diet and lifestyle are possibly important predisposing factors in the development of primary varicose veins.

1.23 <u>Evolution of deep venous disease</u>

The relation between venous thrombosis and leg ulcerations was first noticed by Homans (Homans, 1916; 1917; 1938) who also pointed out that venous thrombosis occurred more often after surgical operations and pregnancy. Homans differentiated between limb ulceration related to simple varicose veins, which could be treated with surgery, and ulceration following deep venous thrombosis. The relation between a previous episode of thrombosis and venous ulceration was confirmed by the clinical studies of Anning (1954). This author found that deep venous thrombosis preceded ulcerations in 20% of the affected limbs within the previous 5 years, in 52% within the previous 10 years and in 79% within the previous 15-20 years. These findings were confirmed by subsequent studies (Linton, 1953; O'Donnell et al, 1979).

The damage to the veins and the valvular system after thrombosis, which is responsible for the subsequent post-thrombotic changes of the leg, has been described by Edwards and Edwards (1937). They observed that once the thrombus is stabilised in the lumen of the vein, the process of fibrosis and recanalisation is initiated. This can result in complete or partial obstruction of the lumen and impairment of function of the valve cusps which become fibrotic, thickened and contracted (Edwards and Edwards, 1937). The obstruction of the deep veins appears to be responsible for the distension of the distal perforating veins, which subsequently become incompetent and allow the passage of high pressure blood flow to the superficial veins. The increased outwards flow of blood through these veins and the persistently raised pressure result in the formation of secondary varicosities because of venous elongation and distension. Secondary varicose veins act as collaterals which by-pass occluded deep veins. However, their valves often become incompetent because the dilatation of the lumen may prevent the closure of the valvular cusps. (Edwards and Edwards, 1937).

The final outcome of an episode of venous thrombosis is often unpredictable. Venous function usually improves to some degree but rarely returns to normal (Hallbook and Gothlin, 1971; Barnes et al, 1972). In a series of post-thrombotic limbs studied with straingauge plethysmography, venous incompetence only was detected in 30%, occlusion only in 24% and a combination of both incompetence and occlusion in 27%. The remaining limbs could not be categorised (Sakaguchi et al, 1972).

The existence of primary deep venous incompetence has been demonstrated on descending venography (Lockhart-Mummery and Hiller-Smith, 1951) when leakage of the contrast medium, through the valve cusps of the deep veins was observed. Dodd and Cockett (1976) made similar observations but they considered that this condition was subclinical because none of the patients they studied had symptoms and signs of severe chronic venous disease. However, Kistner (1978; 1980) and Raju (1983; 1986), performing descending venography by injecting contrast media into the femoral vein in a large number of patients, indicated that deep venous incompetence as a result of deformity of the valve cusps because of primary stretching, is not a rare condition. They considered primary deep venous incompetence to be related to clinical symptoms. These patients tend to improve after valvuloplasty, i.e., surgical correction of the incompetent valve (Kistner, 1975; Taheri et al, 1982).

The significance of primary deep venous incompetence in the development of chronic venous insufficiency remains controversial. It has been observed with ambulatory venous pressure measurements (Shull et al, 1979) that the integrity of the valves of the popliteal vein protects the leg from chronic venous hypertension and ulceration while incompetence of this venous segment produces severe venous hypertension independently from the condition of the femoral valves.

Complete congenital absence of valves in the deep veins was first demonstrated by Luke (1941). This is a very rare condition associated with severe venous incompetence (Lodin et al, 1958; Leu, 1974; Friedman et al, 1987).

Irrespective of deep or superficial venous incompetence, the progressive increase in venous pressure, if left untreated, leads initially to functional changes then, later to organic changes at the level of the most distal venous system and in the microcirculation (Hoare et al, 1981; Scurr and Coleridge-Smith, 1992).

The pathological changes which develop in chronic venous hypertension defined as "venous hypertensive microangiopathy" (Belcaro et al, 1988; Christopoulos et al, 1992) bear similarities to other *high perfusion microangiopathies* (in contrast to *low perfusion, ischaemic microangiopathy*) such as diabetic microangiopathy.

The final event of *high perfusion microangiopathy* is usually an ulceration of the skin which heals very slowly and only if the initial cause (chronic venous hypertension) is abolished or attenuated.

1.24 The microcirculation in chronic venous insufficiency

In recent years chronic oedema and capillary deposition of fibrin have been postulated to be the major factors producing tissue damage, liposclerosis and eventually leg ulceration in patients with post-thrombotic limbs (Browse et al 1982, Burnand et al 1980; 1982). These pathological changes have been considered to be due to chronic venous hypertension on the microcirculation. The effects of a continuous situation of venous hypertension on the skin - particularly of the perimalleolar region - cause microcirculatory disturbances whose significance has been recently better understood. The quantitative measurement of these microcirculatory disturbances has become recently easier using simple, noninvasive techniques such as laser Doppler flowmetry (LDF) (Belcaro et al 1988a,b,c,d,e and 1989a,b; Coleridge-Smith et al 1993) transcutaneous PO_2 ($TcPO_2$)(Franzeck et al 1984) and PCO_2 ($TcPCO_2$) (Belcaro et al 1988a,e) and straingauge plethysmography (Belcaro et al 1989b, Cesarone et al 1991) and the vacuum suction chamber (VSC) device used to assess capillary filtration (Belcaro and Rulo 1988b).

Venous hypertensive microangiopathy is the term used to describe the anatomical and pathophysiological changes that occur in the microcirculation as a result of venous hypertension, which are responsible for the characteristic clinical changes in the skin. In the following pages the microcirculation alterations observed in chronic venous hypertension, the microcirculatory methods available for their quantification and the relative importance of the microcirculatory alterations causing oedema, lipodermatosclerosis and eventually ulceration will be reviewed.

Laser Doppler flowmetry has shown that in limbs with venous hypertension there is an increase in skin flow) Gowland-Hopkins et al, 1983) and in skin red cell flux (flow measured with laser Doppler flowmetry is indicated as flux). This indicates a general increase in skin perfusion at rest (RF= resting flow) with a decrease, abolition or alteration of the normal vasomotor activity. Flux alterations may be associated with a decreased venoarteriolar response (VAR) namely the vasoconstrictory reflex induced by postural changes - i.e. from the supine to the standing position (Hendriksen 1976). This physiological response appears to minimise the number of capillaries exposed to a high flow and pressure in the standing position. Absence or reduction of the VAR possibly exposes a large number of capillaries to high pressure on standing. This appears to be associated with increased capillary leakage and with the formation of ankle and foot oedema. In normal limbs the precapillary resistance in the skin of the foot and of the perimalleolar region increases on standing producing a decrease in capillary blood flow (Hendriksen 1976; Rayman et al 1986; Belcaro et al 1988a,b,c,d,e and 1989a,b). This response limits the increase in capillary pressure determined by the vertical column of blood between heart and foot. It has been suggested that this vasoconstrictory response is mediated by a sympathetic axon reflex (Hendriksen 1976; Rayman et al 1986). Lowering the leg and foot below the horizontal level in normal subject elicits the venoarteriolar response producing a small decrease (20-30%) in skin flux. A greater decrease in skin flux (40-60%) is observed on standing. A small decrease in flux is also observed by sitting up while keeping the legs horizontal. Inflating a thigh cuff to 80 mmHg to occlude the superficial venous system will also elicit a small decrease in skin flux and no further decrease would be observed when the leg is lowered below the horizontal. Lowering one leg may produce a minimal decrease in the skin flux in the opposite limb which is very difficult to quantify. It appears that a sudden increase in venous pressure is an important stimulus for the venoarteriolar response which is mainly the result of a local reflex mechanism (Hendriksen 1976; Rayman et al 1986; Belcaro et al 1989; Levick and Michel, 1978).

It has been calculated that in normal conditions, in the normal skin, only 5-10% of the total skin blood flow is through the nutrient capillaries reaching the outer layers of the dermis (Fagrell et al 1993). The number of nutrient capillary loops per unit area is related to the transcutaneous PO_2 ($TCPO_2$). The smaller the number of nutrient capillary loops per mm², the lower is the $TcPO_2$ (Franzek 1984). Coherent light emitted by the laser Doppler probes penetrates the superficial part of the dermis for a depth ranging between 0.7mm and 1.5mm. Therefore laser Doppler flowmeters measure red cell flux within an average depth of about 1mm. It is thus not surprising that $TcPO_2$ is not always related to the red cell flux as measured by LDF. The thermoregulatory function and capacity of the skin results in great temporal fluctuations in the total skin blood flow. Thus, changes in flow (particularly in the most superficial nutritional layers of the dermis) are not necessarily reflected by changes in LDF measurements (Belcaro and Nicolaides 1993).

The output signal from laser Doppler flowmeters is directly proportional to blood flow in the microcirculation and particularly in superficial skin vessels (localised within a depth of less than 1.5mm) only under certain specific and often not reproducible situations. Comparative studies with television capillaroscopy indicate that laser Doppler flowmetry detects flow in subcapillary plexuses, superficial shunts and capillary loops. Therefore the reflux responses observed by the two techniques are comparable (Tooke et al 1983; Rayman et al 1986). LDF probes record red cell flux (a function of number of red cells, capillary loops and velocity) in small volumes of tissue (of the circumference of approximately 1 mm²). One of the advantages of LDF is the possibility to record and monitor vasomotor activity which produces the rhythmic fluctuations in microcirculation blood flow. This is because vaso-constriction alternating with vasodilation occurs in one area while the opposite may occur in an adjacent area. This vasomotor activity is associated with healthy skin conditions and is a factor determining total skin blood flow. In pathological situations such as inflammation, allergic reactions and in venous microangiopathy, the vasomotor activity can be altered, reduced or abolished with generalised vasodilatation resulting in a marked increase in skin blood flow and LDF flux.

Laser Doppler resting flux, VAR and ambulatory venous pressure measurements (AVP) have been shown to be linearly related to the incidence of venous ulceration (Belcaro and Nicolaides, 1993a,b). There was a poor correlation of the $TcPO_2$ with RF ($r<0.4$) with a significant negative linear relationship between the PCO_2 and VAR ($r= -0.72$). It appears that high skin PCO_2 values are associated with a high RF and a poor VAR (Belcaro et al, 1988a). The question arises whether the increased PCO_2 is responsible for or is the result of the vasodilatation with increased skin flux and the alterations in vasomotor activity (Belcaro 1988a).

It has been also observed that in patients with diabetes and venous hypertension in whom the VAR is impaired, oedema may occur as a result of high capillary pressure on standing. In diabetes the thickening of basement membranes, the histological hallmark of microangiopathy, is promoted by chronically raised capillary pressure (Tooke et al 1983;

Bollinger et al 1982b).

In venous hypertension the increase in capillary leakage and filtration can be demonstrated both by the use of a vacuum suction chamber (Belcaro and Rulo 1988, Belcaro et al 1993b) or by venous occlusion plethysmography (Thulesius 1973; Sigaard-Andersen 1970). The increase in capillary leakage and the following production of oedema are indicated by both methods (Cesarone et al 1992) and the increase in filtration is always associated with a proportional increase in skin flux at rest and often with a decrease in venoarteriolar response (Michel, 1989).

In conclusion the development of different theories concerning the evolution of venous hypertension and its causes and the final processes leading to the characteristic skin changes and ulcerations have followed the development of technology. The evaluation and quantification of the final events happening in the microcirculation is now possible as more sophisticated, non-invasive methods to assess the venous system and the microcirculation are available.

1.3 METHODS OF EVALUATION AND QUANTIFICATION OF CHRONIC VENOUS INSUFFICIENCY AND VENOUS HYPERTENSION

Non-invasive diagnostic tests have been developed and now they are routinely used to evaluate and quantify venous hypertension. They allow us to understand better the pathophysiology of chronic venous insufficiency (Belcaro et al, 1992f; 1993b).

Symptoms and signs of chronic venous insufficiency are produced by persistent venous hypertension which is the result of obstruction, reflux or a combination of both.

Outflow obstruction is found in patients who have had deep venous thrombosis not followed by adequate recanalisation of the affected venous segments and with poor development of a collateral venous circulation. Less frequently it is the result of external venous compression.

Venous reflux is found when the valves are damaged because of venous thrombosis followed by recanalisation with distruction or dilatation of the vein and valvular rings. In this situation the valve cusps no longer properly close causing reflux (Belcaro et. al, 1993).

Varicose veins are often associated with deep to superficial venous reflux caused by valvular incompetence of the superficial or communicating system. This is usually associated with venous dilatation without previous thrombosis (primary varicose veins). Less often it is a consequence of valvular damage following thrombosis and vein recanalisation which causes deep and perforating vein incompetence (secondary varicose veins).

Reflux in the deep veins is usually the result of venous thrombosis and recanalisation with destruction of the venous valves. Rarely, the absence of valves is idiopathic. Recent studies using descending venography have also indicated that idiopathic reflux due to *floppy* valve cusps are found in 30% of patients with venous hypertension. This finding is particularly interesting as some of these valves may be corrected by valvuloplasty (Kistner, 1980).

The final events in chronic venous hypertension either caused by reflux or obstruction, primary or secondary, are skin changes due to venous hypertensive microangiopathy.

The clinical examination with the classical Trendelenburg and Perthes tests can be misleading or impossible when varicose veins are not prominent and can offer relatively little information about the state of the deep veins (obstruction or reflux), although in extreme conditions with a history of pain on walking (venous claudication), severe swelling and prominent veins over the lower abdominal wall, the diagnosis is obvious.

Recently a number of diagnostic investigations have been developed to provide qualitative and quantitative information that can offer answers to most questions posed in a clinical practice. In this section of the thesis a review of the most applied invasive and noninvasive investigations in venous disorders is presented. This section also outlines the usefulness and limitations of each test.

1.31 <u>Ascending venography</u>

Ascending venography displays the anatomy and can give an indication of the basic abnormality (Gryspeert, 1953). Unfortunately venography provide quantitative measurements of any abnormality. The main reasons for doing venograms are to confirm the presence and extent of outflow obstruction with visualisation of the extent of collateral circulation and sites of reflux. Until recently venography has been considered to be the *gold standard* for anatomic visualisation (Bergan & Kistner, 1992). However, the development of high resolution real time ultrasonic imaging equipment combined with Doppler ultrasound (see below under duplex scanning) is now producing a noninvasive *gold standard*. As noninvasive techniques which can be used in combination with duplex scanning give precise quantitative measurements of the severity of obstruction and reflux venography tends to be performed in an increasingly less number of patients. At the present time, venography is generally performed in only 3-4% of all patients with venous problems (Belcaro et al, 1992; 1993b; Nicolaides et al 1978).

1.32 Descending venography

The aim of descending venography is to assess the extent of reflux and by inference the degree of valvular damage in the deep veins of the lower limb. The patient is placed in the 60°, semi-upright position. A venous catheter is positioned in the common femoral vein at the level of the pubic bone. Repeated boluses of contrast are injected. The competence of the common femoral, superficial femoral, profunda femoris, popliteal vein and the saphenofemoral junction are assessed by determining the extent of distal reflux of the contrast material. Initially the examiner identifies spontaneous reflux and subsequently asks the patient to do a Valsalva manoeuvre and then to flex the foot gently and not against resistance as described for ascending venography.

1.321 Grades of Reflux

Five grades of reflux (0-4) have been described

(Ackroyd et al 1986) (Table 1.1). Although reflux through the popliteal vein has been shown to be associated with symptoms, the association is not clear-cut. For example in one study reflux through the popliteal vein was found in one in five limbs with skin changes or ulceration and only in 31% of postphlebitic limbs (Ackroid et al 1986). The poor association between popliteal reflux and symptoms is probably because of the following two reasons in addition to technical errors. It is now well established that skin changes and ulceration can often occur in the presence of reflux in the superficial veins only, when the retrograde venous flow at peak reflux exceeds 7ml/sec (Vasdekis, 1989). It has also been demonstrated that competent popliteal valves do not exclude post-phlebitic changes which may be the result of reflux in the tibial veins and incompetent calf perforating veins (Moore et al 1986). Unfortunately the technique of descending venography as described above will fail to demonstrate reflux in the tibial veins in the presence of competent popliteal or more proximal valves.

The development of duplex scanners has now provided us with a noninvasive method that can not only detect but also quantitate reflux in individual veins (Vasdekis et al, 1989) so that descending venography is no longer necessary unless one is looking *for floppy* valves with the view to valvuloplasty.

Table 1.1

Types of venous reflux demonstrated with descending venography.

Complete competence

The venous system does not leak during full Valsalva manoeuvre

Satisfactory competence

Mild leakage limited to thigh during Valsalva manoeuvre

Moderate incompetence

Prominent leakage into calf veins during Valsalva manoeuvre

Retains centripetal (prograde) flow in iliac vein

Severe incompetence

Cascading retrograde flow during Valsalva manoeuvre

Reflux into calf perforators

1.33 Ambulatory venous pressure measurements

The original observation made in the 1940s of a decrease in venous pressure in the foot during walking (Veal and Hussey, 1940; Pollack and Wood, 1949; De Camp et al, 1951; Van der Hyde, 1961), and its gradual recovery to the resting value when walking ceases, became the basis of ambulatory venous pressure (AVP) measurements. This minimally invasive method has been used to supplement anatomical information provided by venography (Arnoldi, 1965; Arnoldi and Linderholm, 1971). In recent years, AVP measurements has became the haemodynamic *gold standard* used in the evaluation of noninvasive methods used for diagnostic assessment. Figure 1.1 shows an AVP tracing in a subject with venous incompetence. In the presence of competent deep veins the application of a below-knee tourniquet excluding the superficial system normalises AVP (the lowest pressure obtained during the exercise test) and the refilling time (RT) (Nicolaides and Zukowski, 1986). The AVP and RT values in normal limbs and in venous disease are indicated in Table 1.2. A good correlation between AVP and the incidence of venous ulceration (Table 1.3) has been demonstrated (Walker and Loughland, 1959; Nicolaides and Zukowski 1986; Nicolaides et al, 1985).

In the presence of severe outflow obstruction and deep venous reflux (including reflux in the popliteal vein) the value of AVP may actually increase during exercise because of the increased blood flow as a result of the post-exercise hyperaemia. This is observed in patients who complain of venous claudication which may occur even in the presence of competent popliteal valves. Because AVP measurement is

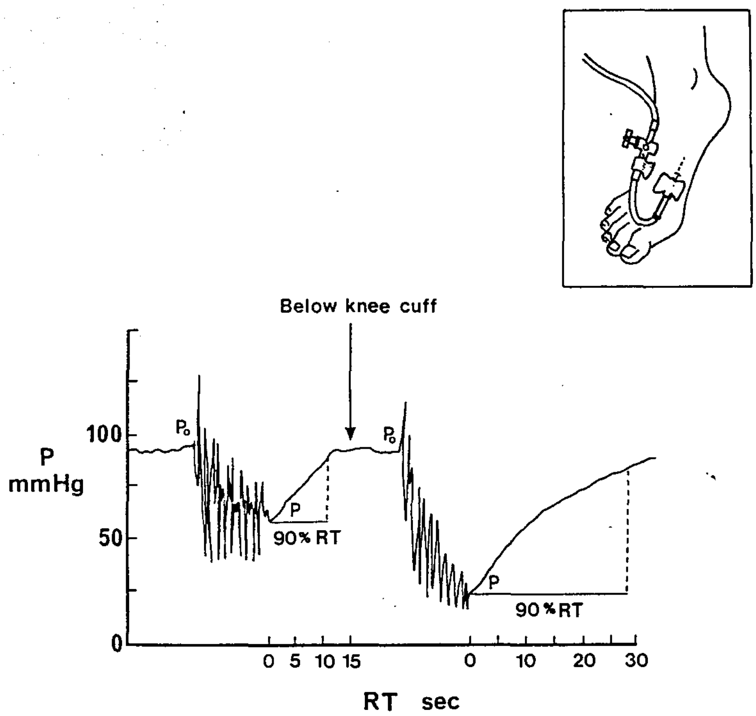


Figure 1.1: An AVP tracing in a subjects with venous incompetence. The application of a below-knee tourniquet excluding the superficial system normalises AVP (the lowest pressure obtained during the exercise test) and the refilling time (RT).

Table 1.2

Ambulatory Venous Pressure (AVP) and Refilling Time (RT)*

Type of Limb	AVP (mmHg)		RT_{90} (Sec)	
	No ankle cuff	Ankle Cuff	No Ankle Cuff	Ankle Cuff
Normal	15-30	15-30	18-40	18-40
Primary varicose veins with competent perforating veins	25-40	15-30	10-18	18-35
Primary varicose veins with incompetent perforating veins	40-70	25-60**	5-15	8-30
Deep venous reflux (incompetent popliteal valves)	55-85	50-80	3-15	5-15
Popliteal reflux and proximal occlusion	60-110	60-120		
Popliteal occlusion and competent popliteal valves	25-60	10-60		

* Standard exercise: 10 tiptoe movements

** In one third of these limbs, AVP remained more than 40 mmHg and RT_{90} less than 15 seconds despite the application of the ankle cuff.

Table 1.3

Incidence of ulceration in relation to ambulatory venous pressure (AVP) in 222 patients (251 limbs)

AVP (mmHg)	N	Incidence of Ulceration
< 30	34	0
30-40	44	11
41-50	51	22
51-60	45	38
61-70	34	59
71-80	28	68
81-90	10	60
> 90	5	100

moderately invasive, it cannot be repeated frequently nor can it be used as a screening test. It is for this reason that noninvasive screening tests such as Doppler ultrasound, calf volume plethysmography, foot volumetry and duplex scanning have been developed.

1.34 <u>Doppler ultrasound</u>

Continuous wave Doppler ultrasound is a useful test for the detection of reflux at the saphenofemoral and saphenopopliteal junctions. It has become an established routine technique in the out-patient clinic because it provides a quick and inexpensive noninvasive method of assessment of the veins of the leg. However it is less useful in the detection and localisation of incompetent thigh and calf perforating veins (Strandness et al, 1967; Sigel et al, 1972; O'Donnell et al, 1979).

One of the most important limitations of continuous wave Doppler ultrasound is that it cannot insonate an individual vessel selectively but it detects velocity from any artery or vein lying in the path of the ultrasonic beam. For example, at the level of the groin venous reflux can be in a tributary of the long saphenous vein, the long saphenous vein itself or the common femoral vein. In these cases Doppler ultrasound cannot identify the exact site of reflux nor can it detect a double long saphenous or femoral vein. In the popliteal fossa, although it can detect reflux it cannot detect the level of the termination of the short saphenous vein (Strandness and Sumner, 1972; 1976). Reflux in the gastrocnemius or the Giacomini vein can give false positive results indicating deep venous reflux despite the presence of competent popliteal valves. These deficiencies have now been overcome by duplex scanning.

1.35 Photoplethysmography

Photoplethysmography (PPG) and light reflection rheography (LRR) are noninvasive techniques that detect changes in the blood content of tissues. They have found their main use in the study of blood flow and blood volume changes in the skin (Hyman and Windsor, 1961). Although the skin is essentially opaque to light, slight light transmission and backscattering in the range of the visible and infrared spectrum does occur. In practice, a probe consisting of a light source and a light sensitive diode is positioned on the skin. Changes in the number of red cells in the dermis affect the backscatter of light and are detected by the light-sensitive probe. Such changes are produced by alterations in venous pressure caused by changes in limb position or proximal venous occlusion. A typical PPG or LRR tracing obtained with the patient in the sitting position and with 10 foot dorsiflexions is shown in figure 1.2. The PPG values in normal limbs and in limbs with superficial and deep venous disease in the standing and sitting position are reported in Table 1.4.

PPG and LRR have found relatively little application because of the inability to calibrate the signal, unless one is using time measurements such as the postexercise refilling time. When the refilling time was measured using both photoplethysmography and venous pressure simultaneously

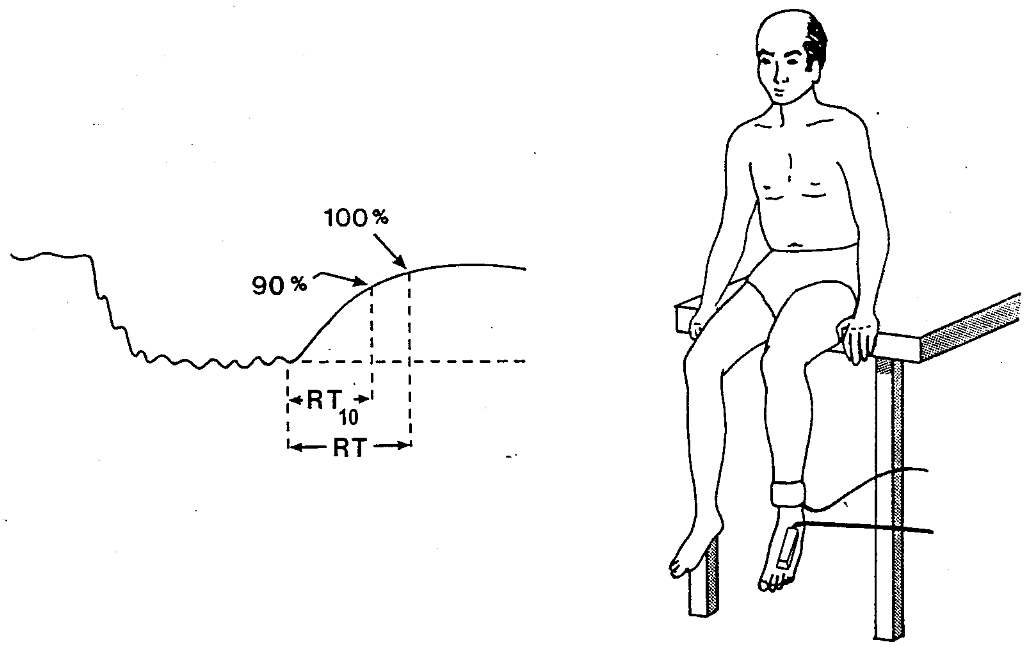


Figure 1.2: A typical PPG or LRR tracing obtained with the patient in the sitting position and with 10 foot dorsiflexions.

Table 1.4

Photoplethysmographic refilling time (RT_{90}) with and without an ankle cuff to occlude superficial veins.

	STANDING (Sec)		SITTING (Sec)	
	No cuff	Cuff	No Cuff	Cuff
Normal	18-80*	18-80	26-100	26-100
SVI	5-18	18-50	2-25	18-50
DVI	3-12	6-18**	2-28	2-30

* $RT_{90} > 18$ seconds without cuff identifies normal limbs.

** $RT_{90} < 18$ seconds with cuff identifies limbs with deep venous incompetence.

in two studies (Abramowitz 1979; Nicolaides and Miles 1987) a high degree of linear correlation was found (r=0.93 and r=0.88). It should be pointed out that although the refilling time without and with occlusion of the superficial veins can provide a means of distinguishing between normal limbs, limbs with superficial venous incompetence and limbs with deep venous incompetence, PPG is not a quantitative index of the severity of deep venous insufficiency (Nicolaides and Miles, 1986; Belcaro et al 1992f). The PPG or LRR refilling time may be below 20 seconds (indicating severe reflux) for a wide range of AVP measurements (i.e. between 35 mmHg, which is a normal value, and 90 mmHg, which is associated with severe venous hypertension) (Miles and Nicolaides, 1981; Norris et al, 1983; Belcaro et al, 1992b,f).

A flow chart summarising the present role of PPG/LRR in the context of non-invasive venous investigations is shown in figure 1.3.

1.36 Duplex scanning

Duplex scanning developed in the early 1980s for the diagnosis of deep venous thrombosis (Talbot, 1982; Sullivan et al 1984) has now been extended to the study of venous valve function (Semrow et al 1986) and venous reflux (Szendro et al 1986; Vasdekis et al, 1989).

Duplex scanning has been shown to be much more accurate than continuous wave Doppler ultrasound because it detects the presence or absence of reflux at anatomically identified

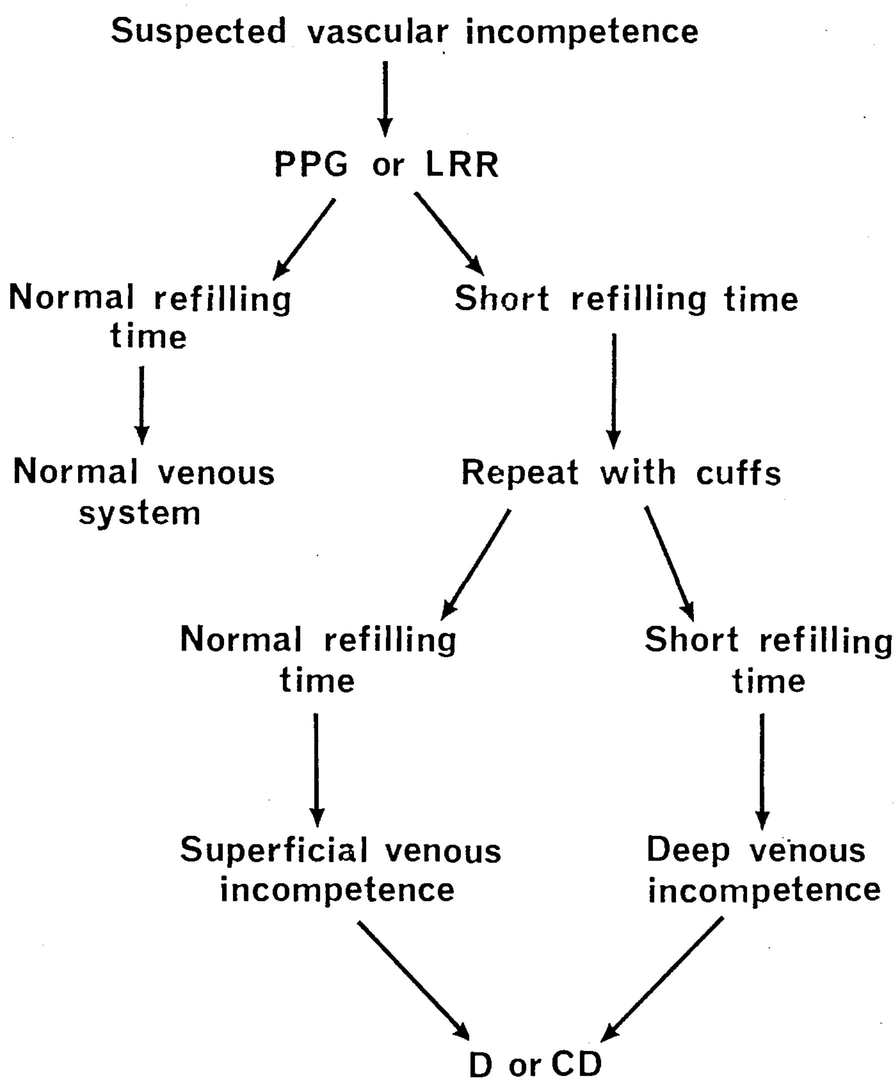


Figure 1.3

Flow chart summarising the role of photoplethysmography (PPG) or light reflection rheography (LRR) in the context of venous, non-invasive investigations.

d/cd = duplex or colour duplex

sites. Duplex scanning allows the examiner to visualise the venous system in real time, detecting single veins, position the sample volume of gated Doppler in them and test for reflux by calf compression and release of the latter. Reflux is the effect of gravity and therefore the patient is examined standing (Szendro et al 1986; Vasdekis et al, 1989; Belcaro et al, 1993b). With duplex scanning it is also possible to quantify reflux in individual veins. By duplex and colour duplex scanning it has been observed that reflux may be localised (i.e. femoral or popliteal veins) or diffuse to the whole deep venous system. Figure 1.4 shows how colour duplex may be used to localise reflux at the saphenopopliteal junction with a simple compression-release manoeuvre. Figure 1.5 shows how duplex scanning and this manoeuvre allows a fast identification of the venous system and its anatomical variations at the popliteal fossa. The evaluation of reflux in individual veins is tedious with black and white duplex as each vein must be individually tested. In contrast colour duplex allows a fast evaluation of all veins in the area with one single manoeuvre. The measurement of retrograde flow in ml/sec at peak reflux in axial veins (long saphenous, short saphenous and femoropopliteal) is also possible by duplex. Vasdekis et al (1989) studied 47 limbs of patients who presented with chronic venous problems (varicose veins, skin changes and/or ulceration). Results indicate that skin changes or ulceration do not occur when the sum of peak reflux in all the veins is less than 10 ml per second.

The incidence of skin changes and/or ulceration is high when

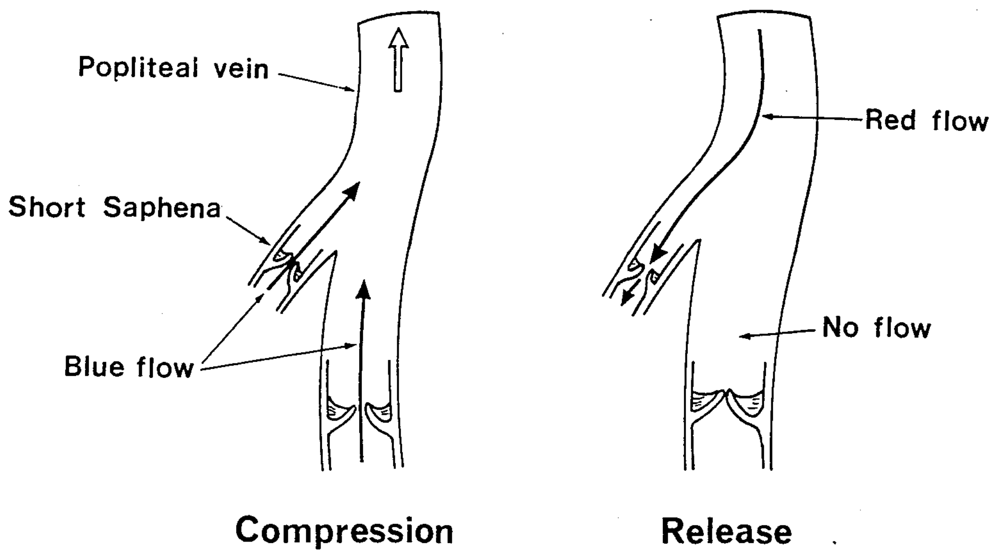


Figure 1.4: Colour duplex is used to localise reflux at the saphenopopliteal junction with a simple compression- release manoeuvre.

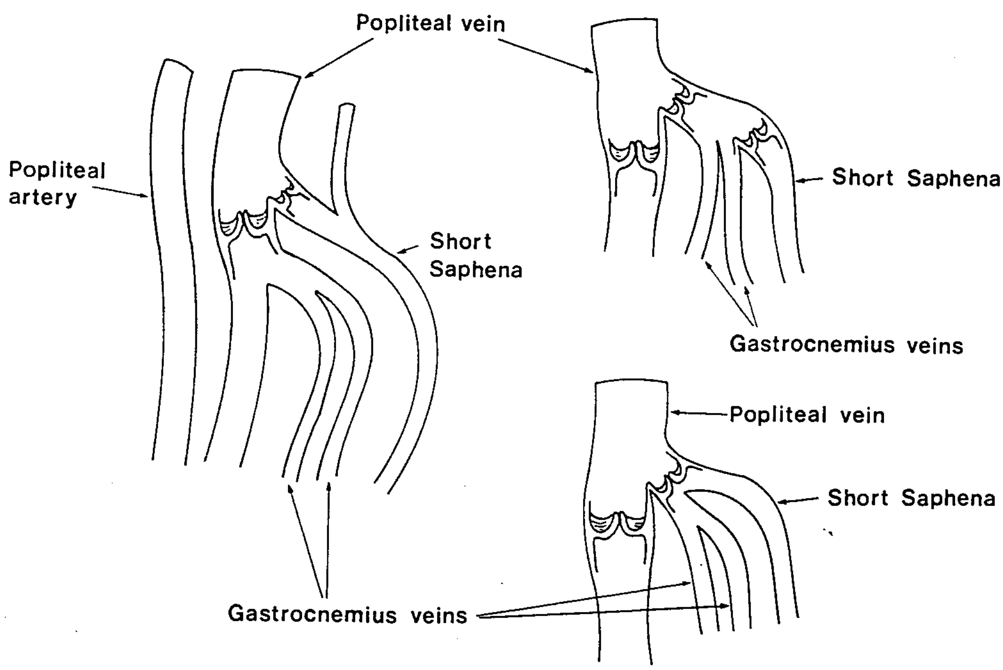


Figure 1.5: Duplex scanning with a compression-release manoeuvre allows a fast anatomical identification of the venous system, its anatomical variations at the popliteal fossa and the sites of reflux.

peak reflux exceeds 10 ml per second irrespective of whether such reflux is in the superficial or the deep veins. These preliminary findings need to be confirmed by larger studies.

Also the evaluation of incompetent perforators (Figure 1.6) is possible and reliable by colour duplex. The deep and superficial veins are identified and the communicating perforating vein is detected and localised by transverse scanning moving the probe along the axis of the limb.

1.37 **Air plethysmography (APG)**

APG has been used in the early 1960s to study relative volume changes in the lower limb in response to postural alterations and muscular exercise (Allan 1964). Recent interest in reconstructive surgery of the deep veins has created a need for the noninvasive quantitative assessment of venous reflux and calf muscle pump ejection.

By calibrating air-plethysmography it has become possible to detect whole leg volume changes as a result of exercise in absolute (ml) as well as relative units, overcoming the limitations of segmental devices and water plethysmography (Christopoulos et al 1987). Segmental volume changes measured with straingauge do not necessarily represent changes in the whole leg. In contrast APG can provide information on the whole leg. In addition, gravitationally induced tissue shifts in response to postural changes that interfere with segmental devices on the calf are less likely to occur with APG because the latter includes all the tissues between the knee and ankle.

The APG consists of a 35cm long tubular polyvinyl

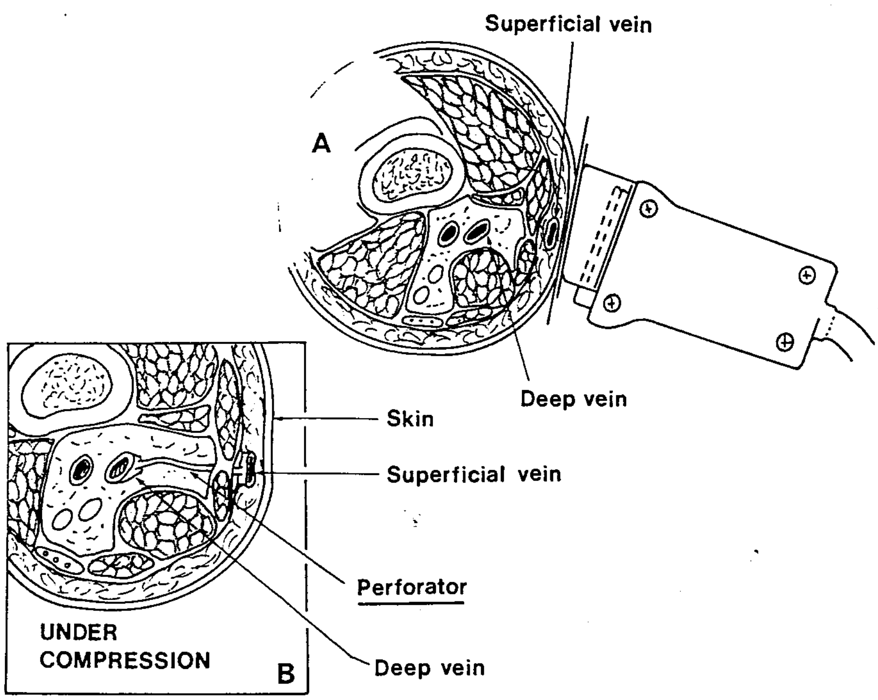


Figure 1.6: With colour duplex the evaluation of incompetent perforators is fast and reliable. The deep and superficial veins are identified and the communicating perforator vein is detected and localised by transverse scanning moving the probe along the axis of the limb.

chloride air-chamber (capacity 5 litres) that surrounds the whole leg from knee to ankle (Figure 1.7). This is inflated to 6 mmHg and connected to a pressure transducer, amplifier and recorder. The pressure of 6 mmHg is the lowest that ensures good contact between the air-chamber and the leg. Calibration is performed by depression of the plunger of the syringe, compressing the air in the system, reducing its volume by 100 ml and observing the corresponding pressure change. The plunger is then pulled back to its original position when the pressure in the air-chamber returns to 6 mmHg. Initially, the patient is in the supine position with the leg elevated (45 degrees) to empty the veins, and the heel resting on a support. After a stable baseline recording is obtained, the subject is asked to stand keeping the weight on the opposite leg, holding onto an orthopaedic frame.

An increase in the leg venous volume is observed as a result of the venous filling (Figure 1.8). This is 100-150 ml in normal limbs and 100-350 ml in limbs with chronic venous insufficiency. The venous filling index (VFI) is defined as the ratio of 90% of the venous volume divided by the time taken to achieve 90% of filling (VFI=90% VV/VFT90). This is a measure of the average filling rate and is expressed in millilitres per second. The range of VFI in normal limbs, limbs with superficial venous incompetence and limbs with deep venous disease is different. A VFI of 2 ml/sec or less indicates absence of significant venous reflux and that the veins are filling slowly from the arterial circulation.

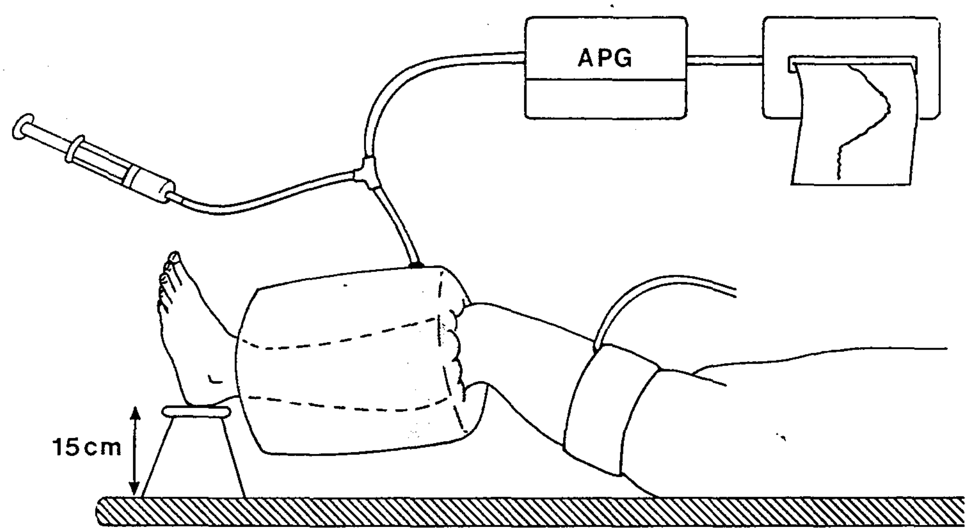


Figure 1.7: APG consists of a 35 cm long tubular polyvinyl chloride air-chamber (capacity 5 litres) that surrounds the whole leg from knee to ankle. The chamber is inflated to 6 mmHg and connected to a pressure transducer, amplifier and recorder.

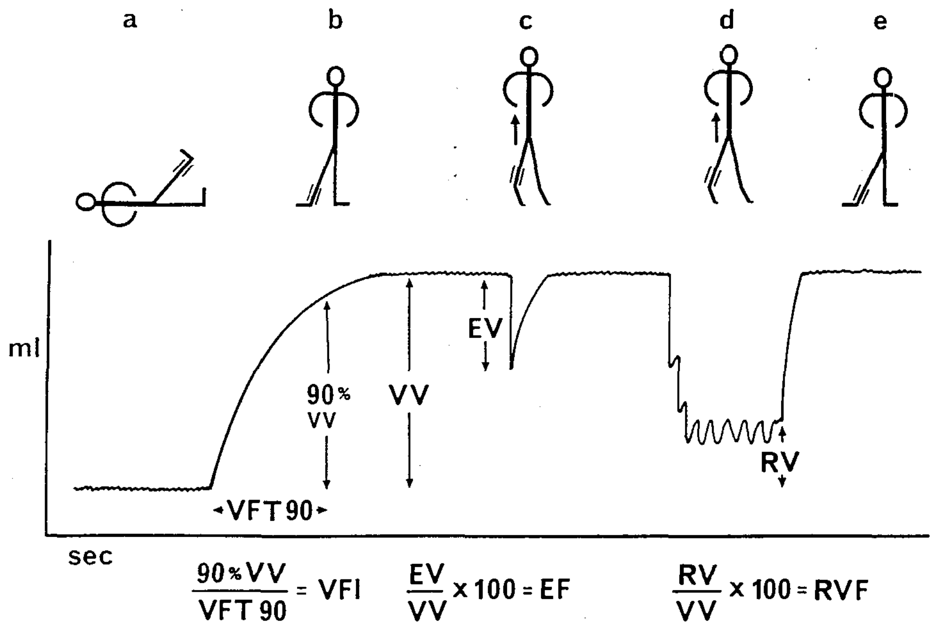


Figure 1.8: An increase in the leg venous volume is observed as a result of the venous filling. This is 100-150 ml in normal limbs and 100-350 ml in limbs with chronic venous insufficiency. The venous filling index (VFI) is defined as the ratio of 90% of the venous volume divided by the time taken to achieve 90% of filling (VFI=90% VV/VFT90). This is a measure of the average filling rate and is expressed in millilitres per second.

A VFI greater than 7 ml/sec is associated with a high incidence of skin changes, chronic swelling and ulceration irrespective of whether the reflux is in the superficial venous system only or in the deep system. The application of a narrow pneumatic tourniquet (2.5 cm wide) which occludes the superficial veins at the knee (long and short saphenous) will reduce VFI to less than 5 ml/sec in limbs with primary varicose veins and competent popliteal valves but not in limbs with incompetent popliteal valves on duplex scan (Christopoulos et al 1988). Also, measurements before and after conventional surgery for superficial venous incompetence have shown that APG is an effective method for demonstrating the abolition of venous reflux.

By asking the patient to do one tiptoe movement with the weight on both legs and then return to the initial position the ejected volume (EV) (figure I.8) and ejection fraction (EF = (EV/VV)x100) as a result of calf muscle contraction are measured. The mean and range of VFI, EF and RVF in normal limbs, limbs with primary varicose veins and limbs with deep venous disease are shown in Figure 1.9. By asking the patient to do ten tiptoe movements one can measure the residual volume (RV) and calculate the residual volume fraction (RFV=(RV/VV)x100) (Figure 1.8).

It has been demonstrated that there is a good linear correlation between RVF and AVP namely the ambulatory venous pressure at the end of exercise (Christopoulos et al 1988). This is not surprising because, at any time, it is the amount of blood in the veins that determines the venous pressure. Table 1.5 shows the values of the most relevant

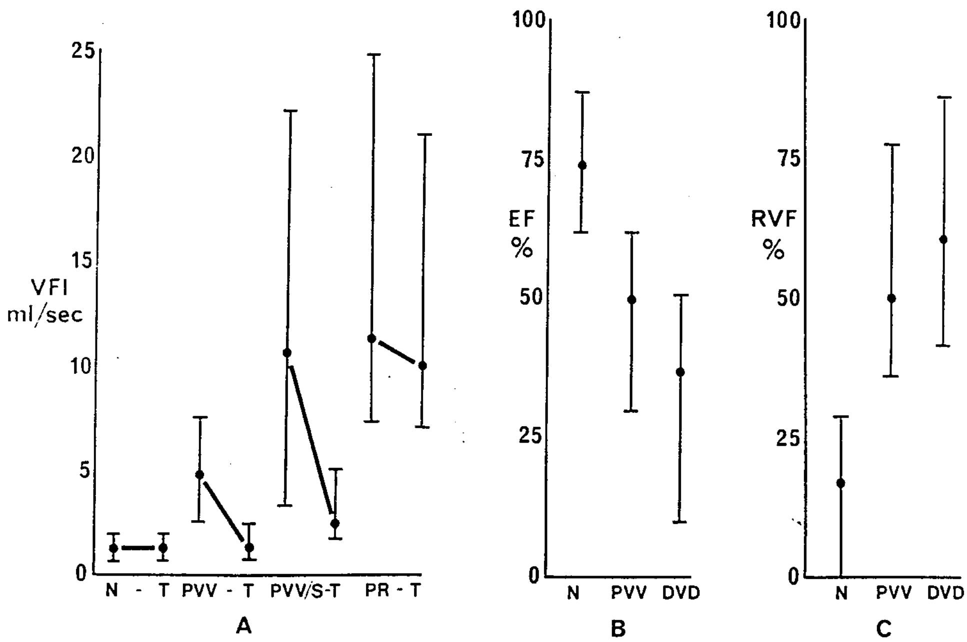


Figure 1.9: the range of the venous filling index (VFI), ejection fraction (EF =(EV/VV)x100) and residual volume fraction (RVF) in normal limbs, limbs with primary varicose veins and limbs with deep venous disease is shown in this figure. T indicates repetition of the measurements with a narrow tourniquet at the knee to control reflux in the superficial veins.

Table 1.5

Air plethysmography

	Coefficient of Variation	Normal Limbs	Primary DVD	VVs
Direct Measurements				
Functional venous volume (VV) (increase in leg volume on standing) mL	10.8-12.5	100-150	100-350	70-320
Venous filling time (VFT90) (time taken to reach 90% of VV) sec	8.0-11.5	70-170	5- 70	5-20
Ejected volume (EJ) (decrease in leg volume as a result of one tiptoe) mL	6.7-9.4	60-150	50-180	8-140
Residual volume (RV) (volume of blood left in veins after ten tiptoes) mL	6.2-12	2-45	50-150	60-200
Derived Measurements				
Venous filling index (VFI) (Average filling rate: 90% VF/VFT90) mL/sec	5.3-8	0.5-1.7	2-25	7-30
Ejection fraction (EF=[EV/VV] x 100) %	2.9-9.5	60-90	25-70	20-50
Residual volume fraction (RVF = [RV/VV] x 100) %	4.3-8.2	2-35	25-80	30-100

VV's = Varicose veins DVD = Deep venous disease

APG parameters in normal limbs, the values in primary venous disease and the coefficient of variation of the different measurements. It has also been reported that the incidence of venous ulceration increases in relation to the residual volume fraction (Christopoulos et al, 1990).

The above volume measurements have been used to study the efficacy of the calf muscle pump and quantitatively assess the effect of therapeutic measures such as compression and surgical intervention. They should be used not only to assess the effects of deep venous reconstruction, but also to select the patients who are most suitable for such reconstruction.

1.38 Measurement of outflow obstruction

Outflow obstruction may be suspected because swelling and increased limb size are the predominant signs which could be associated with a history of deep venous thrombosis and the finding of prominent collateral venous channels in the groin above the pubis or the anterior abdominal wall.

It should always be suspected and investigated for, in patients with post-thrombotic limbs. Simple leg elevation with the patient supine can provide an estimate of the resting venous pressure by observing the height (in cm) of the heel from the heart level at which the prominent veins collapse.

1.381 Doppler ultrasound

Doppler ultrasound examination with the legs horizontal and the trunk of the patient semisupine (45°) as for deep venous thrombosis may indicate occlusion of the deep veins by the absence of flow which is phasic with respiration, absence of augmented flow on calf compression or the presence of suprapubic collateral flow, which is abolished by manual compression of the femoral vein in the opposite groin.

1.382 Maximum Venous Outflow

Confirmation of deep venous obstruction and the extent of collateral circulation is obtained by venography. However, the functional severity of the obstruction is difficult to assess from the venogram. Quantitative measurements (maximum venous outflow - MVO), can be obtained using straingauge plethysmography or air plethysmography; also by measuring foot to arm pressure differential. For the first two methods a thigh cuff is inflated with the limb elevated 10° and the veins are allowed to fill. The cuff is suddenly deflated and measurements are made from the outflow curve. Using a straingauge and the 1 second outflow method normal limbs have an MVO greater than 45 ml/100ml/min. Measurements of MVO with straingauge plethysmography are useful not only in determining the severity of outflow obstruction, but also in following-up the development of collateral circulation (Belcaro et al 1992f). In approximately 90% of patients who have an abnormally low MVO soon after deep venous thrombosis, values close to the lower limit of normal will be found one year later presumably because of recanalisation and development of collateral channels. However, in 10% of patients the MVO will remain grossly abnormal and it is these patients who are severely incapacitated often from persisting venous claudication (Table 1.6).

More recently (Christopoulos et al, 1991) the one second venous outflow has been measured using air-plethysmography. It has been found that this is more than 40% of the venous volume in normal limbs. It is 30-40% in limbs with mild to moderate obstruction and less than 30% in limbs with severe obstruction (Belcaro et al, 1992f).

1.383 Arm/Foot Pressure Differential

The arm/foot pressure differential has been used by Raju as another method of assessing the severity of outflow obstruction (Raju, 1986). This method consists of recording the venous pressure in the veins of the foot and hand simultaneously with the patient in the supine position at rest. The measurements are repeated after inducing reactive hyperaemia. In normal limbs the arm/foot pressure differential (P) is less than 5 mmHg. A rise of up to 6 mmHg is observed during reactive hyperaemia. Patients with venographic evidence of obstruction and P<5 mmHg at rest and an increment of less than 6 mmHg during reactive hyperaemia are considered to be fully compensated (Grade I). Using such measurements Raju has classified limbs with outflow obstruction into four grades (Table 1.7).

In conclusion the measurements of MVO or arm/foot pressure differential can provide a quantitative indication of the severity of outflow obstruction. Their main applications are in the objective study of the natural history and efficacy of surgical reconstructive procedures that improve outflow.

Table 1.6

Maximum Venous Outflow (MVO)

OBSTRUCTION	NORMAL	MODERATE	SEVERE
MVO Straingauge (1 sec) (mL/100mL/min)	45	45-30	30
1 sec outflow fraction (OF) Air plethysmography (% of VV)	38	38-30	30

VV = venous volume

Table 1.7

Arm-Foot Differential (P mmHg) in limbs with outflow obstruction (10)

GRADE	PRESSURE AT REST	PRESSURE INCREMENT DURING HYPERAEMIA
I: Fully compensated	< 5	< 6
II. Partially compensated	< 5	< 6
III: Partially decompensated	> 5	> 6 (often 10-15)
IV: Fully decompensated	>>>5 (often 15-20)	No further increase)

1.4 THE PLACE OF THE VARIOUS TESTS IN EVALUATING CHRONIC VENOUS HYPERTENSION

In the evaluation of patients with chronic venous problems it is important to determine the presence or absence of outflow obstruction and/or reflux in the venous system in the first instance. The history and clinical examination will indicate the patient's problems and clinical picture. The use of Doppler ultrasound in out-patients by the physician will confirm the presence of obstruction and, or reflux indicating its sites.

The most important obstruction may be femoro-popliteal or iliofemoral and the most important reflux is generally at the saphenofemoral junction, saphenopopliteal junction, at the level of thigh incompetent perforating veins or at the popliteal vein in most (90%) patients.

The remaining 10% includes complicated cases many of which had a previous operation on their veins or in which the results of Doppler ultrasound are not clear. Also venography is used in a small group in which incompetent calf perforating veins are suspected and their presence needs to be confirmed.

In the majority of these patients MVO measurements (straingauge) and air plethysmography repeated with a tourniquet at different levels will provide the answer.

1.41 Localisation of obstruction and/or reflux

Accurate localisation of venous obstruction because of planned surgery will require a venogram although Duplex scanning is proving equally helpful particularly for lesions distal to the common femoral vein. Until recently, accurate localisation of the sites of deep to superficial reflux (saphenofemoral, saphenopopliteal, incompetent thigh perforating veins, calf perforating veins) and reflux in the deep veins (femoral, popliteal, tibial) could only be demonstrated by venography. Duplex scanning is proving to be a simpler and functionally more accurate test so that ascending functional or descending venography is now rarely performed. As far as localisation of the site of incompetent perforating veins and the junction of the short saphenous with the popliteal vein, Duplex scanning is the method of choice.

The above tests diagnose and quantify obstruction and, or reflux and therefore they are very often adequate for the rational planning of management.

1.42 <u>Quantitative measurements of obstruction and reflux</u>

Quantitative measurements of outflow obstruction and, or reflux are needed for research purposes, particularly for the study of the natural history of patients with different forms of chronic venous insufficiency and for the assessment of established and new methods of treatment. These quantitative measurements have now opened new avenues leading to a better scientific basis for the management of patients.

Until recently, the measurement of ambulatory venous pressure had been the only quantitative test available. It was invasive, but it provided an indication of the severity of venous hypertension. It was a measure of the end-result of both outflow obstruction and reflux. However, the new tests can separate and dissect out the relative contribution of different abnormalities such as venous obstruction, reflux in the superficial and, or in the deep veins. Also, the function of the calf muscle pump and its role in causing or aggravating the problem can be quantitatively evaluated.

1.5 DYNAMIC METHODS USED TO ASSESS THE MICROCIRCULATION

1.51 **Laser Doppler flowmetry: principles of technology and clinical applications**

1.511 Introduction

Noninvasive optical methods to evaluate skin flow have been used for many years. The most used method is possibly photoplethysmography which records variations in the blood volume of the skin.

With the exception of time dependent parameters (e.g., refilling time, pulse rate) only qualitative data may be obtained. Quantitative data are difficult to obtain and standardise. Fluctuations in venous volume, i.e., due to postural changes or motion artefacts alter the signal and make the interpretation of skin flow variations difficult. Also, attempts to calibrate it by several teams have not been successful. As a result the use of PPG has been mainly limited to complementary diagnostic methods applied to evaluate some aspects of vascular disease i.e. skin flow pulsatility in Raynaud's disease or the refilling time after venous emptying following an exercise test.

Furthermore the light beam in PPG systems penetrates the skin for a variable depth (2-6 mm) including different skin circulatory elements - i.e. thermoregulatory capillary loops and more superficial nutritional capillaries - without separating their flow.

Laser Doppler flowmetry (LDF), a more sophisticated method, has been developed in the last 15 years from scientific wizardry to a research tool and in the last few years to a clinical diagnostic technique that can assess tissue viability and perfusion (Almond et al, 1985; Boggett et al, 1985; Almond et al, 1988; Almond, 1994). The fundamental principle of LDF as applied to the measurements of tissue perfusion have been described in detail in several publications (Bonner and Nossal, 1981; Engelhart and Kristensen, 1983; Boggett et al, 1985; Borgos, 1990; Belcaro et al, 1994).

The measurement of blood velocity in single, large vessels and the measurement of skin perfusion can be both obtained using LDF. However the technology required for each of these two applications is completely different. In this chapter we refer only to the measurement of microvascular perfusion.

1.512 <u>Theory of laser Doppler flowmetry</u>

A detailed technical description of the instrumentation is beyond the aims of this chapter. However some simple concepts are needed to understand the method, its applications and possible limitations. Most commercially available laser Doppler instruments utilise helium-neon gas or gallium aluminium arsenide elements to produce a weak laser beam with low tissue penetration. This type of laser light does not alter the tissues under evaluation or produce increase in tissue temperature. Most tissues (i.e. skin) are relatively opaque as they contain particles which refract (scatter) light in various and random directions.

Excluding blood within large vessels, blood itself constitutes only a small fraction of tissue volume so that most light scattering is due to small particles and to stationary tissue elements. Only moving parts in the sample volume (blood cells) will cause a Doppler shift in the light frequency.

The scattering angles and red cell velocities are variable and they can be determined only in a statistical sense (Weis et al, 1989).

Therefore the LDF signal is a stochastic representation of the number of cells in the sample volume multiplied by their velocities. The technology of LDF using coherent laser light overcomes some problems observed with other optical and non-optical methods used to record skin blood perfusion. The helium-neon laser which emits a red light and is used in many LDF instruments detects very small changes in the wavelength of the laser light as a result of red blood cell movements (Doppler effect), well below the resolution of the optical spectroscope (Almond et al, 1985; Almond, 1994).

The frequency distribution of the signal is defined by computerised spectral analysis of the output that produces a power spectrum with a separation between the noise and the true signal due to blood cell motion. Some components of the

LDF signal are due to external biological or instrumental elements (e.g., vibration) and some to internal (mainly electronic noise) factors. The LDF photodetector signal contains all the Doppler frequencies arising from the laser interaction with moving particles in the tissue and static components.

An elaborate electronic processing and filtering system is needed to transform the LDF signal into a physiologically reproducible, meaningful and useful parameter so that the LDF output varies linearly with the blood flow within the sample volume.

Considering the LDF output, as seen above, the total power in the signal depends on the number of the moving particles producing a laser Doppler shift of frequency. Therefore a laser Doppler flowmeter must be capable of measuring the mean frequency shift in the signal. Some LDF flowmeters digitise the signal and analyse it with a fast Fourier transform from which the mean frequency shift can be measured. Other systems employ analogue signal processing circuitry.

Electronic components are needed to normalise the signal and to compensate for noise. In most instruments the noise level remains relatively stable and theoretically it can be extracted from the LDF output by subtracting a constant offset. Different technical solutions have been applied in low noise lasers or laser diodes (Nilsson et al, 1980; Bonner and Nossal, 1981; Johnson et al, 1984; Boggett et al, 1985).

This simple and brief preliminary outline of laser Doppler flowmetry technology may be useful to comprehend the basic concepts. More specific technical information and details on the structure of laser Doppler flowmeters can be found in more specialised reports (Bonner and Nossal, 1981; Almond et al, 1985; Almond, 1994).

1.513 **Calibration**

Many studies have demonstrated a good correlation between LDF measurements and other methods of blood flow measurements (Almond, 1994). However some studies have shown a poor correlation between LDF and isotopic methods (i.e. xenon clearance) (Borgos, 1990) in the presence of arteriovenous shunts such as in skin of the fingers (Engelhart and Kristensen, 1983) or when measurements are made in the bone (Hellem, 1983).

The major problem at this stage is that there is no gold standard, particularly in the skin, against which LDF can be compared. Because each type of LDF instrument gives its own values and it is difficult to compare results obtained with one instrument from one manufacturer to results obtained from another. Therefore relative changes (i.e., before and after treatment, after thermal or postural changes or after arterial occlusion to cause reactive hyperaemia) are clinically more useful than absolute flux measurements. A universal calibration does not appear possible at the moment as in different tissues, several factors (i.e. light penetration, diffusion and reflection and characteristics of the used technology) make the calibration relevant only to that single tissue.

Despite these limitations LDF has many positive aspects which have progressively enlarged its fields of application from experimental and clinical physiology to clinical practice.

Instrumental baseline and the biological zero. The zero flux baseline is obtained by positioning the probe against a white surface. An "instrumental zero" is different from the "biological zero", which can be obtained from the skin (Fagrell, 1994; Tonnesen, 1993) by complete occlusion of the arterial supply.

When blood flow in the skin is completely abolished, the LDF signal decreases to 20-50% of the tissue flux measurement (Figure 1.10). The relative ratio between the normal resting flux state and the occlusion state values are variable from region to region and also from organ to organ. It has been observed that in a fingertip the ratio is 5-7% and that in closely related areas the biological zero is very similar (Wardell et al, 1991) (Figure 1.11).

The origin of the signal that is responsible for the biological zero is not clearly understood. Studies on excised tissue have shown an elevated baseline from the instrumental zero even several hours after excision. However, the elevated biological zero disappeared after a few days. Freezing tissues abolishes the biological zero baseline lowering the values to a level very similar to the instrumental baseline (Belcaro et al, 1994).

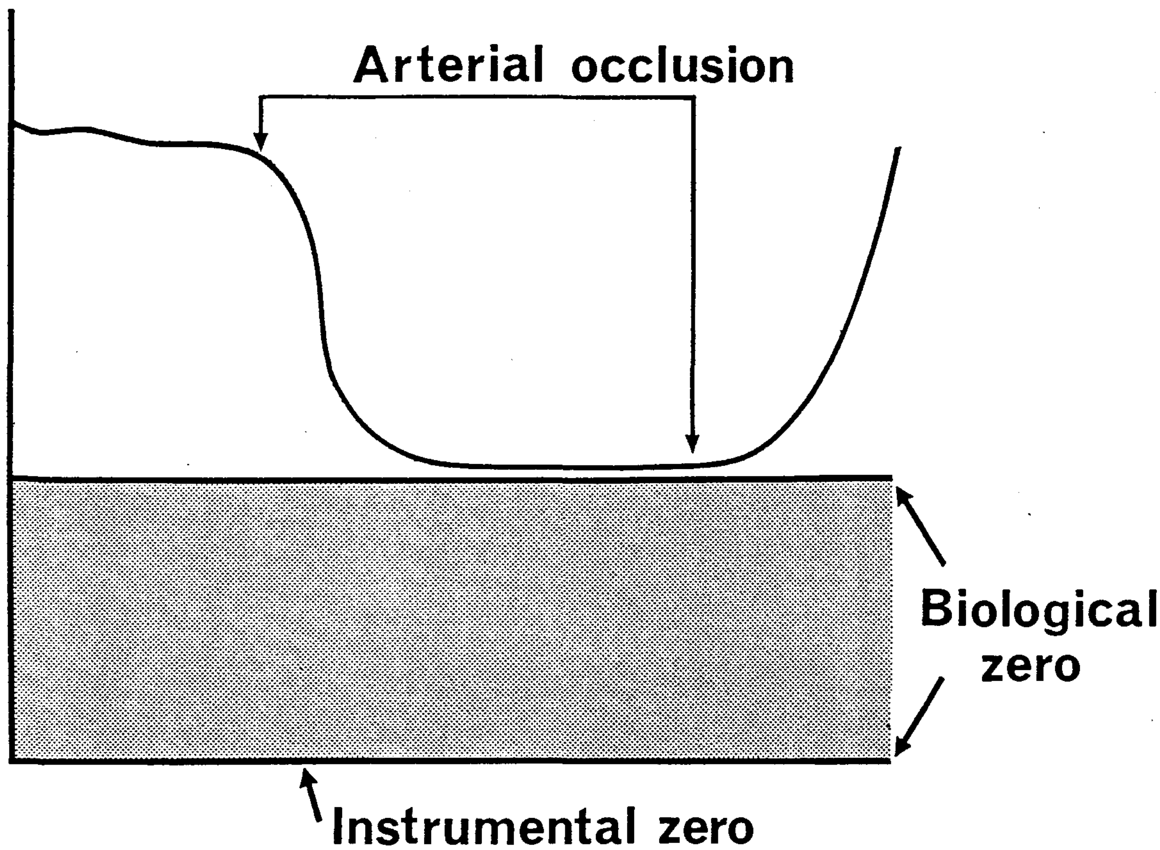


Figure 1.10

The instrumental baseline and the biological zero. The flux zero baseline is obtained by positioning the probe against a white surface. An "instrumental zero" is different from the "biological zero", which can be obtained from the skin by complete occlusion of the arterial supply. When blood flow in the skin is completely abolished, the LDF signal decreases to 20-50% of the tissue flux measurement.

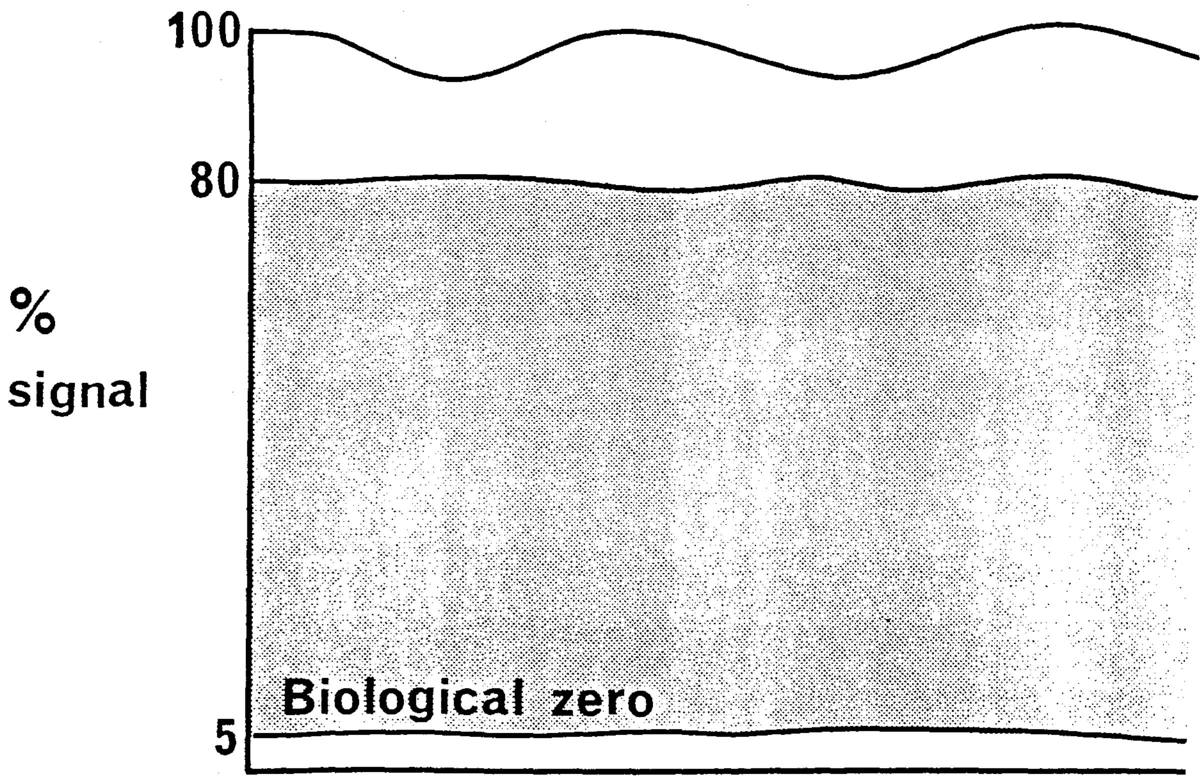


Figure 1.11: The ratio between the normal resting flux state and the occlusion state values are variable from region to region and also from organ to organ. In the normal fingertip the ratio is 5-7%; in closely related areas the biological zero is very similar. The scale (0-100) indicate the total LDF signal output.

In situations of inflammation of human skin it has been shown that the biological zero is increased up to approximately 50-70% (Fagrell, 1990). The actual clinical implications of these findings are still unclear and further studies in this field are essential. However, in the practical clinical evaluation of limbs, particularly in low perfusion states, it is recommended that each measurement should be associated with an estimation of the instrument zero baseline and of the biological zero.

Depth of measurements and volume in the skin. The sensitivity of the reflected LDF measurements decreases exponentially with the distance from the probe (Weis et al, 1989). It has been estimated that the theoretical average depth of sampling in the skin is 0.14 mm but in artificial models it has been estimated that it is 1.5 mm (Fagrell, 1993). However, these values have little importance in clinical applications. There is also evidence that in intestinal models the measuring depth can be greater than 6mm and that by placing a mirror on the opposite side of the intestinal wall the signal output can be increased from 85 to 100% (Almond et al, 1988). The above observations indicate that the measuring depth is not a fixed value for the skin but most probably a continuous variable as in other tissues. As reported by Fagrell (1990) the microcirculation - particularly skin microcirculation - can be considered to consist of a more superficial, thin layer supplied by nutritional capillaries and in a deeper, thicker layer with thermoregulatory vessels.

Figure 1.12 shows the localisation of the nutritional

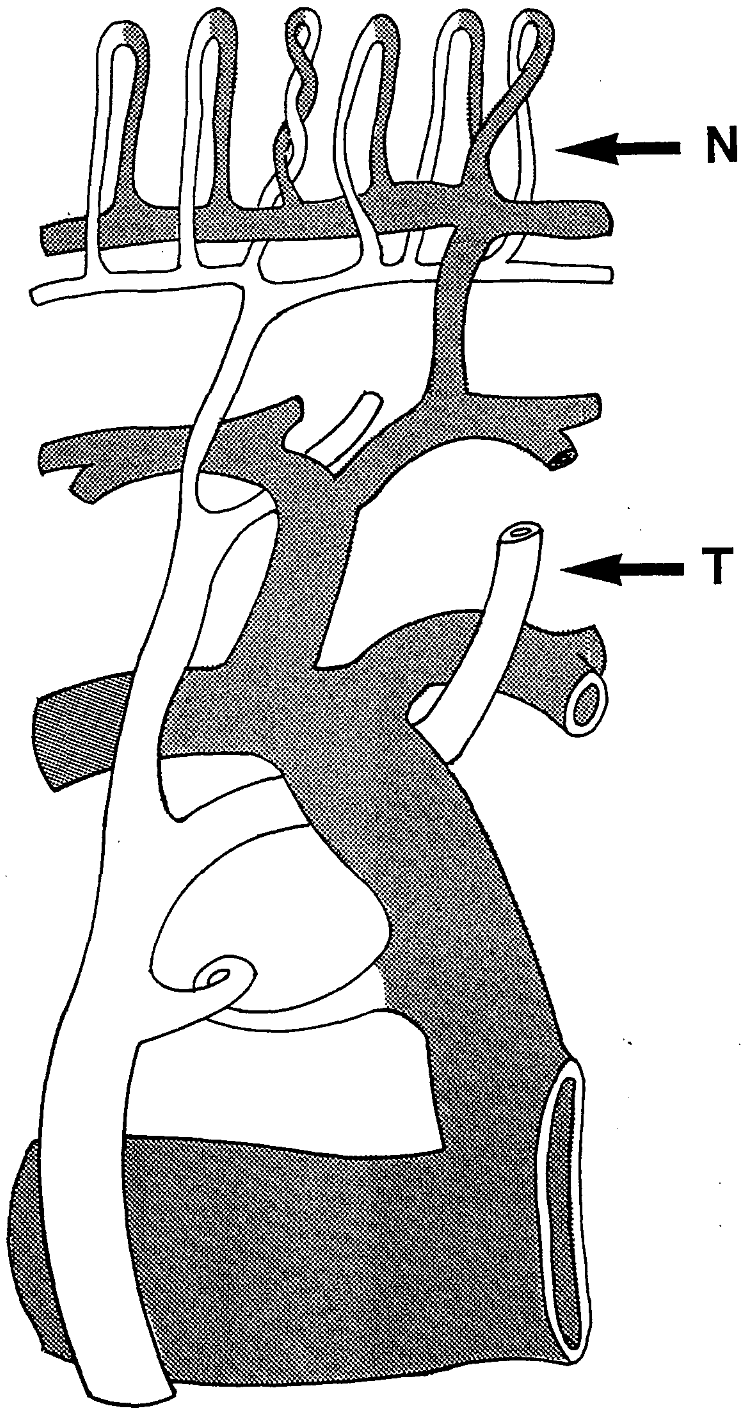


Figure 1.12: The nutritional capillaries (N) are the most superficial ones (0.1-0.05 mm from the skin surface) and in normal conditions only a very small amount of the total skin blood flow (5-10%) passes through them. Laser Doppler flux measurements include flux components from the most superficial and also from the deeper, non-nutritional, mainly thermoregulatory layers (T).

capillaries (0.1-0.05 mm from the skin surface).

In normal conditions only a very small amount of the total skin blood flow (5-10%) passes through the nutritional capillaries. At least theoretically (Belcaro et al, 1994) it is possible to (Belcaro et al, 1995) measure the superficial nutritional flux using a polycarbonate plastic spacer applied between the probe and the skin surface (Figure 1.13). The polycarbonate spacers have the same optical density of the skin and may contribute to isolate the most superficial nutritional flux from the whole flux in the capillary layer and subpapillary plexus. However only a limited amount of information is so far available and the method has still to be clearly defined.

It is also important when considering and analysing the laser Doppler waveform (Figure 1.14) to know that the capillary nutritional flux is represented by about 10% of the upper part of the tracings while the subpapillary flow constitutes about 90% of the width of the tracings. In the subpapillary, mostly thermoregulatory bed (0.05-2.0 mm in depth) the most common (95%) vessels are venules a small portion being arterioles.

In this bed at least 95% of skin blood flow can be responsible for the LDF output while in the nutritional bed only a small percentage of flow (5-10%) contributes to the global output.

Therefore LDF measurements in the skin - measuring within 1-2 mm of skin depth - may record a signal in which the

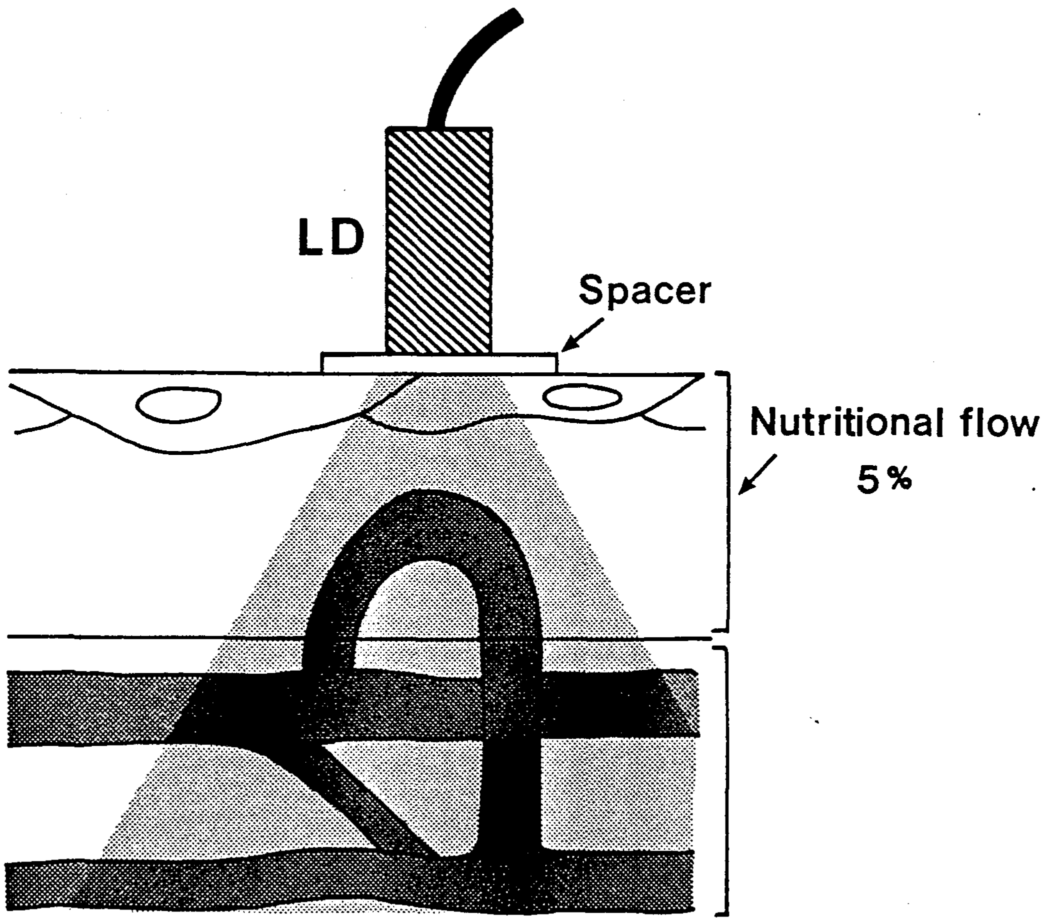


Figure 1.13: Theoretically it is possible to measure the superficial nutritional flux using a polycarbonate plastic spacer between the probe and the skin. The polycarbonate spacers have the same optical density of the skin and may contribute to isolate the most superficial nutritional flux from the whole flux in the capillary layers and subpapillary plexus.

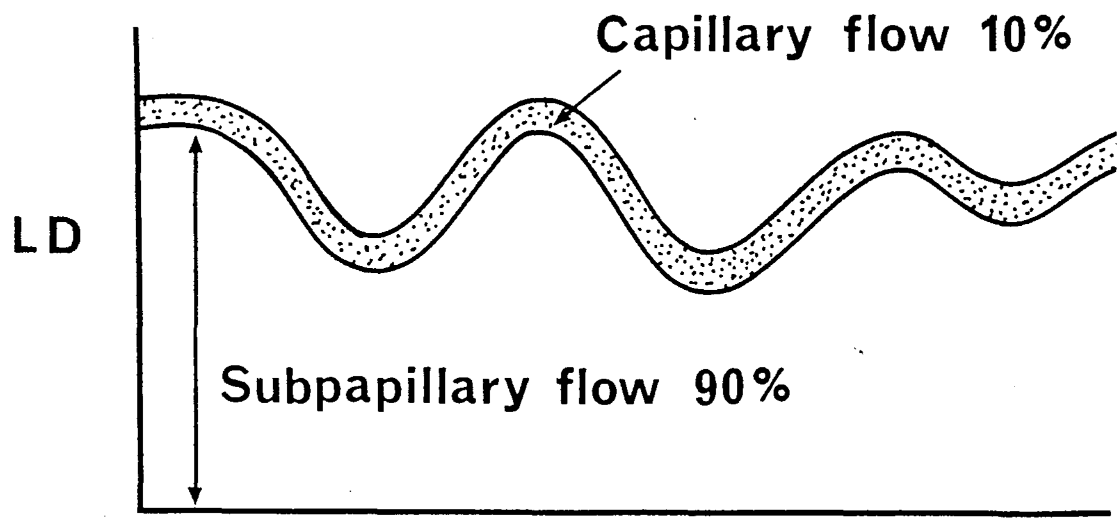


Figure 1.14: In laser Doppler waveforms the capillary nutritional flux is represented by about 10% of the upper part of the tracings and the subpapillary flow constitutes about 90% of the width of the tracing.

thermoregulatory flow component is predominant and the nutritional flow a small component. New microprobes may reduce the measuring depth and selectively evaluate the most important superficial nutritional capillaries but so far clinically relevant data are not available.

Vasomotion. As LDF measures flux continuously, flux motion can also be easily evaluated. During LDF monitoring in normal conditions the skin vessels in the microcirculation fill up with blood rhythmically as a consequence of pressure and flow changes due to cardiac action respiration and vasomotion. The LDF output therefore shows a continuous variation.

Flux motion patterns are often markedly altered in patients with peripheral vascular disease who frequently present a high frequency flux motion component. The prevalence of high frequency motion waves is significantly increased in low perfusion states and it is proportionally more evident with increased levels of ischaemia.

The presence of high frequency flux motion waves at the forefoot has been evaluated by Hoffman et al (1994) in patients with peripheral limb ischaemia before and after percutaneous transluminal angioplasty. In successfully treated patients a significant decrease in high frequency flux waves was observed after angioplasty. However the persistence of such waves after angioplasty was associated with severe persisting chronic ischaemia.

Different patterns of vasomotor waves were detected by Hoffman (Hoffman et al, 1994) in different conditions of perfusion. Flux motion in normal individuals was characterised by low frequency and pulsatile flux waves.

Occasionally an additional high frequency wave component appeared in the recording. Flux motion patterns in ischaemia showed almost no pulsatile flux waves whereas high frequency waves were frequently observed in severe ischaemia. In the most severe cases of ischaemia no flux motion was observed. By contrast patients with intermittent claudication showed variable vasomotion patterns.

Therefore, using frequency analysis, it appears theoretically possible to qualitatively differentiate degrees of ischaemia. However, while there is little doubt that the alteration of vasomotion in low or high perfusion states is clinically relevant in indicating microcirculatory disturbances no definite, clinically practical application of the analysis of vasomotion has been found so far (Nicolaides and Belcaro, 1993).

1.514 LDF in clinical practice

LDF is noninvasive and does not interfere with the microcirculation when measuring local blood flow (Weis et al, 1989). LDF is also particularly useful as it produces a continuous output which can be used for prolonged monitoring of tissue viability - i.e. after plastic surgery or to record skin flow perfusion during sleep or in the newborn - a technique which is impossible to obtain with any other noninvasive technique. LDF monitoring is also relatively stable, reproducible and easy to learn and apply.

The technology of clinically usable LDF instrumentation is continuously improving. Multiple channel systems capable of measuring several distant tissue areas at the same time are now being produced by different manufacturers. LDF imagers (Wardell et al, 1991) and multi-wavelength systems (Almond, 1993) are currently being developed and may be used for more accurate and informative applications.

So far LDF has been extensively used for clinical and physiological evaluations and in humans. The technique is easy, noninvasive and has become very popular but at times the interpretation of clinical results has often been uncritical (Fagrell, 1994).

LDF, as seen above, measures minute particle motion. In living tissue such particles include mainly blood cells which will constitute the major component of the LDF output. However it is obvious that in situations of altered microcirculation or alteration of the blood hematocrit (i.e. in inflammation or leukaemia), the number of particles can change, producing a different output. Thus, the LDF signal can be considered a stochastic representation of the motion of all the particles in the sample volume (Stern, 1975; Weis et al, 1989), and although this measurement cannot be correctly defined as flow in certain tissues and under certain conditions, it is proportional to, and closely related to flow (Fagrell, 1994) as measured with isotopic methods.

Also, the precise sampling volume is not easy to define and this is another reason why true volume flow cannot be exactly measured (Fagrell, 1993).

Because of the above considerations, the LDF output signal recorded has been defined as flux, but possibly the most correct expression in clinical application should be "relative perfusion units "(Fagrell, 1993). Other terms used to express output signal such as Volt or mV, arbitrary units and other terms need to be unified. This appears to be difficult at the moment as there is no dialogue among manufacturers concerning a common LDF standard. However, when referring to flow in certain contexts and considering the above limitations, the term "flow" may be used to express a concept which is more familiar to most physicians.

1.515 Conclusions

The use of laser Doppler flowmetry is progressively increasing in the fields of physiology, pharmacology and in the practical daily clinical evaluation of vascular disease. The monitoring of the effects of treatment on the microcirculation appears to be one of the most promising fields of application of LDF.

The technical development of LDF combined with its extensive clinical research applications and coupled with frequency analysis systems will probably make this method one of the most interesting noninvasive techniques of investigation in vascular disease (Holloway and Watkins, 1977).

1.52 **Transcutaneous PO_2 and PCO_2 measurements**

Transcutaneous (Tc) PO_2, originally developed for intensive care and neonatal monitoring (Huch et al, 1983) has been also used in the past to study the microcirculation in venous hypertension comparing skin oxygen tension with capillary morphologic characteristics and density (Franzeck et al 1984).

$TcPO_2$ and PCO_2 measurements use a polarographic determination of molecular oxygen (and CO_2) diffusing to the skin surface, by means of a modified Clark-type electrode. Local hyperaemia is necessary to measure PO_2 on the skin surface. The obtained measurements have a close relationship to changes in capillary arterial PO_2 and PCO_2 (Franzeck et al, 1984). The hyperaemic condition is achieved by heating the silver/chloride anode of the electrode to 44-45°C. The resulting PO_2 and PCO_2 values are determined by the reduction in current at the platinum cathode which is proportional to the amount of oxygen diffusing to the skin surface.

It has been observed that in avascular skin areas (scar tissue, white atrophy) PO_2 is at very low levels (just above zero). In areas of hyperpigmentation, induration and hyperkeratosis PO_2 is significantly decreased (Franzeck et al 1984). More recently the combined evaluation of transcutaneous PO_2, PCO_2 and laser Doppler skin flux on intact skin indicated that in venous hypertension the increase in skin flux was associated with normal levels of PO_2 but with abnormally increased levels of PCO_2 (Belcaro et al 1988a).

The correlation between LDF parameters (RF and VAR) and transcutaneous (tc) PO_2-PCO_2 at the internal perimalleolar region in postphlebitic limbs were evaluated measuring skin flux and PO_2 and PCO_2 at the same site (Belcaro et al, 1988a). All measurements, performed in a temperature controlled room (22°C), after acclimatisation indicated an increase in flux related to an increase in PCO_2 and a decrease in PO_2. The flux and PCO_2 increase were inversely correlated to the decrease in VAR (Belcaro et al, 1988a).

1.53 **Straingauge plethysmography to assess capillary filtration**

In venous hypertension fluid filtration into the extracapillary compartment is increased (Michel, 1989). The increase in filtration observed in venous microangiopathy is associated with a decreased venoarteriolar response (Michel, 1989). The filtration from the intracapillary to the extracapillary compartment may be artificially induced by acute venous occlusion obtained with a cuff occluding the venous system (Brugmans et al, 1977). This situation reproduces venous hypertension. Straingauge plethysmography has been used for many years to assess volume changes in venous diseases (Hyman and Windsor, 1961). This method has also been used to study capillary filtration (Rotzocil et al, 1977). To quantify capillary filtration two methods based on straingauge plethsymography have been developed by our group - as the evolution of previously used methods (Belcaro et al, 1989b; Cesarone et al 1992; Belcaro et al 1990 a and b).

1.531 Venous occlusion plethysmography

A 23 cm wide cuff placed at the lower third of the thigh is inflated at 120 mmHg to occlude the venous system for 10 minutes (Figure 1. 15). The resulting curve (Figure 1.16) is divided in three parts: the first part (venous filling) is due to the venous volume increase following occlusion and

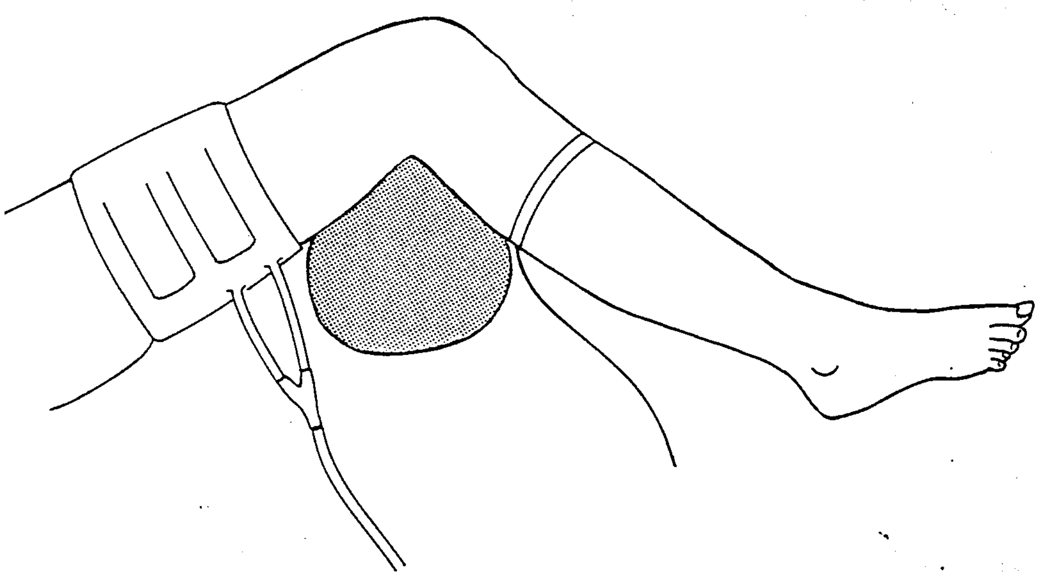


Figure 1.15: A 23 cm wide cuff is placed at the lower third of the thigh ed inflated to occlude the venous system (120 mmHg) for 10 minutes.

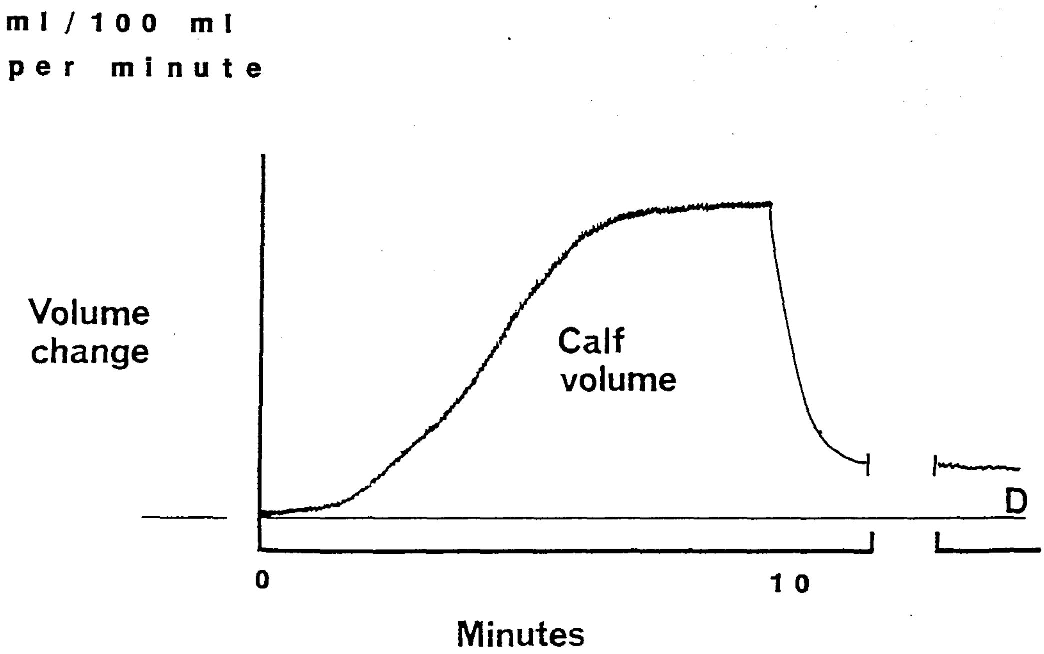


Figure 1.16: The volume increase curve can be theoretically divided in three parts: the first part is due to venous filling and the second part is due to venous stretching. The third part is characterised by a very slow, minimal volume increase and it is considered to be related to filtration of fluid from the capillary into the extracapillary compartment.

it is characterised by a fast increase in volume (time 0 to 3 minutes). The second part, defined as venous stretching, is due to venous distension and is characterised by a slower volume increase (4th to 6th minute). The third part of the curve can be defined as the capillary filtration phase and is characterised by a very slow, almost minimal volume increase, observed after the 7th minute. The curve in this phase reaches almost a plateau level with a very small increase in volume due to filtration of fluid into the extracapillary compartment. The assumption that this phase can be considered related to capillary filtration and permeability derives from some previous reports from different groups (Roztocil et al, 1977; Thulesius et al, 1973; Thulesius et al, 1973; Belcaro et al, 1989a).

In normal subjects capillary filtration calculated from the tangent to the part of the curve between the 7th to the 10th minute is on average 1.12 ml/min (SD 0.082) per 100 ml per minute (Belcaro et al, 1992a). It is possible to show by straingauge plethysmography in standard situations (constant temperature and humidity and well calibrated instruments) that after rapid deflation of the occlusion cuff the small increase in volume measured in comparison with the baseline value is proportional, if not equivalent, to the calculated capillary filtration. This difference from the baseline volume (D in Figure 1.16) is considered to be the residual increased volume due to the fluid filtrated from the intra- to the extravascular compartment. This small volume of fluid is proportional and equivalent to the filtration value obtained from the tangent to the curve (7th to 10th minute).

1.532 Rate of ankle swelling (RAS)

The second method to evaluate filtration is defined rate of ankle swelling. It analyses a normal physiological situation such as the filtration following the transition from the supine to the standing position. In this situation a curve very similar to the curve described before can be observed. After the first period of venous filling and the second period of venous stretching the filtration period between the 7th and 10th minute is indicated by a very slow volume curve increase with the curve approaching a plateau level in normal subjects. Different slopes are obtained in normal limbs and in patients with venous hypertension (Figure 1.17). This method is comparable to the previous one and proportionally similar results can be obtained with the two methods. However the second method does not require occlusion, is better tolerated and possibly more physiological (Belcaro et at 1989b).

1.54 Evaluation of local capillary filtration with the vacuum suction chamber

The filtration in the whole limb and in the distal segments of the lower limbs is possibly increased to a different extent in venous hypertension. Local capillary permeability in patients with lower limb oedema due to venous hypertension is particularly increased (Rotzocil et al, 1977; Belcaro et al, 1989b; Belcaro et al 1988b; Thulesius et al, 1973) at the perimalleolar region.

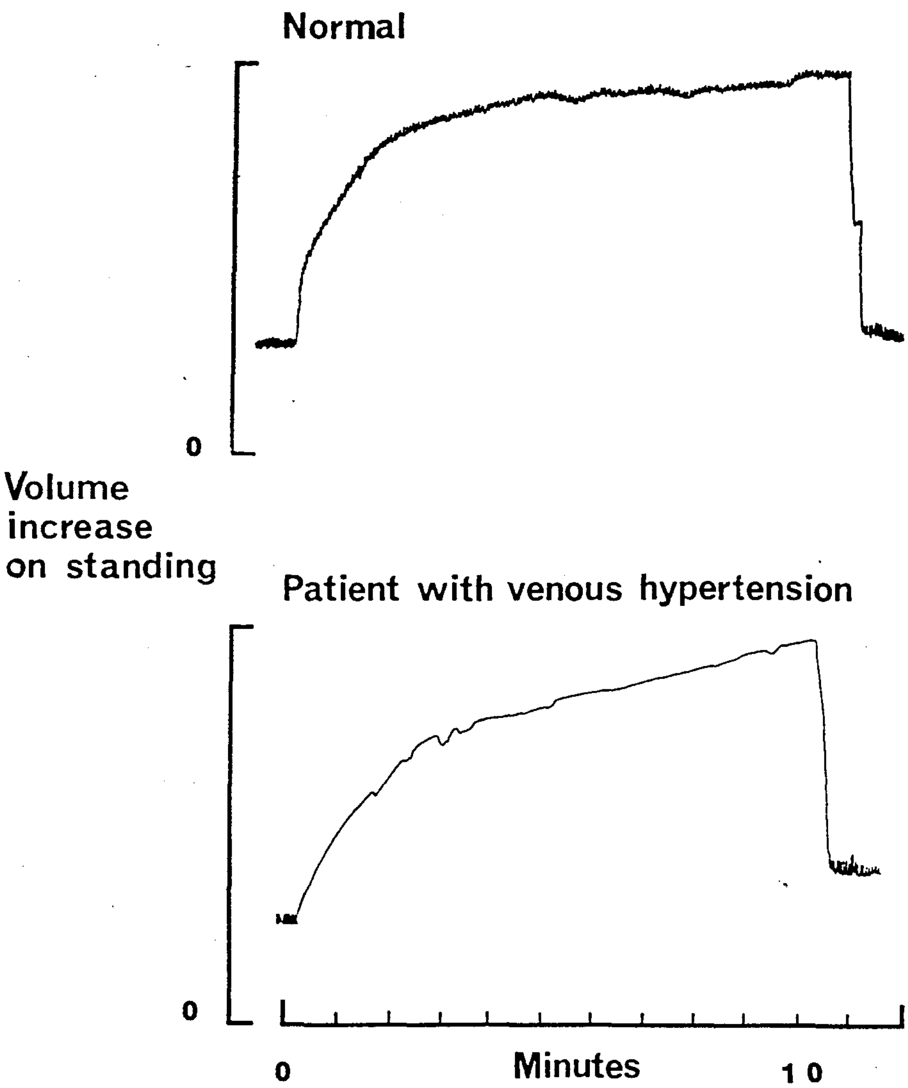


Figure 1.17: Example of curves obtained by measuring the the rate of ankle swelling (RAS). This method analyses a normal physiological response such as the passage from the supine to the standing position. In this situation a curve very similar to the curve described before can be observed. After the first period of venous filling and the second period of venous stretching the filtration period between the 7th and 10th minute is indicated by a very slow volume curve increase.

The increased filtration in association with increased skin flux measured by laser Doppler flowmetry (Belcaro et al, 1989a) can be evaluated with straingauge plethysmography (Cesarone et al, 1992) or with a vacuum suction chamber (VSC) (Belcaro and Rulo, 1988b; Belcaro et al, 1992b).

The VSC system is composed of a plastic chamber (2cm in diameter) applied to the skin. A decrease in air pressure is obtained for 10 minutes using a small air pump (Figure 1.18) producing a constant pressure decrease of 30 mmHg in the chamber. A weal (rounded flat-topped, pale-red, evanescent elevation in the skin which disappears in minutes or hours) is produced on the skin by the VSC (Figure 1.19A and B).

Weals are caused by localised oedema in the upper layer of the dermis due to filtration as a result of the negative pressure. The increase in capillary permeability increases the passage of fluid from the intravascular to the extravascular component of the extracellular fluid space. The localised oedema produced by the VSC disappears completely in normal skin, in standard environmental conditions, in less than 60 minutes (Belcaro and Rulo, 1988a; Belcaro et al 1992b). Previous work (Belcaro et al 1992b) comparing measurement of skin flux with laser Doppler flowmetry and the VSC disappearance time (Figure 1.20) has shown that there is a good correlation between the time of disappearance of the weal and ambulatory venous pressure measurements. Also when rate of ankle swelling and VSC disappearance time were evaluated in the same limbs the two measurements were well correlated (Laurora et al, 1992; Cesarone et al, 1992).

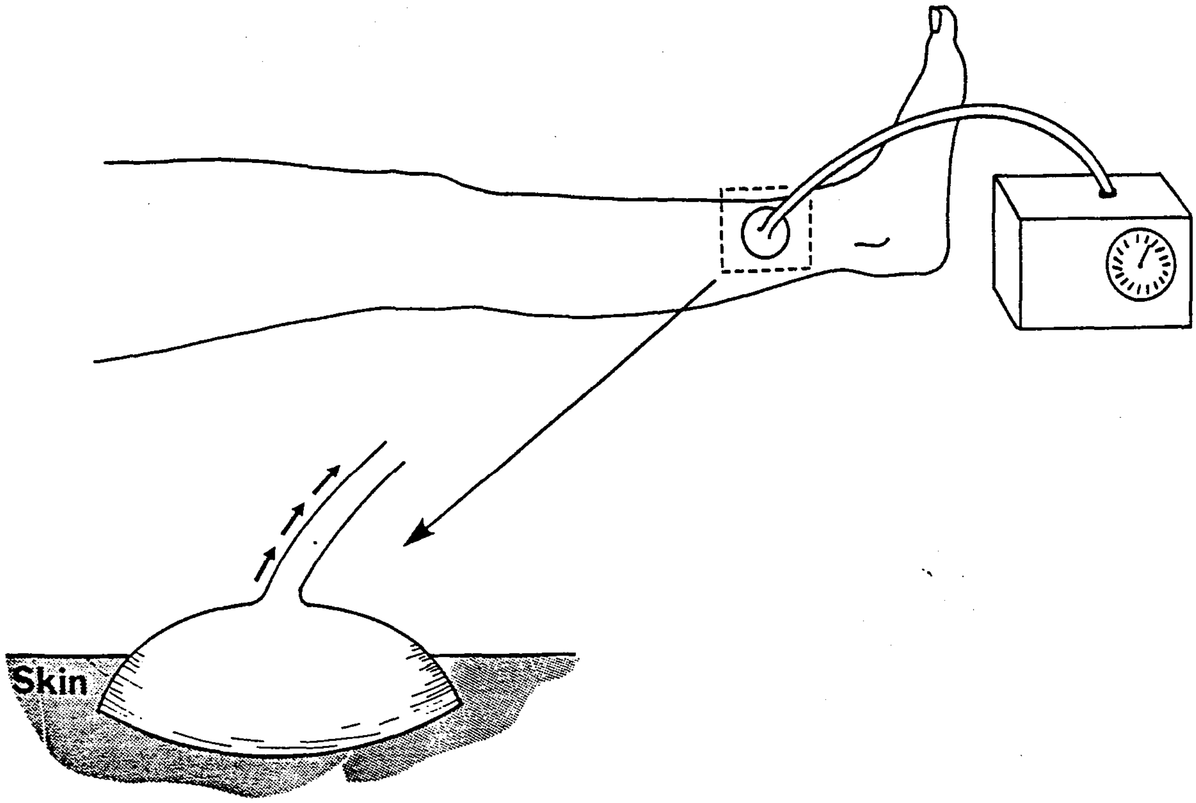
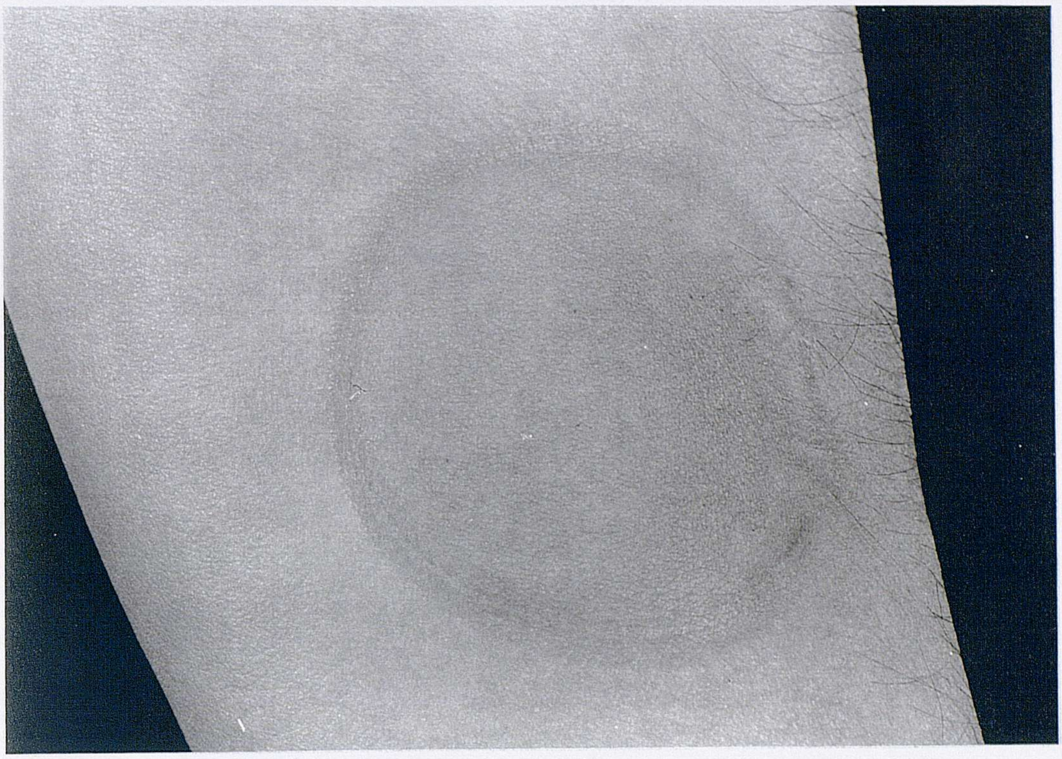


Figure 1.18: The vacuum suction chamber (VSC) is composed of a plastic chamber applied to the skin. A decrease in air pressure is obtained for 10 minutes using a small air pump, producing a constant pressure decrease of 30 mmHg in the chamber.



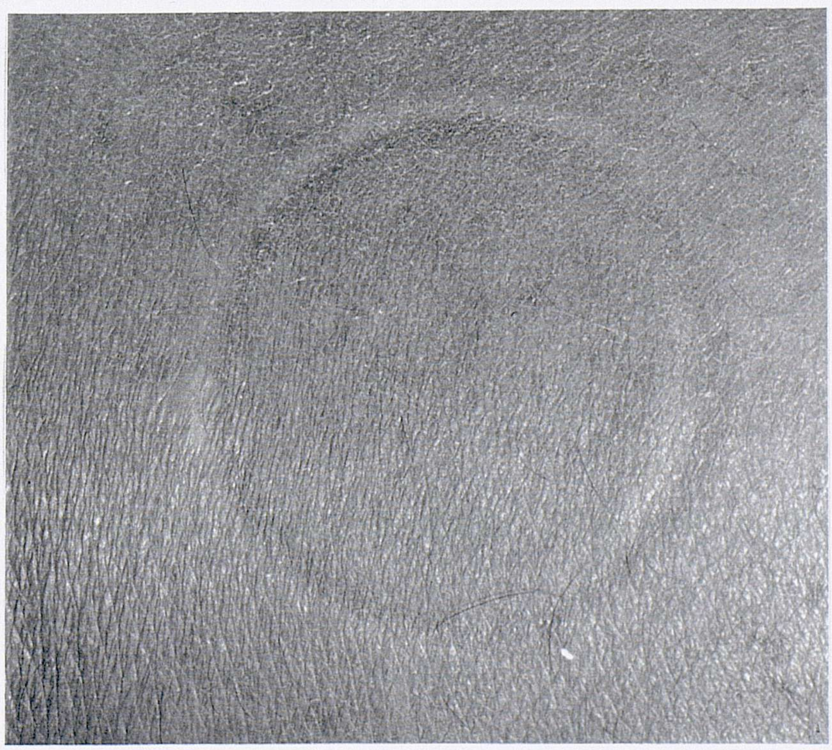


Figure 1.19: Weals produced by the VSC at the forearm (A) and at the internal perimalleolar region.(B)

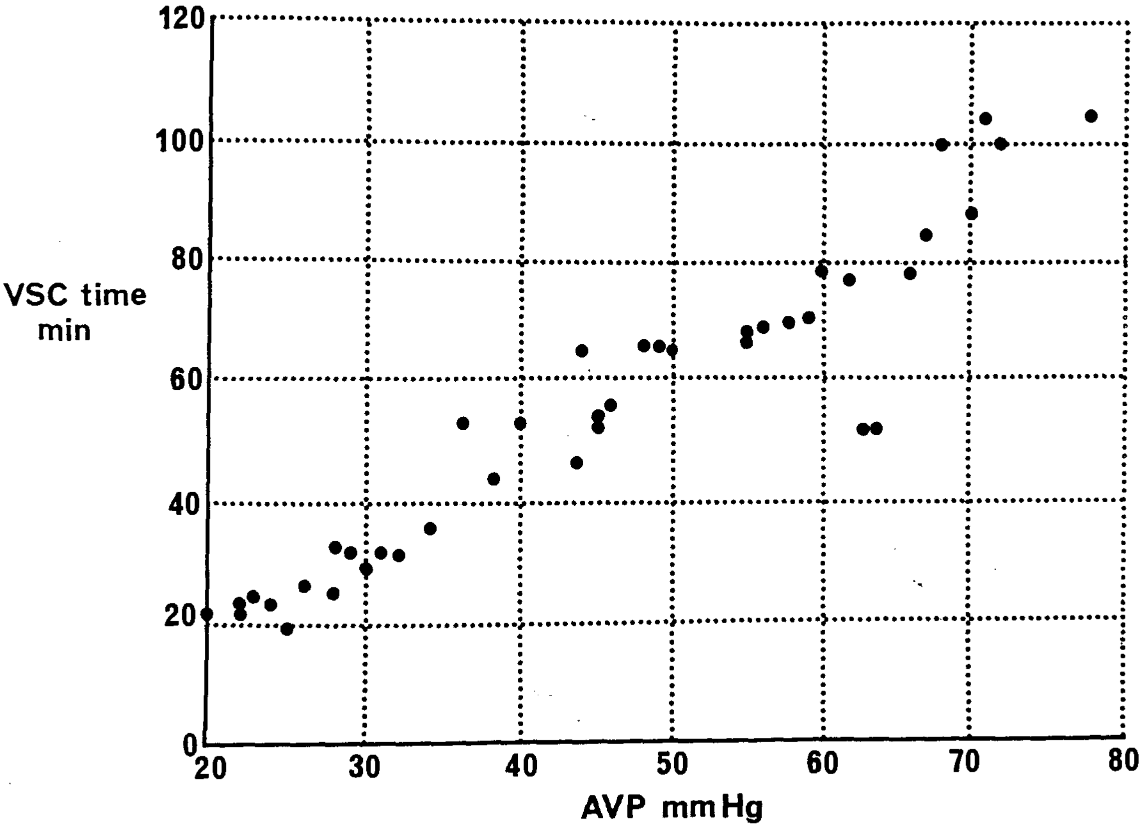


Figure 1.20: The correlation between the weal disappearance time and ambulatory venous pressure (Belcaro et al, 1992).

1.6 OTHER METHODS USED TO STUDY THE MICROCIRCULATION

1.61 **Skin flux and histology**

Skin histology in limbs with chronic venous hypertension studied by different authors has indicated the presence of fibrin deposits within the skin affected by chronic venous hypertension (Browse et al, 1977; Browse et al, 1982; Burnand et al, 1977; Burnand et al, 1980; Burnand et al 1981; Burnand et al, 1982). Fibrin deposits have also been detected with immunofluorescence according to the method described by Neumann and Van der Broek (1991) and by Hammersen (1977) and Uitto et al (1987). Studies from other groups (Neumann and Van der Broek,1991; Hammersen, 1977, Uitto et al, 1987) have shown in histology specimens from the skin of patients with postphlebitic limbs the following distinctive findings:

a. An apparent increase in the number of capillaries.

b. The capillaries were dilated and tortuous with a glomerular-like aspect.

c. The capillary wall was thickened and surrounded by a pericapillary halo composed of protein, neutral polysaccharides, haemosiderin and fibrin.

d. In some specimens, collagen IV layers have been observed on the basal membrane and around most capillary walls (Neumann and Van der Broek,1991; Hammersen, 1977). Collagen IV deposits are not seen normally in normal subjects (Uitto et al, 1987).

e. Fibrin deposits were detected with immunofluorescence in only a few (some 50-30% of histology specimens). They were not seen in normal subjects (Laurora et al, 1993).

f. Haemosiderin and histiocytes were observed in liposclerotic skin only (all histology sections).

More recently Laurora et al, (1993) studied histology using a perimalleolar punch biopsy in normal volunteers and in subjects with venous hypertension and lipodermatosclerosis due to postphlebitic syndrome.

Elongation and dilatation of capillaries with thickening of the capillary wall and a glomerular-like aspect of the perimalleolar capillary network was seen in the skin of all patients with postphlebitic limbs. These aspects were not observed in normal skin biopsies. However fibrin deposition or a fibrin cuff was not observed in Laurora's study.

1.62 **Videomicroscopy**

Capillaroscopy, videomicroscopy and fluorescence videomicroscopy has been used by several research groups to study venous microangiopathy (Moneta et al, 1987, Bollinger et al, 1979; Bollinger at al, 1981; Bollinger at al,1982 a and b; Fagrell, 1979 and 1982; Franzeck et al, 1984; Moneta et al 1986; Leu et al, 1993; Hasselbach et al, 1986; Huch et al, 1983).

With vital videomicroscopy in healthy subjects the cutaneous capillaries usually appear to run vertically to the skin surface. They appear as a point or comma corresponding to the apex of the capillary loop. In patients with venous microangiopathy most capillaries are dilated, elongated and tortuous. The microvessels resemble trees or glomeruli. Pigmentation areas are more frequent and more pronounced than in healthy controls. The pigmentation is generally located at the halo borders forming web-like structures (Leu et al,1993). Fagrell observed that the terminal capillary loops appeared to be decreased in number and, around them pericapillary oedema often formed a halo (Fagrell, 1982). These changes were considered to be the direct cause of trophic lesions and were demonstrated in most limbs with venous microangiopathy (Fagrell, 1982).

Videomicroscopy in combination with transcutaneous PO_2 measurements (Franzeck et al, 1984) indicated that areas of venous microangiopathy and capillary rarefaction are also poor in transcutaneous PO_2. In limbs with early disease, in areas close to incompetent perforators, with the skin without major trophic changes videomicroscopy showed dilated and tortuous capillaries surrounded by a halo of oedema. In areas of hyperpigmentation, induration and hyperkeratosis, a significant decrease in the number of capillaries was associated with very low transcutaneous PO_2 levels. In avascular skin areas (scar tissue, white atrophy) PO_2 was close to zero and no capillaries or very few were seen by videomicroscopy.

1.7 EFFECT OF THERAPEUTIC MEASURES ON VENOUS HYPERTENSIVE MICROANGIOPATHY. ASSESSMENT BY LASER-DOPPLER FLOWMETRY

1.71 Introduction

The effects of treatments on limbs with venous hypertension have been mainly focused on clinical aspects

(Jones et al, 1980). A few studies have been focused on the qualitative and quantitative effects of treatments in chronic venous hypertension (Belcaro et al, 1987; Christopoulos et al 1990 and 1991). The possibility of evaluating with quantitative methods venous hypertension and its effects on the macro and microcirculation (particularly using laser Doppler flowmetry) (Christopoulos et al, 1991) and LDF in combination with transcutaneous PO_2 and PCO_2 measurements (Belcaro et al, 1987 and 1989) is a recent development.

The chronic effects of elastic stockings (Belcaro et al, 1988d) and the acute effects of the sequential compression device (SCD) and of graduated compression stockings have been recently analysed using microcirculatory methods in pilot studies (Belcaro et al, 1993a).

Recent studies have demonstrated that in patients with chronic venous insufficiency and venous hypertensive microangiopathy, elastic compression has a beneficial effect not only on the venous haemodynamics of the lower limb (Christopoulos et al, 1990; Christopoulos et al, 1991) but also on the microcirculation (Belcaro et al, 1988d; Belcaro et al, 1993a; Christopoulos, 1991).

Additionally it had been previously demonstrated that intermittent pneumatic compression using a sequential compression device intermittently (3 hours per day in addition to low compression, graduated elastic stockings) accelerates the rate of healing of leg venous ulcers approximately tenfold (Kolari and Pekanmaki, 1987; Coleridge-Smith et al, 1988) but until recently little has been known about its mode of action on the microcirculation.

This finding has now been confirmed by the observation that the SCD acutely reduces the abnormally increased skin flux and improves vasomotion in limbs with venous hypertensive microangiopathy (Belcaro et al, 1993a).

The chronic effects of drugs such as flavonoids (Belcaro et al, 1988a), the total triterpenic fraction of centella asiatica (TTFCA) (Belcaro et al, 1989a; Belcaro et al, 1989b) and an oral profibrinolytic drug (defibrotide) (Belcaro and Marelli, 1989) in subjects with venous hypertension have been evaluated using laser Doppler flowmetry and other combined methods (Belcaro et al, 1993).

1.72 **Discussion**

The aim of these interventional studies was to evaluate whether laser Doppler flowmetry was effective in detecting the changes produced by treatments in subjects with venous hypertensive microangiopathy. As the main observation from previous studies was that venous microangiopathy is generally associated with high flux in the perimalleolar region the main endpoint in all these treatment trials was to show the efficacy of the treatment in reducing the abnormally increased skin flux. The second endpoint was to show the action of the treatments on the increased capillary filtration observed in venous hypertension.

In conclusion the chronic effects of venous hypertension on the skin of the perimalleolar region cause microcirculatory disturbances that may be defined as venous hypertensive microangiopathy. The complex meaning of the different microcirculatory factors causing venous microangiopathy has only recently been investigated and partially understood. The quantitative noninvasive assessment of microcirculatory disturbances has become possible with the development and clinical applications of laser Doppler flowmetry in combination with transcutaneous PO_2 and PCO_2 measurements, straingauge plethysmography and other methods used to assess capillary filtration.

Noninvasive methods, now widely available can document and quantify the microcirculation changes produced by treatments, offering the possibility of further research to establish the optimum *dose* for both mechanical and pharmacological methods.

Laser Doppler flowmetry is not generally used to evaluate changes produced by treatments in single subjects but the data produced are useful in evaluating the natural evolution of microangiopathy (whether venous or diabetic) in groups of subjects or to observe the qualitative and quantitative effects of treatment.

PART II

CHAPTER 2

METHODS

2.1 INTRODUCTION

The noninvasive methods used in the clinical studies presented in this thesis are described in this section. They have been grouped here to avoid repetition as many of them are used in several clinical studies presented in different chapters of the thesis.

2.11 Doppler ultrasound examination

In the preliminary evaluation of the subjects included in this thesis a pocket Doppler ultrasonic blood flow velocity detector, with a 8 MHz probe (Parks, USA) was used as the first screening test.

The first procedure in all patients was the assessment of a normal arterial supply. The posterior and anterior tibial artery Doppler pressures were measured to exclude peripheral arterial disease. Subjects with an ankle-brachial Doppler pressure index below 0.9 were considered to have arterial disease.

The initial venous examination was performed with the probe at an angle of 40-60 degrees to the skin, in order to obtain optimum signals. Water soluble gel was used to facilitate the transmission of ultrasound from the probe to the tissues.

2.111 Detection of chronic venous occlusion

The subject was examined lying on a couch with the knee slightly flexed and the leg externally rotated. The probe was positioned medial to the femoral artery. In normal limbs the signal of the femoral vein is spontaneous, phasic with respiration and augmented with compression of the thigh and calf (Sumner, 1981). Compression of the calf was repeated with manual occlusion of the long saphenous vein to ensure that the outflow from the calf was through the popliteal vein. When the signal was absent or continuous, non-phasic with respiration and not augmented with calf compression, it was considered suggestive of venous occlusion with increased flow through collaterals or partially recanalised deep veins. Abolition or diminution of the abnormally increased continuous flow with digital compression on the opposite groin or pubis, indicated iliac or femoral vein occlusion of the examined side and outflow through collateral suprapubic veins. Absence of augmentation of the venous signal at the groin by calf compression indicated occlusion at the level of the popliteal and, or superficial femoral vein. Augmentation with this manoeuvre, only when the long saphenous was not manually occluded, indicated that the long saphenous was acting as an important collateral.

2.112 Detection and localisation of venous reflux

The patient was examined in the standing position with the weight on the opposite leg, so that the examined leg was relaxed. The probe was placed in the groin over the femoral vein and at the popliteal fossa. The calf of the examined limb was manually compressed in order to produce ejection of venous blood towards the heart. A proximal flow was then detected in the femoral vein. If the valves of the common femoral and long saphenous veins and of the popliteal vein were competent, no signal of reversed flow could be detected on release of the compression. This criterion was considered diagnostic of absence of venous reflux in the vein of the area. On the other hand, the presence of retrograde flow was considered to be indicative of reflux.

If no reflux or no obstruction were documented with the pocket Doppler then the patient was considered free from reflux (or severe incompetence) and therefore colour duplex scanning and all the other investigations were not performed (Nicolaides et al, 1981a).

2.12 Duplex scanning and colour duplex scanning

Duplex scanning (performed with an ATL, UltraMark 4 scanner) and colour duplex scanning (using a Quantum, USA scanner) were used to visualise the veins by high resolution, B-mode real time and colour duplex ultrasound using a linear 7.5 MHz probe. Flow velocity variations appeared within the vessel as a colour-coded scale of velocity. The cephalad flow was coded in different degrees of blue and the flow towards the distal part of the limb in red. With the compression-release manoeuvre (performed by quick compression of the calf, with the patient standing) the presence of retrograde flow indicating reflux appeared in red in the deep or superficial veins under examination (Vasdekis et al, 1989; Szendro et al 1986). The compression with the probe on skin overlying a vein and its complete collapse and the disappearance of the colour flow indicated a patent venous lumen. The femoral, popliteal and superficial veins were examined in patients standing (Szendro et al, 1986; Belcaro et al, 1993b) and holding on to a frame. The examined leg was relaxed, with the knee slightly flexed and the weight mainly on the opposite leg. To evaluate the popliteal vein the probe was placed behind the knee pressing lightly on the skin and its position was adjusted so that three structures could be identified on a longitudinal ultrasonic section of the popliteal fossa: the popliteal artery lying deepest, the popliteal vein more superficial and parallel to it and the short saphenous vein most superficial. The latter has a smaller diameter and usually takes an oblique course, joining the popliteal vein at the saphenopopliteal junction (Hobbs, 1985).

Duplex and colour duplex were used in all subjects to indicate and localise competence or incompetence of superficial and deep veins and to detect obstruction.

2.13 Ambulatory venous pressure measurements (AVP)

A 21-gauge, butterfly needle was inserted into a vein on the dorsum of the foot and connected to a pressure transducer-amplifier (S&W, Type 8041) and recorder (MedaSonics SP32) which provided a continuous recording of venous pressure. The resting pressure was initially recorded with the patient in the standing position, holding on to a frame. The patient then performed a standard exercise of ten tip-toe movements at the rate of one per second. At the end of the exercise, the patient remained still until the pressure returned to the resting level. The test was repeated after inflating a 2.5 cm wide pneumatic tourniquet at the ankle to occlude the superficial veins. The tourniquet pressure was 80 mmHg. Limbs with an ambulatory venous pressure (AVP) less than 45 mmHg when the ankle tourniquet was inflated were considered to have superficial incompetence (primary varicose veins). In absence of obstruction limbs with an AVP greater than 45 mmHg, even when the tourniquet was inflated, were considered to have an incompetent deep venous system (Nicolaides et al, 1981b).

2.14 Laser Doppler flowmetry (LDF)

A description of the method and its clinical applications have been given in Chapter 1 and have been recently reported in detail (Belcaro et al, 1994).

LDF output signals recorded for the experiments described in this thesis were defined as flux. All recordings were obtained with three instruments: the Periflux PF2 (Perimed Sweden), the TSI-BPM (TSI, USA) and the Vasamedics BPM (Vasamedics, USA). A standard skin probe was used according to the technique used by our group and previously described (Belcaro et al, 1988 a to e; Belcaro et al, 1989 a; Belcaro et al, 1989 a and b). The probe was applied on to the perimalleolar skin using double-adhesive rings, placing a minute quantity of Aquasonic ultrasound gel between the probe and the skin surface to improve laser light transmission. Patients sensorial stimulation was kept to a minimum avoiding noise, light changes, talking and postural changes.

The following main parameters have been defined and used in the experiments reported in this thesis.

2.141 Resting skin flux (RF)

Resting flux was determined by measuring the average skin flux at the internal perimalleolar region at least 2 cm away from the edge of any skin lesion or alteration (including ulcerations). The skin flux within three minutes after 30 minutes of supine rest and acclimatisation in a room at constant temperature (22±1°C) was considered as the RF.

2.142 Standing flux (SF), flux on dependency (DF) and the venoarteriolar response (VAR)

After the resting flux had been determined the subjects were asked to stand, holding on to an orthopaedic frame. After the first minute during which the motion artefact due to the change in posture was ignored the average skin flux was recorded for the subsequent three minutes at the same spot, with the probe maintained in the same position. This measurement was defined as the flux on standing (SF).

The venoarteriolar response (VAR) was calculated from: VAR=[(RF-SF)/RF]x100).

As an alternative measurement in some experiments when the subject under examination could not stand easily or to avoid as much as possible motion artifacts the VAR was measured asking the subjects to lower the limb under investigation 90 degrees by the side of the couch keeping the limb at least 45 cm below the heart level. This parameter was defined as flux on dependency (DF).

Vasomotion was analysed in one of the experiments examining the number of cycles (periodical flux variations per minute) present in the LDF tracings.

2.15 **Transcutaneous PO_2 and PCO_2 measurements**

All measurements were performed in a temperature controlled room (22°C) after 30 minutes acclimatisation with the patient resting supine on the couch with bare legs. All measurements were performed before 10 a.m. to avoid the effects of a day of standing or working and particularly of oedema. Five minutes after the laser Doppler evaluation had been completed PO_2 and PCO_2 measurements were recorded at the same perimalleolar internal region. PO_2/PCO_2 measurements were recorded with the probe heated at 43°C, fixed to the skin with a double-adhesive ring using a Microgas (Kontron, UK) analyser connected with a CombiSensor probe. This multiple sensor allowed simultaneous measurements of PO_2 and PCO_2 over the same site of skin (Belcaro et al, 1988). The readings were recorded 30 minutes after the placement of the probe to allow skin capillarisation and O_2 and CO_2 diffusion through the probe membranes. The transcutaneous PO_2 and PCO_2 were measured as the average within 5 minutes (from minute 30 to 35) after the placement of the probe.

2.16 Straingauge plethysmography to assess capillary filtration

Two methods of assessing capillary filtration have been developed. In both methods straingauge plethsymography (using a MedaSonics SPG-16 straingauge) was applied.

Before measuring capillary filtration all subject were asked to rest supine for 30 minutes. The straingauge was applied on a 2 cm wide, flexible plastic band to avoid contact with the skin. Direct contact, particularly in oedematous limbs, produces deepening groove of the straingauge into the skin causing calibration problems.

After placing the straingauge at the smallest ankle circumference five minutes of stabilisation were recorded. The five minutes of recording were averaged to obtain the baseline volume level. The thigh cuff was then inflated or the subject was asked to stand, holding on to a frame to avoid motion artifacts depending on which method was used. The full weight of the body was sustained by the contralateral limb and the limb under examination was placed on the floor without bearing weight. Both methods of measuring capillary filtration were used in a room maintained at constant temperature (22±1°C) and after 30 minutes of acclimatisation.

The straingauge plethysmograph - MedaSonics SPG16, (Mountain View, USA) coupled with a MedaSonics chart recorder and a computerised curve calculation system based on an IBM-PS2 personal computer - was used for all subjects and tests. A set of 25 straingauges of different length (ranging from 12 cm to 35 cm) was used for the experiments described in this thesis. Different lenghts were needed to approximate as much as possible limb circumferences.

2.161 <u>Venous occlusion plethysmography</u>

A 23 cm wide cuff was placed at the lower third of the thigh and inflated at 120 mmHg to occlude the venous system for 10 minutes. The last part of the volume increase curve was defined as the capillary filtration phase and it was characterised by a slow, almost minimal volume increase, observed after the 7th minute. The small increase in volume was due to extrafiltration of fluid into the extracapillary compartment. The assumption that this value is related to capillary filtration derives from previous observations (Thulesius, 1973; Thulesius and Norgren, 1973; Roztocil et al, 1977; Cesarone et al, 1992). With this method in our laboratory, in normal subjects capillary filtration, calculated from the tangent to the the curve between the 7th to the 10th minute, is on average 1.12 ml/min per 100 ml (Belcaro et al, 1992a and 1993a).

2.162 Rate of ankle swelling (RAS)

The second method measured the rate of ankle swelling which occurred when the patient moved from the supine to the standing position. A curve similar to the curve obtained with the previously described method was recorded (see figure 1.17). Capillary filtration was considered to be proportional to the tangent on the curve between the 7th and 10th minute. This method did not require occlusion, was better tolerated and therefore it was chosen as the main method of evaluating capillary filtration in this thesis.

2.17 Evaluation of local capillary filtration with the vacuum suction chamber (VSC) device

The VSC system has been described in Chapter 1 (page 92). It was applied on the skin of the perimalleolar region at least 3 cm from any skin lesion or ulceration. After applying the laser Doppler probe and the VSC chamber as shown in figure 2.1 the skin flux was measured. A negative pressure in the chamber was maintained for 10 minutes using a small air pump. After removing the chamber the length of time needed for the disappearance of the weal was measured

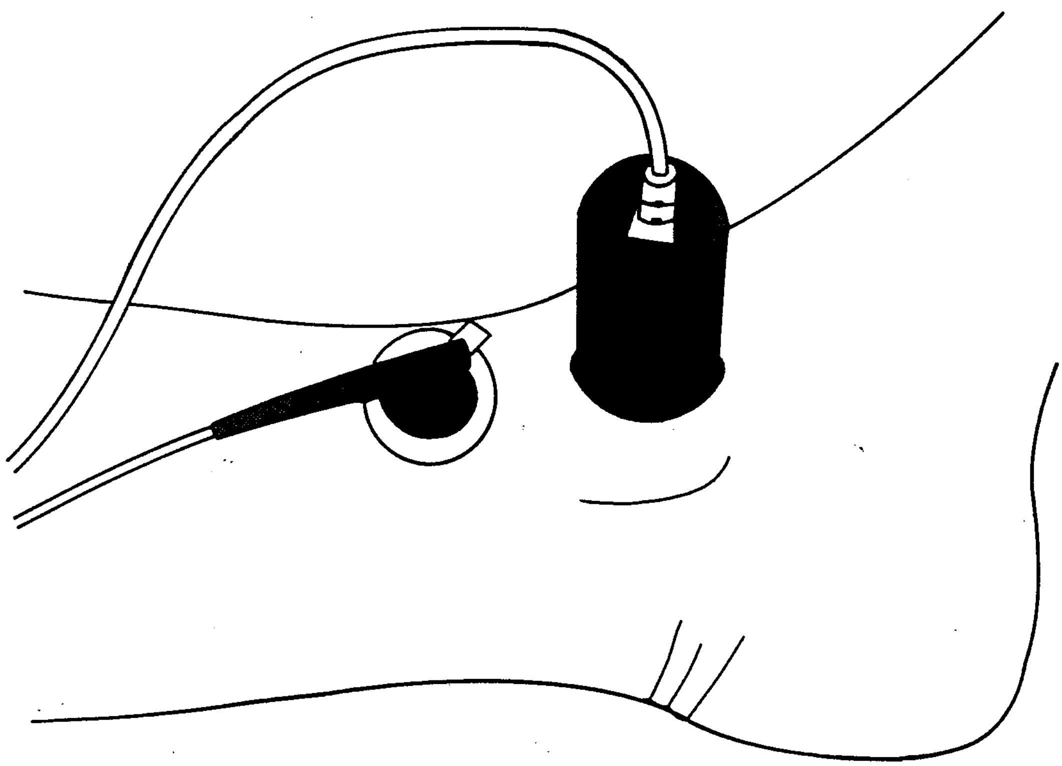


Figure 2.1: the vacuum suction chamber and the laser Doppler probe applied at the internal perimalleolar region.

in minutes (Belcaro et al 1992a). The weal disappearance time was recorded at constant temperature (21±2°C), after acclimatisation. Photographs of the weal were taken every 5 min up to 120 min or until the weal was not visible on photographs. The weal disappearance time, defined as the VSC time, was expressed in minutes. After completing the VSC test the capillary filtration rate was measured by evaluating the rate of ankle swelling.

2.18 **Skin flux and histology: methods**

After informed consent, and skin infiltration of local anaesthetic (1 ml of Carbocain 2% without adrenaline) a small biopsy was performed using a stitch cutter curved blade (Swann-Morton). A single biopsy was made in each limb. Before the biopsy all patients had been fully acclimatised at 22°C for 30 minutes. A washout period without any treatment had been observed. Patients had been asked not to wear elastic compression and not to use drugs for one week. Before the biopsy the laser Doppler probe had been applied on the biopsy area. The resting flux had been recorded as the average o four recordings. The laser Doppler sampling point had been marked with a skin marker and the biopsy was performed at the point where the highest flux had been found. A previous study (Laurora et al, 1993) had shown a significantly increased capillary network in areas of increased skin flux. All biopsies were from non-infected, liposclerotic skin of the internal perimalleolar region at least 2 cm from scars of previous ulcerations and at least 3 cm from the medial malleolus.

A vertical thickness of 0.4 cm of skin was biopsied and a standard haematoxylin-eosin stain was used. Commercially available stains for collagen IV deposits (anticollagen IV serum) and fibrinogen were used (Neumann and Van der Broek,1991; Hammersen et al,1977; Uitto et al; 1987).

Fibrin deposits were detected with immunofluorescence according to the method described by Neumann and Van der Broek (1991) and by Hammersen (1977) and Uitto et al (1987). After the biopsy was performed the histology specimen was immediately fixed with a standard formalin solution.

All histology sections were prepared and analysed within 48 hours of staining.

The site of the biopsy was compressed for a few minutes and a small compressive bandage was applied.

2.2. TREATMENT METHODS USED IN THE THESIS

In the treatment studies evaluating both surgery and sclerotherapy, criteria of exclusion were any form of previous surgery or sclerotherapy, any systemic disease and leg pathology not due to venous insufficiency.

2.21 Superficial venous surgery

Selective surgery of the incompetent superficial veins was performed under general anaesthesia, after localising the sites of incompetence with colour duplex (Belcaro, 1986; Belcaro and Errichi, 1992; Belcaro, 1993 c, Ricci et al).

The ligation and division of the incompetent venous sites were guided by marking their localisation on the skin whith the patient standing. The ligation was always associated with division of the veins. All patients were fully mobile within 24 hours after surgery and no drug was used either during or after the procedure (excluding drugs used for anaesthesia). In the protocols used in this thesis stripping was not used as a method of treatment of superficial venous incompetence.

2.22 **Sclerotherapy versus selective surgery**

Sclerotherapy was performed after localising the sites of venous incompetence with colour duplex. Therapy consisted of sclerotherapy of the incompetent veins with Polidocanol (40 mg/ml) associated. After injection of the sclerosing agent into the vein local compression of the injected veins with small cotton balls was achieved. Then continuous compression was achieved using medium compression (pressure at the ankle 25 mm) stockings (Sigvaris, Ganzoni, St Gallen, Switzerland) (Leu et al, 1993). The stockings were worn during the days after treatment as described by Leu et al (1993). All treated patients used stockings for 3 weeks after sclerotherapy (Williams and Wilson, 1984; Hobbs 1974 and 1975). According to the size of the veins to inject a solution with a 3% concentration of polidocanol with three weeks of compression were used for veins of a diameters of 3 mm or more. A 2% solution and 2 weeks of compression were used for veins of diameter ≈ 2 mm while a 1% solution and 1-week compression were used for veins of diameter ≈ 1 mm.

In the protocol used in this thesis all major incompetent veins were treated in a three-week period.

PART III

CLINICAL STUDIES

CHAPTER 3

LASER DOPPLER FLOWMETRY IN VENOUS HYPERTENSION

3.1 INTRODUCTION

The increase in skin flux in the perimalleolar region in limbs with venous hypertension and the decrease in VAR (Belcaro et al, 1989 and 1993; Coleridge Smith et al, 1993) have been previously observed in limited experiments. It had been suggested that the increased skin flux is an index of venous hypertension. Previous findings support the suggestion that in venous hypertension the microcirculation in the skin behaves in many aspects as seen in a chronic inflammatory reaction. A practical clinical observation is that the finding of resting flux in the perimalleolar region higher than a certain flux unit number (i.e. 2 flux unit with the Vasamedics, BPM, laser Doppler, in standard environmental and experimental conditions) suggests an abnormality of the venous system. Also the finding of a decreased venoarteriolar response (<30%) may indicate the presence of severe microcirculatory abnormality.

3.2 RATIONALE AND AIMS

The aims of the experiments presented in this part were:

A. to determine the correlation between ambulatory venous pressure and LDF measurements.

B. To identify whether any clinical cut-off point in laser Doppler measurements could be used as an indication of an abnormal venous system.

3.3 MATERIAL AND METHODS

3.31 Materials

Five groups of subjects were studied.

1. Normal subjects;
2. Patients with varicose veins;
3. Patients with deep venous insufficiency

   a. without skin lesions;

   b. with lipodermatosclerosis, skin pigmentation and induration but no ulcerations present at the moment of the evaluation or in the past.

   c. with venous ulcerations.

3.32 Methods

Arterial disease was excluded by Doppler ankle pressures measurements (ankle pressure index > 0.9).

The correlation between ambulatory venous pressure (AVP) measurements, refilling time (RT), skin flux at rest at the internal perimalleolar region (RF) and the venoarteriolar response (VAR) were studied in 10 normal subjects and in 88 limbs with various degrees of venous incompetence. The parameters obtained with ambulatory venous pressure (AVP) measurements - namely P (the lowest pressure, in mmHg, during the exercise test) and the venous refilling time (RT) - were correlated to RF and to the venoarteriolar response (VAR). Colour duplex was performed in all examined limbs. It excluded venous obstruction or deep venous thrombosis and confirmed (Table 3.1) AVP findings indicating the presence or absence of superficial and, or deep venous incompetence.

As criteria of exclusions, subjects with any clinical cardiovascular disease or any other concomitant clinical condition, under any pharmacological treatment within the previous two weeks, obese subjects and subjects with bone or joint problems or otherwise unable to perform the AVP exercise test were excluded.

All patients were studied with duplex scanning to determine the state of the superficial and deep veins, AVP measurements with and without a tourniquet and laser Doppler as described in Chapter 2 (pages 108-110 and 110-111 respectively). On the basis of the clinical and duplex findings patients were divided into those with reflux confined to the superficial veins and those with deppe venous insufficiency. The latter was subdivided into three subgroups (as indicated above): those without skin lesions (A); those with lipodermatosclerosis, skin pigmentation and induration but no ulcerations (B) and ulcerations (C).

All measurements were recorded before 10.00 a.m. to avoid or reduce the potential effects of oedema on the skin microcirculation (more evident in the afternoon or in the evening). All included subjects had been asked not to wear stockings and not to use any drug for at least 5 days before the tests. All ulcerations at the time of evaluation were not inflamed, non-septic, clean, without necrotic material and not larger than 3 cm at the maximum width. The laser Doppler probe was placed at least 2 cm proximally or distally to the edge of the ulceration on intact skin. The average area of the ulcerations was 3.2 ± 0.86 cm^2. All ulcerations were at the internal perimalleolar region.

3.4 **RESULTS**

The demographic characteristics are shown in Table 3.1. The groups of subjects were comparable for age and sex distribution. The mean AVP in the groups is shown in figure 3.1.

There was a significant difference between normal subjects and patients ($p<0.05$) and between limbs with superficial and deep venous incompetence ($p<0.05$). The mean skin RF in the groups is shown in figure 3.2. There was a significant difference ($p>0.05$) between normals and patients with DVI. However there was no difference between normal subjects and those with varicose veins. Also there was no difference between the subgroups of patients with DVI.

The mean VAR in the groups is shown in figure 3.3. The only significant difference in VAR was observed between subjects with varicose veins and those with DVI.

A linear relationship ($r=0.712$) was observed between AVP and RF indicating an increase in flux with an increase in ambulatory venous pressure (Table 3.2).

There was also a negative correlation between RT and RF ($r=-0.57$) and a low, not significant correlation between AVP and VAR and RT and VAR (Table 3.2).

Table 3.1

Age and sex distribution and colour duplex competence (comp) or incompetence (incomp) of the studied subjects.

				COLOUR DUPLEX	
	n	Age	M:F	Super.	deep
Normal subjects	10	41±5	5:5	comp	comp
Varicose veins	14	42±7	7:7	incomp	comp
Deep incomp					
(A)No skin lesions	14	41±6	8:6	comp	incomp
(B)Lipodermatoscl.	30	42±9	14:16	incomp	incomp
(C)Ulcerations	30	41±8	16:14	incomp	incomp
TOTAL	98	41.4±7	50:48		

Table 3.2

Data of all limbs evaluated with AVP and laser Doppler flowmetry.

TOTAL:	AVP	RT	RF	VAR
Mean	51.34	10.6	1.8	33.03
SD	13.42	4.7	0.87	10.9
Range	22-73	4-26	0.4-4.1	0-54
Median	51	9.5	7.05	34

Correlation coefficients (all limbs):

AVP - RF	0.712*
AVP - VAR	-0.18
RT - RF	-0.57
RT - VAR	0.33

* p<0.05

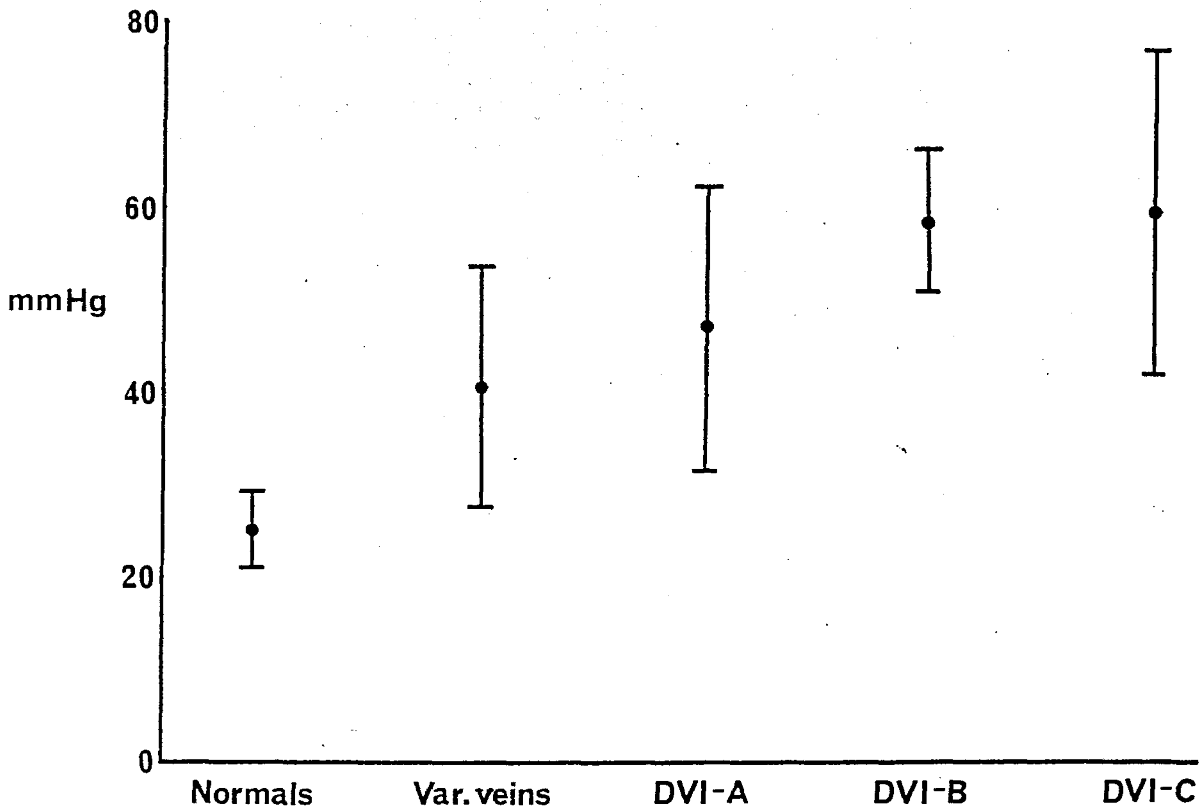


Figure 3.1: Ambulatory venous pressure in the different groups (mean ± 2 sd). A indicates no skin lesion; B indicates lipodermatosclerosis and C indicates ulcerations.

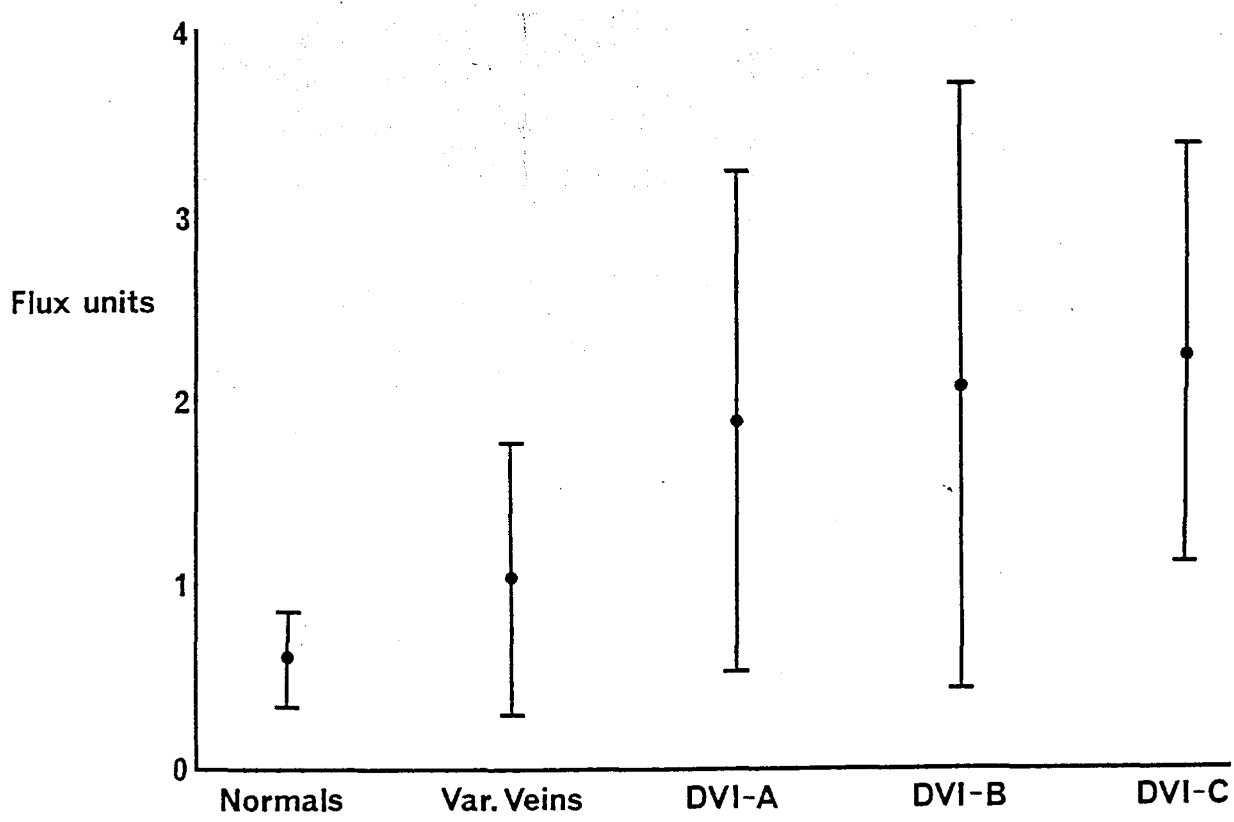


Figure 3.2: Perimalleolar skin flux (mean ± 2 sd). A indicates no skin lesion; B indicates lipodermatosclerosis and C indicates ulcerations.

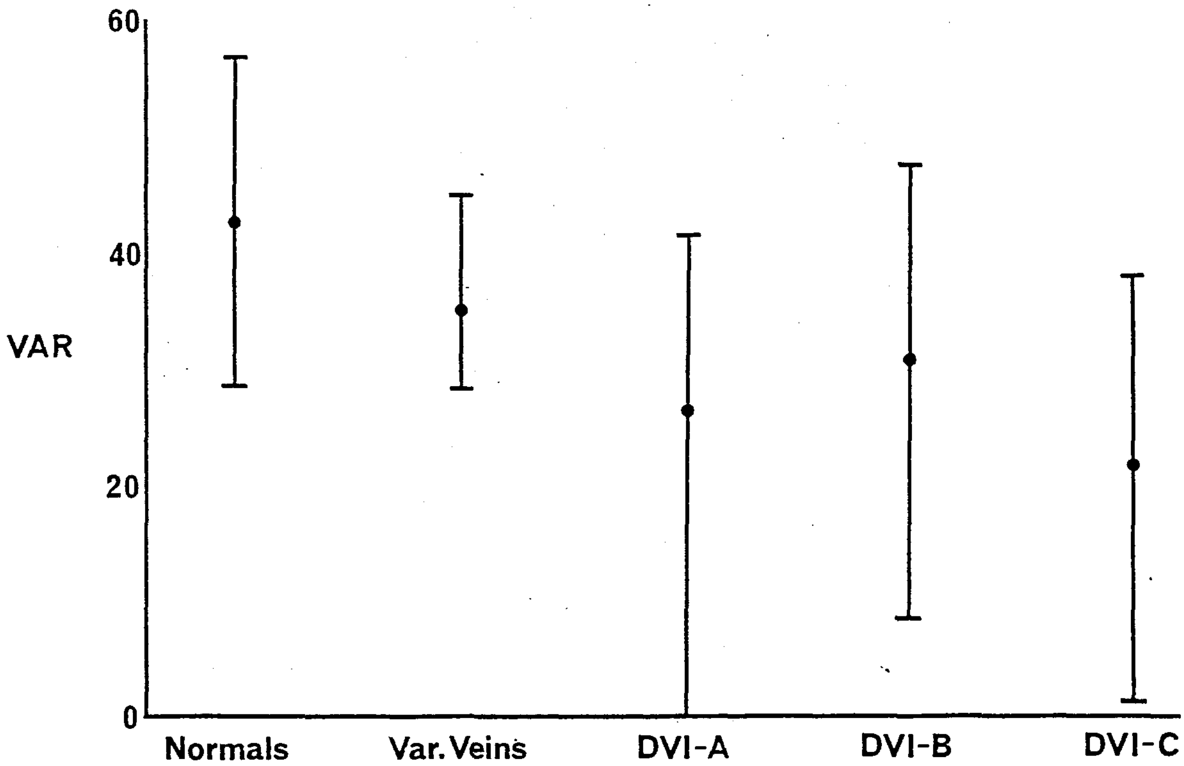


Figure 3.3: The venoarteriolar response (in percentage; median and range presented in the figure) in the same groups. A indicates no skin lesion; B indicates lipodermatosclerosis and C indicates ulcerations.

The average of all data from the five groups (normals, varicose veins and the three subgroups with deep venous insufficiency are shown in Table 3.2 with the correlation coefficients including the data from all limbs. The best correlations observed were the correlation between AVP and RF ($r=0.712$; $p<0.05$; Figure 3.4) and the correlation between RT and RF ($r=-0.57$).

3.5 CONCLUSIONS

These results indicate that there is a linear relationship between AVP and RF when normal limbs and limbs with different degrees of venous disease are included. The correlation between VAR, AVP and RT was poor and did not confirm previous findings observed in smaller studies (Belcaro et al 1987 and 1989). In standard environmental conditions laser Doppler measurements are reproducible (see Chapter 1, pg 74) but careful management of calibration and operative procedures should be followed. The observation of increased skin flux in venous hypertension can be observed with any available instrument even if calibration among instruments is not comparable. On the basis of these observations it appears that the increase in RF can be generally considered an index of venous hypertensive microangiopathy.

The aim of the study presented in this Chapter had been the evaluation of the relationship between venous pressure and flux. According to the results the increase in RF is well correlated to the AVP. On the contrary, due to the large overlap the VAR is a poor indicator of the severity of venous microangiopathy.

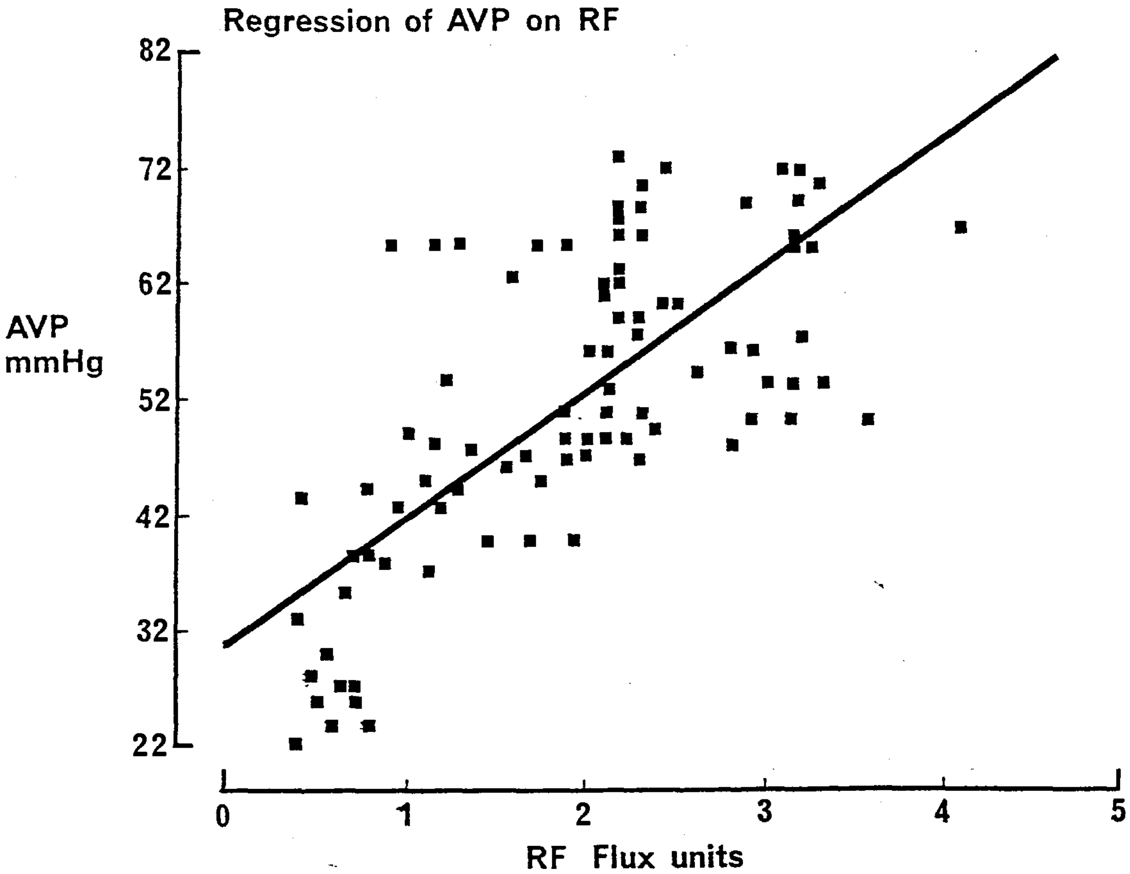


Figure 3.4: Correlation between ambulatory venous pressure (mmHg) and resting flux (flux units) in normal subjects and patients with superficial and,or deep venous incompetence.

The evaluation of RF by laser Doppler flowmetry is noninvasive and easier to perform than AVP. Therefore RF can be effectively used as a parameter to evaluate, quantify and monitor venous microangiopathy and its evolution and to quantify the effects of therapy.

CHAPTER 4

THE RELATIONSHIP BETWEEN LASER DOPPLER FLUX AND TRANSCUTANEOUS PO_2 AND PCO_2 MEASUREMENTS IN LIMBS WITH CHRONIC VENOUS HYPERTENSION

4.1 INTRODUCTION

The clinical study described in this Chapter deals with the problem of the increased skin flux on skin nutrition. As described in the review (pages 31-36) several investigations have demonstrated a decrease in transcutaneous PO_2 and an increase in transcutaneous PCO_2 in the skin of the perimalleolar region in areas close to lipodermatosclerosis and ulcerations. The aim of this experimental study was to assess whether the changes in tc PO_2 and PCO_2 in limbs with severe venous hypertension are associated with an increase in perimalleolar skin flux shown by laser Doppler flowmetry (LDF). The measurement of transcutaneous PO_2 and PCO_2 is tedious and time consuming. In contrast the measurement of laser Doppler parameters is relatively simple. Therefore a second aim of this study was to determine whether the measurement of skin flux by LDF is a better indicator of venous microangiopathy than the alterations in tc PO_2 and PCO_2.

4.2 MATERIALS AND METHODS

The relationship between laser Doppler parameters (RF and VAR) and transcutaneous (tc) PO_2-PCO_2 measurements in the internal perimalleolar region in patients with chronic venous hypertension was evaluated in a prospective study.

Twenty limbs of 20 normal subjects and 50 limbs of 50 patients with severe venous hypertension were studied. The two groups were matched for age and sex distribution (Table 4.1). In all limbs evaluated venous hypertension was a consequence of the postphlebitic syndrome. Incompetence of the popliteal vein was present in all limbs.

Table 4.1

Details of the subjects in the two groups (normal subjects and patients with venous hypertension. Values are expressed as means (± SD).

	Age (yrs)	M:F	AVP (P) mmHg	RT sec
Normals	52.3±8.1	10:10	22±9	18.9±9
Patients	52±8	25:25	62±11	7.2±4

P is the lowest pressure obtained at the end of the exercise test.

RT = refilling time.

All patients had been assessed by colour-duplex scanning which had demonstrated deep venous incompetence and absence of obstruction and by ambulatory venous pressure (AVP) which had indicated severe deep venous incompetence (Table 4.2). No ulcerations were present in these patients although oedema, skin changes and dischromic patches were present at the internal perimalleolar region.

As criteria of inclusion, peripheral arterial pressures were normal and none of these patients had diabetes or peripheral neuropathy, hypertension or any systemic disease or skin lesion which could affect the microcirculation.

While recording laser Doppler resting flux, tc PO_2 and PCO_2 were recorded in the same skin area. In this study a Laserflo BPM1 (Vasamedics, St.Paul, USA) laser Doppler flowmeter was used. All measurements were recorded at the internal perimalleolar region and expressed in flux units.

The combined tc PO_2 and PCO_2 (CombiSensor, Kontron, U.K.) probe was placed at least 4 cm from the laser Doppler probe to avoid the effect produced on the local skin microcirculation by the heated PO_2 and PCO_2 sensor.

Statistical analys of the results was performed using the Mann-Whitney U-test.

4.3 **RESULTS**

The results obtained in this study (table 4.2) indicate that RF was significantly increased in patients ($p<0.05$) while the VAR was decreased in patients as compared to normal subjects ($p<0.05$). No significant differences in PO_2 (table 4.2) were observed.

Table 4.2

Results of skin flux and venoarteriolar response in the 20 normal limbs (nor) and in the 50 limbs with chronic venous hypertension (pat). RF is expressed in flux units and PO_2 and PCO_2 in mmHg).

	RF		VAR		PO_2		PCO_2	
	Nor	Pat	Nor	Pat	Nor	Pat	Nor	Pat
Mean	0.72	2.1	36	24	61	62	26	35
sd	0.16	0.9	--	--	8.3	10.5	2.3	4.9
Median			34	27				
Range			19-65	6-44				
	$p<0.05$*		$p<0.05$*		N.S.*		$p<0.05$*	

(Mann-Whitney U-test)

* difference between normal limbs and limbs with chronic venous hypertension.

$TcPCO_2$ was significantly increased ($p<0.05$) in patients with chronic venous hypertension.

When a multiple correlation system (Statgraphics STSC, USA) was used to correlate all parameters observed in normal limbs (RF, VAR, PO_2, PCO_2) (Figure 4.1) no significant linear relationship was found (all correlation coefficients were low ($r<0.4$).

The correlation in limbs with chronic venous hypertension is shown in Figure 4.2. In these limbs multiple correlations indicated a significant inverse linear relationship between VAR and RF ($r=-0.65$; $p<0.05$) but all other correlation coefficients were low ($r<0.4$). These results suggest that in the skin of limbs with chronic venous hypertension with increased flux there is a moderate increase in skin PCO_2 but the PO_2 appears to be within normal limits.

4.4 DISCUSSION

The results from this study do not confirm completely previous data (Franzeck et al, 1984) indicating a correlation between the degree of lipodermatosclerosis and the decrease in skin tc PO_2. The severe decrease in transcutaneous PO_2 in patients with severe degrees of venous hypertension were not confirmed by this study.

The demonstration of an association between very low skin PO_2 levels, reduced microscopy capillary density and severely altered morphologic characteristics of the skin capillaries (Franzeck et al, 1984) has been observed in skin with healed ulcerations and scarring therefore with fibrotic tissue.

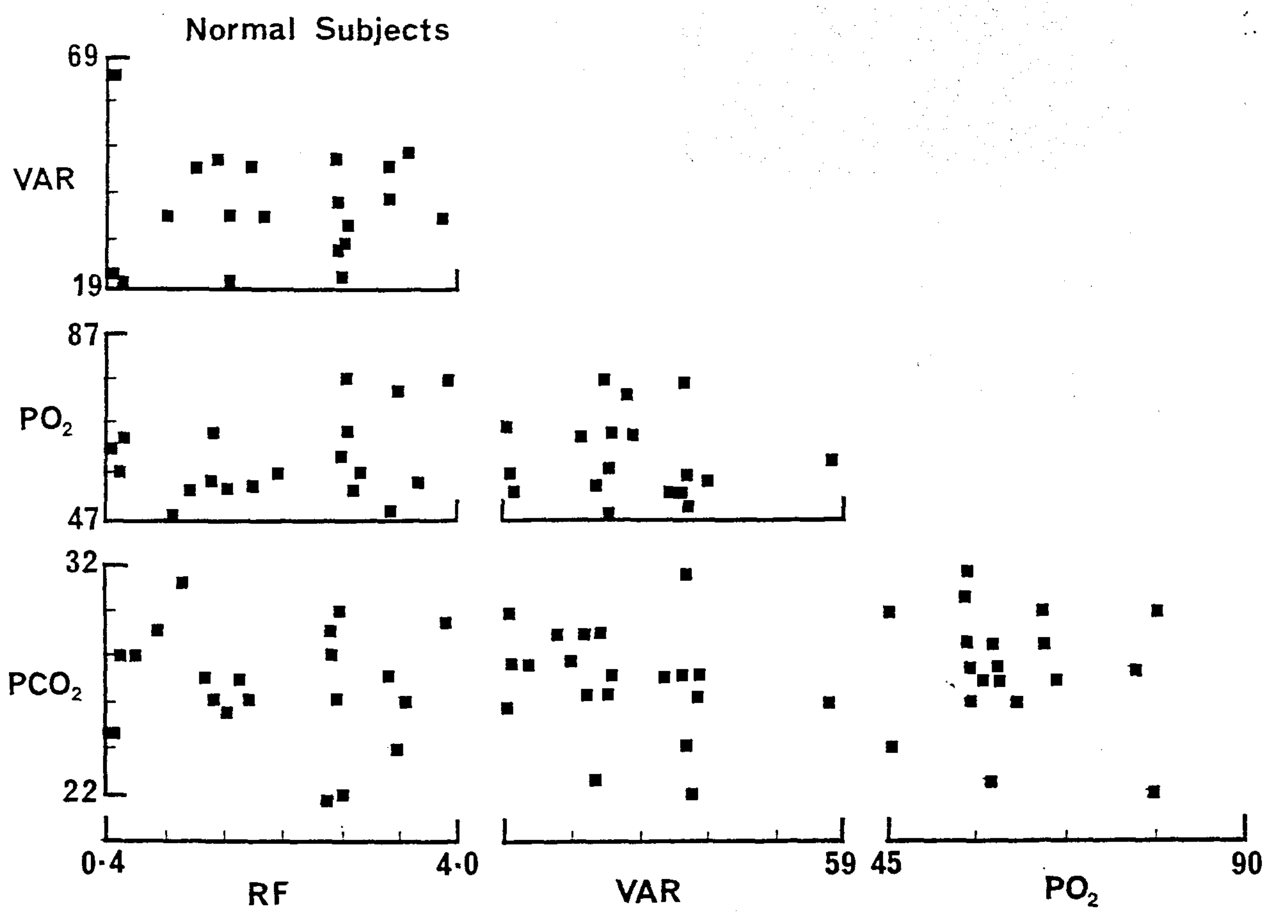


Figure 4.1: Multiple correlation among tc PO_2 and PCO_2, the venoarteriolar response, and laser Doppler resting flux in normal subjects.

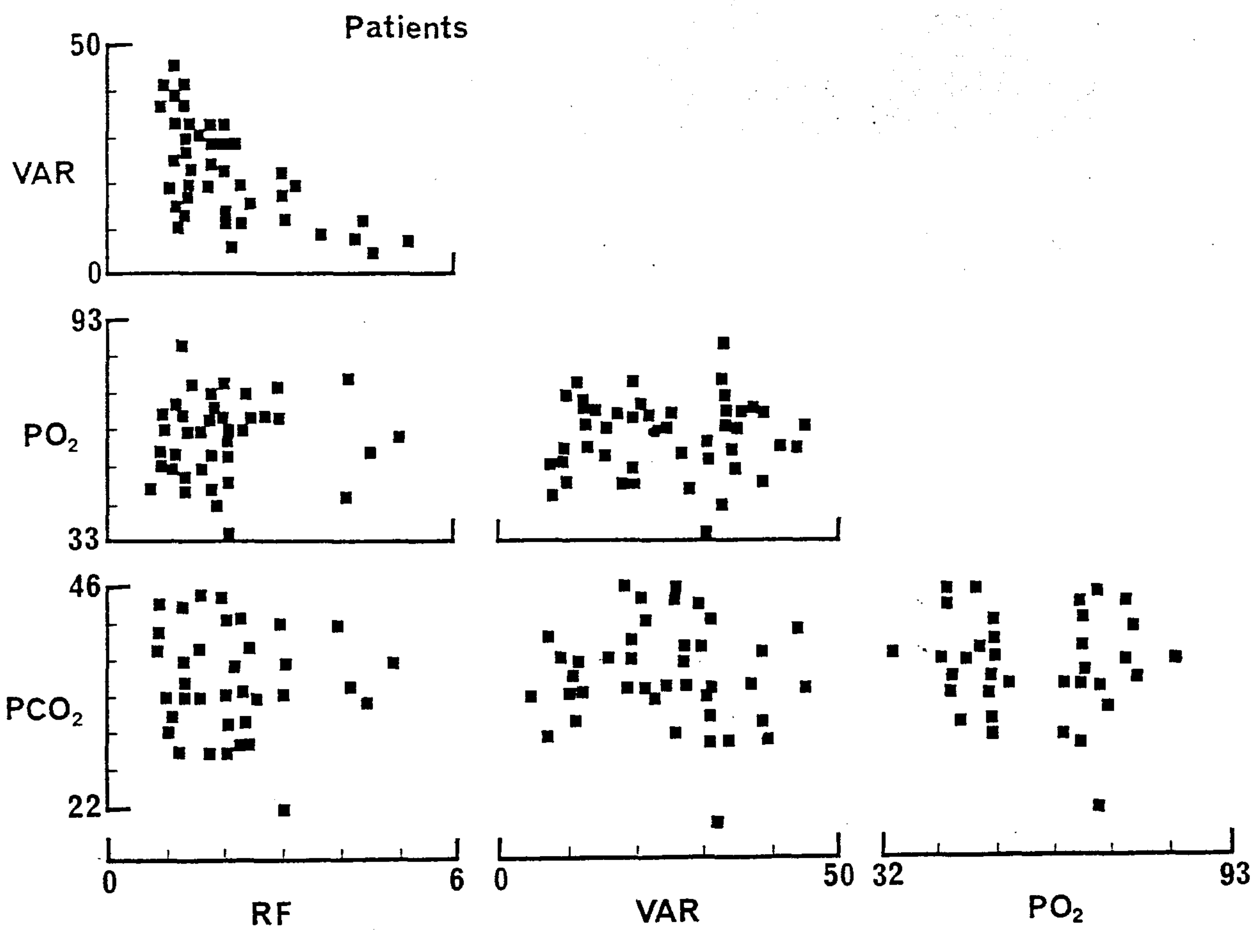


Figure 4.2: Multiple correlation among tc PO_2 and PCO_2, the venoarteriolar response, and laser Doppler resting flux in patients with severe venous hypertension.

The subjects included in this study had no venous ulcerations or skin scarring and fibrosis and it is possible that the selection of patients included in the present study had lower degrees of venous hypertension and consequently of skin microcirculation alterations than in Franzeck's study.

In conclusion, the combined evaluation with laser Doppler flowmetry and transcutaneous PO_2 and PCO_2 measurements in the perimalleolar region in subjects with chronic venous hypertension indicates that differences in RF appear to be generally more reliable than PO_2 and PCO_2 measurements both in separating groups of subjects with chronic venous microangiopathy from normal subjects and in quantifying the degree of venous microangiopathy.

The first aim of the study - to evaluate whether or not the changes in transcutaneous PO_2 and PCO_2 in venous hypertension were correlated with the increase in skin flux - were not achieved. However the evaluation of skin flux is possibly a better and more reliable indicator of venous microangiopathy than the alterations in transcutaneous PO_2 and PCO_2 which may be present only in very late stages of venous microangiopathy.

CHAPTER 5

SKIN FLUX AND CAPILLARY FILTRATION IN VENOUS HYPERTENSION

5.1 INTRODUCTION

In Chapter 3 it was observed that ambulatory venous pressure is related to the increase in perimalleolar skin flux. In patients with venous hypertension the elevation in flux appears to be clinically related to the development of oedema which is a common and early sign in subjects with venous hypertension. The correlation between skin flux changes and the changes in capillary filtration was evaluated in a clinical study which included 20 subjects with chronic venous hypertension. As no agreement exists at this stage on a standard method to assess capillary leakage, three different methods to assess capillary filtration (CF) were used as described in Chapter 2.

1 - venous occlusion plethysmography (VOSGP) (pg 88);

2 - rate of ankle swelling (RAS) using straingauge plethysmography (pg 92);

3 - the vacuum suction chamber (VSC) device (pg 92).

The aim of this study was to demonstrate that in chronic venous disease an increase in capillary filtration is associated with an increase in skin flux. The main aim of the study was to test the hypothesis that there is an association between the increase in skin flux shown by laser Doppler and the rate of capillary filtration (CF) into the extracapillary space.

5.2 MATERIAL AND METHODS

Twenty subjects with chronic deep venous incompetence were selected. The deep venous incompetence had been detected with colour duplex and quantified with ambulatory venous pressure measurements (AVP) as described in Chapter 2.

Also other inclusion criteria were an intact skin (no ulceration present and no history of previous ulcerations) with skin dystrophic changes due to venous hypertension, and increased skin flux at the internal perimalleolar region.

Patients with arterial disease, obesity, diabetes, any systemic disease or under any drug treatment were excluded.

A TSI, Laserflo (TSI, USA) laser Doppler flowmeter was used. Skin flux was measured in relative flux units.

Capillary filtration was measured in ml/minute per 100 ml of tissue.

In this study after evaluating resting skin flux the sequence of the three tests of capillary filtration was for all patients as follows:

capillary filtration by venous occlusion plethysmography was the first test;

rate of ankle swelling the second measurement;

vacuum suction chamber time was the last test.

The correlation coefficients were assessed with a statistical package Statgraphics System (STSC, USA).

5.3 RESULTS

The mean age of the 20 patients (10 males and 10 females) was 47.8 (SD 11; range 34-61). Table 5.1 shows the mean, SD and range of the evaluated parameters.

Results are also shown in Figure 5.1.

Table 5.1

Ambulatory venus pressure (AVP), laser Doppler skin flux at rest (RF), capillary filtration (CF), rate of ankle swelling (RAS) and the vacuum suction chamber (VSC) time. CF and RAS are expressed in ml/100 cc of tissue per minute. VSC time is expressed in minutes.

	AVP mmHg	RF flux	CF	RAS	VSC
MEAN	61	3.5	1.73	1.557	46
SD	7.3	1.1	0.316	0.34	1.1
RANGE	43.71	0.8-5.1	1.34-2.3	1.04-2.05	0.8-5.1

CORRELATIONS: RF vs RAS = 0.70 ($p<0.05$)

RF vs CF = 0.75 ($p<0.05$)

RF vs VSC = 0.79 ($p<0.05$)

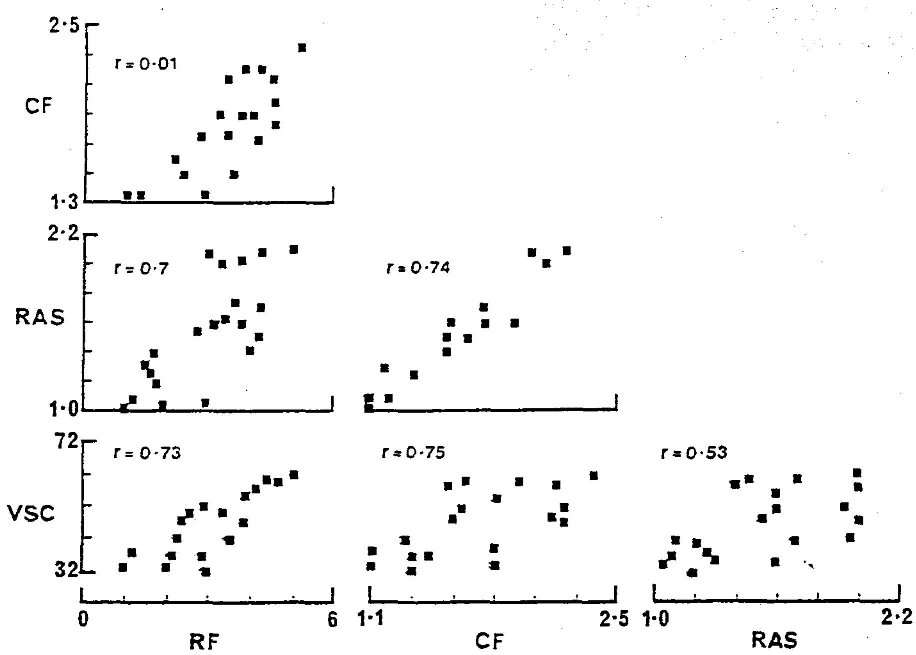


Figure 5.1: Multiple correlation between laser Doppler resting flux (RF) in flux units, capillary filtration (CF) and rate of ankle swelling (RAS) in ml/min per 100 cc of tissue and the vacuum suction chamber (VSC) time in minutes. The relative r value of the correlations is indicated.

There was a linear relationship between RF and the capillary filtration measured with any of the described methods ($r \geq 0.7$; $p < 0.05$).

These results indicate that there is an increased oedema formation associated with increased filtration and capillary leakage in limbs with chronic venous hypertension which is also associated to the flux elevation in the perimalleolar region.

This observation is related to the clinical presence of oedema which was evident in the evening in all included limbs.

5.4 DISCUSSION

According to the results from this study there is a linear relationship between the abnormal increase in skin flux and the increased capillary filtration.

In conclusion the evaluation of RF gives also an indirect but good estimate of capillary filtration in the limb with venous hypertension and oedema.

Chronic increase in capillary permeability and filtration and their role in causing chronic peripheral oedema in venous hypertensive microangiopathy are still unclear.

With the VSC method it is now possible to evaluate the role of local capillary filtration in venous hypertension directly at the perimalleolar region.

The weal produced by the VSC device has different patterns of evolution in normal subjects, patients with moderate venous hypertension and in patients with severe venous hypertension.

The increase in skin flow and laser Doppler flux in the foot and the decrease in venoarteriolar response in patients with venous hypertension as well as in subjects with diabetic microangiopathy has been shown to be associated with foot oedema due to locally increased capillary filtration (Rayman et al, 1986).

Oedema is an early sign indicating microangiopathy which is observed both in limbs with venous hypertension and diabetic subjects (Belcaro et al, 1989).

According to our study the increased filtration, the increased skin flux and the formation of oedema are all related and are an important indication of microangiopathy.

CHAPTER 6

PERIMALLEOLAR SKIN FLUX AND HISTOLOGY

6.1 INTRODUCTION

In patients with chronic venous hypertension the increase in skin blood flux in the perimalleolar region and, in some subjects, the impairment of the venoarteriolar response are associated with chronic oedema (Hammersen, 1977; Uitto et al, 1987) and with characteristic histological changes typical of venous hypertensive microangiopathy as previously described (Laurora et al, in 1993).

The aim of this chapter was to test the hypothesis that there is a correlation between histological findings and the alterations in skin flux observed in venous hypertension.

6.2 MATERIAL AND METHODS

6.21 Selection of patients

Thirty limbs of thirty patients with chronic venous hypertension due to deep venous incompetence, without active ulcerations or history of ulcerations in the previous 12 months were studied and compared with normal limbs. Venous reflux in the depp veins had been diagnosed with colour duplex imaging. In all subjects foot pulses were palpable and peripheral vascular disease had been excluded by Doppler ultrasound (ankle/brachial index >0.9).

On the basis of ambulatory venous pressure (AVP) measurements only patients with severe deep venous incompetence - AVP higher than 55 mmHg (66±12) and a venous refilling time (RT) shorter than 14 seconds (12±8) - were included in this study.

6.22 **Methods**

The laser Doppler flowmeter (BPM1, Vasamedics, USA) probe was placed on the skin of the internal perimalleolar region, 3 to 6 cm proximal to the medial malleolus. RF was measured in flux units as described in Chapter 2 (pages 84-86).

After all subjects had given informed consent a small biopsy of the skin was taken under local anaesthesia. The biopsies were from liposclerotic skin of the internal perimalleolar region at least 2 cm from scar tissue of any previous ulcerations. An haematoxylin-eosin stain was used. Also commercially available stains for collagen IV deposits (anticollagen IV serum) and fibrinogen were used. Fibrin deposits were studied with immunofluorescence as described by Hammersen in 1977 and Uitto in 1987. After obtaining informed consent a perimalleolar skin biopsy was also performed in six randomly selected normal volunteers in the perimalleolar region.

6.3 **RESULTS**

Details of the normal subjects and the patients are shown in Table 6.1. Results of laser Doppler measurements are shown in Table 6.2. In postphlebitic limbs the mean resting flux was significantly increased ($p<0.05$) in comparison with normals.

6.31 **Histopathology**

In all histology specimens obtained from limbs with venous hypertension (figure 6.1) three major features were consitently observed in comparison with normal skin:

Table 6.1

Details of the two groups of patients

	Normal subjects	Postphlebitic limbs
No	6	30
Age (mean±sd)	47.5±9	47±8
M:F	15:15	14:16
Punch Biopsy	6	30

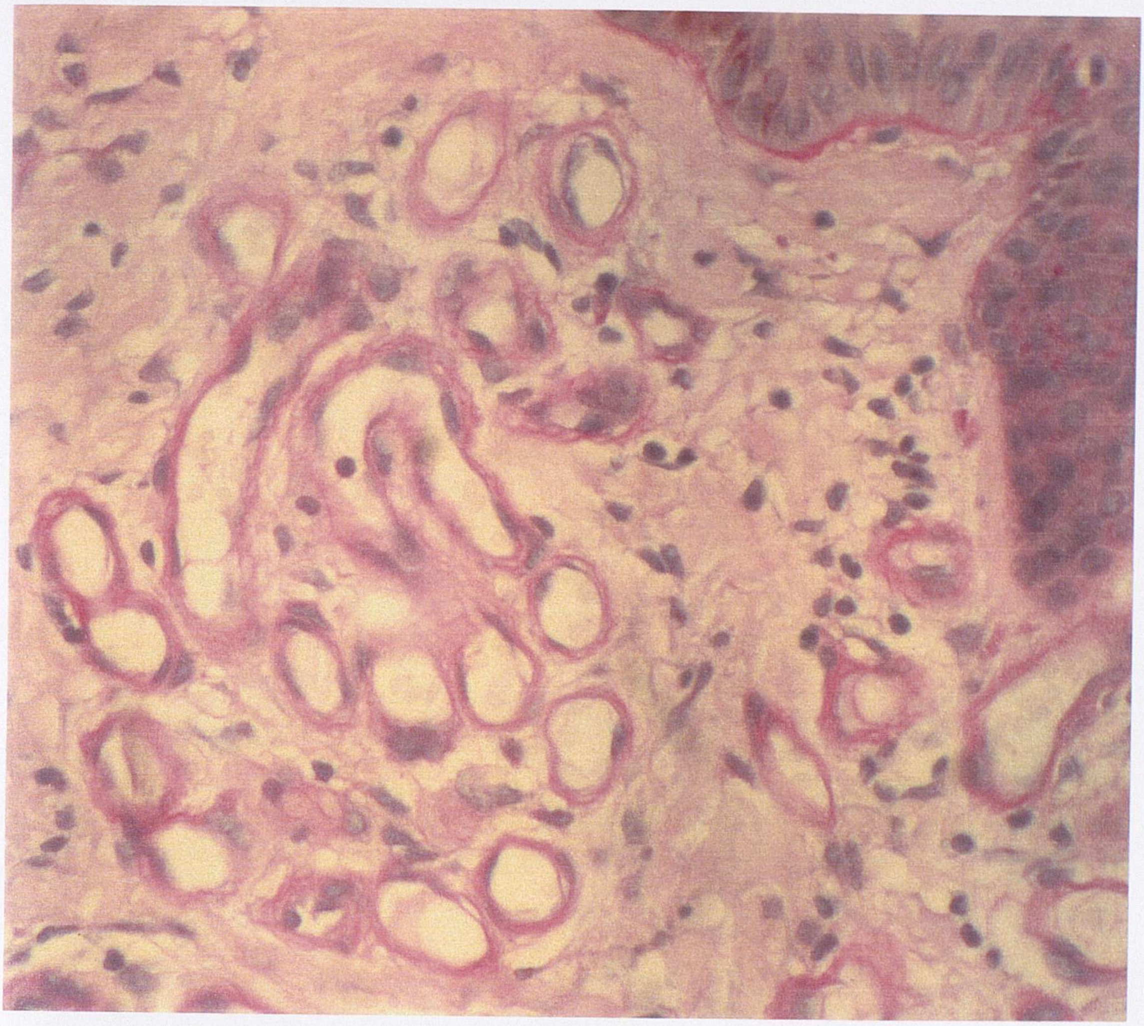
Table 6.2

Resting (RF) flux in normal limbs and in limbs with venous hypertension due to postphlebitic syndrome.

SKIN RESTING FLUX

NORMALS	mean	0.61
	SD	0.095
	range	0.4 to 0.81
POSTPHLEBITIC LIMBS	mean	2.33*
	SD	0.93
	range	0.95 to 4.2

* $p < 0.05$ difference in flux



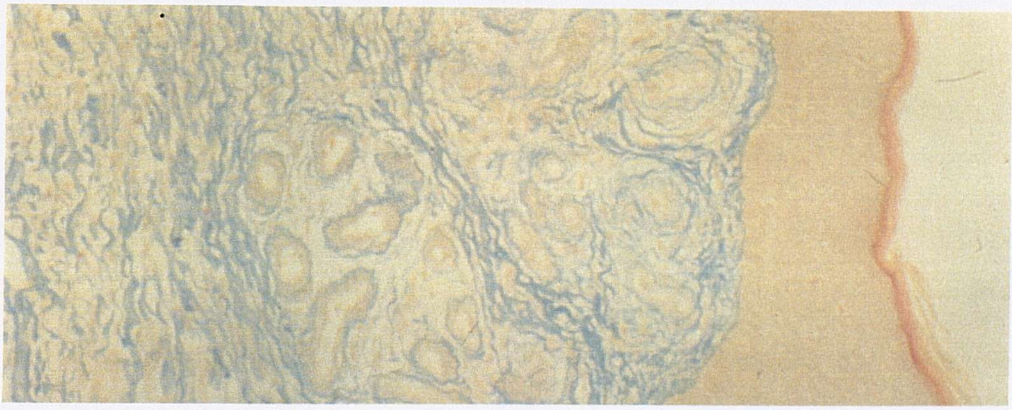


Figure 6.1: The apparent increased number of capillaries is visible in these sections. The elongation and tortuosity of the dilated skin capillaries and the *glomerular* aspect of the capillaries are visible.

a. An apparent increased number of capillaries as shown in figure 6.1.

b. The capillaries were dilated and tortuous as shown in figure 6.2.

c. The capillary wall was thickened and surrounded by a pericapillary halo composed of proteins, neutral polysaccharides, haemosiderin and fibrin (Figure 6.3).

Figures 6.4 and 6.5 show the clinical appearance of the skin and the relative histology section. The biopsy in these patients were taken from skin just at the edge of the lipodermatosclerotic and pigmented area.

In 18 (60%) specimens, collagen IV layers were observed on the basal membrane and around capillary walls. Collagen IV deposits were not visible in normal skin.

Fibrin deposits studied with immunofluorescence were detected in only 8 (26%) of the 30 specimens. They were not visible in normal skin.

Also haemosiderin and histiocytes were only observed in liposclerotic skin, in all specimens.

6.4 DISCUSSION

The results indicated that high skin flux is associated with high capillary density in liposclerotic areas.

The apparent increased number of capillaries in comparison with normal skin has been previously documented (Leu, 1991; Van Den Scheidt et al, 1991; Laaf et al, 1991; Laurora et al, 1993) and it was confirmed by this study.

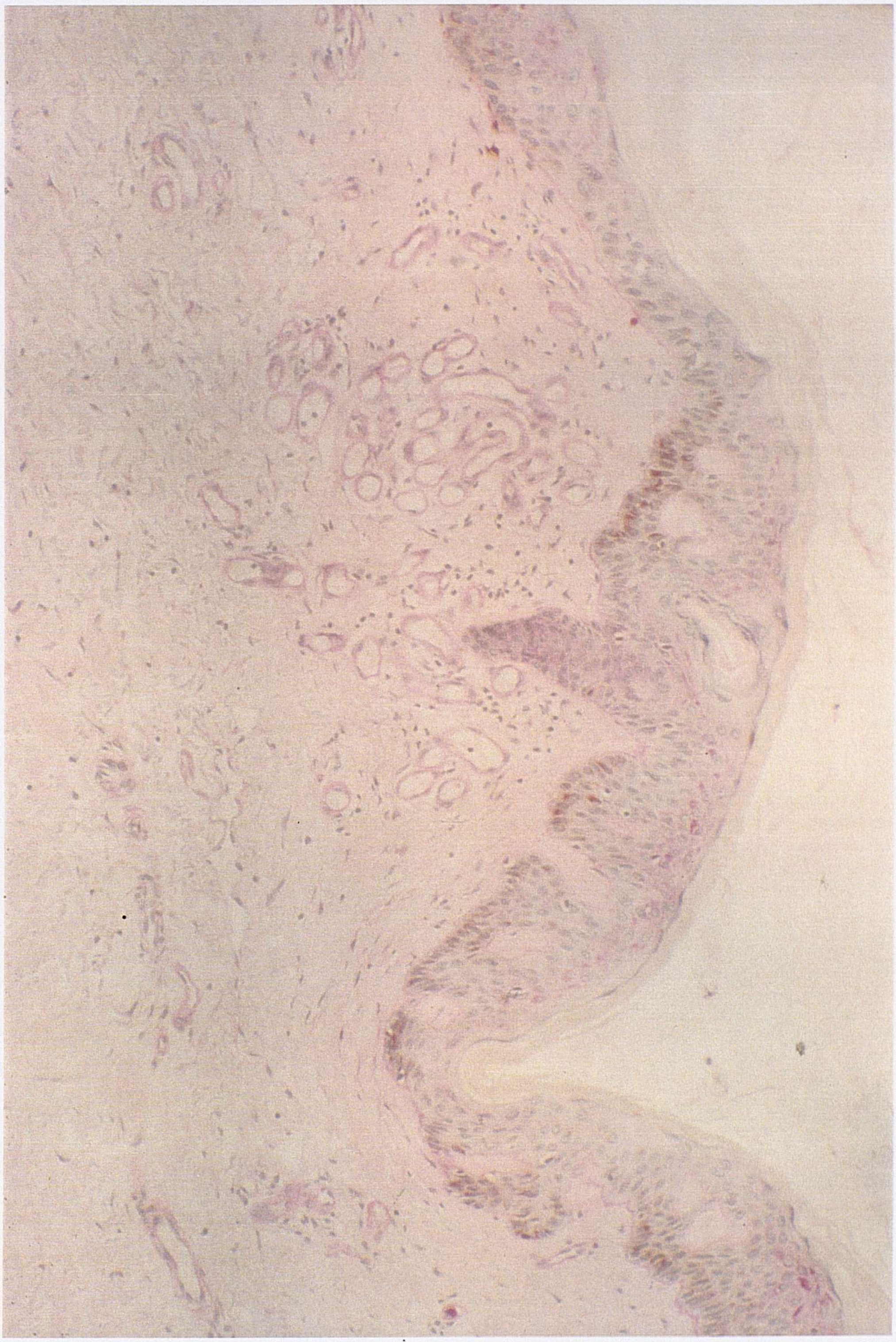


Figure 6.2: The capillaries were dilated and tortuous with an abnormal glomerular-like aspect.

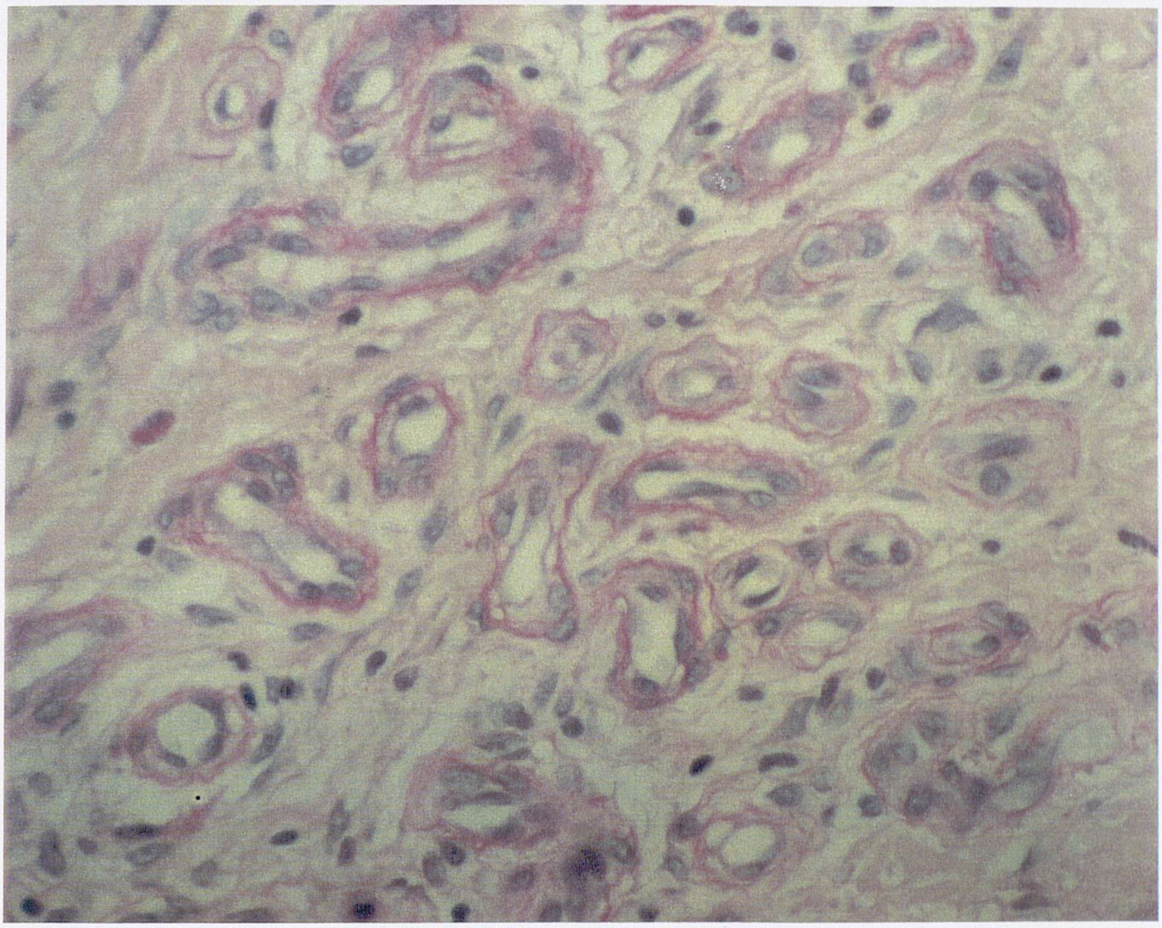


Figure 6.3: The capillary wall was generally thickened in areas of venous hypertensive microangiopathy in the perimalleolar region. In this section the capillaries are surrounded by a pericapillary halo which has been found to be composed of proteins, neutral polysaccharides, haemosiderin and fibrin.

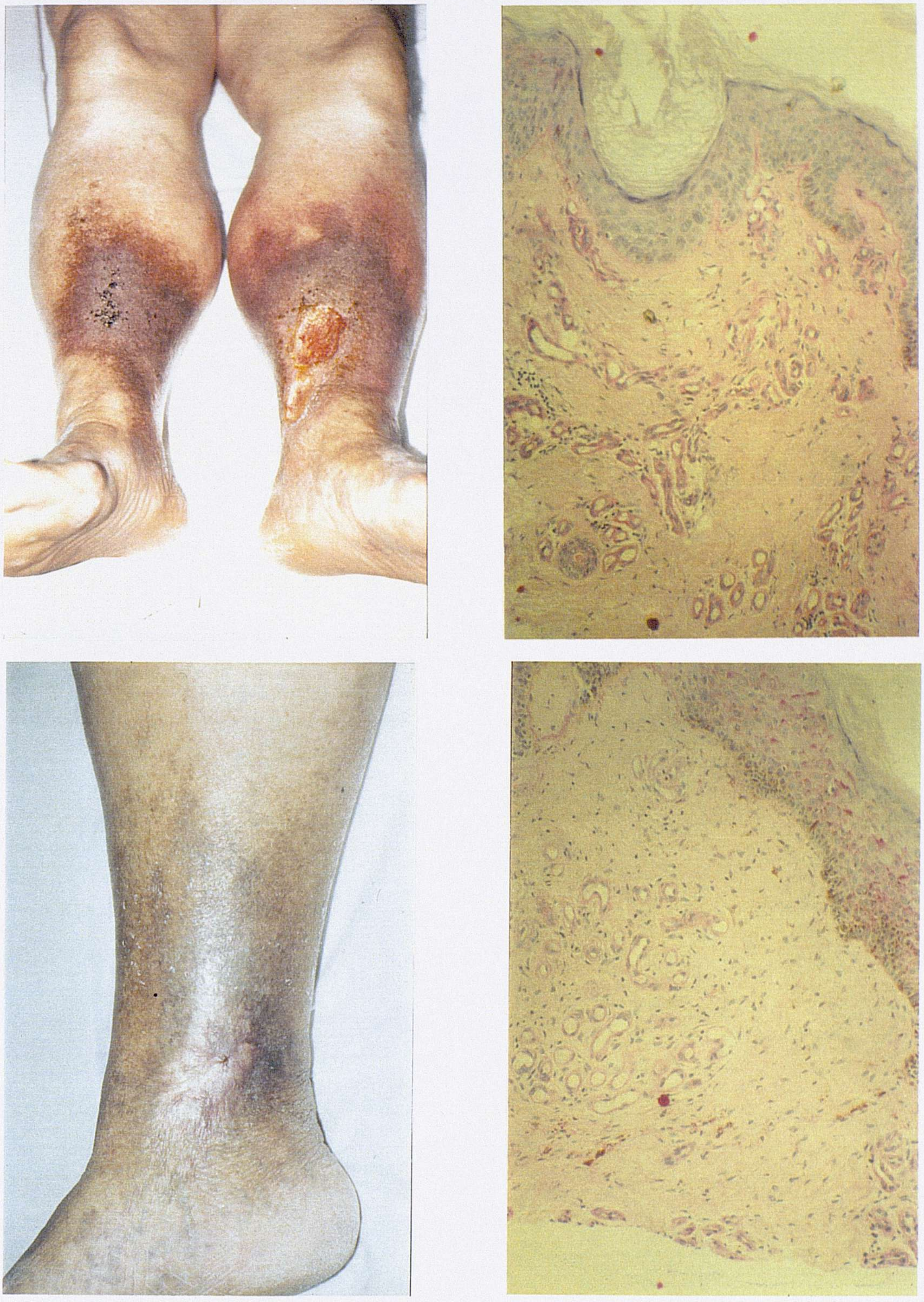


Figure 6.4: (Above): The clinical appearance of the skin in a subject with bilateral post-thrombotic syndrome due to massive caval and iliac thrombosis and the relative histology section. (Below): The clinical aspect and the skin section of a subjects with an healing ulceration.

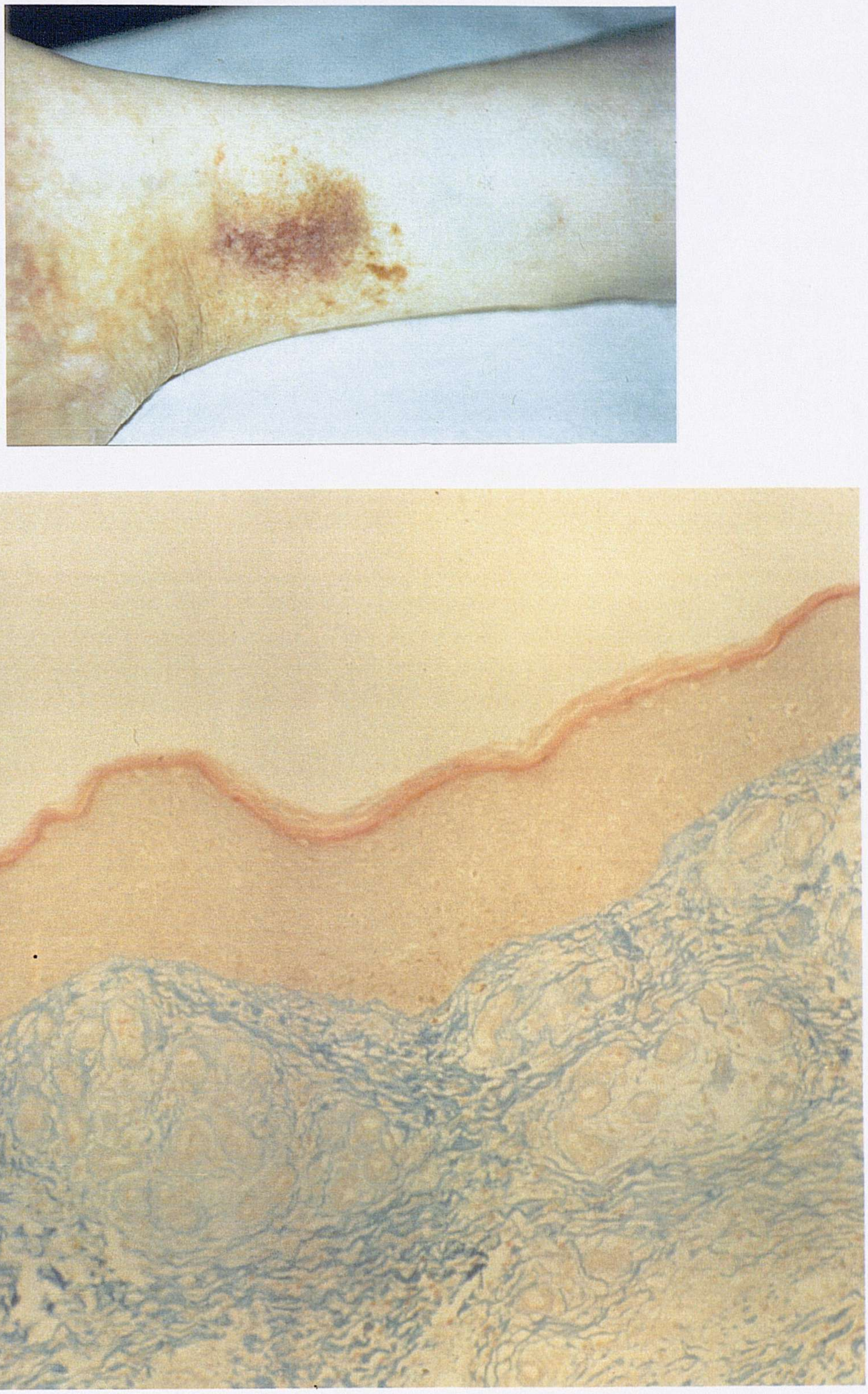


Figure 6.5: The clinical aspect of the skin and the histology skin section in a young subject with severe popliteal incompetence.

In this study collagen IV deposits were observed in almost all patients while fibrin was clearly documented only in 26% of all specimens.

It has been previously observed that the increase in collagen IV in limbs with venous hypertension was found in all specimens while the increase in fibrin deposits was seen in most specimens of liposclerotic skin in previous studies probably in subjects with mode advanced disease (Hammersen, 1977; Burnand et al, 1982; Uitto et al, 1987; Thani et al, 1989; Falanga et al, 1991).

It is possible that the reactive hyperplasia of the normal collagen IV may be the result of high capillary pressure in chronic venous hypertension as indicated by Neumann and Van der Broek, 1991.

Within the group of 30 patients with venous hypertension included in this study 10 patients (6 females) were heavy smokers (without vascular disease).

Comparable ultrastructural changes in the vein wall of the proximal saphenous veins have been also documented recently and associated with smoking (Higman et al, 1994).

In conclusion the finding of an increased skin flux in the perimalleolar region seems to be consistently associated with the histological findings characteristic of long-standing, chronic venous hypertension.

CHAPTER 7

EFFECT OF ELASTIC COMPRESSION ON VENOUS HYPERTENSIVE MICROANGIOPATHY: ASSESSMENT WITH LASER-DOPPLER FLOWMETRY

7.1 INTRODUCTION

In the past assessment of the effects of different treatments on the skin of the perimalleolar region in limbs with venous hypertension has been focused on the purely clinical and subjective effects of therapy. However the qualitative and quantitative effects of therapy on the microcirculation in chronic venous hypertension can now be studied by LDF or by a combination of LDF and other microcirculatory methods such as tc PO_2 and PCO_2 measurements, and by the assessment of capillary filtration.

The following experimental study was planned to evaluate whether laser Doppler flowmetry (LDF) is effective in detecting and quantifying the acute and chronic microcirculatory changes produced by a commonly used and accepted treatment such as elastic compression stockings.

The aim of the study was to evaluate whether elastic compression stockings are useful in reducing the abnormally increased resting skin flux in the perimalleolar region and in improving the venoarteriolar response in subjects with venous hypertension.

7.2 MATERIAL AND METHODS

Below-knee elastic compression stockings (Sigvaris 802; Ganzoni, Switzerland) producing 25 mm of pressure at the ankle level were tested. The stockings were worn for four weeks at least 8 hours daily between 10 a.m. and 8 p.m.

All subjects were evaluated with colour duplex, ambulatory venous pressure (AVP) measurements, laser Doppler flowmetry (BPM,TSI,USA) and with tc PO_2 measurements. These tests were performed at the onset of the study and repeated after 4 weeks.

Thirty-two patients with large, primary varicose veins (12 males; mean age 48; SD 11.4; range 34 to 65), 31 patients with deep venous incompetence (11 males; mean age 48.5; SD 10; range 39 to 66) and 15 normal volunteers (4 males; mean age 49.2; SD 9; range 37 to 66) acting as controls were included. In this study only subjects with venous hypertension (shown by AVP) and chronic venous microangiopathy characterised by increased perimalleolar skin flux (> 2 flux units) and a decreased venoarteriolar response (>20%) were selected.

7.3 RESULTS

Table 7.1 shows the parameters evaluated in the study.

No significant changes in AVP were observed.

After 4 weeks there was a change towards normality in LDF skin resting flux which decreased (figure 7.1) ($p<0.05$) in all included patients. The venoarteriolar response was increased ($p<0.05$) while transcutaneous PO_2 increased ($p<0.05$) only in subjects with deep venous incompetence.

A comparable trend in the increase in $tcPO_2$ was observed but significant values were observed only in subjects with deep venous incompetence.

7.4 DISCUSSION

LDF data indicated that elastic compression stockings reduce the abnormally increased resting skin flux in the perimalleolar region and improve the venoarteriolar response. This may be possibly associated with a better skin perfusion - as documented by the increased transcutaneous PO_2 after 4 weeks of treatment - in patients with the most severe degrees of venous incompetence.

The changes in the microcirculation were not determined by variations in AVP which remained constant. Therefore it appears that there is a direct effect of compression on the skin microcirculation in limbs with venous hypertension which consists of a decrease in the abnormally high skin perfusion. This may be associated with an improved perfusion and nutrition of the skin as documented by the increased transcutaneous PO_2.

The evaluation of the effects of elastic compression on the skin of subjects with venous hypertension explains the action of compression which seems to act with a local mechanism of the skin microcirculation associated with the chronic limitation in venous pressure which may be achieved with stockings.

Table 7.1

Effect on venous hypertension at the perimalleolar skin of graduated elastic compression (25 mmHg at the ankle) for 4 weeks (in subjects with primary varicose veins (VVs) and deep venous disease (DVD).

		Primary VVs		DVD	
	Normal subjects	Before	After	Before	After
Number of limbs	15	32	32	31	31
AVP (mmHg)					
Mean	25	46	47	59	57
Range	>30	39-57	39-57	43-79	43-79
LDF-RF					
Mean	0.65	0.93	0.72*	1.12	0.83*
SD	(0.3)	(0.2)	(0.1)	(0.49)	(0.3)
VAR	37%	19%	26%*	3%	16%*
PO_2 (mmHg)					
Mean	74	65	69 ns	52	66*
SD	8	8	7	9	7

ns = not significant

* = $p < 0.05$

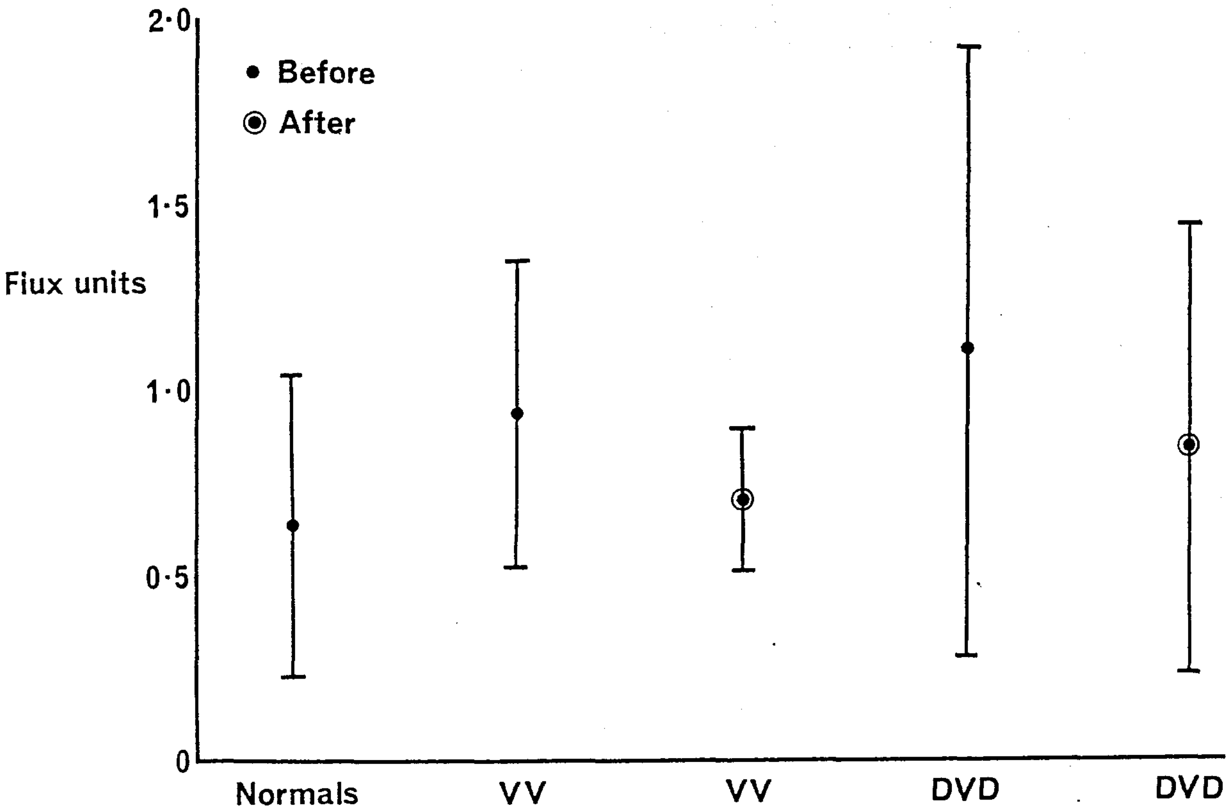


Figure 7.1

Effects of compression on perimalleolar skin flux in limbs with varicose veins (VV) and deep venous disease (DVD) and chronic venous incompetence before and after 4 weeks of compression (mean and 2 sd). The value of RF in normal limbs (NORM), of subjects comparable for age and sex distribution is also shown.

CHAPTER 8

EFFECTS OF INTERMITTENT, PNEUMATIC, SEQUENTIAL COMPRESSION ON VENOUS HYPERTENSIVE MICROANGIOPATHY

8.1 INTRODUCTION

Intermittent, pneumatic compression is obtained with the sequeltial compression device designed for use as mechanical prophylactic method in patients at high risk of venous thromboembolism (Nicolaides at al, 1997).

Previous experimental studies (Kolari and Pekanmaki, 1987) have suggested that this method may be used to improve the microcirculation in patients with chronic venous insufficiency.

The aim of this study was to evaluate the acute effects of the SCD on the microcirculation of the skin of the gaiter area in patients with venous hypertension lipodermatosclerosis and venous ulceration.

8.2 MATERIAL AND METHODS

Sixteen limbs (11 patients, including 6 males; mean age 45.6; SD 8) with chronic venous hypertension and 12 limbs of 12 healthy volunteers (including 6 males; mean age 46; SD 9) were studied.

Laser Doppler resting skin flux (RF) was measured with a Laserflo BPM, laser Doppler flowmeter (Vasamedics, USA) before, during and after sequential compression. The probe was placed at least 2 cm from the edge of the venous ulceration outside the plastic legging. The venoarteriolar response (VAR) was measured lowering the limb 45 cm below the heart level while the subject was resting supine. The occurrence of vasomotor waves was also observed. On completion of the above measurements, the SCD was applied for 30 minutes while the patient was resting supine.

Continuous monitoring of the skin flux was performed with the laser Doppler during the period of sequential compression. The time of onset of rhythmic vasomotor waves and the rate and amplitude of its waves were noted. At the end of the compression RF and VAR were measured. The patient was then asked to rest supine again and monitoring of the skin flux was continued for 2 hours.

The sequential compression device (SCD) Model-5315 (Kendall, USA) used in this study consists of a air compression and control unit linked by plastic tubing with multiple air chamber leggings. The soft plastic leggings, encompassing all the leg from the upper thigh to the ankle - inflate sequentially from the ankle towards the thigh. The pressure in any chamber is at all times lower than the pressure in the adjacent distal chamber. The compression period is 11 seconds with a decompression period of one minute. The pressure is adjustable with a maximum pressure of 65 mmHg at the ankle.

8.3 RESULTS

In limbs with venous hypertension, the mean skin blood flux at rest (RF) was 1.45 flux units, higher than in normal controls ($p<0.05$) (Table 8.1). The VAR was lower (6.8%) than in controls (35%) ($p<0.05$). The vasomotor activity and the amplitude of vasomotor waves were greatly reduced or absent in comparison with normal limbs (Table 8.1; Figure 8.1).

Table 8.1

Skin red cell flux at rest and changes on standing before, during and after sequential compression in 16 limbs with venous hypertension and in 12 limbs of normal controls

	RF MEAN ± SD NORMALS	PATIENTS	VAR MEDIAN AND RANGE NORMALS	PATIENTS	VASOMOTION PATIENTS
After 30' rest	0.56±0.1	1.45±0.1*	35 15-38	6.8 2-11	reduced or abolished
10 minutes after starting SCD	0.59±0.13	1.1±0.3*#	-	-	Present, increased
30 minutes after starting SCD	0.67±0.03	0.90±o.5*#	-	-	Present, increased
30 minutes after stopping SCD	0.47±0.1	0.85±0.2*#	38 15-36	23 9-29)*##	Present, increased
60 minutes after stopping SCD	0.44±0.1	1.10±0.2*#	38 14-48 Present, increased	14 7-27	

* $p < 0.05$ compared with controls

\# $p < 0.05$ compared with baseline

\#\# $p < 0.025$ compared with baseline

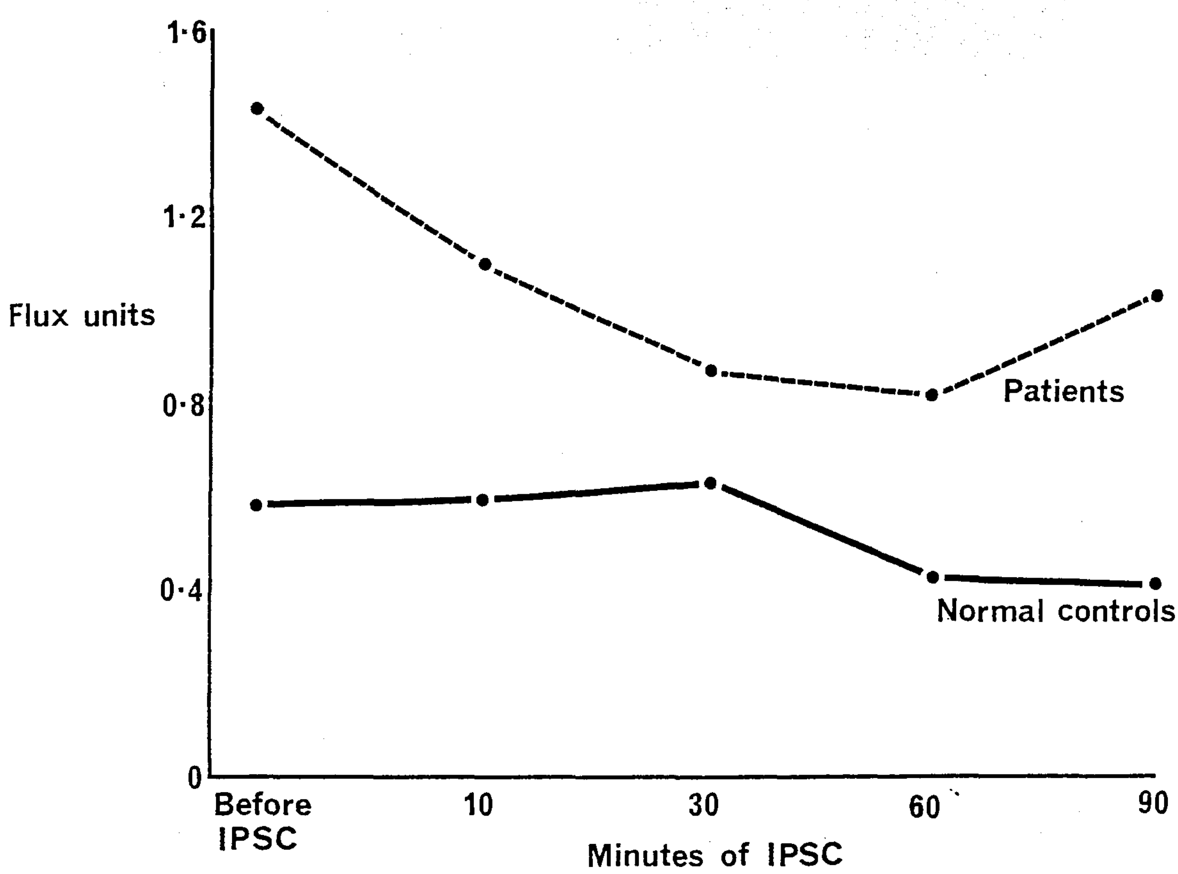


Figure 8.1: Variation in the average resting skin flux (RF) before, during and after sequential compression applied for 30 minutes. The decrease in the average RF was present even 30 and 60 minutes after the end of the compression session (time 60 and 90 minutes).

During sequential compression there was a marked change towards normality in RF, the vasomotor activity increased and vasomotor waves were observed.

The improvement in these parameters was still present at 30 and 60 minutes after stopping the sequential compression (Figure 8.1).

Also, the mean VAR was significantly improved from 6.8% before the sequential compression to 23%

8.4 DISCUSSION

The improvement in resting flux and venoarteriolar response and the induction of vasomotor activity by stimulating the lower limb with sequential compression results in a decrease in skin blood flow since some areas vasoconstrict. An induced, local decrease in skin flux may be a stimulus to further vasomotion and possibly tends to perpetuate this phenomenon.

It appears that elastic compression (Belcaro et al, 1988d) and pneumatic, intermittent sequential compression (Kolari and Pekanmaki, 1987) induces vasomotor activity which persists for some time after the cessation of the sequential compression.

Therefore the application of intermittent sequential compression in venous hypertensive microangiopathy improves the microcirculation and induces vasomotion with a self-perpetuating tendency.

The induction of vasomotor activity by intermittent sequential compression indicates a return of local blood flow regulation towards normal. This response may be due to a direct stimulatory effect on the microcirculation.

Another possible explanation of the microcirculatory response to intermittent, sequential compression is that compression enhances the washout of metabolic or inflammatory mediators that cause the chronic vasodilatation seen in these patients.

This data offer a possible explanation for the accelerated healing of venous ulcers treated with the SCD (Coreridge-Smith et al, 1988).

The persistence of the vasomotor activity after the compression has been stopped is an important finding which needs further investigation in order to determine the "dose" of such treatment, i.e., what is the optimum compression (pressure and cycle), duration and frequency of treatment for use in clinical prectice.

CHAPTER 9

ACUTE EFFECTS OF GRADUATED COMPRESSION STOCKINGS ON VENOUS HYPERTENSIVE MICROANGIOPATHY.

9.1 INTRODUCTION

Graduated elastic compression stockings are commonly used in patients with chronic venous insufficiency and, for the prevention of thrombosis and pulmonary embolism, in patients undergoing surgery.

The aim of this study was to evaluate whether any acute effects of elastic compression with the TED graduated compression stockings (Kendall, USA) on the microcirculation of the skin of the perimalleolar region were visible even after a short period (1 to 3 hours) of treatment in subjects with chronic venous hypertension .

9.2 MATERIAL AND METHODS

In this experiment 20 patients (10 males; mean age 45.5; SD 9.4) with venous hypertension due to deep venous incompetence, with ambulatory venous pressure (AVP) higher than 55 mmHg and lipodermatosclerosis were included.

On the inclusion day resting skin flux was measured at the internal perimalleolar region with a TSI-BPM (TSI, USA) laser Doppler flowmeter. The measurement was repeated after 1 and 3 hours.

The graduated compression stocking was applied to the limb and skin flux was measured again with the same method and sequence after 1 and 3 hours through a small (2 mm) hole in the stocking. During this period the patient was resting supine for the first hour and sitting in an armchair for the following two hours.

9.3 RESULTS

Table 9.1 and figure 9.1 show the results in the treated limbs.

Resting skin flux values in the same limbs when studied without the application of compression had remained unchanged. There was a significant decrease in skin flux in the perimalleolar region at the site of the stocking hole after one hour and three hours ($p<0.02$) of TED compression. The comparison between the effects of compression on skin flux and the absence of variations in the control experiment is shown in figure 9.2).

9.4 DISCUSSION

These results indicate an important, measurable, acute effect of graduated elastic compression on the perimalleolar skin flux. The decrease in skin flux was fast and significance was obtained after only one hour of compression. Also it appeared that the decrease in skin flux obtained in one hour did not significantly change in the following two hours. However this is the first time that it was possible to show and quantify that even a short period of application of graduated compression may be useful in reducing the abnormally increased skin flux in the perimalleolar region in venous hypertension.

Table 9.1

Perimalleolar skin flux variations in the perimalleolar region with the TED graduated compression stockings.

RESTING SKIN FLUX TED	Baseline	1 hour	3 hours
Mean	3.95	1.82	1.72
sd	0.8	0.4	0.5
Range	1.5-4.8	0.7-4.0	0.7-3.2
CONTROLS			
Mean	3.89	3.99	4.1
sd	0.47	0.63	0.5
Range	1.1-4.9	1.1-5.2	1.5-6

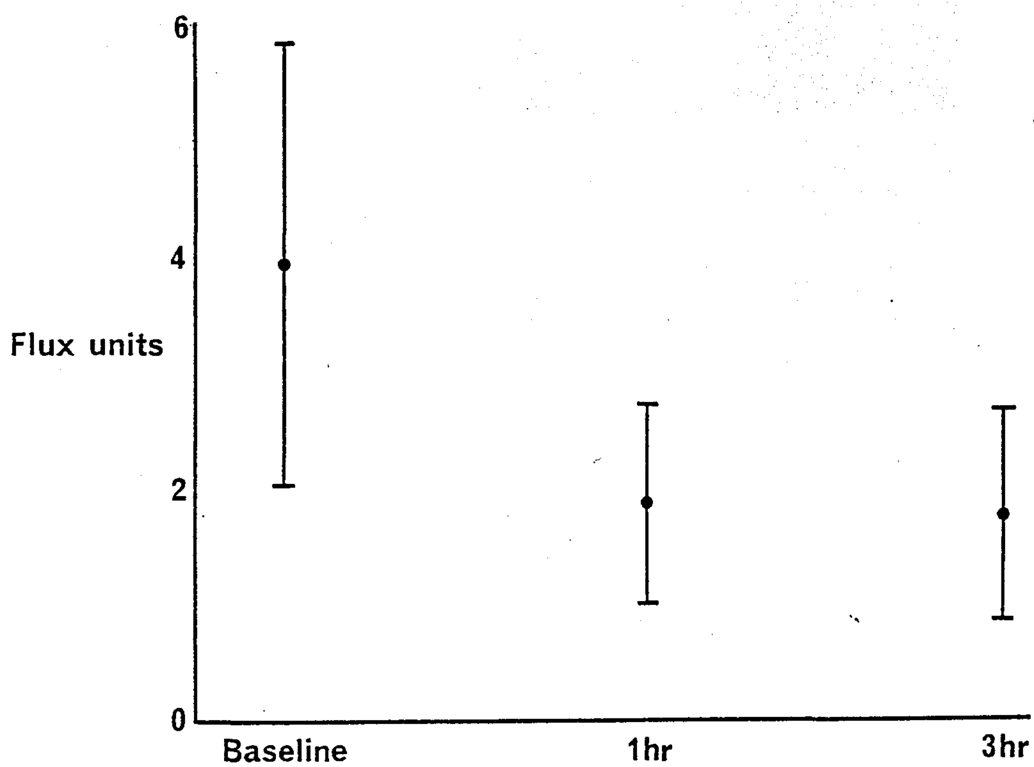


Figure 9.1: Acute variations in skin flux at the perimalleolar region during the application of graduated compression (TED) stockings.

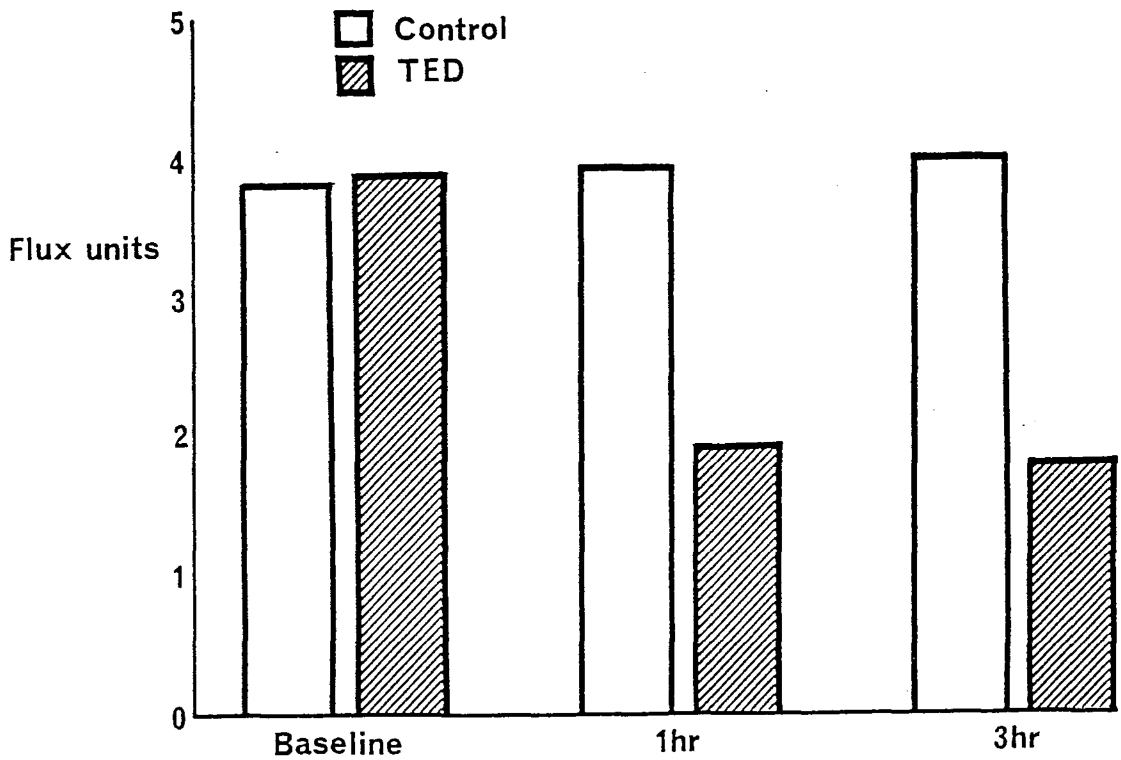


Figure 9.2: Acute variations in the average RF with compression. The comparison with RF in the same limbs studied without compression is shown.

CHAPTER 10

EFFECT OF FLAVONOIDS ON VENOUS HYPERTENSIVE MICROANGIOPATHY. ASSESSMENT WITH LASER-DOPPLER FLOWMETRY AND TRANSCUTANEOUS PO_2 AND PCO_2 MEASUREMENTS

10.1 INTRODUCTION

Flavonoids have been used for many years to treat patients with signs and symptoms associated with varicose veins and deep venous insufficiency. Studies have reported symptomatic relief by the administration of oral preparations (Belcaro et al, 1988e). However, until recently, objective microcirculatory measurements demonstrating the efficacy of these drugs have been lacking.

The aim of this prospective study was to demonstrate whether an oral flavonoid (Paroven or Venoruton, Zyma, Switzerland) was effective in improving the microcirculation in patients with venous hypertension and high skin flux in the perimalleolar region.

10.2 MATERIAL AND METHODS

In this study 35 patients with venous hypertension referred for ankle swelling and lipodermatosclerosis but without ulceration were included. Venous hypertension was the result of deep venous incompetence.

Reflux in the popliteal vein had been documented by colour duplex scanning in all patients.

Patients were randomised into a treatment and a placebo group. As criteria of inclusion all patients had AVP greater than 55 mmHg and venous hypertensive microangiopathy at the limb under evaluation. Patients in the treatment group received a flavonoid (hydroxyethylrutosides, Venoruton) as an oral preparation, 1 g twice a day. The placebo group received the same dose (1 g) of lactose similar in appearance and taste to the active preparation. Elastic compression was not used during the study.

Measurements of RF, VAR, and tc PO_2 and PCO_2 were made before and after six weeks of treatment. A Periflux 1 (Perimed, Sweden) laser Doppler flowmeter was used. Tc PO_2 and PCO_2 measurements were measured with a Microgas Analyser with a combined sensor (CombiSensor, produced by Kontron, U.K.) which detects in the same skin area simultaneously PO_2 and PCO_2

The two groups of patients were comparable for age and sex distribution. Twenty patients were included in the treatment group (mean age 48; SD 79;10 males) and 15 in the placebo group (mean age 48; SD 6; 8 males).

10.3 RESULTS

No drop-outs occurred and no side effects were observed. Results are shown in Table 10.1. There were no significant differences in the mean values of all measurements between the placebo and the treatment group at inclusion into the study.

No significant changes between the baseline value and the measurements performed after six weeks in the placebo group were observed. However, significant changes were observed between the baseline values and measurements performed after six weeks in the treatment group.

Table 10.1

Measurements (mean and SD) in the treatment and placebo groups before and after 6 weeks of oral hydroxyethylrutosides administration.

Treatment group

	Baseline	6 weeks	Normal Values*
RF (mV)	372±48	271± 63*	90-270
VAR median	28	33	43
PO_2 (mmHg)	66±4.4	75±5.6*	81±7
PCO_2 (mmHg)	31±2.6	27±2.4*	25±5

*= $p<0.05$

Placebo group

	Baseline	6 weeks	
RF (mV)	344±34	373± 43	76-270
VAR median	29	30	28
PO_2 (mmHg)	68±6	66±8	65±5
PCO_2 (mmHg)	33±5	34±4	33±6

*** Normal values obtained in standard environmental condition from 10 normal subjects comparable for age and sex distribution (mean age 47; SD 11; 10 males).**

By plotting PCO_2 against the resting skin flux (RF) before and after treatment a linear relationship was found ($r = 0.78$) considering all the readings (figure 10.1). This finding seems to indicate a correlation between the increased skin flux and the increase in skin PCO_2.

10.4 DISCUSSION

The effects of *venoactive drugs* on the skin of the perimalleolar region in limbs with venous hypertension have been mainly focused on the clinical or subjective effects of treaments. The quantitative effects of Venoruton on the skin microcirculation in chronic venous hypertension can be quantitatively demonstrated using LDF or the combination of LDF and tc PO_2 and PCO_2 measurements.

According to the data recorded in the present study it seems that the positive effects of the drug on the microcirculation are associated with a decrease in skin flux comparable to the effects observed with elastic compression, a decrease in skin PCO_2 and an improvement of the venoarteriolar response. The mechanism of these positive changes - related to the clinical improvement of patients with venous hypertension - are still not fully understood.

A larger study including more patients, for a longer period of time is needed. Also it would be interesting to observe whether and how long the microcirculatory improvement persists after the end of the treatment period.

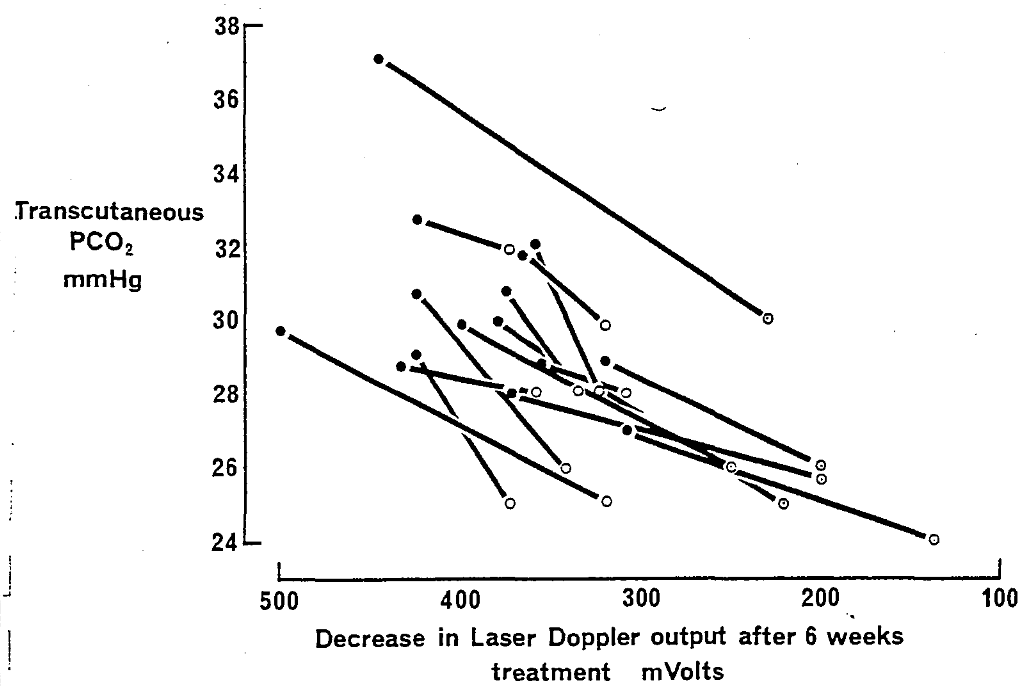


Figure 10.1: Correlation between laser Doppler RF (Perimed) and transcutaneous PCO_2 measurements. The decrease in skin flux is well correlated (r=0.72) to the decrease in transcutaneous PCO_2.

• = before treatment; o = after treatment

CHAPTER 11

EFFECTS OF THE TOTAL TRITERPENIC FRACTION OF CENTELLA ASIATICA (TTFCA) ON VENOUS HYPERTENSIVE MICROANGIOPATHY

11.1 INTRODUCTION

TTFCA has been used in France for many years to treat signs and symptoms associated with venous insufficiency, varicose veins and deep venous disease. Several studies have reported symptomatic relief and a decreased capillary filtration by the administration of the oral preparations (Belcaro et al, 1990a,b; Cesarone et al, 1991).

The aim of this study was to demonstrate whether an oral preparation of TTFCA (Syntex, France), was effective in improving the microcirculation in patients with venous hypertension, venous microangiopathy and high skin flux in the perimalleolar region.

11.2 MATERIAL AND METHODS

In this experimental, clinical study 40 patients with venous hypertension (mean age 44; SD 6; 21 females) with ankle swelling and lipodermatosclerosis were included.

Reflux in the popliteal vein had been shown by colour duplex and AVP was significantly increased all patients having an AVP higher than 60 mmHg.

Patients were randomised into a treatment or placebo group. Patients in the treatment group received TTFCA (tablets, 60 mg b.i.d.) and the placebo group received similar tablets according to the same scheme.

Elastic compression was not used during the study.

Measurements of RF, and capillary filtration - measured as rate of ankle swelling (RAS) by straingauge plethysmography (see Chapter 2, page 112) - were made at inclusion and repeated after six weeks of treatment. A TSI laser Doppler flowmeter (TSI, USA) was used to measure skin flux in the perimalleolar region (as indicated in Chapter 1, pages 84-86).

11.3 **RESULTS**

The two groups of subjects were comparable for age and sex distribution. The mean age was 48 years (SD 9) in the treatment group (22 patients) and 47.6 (SD 7) in the placebo group (18 patients).

Results are shown in Table 7.5. There were no significant difference between the mean values of all measurements between the placebo and the treatment group on admission into the study. There was no significant change between the baseline values and measurements performed after 8 weeks in the placebo group. A significant decrease ($p<0.05$) in RF and RAS was observed in the treatment group (Table 7.5).

11.4 **DISCUSSION**

This study has demonstrated that the oral treatment with TTFCA is effective in improving the microcirculation in limbs with venous hypertension causing microangiopathy characterised by high skin flux and high RAS in the perimalleolar region.

The effects of TTFCA on skin flux and on the rate of ankle swelling and therefore on capillary filtration may be observed even in a limited sample of patients.

Table 11.1

Measurements (mean and SD) in the treatment group before and after 8 weeks of treatment with oral TTFCA. Skin flux normal values with the same equipment, method and in a comparable group of healthy subjects is 0.6±0.11 and RAS is 1.033 ± 0.12.

Treatment group:

	Baseline	after 8 weeks
RF (flux units)	1.93±0.7	1.1±0.4*
RAS (ml/min per 100 ml)	2.16±0.12	1.432±0.122*

Placebo group:

	Baseline	after 8 weeks
RF (flux units)	1.81±0.5	1.7±0.4* #
RAS (ml/min per 100 ml)	2.1±0.11	2.212±0.12* #

* $p<0.05$ = difference before and after treatment

# $p<0.05$ = difference between the two groups

The decrease in local capillary filtration and possibly in the occurrence of oedema may be associated to the symptomatic improvement previously observed in patients treated with TTFCA (Belcaro et al, 1990b).

However large prospective studies, for a longer period are necessary to evaluate the effects of this compound.

It would be interesting to evaluate whether the effects of TTFCA on skin flux and RAS are temporary or may last for some time after the treatment period.

CHAPTER 12

EFFECTS OF SUPERFICIAL VENOUS SURGERY ON VENOUS HYPERTENSIVE MICROANGIOPATHY

12.1 INTRODUCTION

Surgery is commonly used to treat superficial venous insufficiency as this condition may lead to ulceration as well as deep incompetence.

Symptomatic relief possibly due to a reduction in venous hypertension is often observed after surgical treatment of varicose veins and of the sites of superficial venous incompetence such as the saphenofemoral junction, the junction between the short saphenous vein and the popliteal and of the incompetent perforating veins. However the effects of surgery on venous hypertension and microangiopathy is unknown.

The aim of this study was to evaluate whether superficial venous surgery was effective in improving the microcirculation in patients with venous hypertension, venous microangiopathy and lipodermatosclerosis with high skin flux in the perimalleolar region; also whether the effects of surgery were more permanent than the effects produced by compression alone.

12.2 MATERIALS AND METHODS

In this study 100 consecutive patients referred for varicose veins with ankle swelling, lipodermatosclerosis and venous hypertension and microangiopathy were recruited and studied.

As criteria of inclusion, reflux at the saphenofemoral junction had been demonstrated with colour duplex which also excluded deep venous incompetence and, or obstruction.

Also AVP was significantly increased (AVP higher than 50 mmHg) but normalised by a below knee cuff. This indicated pure superficial venous incompetence.

Patients were randomised into a surgical treatment and a control group. Patients in the treatment group were treated with selective surgery of the incompetent venous sites (ligation of the saphenofemoral or saphenopopliteal junction and of the incompetent perforating veins). The sites of incompetence had been detected and marked on the skin on the guide of colour duplex. After surgery patients were asked to wear below-knee elastic stockings (Sigvaris 802, producing an ankle compression of 20 mmHg) at least 8 hours daily for two weeks. The control group was treated only with the same type of elastic compression stockings.

After 6 months the effects of either compression alone or the combination of compression and surgery were compared. Patients were seen again after a second period of 6 months without any form of treatment to evaluate whether the effects of the treatment in the first 6 months after inclusion was temporary or still persisting.

The perimalleolar skin flux was measured in both groups with a BPM (Vasamedics, USA) laser Doppler flowmeter at inclusion and after 6 and 12 months.

12.3 **RESULTS**

The two groups of subjects were comparable for age and sex distribution. The mean age was 47.8 years (SD 8) in the combined treatment group including 48 subjects (23 females) and 48.2 (SD 9) in the compression group including 52 subjects (24 females).

No complications and no drop-outs occurred in the period of observation.

Results are shown in Table 12.1 and figure 12.1

There were no significant differences in RF between the control and the treatment group at inclusion.

A small but significant change between the baseline values and measurements performed after 6 months was observed in the compression group while a significantly higher decrease in RF was observed in the surgery and compression group (Table 12.1).

After 12 months skin flux in the perimalleolar region (figure 12.1) in patients treated with surgery was on average 1.2 (SD 0.4) flux units while in subjects treated only with compression it was 2.33 (SD 0.7) significantly higher than in the surgical group ($p<0.05$).

12.4 DISCUSSION

Results indicated that surgery of incompetent varicose veins is more effective than compression alone in improving the microcirculation in limbs with venous hypertension and microangiopathy, with high skin flux in the perimalleolar region. The decrease in skin flux appears to be associated with the significant decrease in AVP ($p<0.05$) and a longer refilling time ($p<0.05$) achieved after surgery (table 7.6).

These results also indicate that the effects of surgery still persist after 12 months while the effects of elastic compression alone appear to be limited and temporary.

Table 12.1

Perimalleolar skin flux (mean and SD) and ambulatory venous pressure measurements (AVP) and refilling time (RT) in the compression and in the combined (compression and surgery) treatment groups before and after 6 and 12 months. Skin flux normal values with the same equipment, method and in a comparable group of healthy subjects was 0.6±0.11.

Compression treatment group:	Baseline	after 6 months	after 12 months
RF (flux units)	2.36±0.9	1.8±0.5*	2.33±0.7
AVP	44±6	45±7	-----
RT	8±3	8±4	-----
Surgery and compression group:			
RF (flux units)	2.4±0.8	0.9±0.3*#	1.2±0.4*#
AVP	46±7	35±5*#	-----
RT	8±4	19±6*#	-----

* p<0.05 = difference before-after treatment

# p<0.05 = difference between the two groups

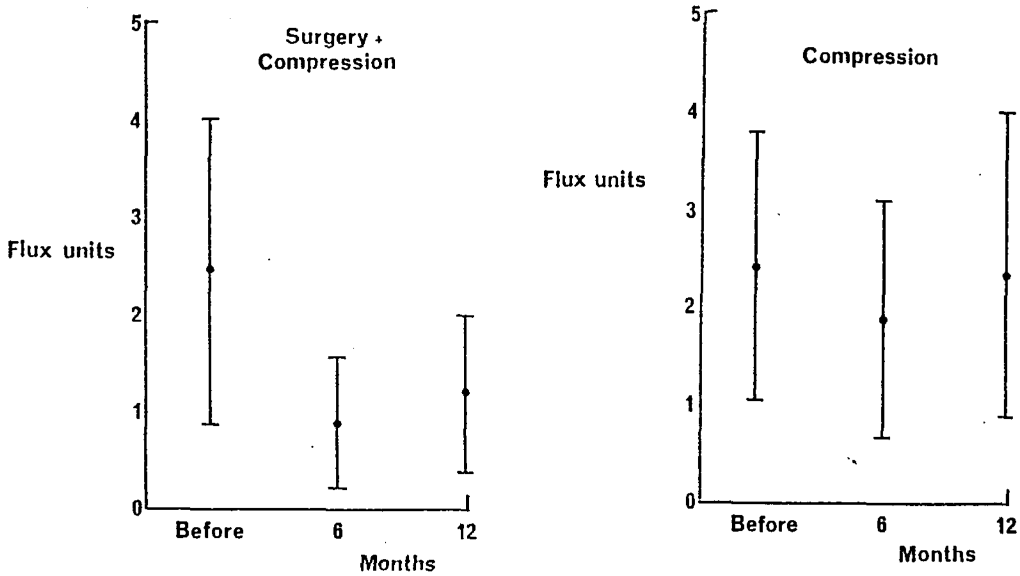


Figure 12.1: Effects of surgery and 6 month compression on the perimalleolar skin flux (left) at inclusion and at 6 and 12 months after inclusion in comparison with mean skin flux (±2 SD) in control limbs (treated only with elastic compression for 6 months). Between the 6th and 12th month no treatment was applied. The effects of surgery still persisted after 12 months (left part of the figure).

In conclusion, the effects of surgery on the skin microcirculation in venous hypertensive microangiopathy appear related both to a decrease in venous pressure and skin flux of the perimalleolar region.

CHAPTER 13

EFFECTS OF SCLEROTHERAPY ON SUPERFICIAL VENOUS INCOMPETENCE CAUSING HYPERTENSIVE MICROANGIOPATHY

13.1 INTRODUCTION

Sclerotherapy is used to treat superficial venous insufficiency as this condition may lead to ulceration as well as deep incompetence. Clinical improvement and reduction of venous hypertension after sclerotherapy of incompetent superficial venous sites have been recently reported (Leu et al, 1993).

The aim of this study was to demonstrate whether sclerotherapy was effective in improving the microcirculation in patients with venous hypertensive microangiopathy and lipodermatosclerosis.

Another aim of the study was to evaluate whether the effects of sclerotherapy were more persistent that the effects of stockings alone. Therefore in a second observation period - between the 6th and 12th months after onset - the stockings were not used.

13.2 MATERIAL AND METHODS

In this study 50 patients referred for recurrent, below-knee varicose veins with ankle swelling, lipodermatosclerosis and venous hypertension were included and studied.

Criteria of inclusion were competence of the deep system with venous reflux in more than four venous sites (incompetent perforating veins) had been demonstrated with colour duplex scanning. Also AVP measurements were indicated a significantly increased venous pressure as all included limbs had AVP higher than 50 mmHg with a refilling time shorter than 10 seconds.

The normalisation of AVP when repeating the exercise test with an ankle tourniquet - applied to exclude the superficial venous system - indicated pure superficial venous incompetence.

After giving informed consent patients were randomised into a sclerotherapy group and into a control group. Patients in the treatment group were treated with selective sclerotherapy of incompetent perforators. The sites of incompetence had been detected and marked on the skin using colour duplex scanning. A comparable control group was included and treated with elastic compression only. In the sclerotherapy group an elastic bandage was used for 2 weeks after injection. After inclusion (and after sclerotherapy for the first group) both groups were treated with elastic compression with thigh-length graduated compression (Kendall-TED stockings).

After 6 months the effects of either compression alone or the combination of compression and sclerotherapy were assessed. The patients were seen again after 12 months. Between the 6th and 12th month after inclusion no compression was used.

The perimalleolar skin flux was measured in both groups with a BPM (Vasamedics, USA) laser Doppler flowmeter at inclusion and again using the same method after 6 and 12 months.

Sclerotherapy was performed by injection in the empty veins of a sclerosing agent (Aethoxysclerol at 2% and 3% concentration). The patient was standing and the vein was compressed between two fingers to keep it empty. Varicose veins large 3 mm or more (when the patient was standing) were treated with the 3% solution while veins of a diameter close to 2 mm were treated with the 2% solution.

The sclerosing agent was injected in more than one venous site (between 5 and 8 in each sclerotherapy session). A small cotton swab was applied onto the injection site and a piece of adhesive elastic bandage (Tensoplast) was then applied. Finally an elastic bandage was applied and the patient was asked to walk slowly for about 15 minutes.

13.3 **RESULTS**

The two groups of subjects were comparable for age and sex distribution. The mean age was 52.4 years (SD 11) in the combined treatment group including 27 subjects (16 females) and 53 (SD 10) in the compression group including 23 subjects (13 females). Results are shown in Table 13.1 and in Figure 13.1. There were no differences in the mean RF between the sclerotherapy and the control group at inclusion. A significant change between the RF baseline values and RF measurements at 6 months was observed in controls and a significantly higher decrease in RF was observed in the sclerotherapy group (Table 13.1; Figure 13.1). In this group the decrease in RF was associated with a decrease in AVP ($p<0.05$) and to a longer refilling time ($p<0.05$).

No AVP changes were observed in the control group.

Table 13. 1

Perimalleolar skin flux (mean and SD) in the compression and in the combined (compression and sclerotherapy) treatment group before and after 6 and 12 months. RF is expressed in flux units, AVP in mmHg and RT in seconds.

Compression treatment group:

	Baseline	after 6 months	after 12 months
RF	2.44±0.7	1.9±0.7*	2.47±0.8
AVP	57±7	58±9	57±11
RT	8.3±4	9±5	7±3

Sclerotherapy and compression group:

	Baseline	after 6 months	after 12 months
RF	2.34±0.7	0.8±0.6*#	1.13±0.4*#
AVP	58±4	37±6	38±9
RT	8±2	15±6	14±4

* $p<0.05$ = difference before-after treatment

# $p<0.05$ = difference between the two groups

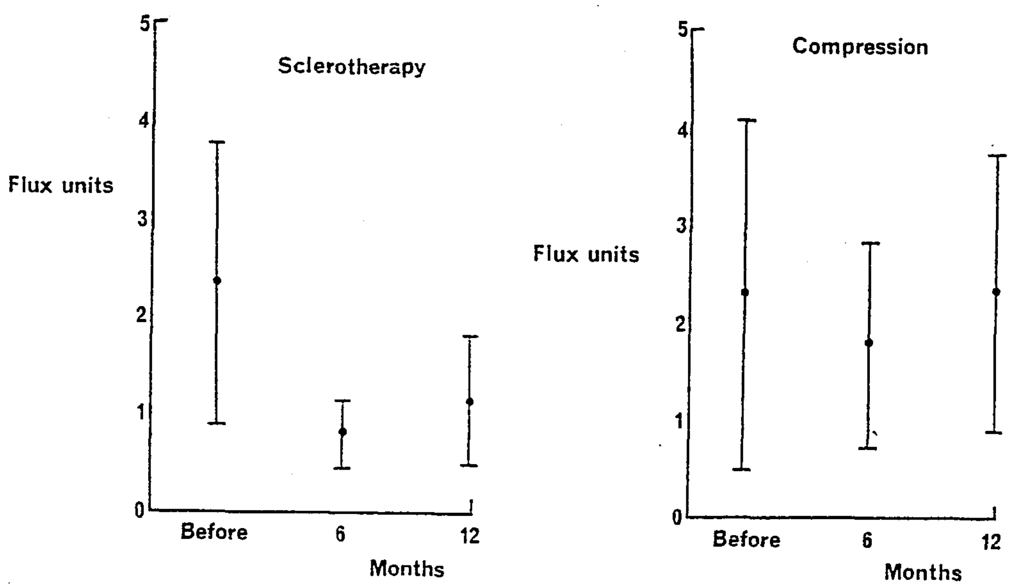


Figure 13.1: effects of sclerotherapy (Scl) (left part of the figure) and 6 month compression on the perimalleolar skin flux at inclusion and at 6 and 12 months after inclusion in comparison with skin flux in control (C) limbs (treated only with elastic compression for 6 months). Between the 6th and 12th month no treatment was applied. The effects of sclerotherapy still persisted at 12 months.

After 12 months the decrease in AVP and RF and the increase in RT in the sclerotherapy group were still present and significant ($p<0.05$). The decrease in RF in controls was lost after 6 months without compression (RF was comparable to the average RF at inclusion as shown in Table 13.1 and Figure 13.1).

13.4 DISCUSSION

This study has demonstrated that sclerotherapy of incompetent venous sites is more effective than graduated compression alone in improving the microcirculation in limbs with venous hypertension and microangiopathy associated with increased skin flux in the perimalleolar region.

The more important and permanent effects of sclerotherapy on the microcirculation were also associated with a significant decrease in AVP and with a longer RT. The improvement was still present after 12 months while in the control group the positive effects of graduated compression were lost when compression was discontinued.

Therefore, in conclusion, the effects of sclerotherapy on the skin microcirculation in venous hypertensive microangiopathy appear to be related both to a decrease in venous pressure and skin flux in the microcirculation of the perimalleolar region.

CHAPTER 14

EFFECTS OF SCLEROTHERAPY VERSUS SELECTIVE SURGERY ON SUPERFICIAL VENOUS INCOMPETENCE IN PATIENTS WITH VENOUS HYPERTENSIVE MICROANGIOPATHY

14.1 INTRODUCTION

Sclerotherapy and venous surgery are commonly used to treat severe superficial venous insufficiency as this condition may lead to lipodermatosclerosis and eventually to ulceration even in the presence of normal deep veins (Bjordal 1972a,b).

In this clinical study we evaluated and treated subjects with severe venous insufficiency and large varicose veins causing chronic venous hypertension and lipodermatosclerosis.

The aim of the study was to evaluate whether sclerotherapy was as effective as selective surgical ligation of incompetent perforating veins in improving the microcirculation in patients with venous hypertension and venous microangiopathy and lipodermatosclerosis.

A secondary aim of the study was to show that the effects of surgery and sclerotherapy were more persistent that the effects of stockings alone. Therefore (as in the previous study reported in Chapter 13) during a second period of 6 months the stockings were not used with the aim of evaluating the persistence of the effects of the two treatments on the microcirculation.

14.2 MATERIAL AND METHODS

In this study 60 patients referred for venous hypertension, associated with recurrent, below-knee varicose veins, lower limb oedema, ankle swelling and, lipodermatosclerosis were included and studied. The following criteria of inclusion were used in selecting patients:

a: the deep system was competent

b. reflux was present in more than 4 venous sites - i.e. varicose veins or incompetent perforators (indicated by colour duplex and AVP measurements;

c: AVP measurements were significantly increased (all limbs had AVP higher than 45 mmHg and the RT was shorter than 10 seconds;

d. no incompetence of the saphenofemoral or saphenopopliteal junction was present;

e. all subjects had high skin flux in the perimalleolar region;

f. AVP measurements were normalised after repeating the exercise test with an ankle tourniquet excluding the superficial venous system. This indicated pure superficial venous incompetence.

Patients were randomised into a sclerotherapy group, a surgery group and a control group treated only with compression. Patients in the sclerotherapy group were treated with selective compression sclerotherapy of incompetent perforators and varices. Patients in the surgical group were treated with selective surgery of the incompetent perforators and larger varicose veins under local anaesthesia using small (1-2 cm) surgical incisions. The sites of incompetence in both groups had been detected with colour duplex and marked on the skin.

After treatment in all groups elastic compression with thigh-length graduated compression (Kendall-TED stockings) was used. In the sclerotherapy group an elastic bandage was used for 2 weeks after injection. After 6 months the effects of compression, of the combination of compression and sclerotherapy or compression+surgery were assessed evaluating the perimalleolar skin flux. During a second period of 6 months no compression or other treatment was used in the three groups.

The perimalleolar skin flux was measured with a BPM (Vasamedics, USA) laser Doppler flowmeter at inclusion and after 6 and 12 months.

14.3 **RESULTS**

The three groups were comparable for age and sex distribution. The mean age was 49.5 years (SD 8) in the control (compression) group including 21 subjects (10 females; 11 males). It was 47 (SD 7) in the compression and sclerotherapy group (18 subjects including 12 females) and it was 49 (SD 8) in the compression+surgery group including 21 subjects (13 females). Results are shown in Table 14.1. There were no significant differences in RF at inclusion. A significant change between the baseline values and measurements repeated after 6 months was observed in all groups (figure 14.1). A significantly more important decrease in RF was observed in the sclerotherapy and surgery groups (Table 14.1). The difference between these two groups was not significant. The decrease in RF was associated with a comparable decrease in AVP in the sclerotherapy and surgery groups while no variations in AVP were observed in the elastic compression, control group.

Table 14.1

Perimalleolar skin flux (mean and sd) in the compression group, and in the combined compression-sclerotherapy treatment group and in the compression-selective surgery group before and after 6 months. RF is expressed in flux units, AVP in mmHg and RT in seconds.

Compression	Baseline	after 6 months	after 12 months
RF	4.27±1	2.2±0.5*	4.2±12
AVP	54±8	57±5#	55±6#
RT	8±3	8±4#	8±3#
Sclerotherapy + compression			
RF	4.3±1.2	2.8±0.6*	1.8±0.2
AVP	57±4	31±8	32±4
RT	7±3	16±4	18±4
Surgery+ compression			
RF	3.8±0.5	1.8±0.6*	1.63±0.2
AVP	55±4	30±4	29±5
RT	8±4	18±5	19±3

* p<0.05 = difference before-after treatment

# p<0.05 = difference between the treatment groups and the control group

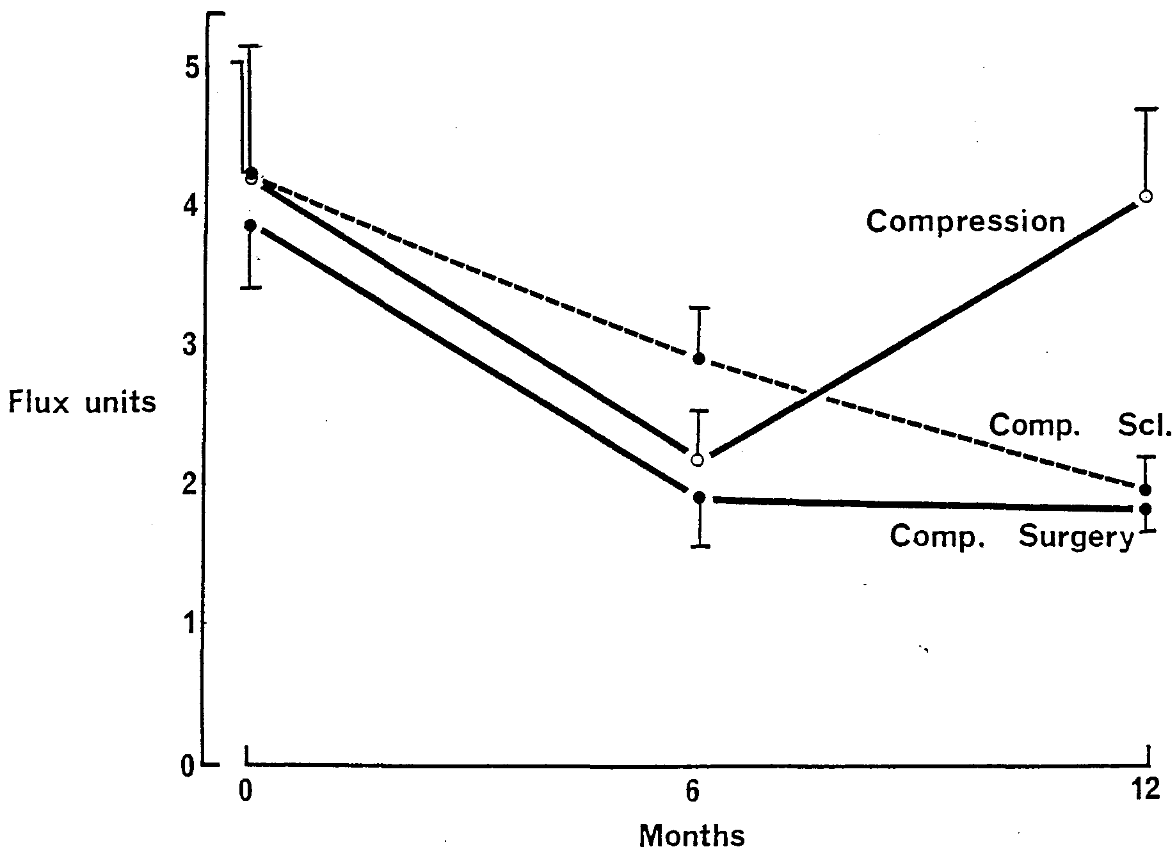


Figure 14.1: Variations in the average perimalleolar skin flux (mean and 1 SD) after 6 months of graduated compression, or sclerotherapy and compression or selective surgery and compression. The effects of compression alone do not last while sclerotherapy and surgery even after compression is no longer used are still clear after 12 months.

After 12 months the new evaluation of skin flux indicated persisting low RF values in the sclerotherapy and surgery groups. However in the control group skin flux increased to levels not significantly different from the values observed at inclusion.

14.4 DISCUSSION

These results indicated that sclerotherapy or selective surgery of the incompetent venous sites are more effective than graduated compression alone in improving the microcirculation in limbs with venous hypertensive microangiopathy and high skin flux in the perimalleolar region. The improvements in the microcirculation are associated with the decrease in AVP and with a longer RT. Therefore the good clinical effects of sclerotherapy and selective venous surgery on the skin microcirculation in venous hypertensive microangiopathy appear to be related to a decrease in venous pressure and a consequent decrease in skin flux in the microcirculation of the perimalleolar region.

In conclusion the microcirculatory effects of treatments persist and last well after compression is no longer used, while the effects of compression for 6 months are temporary and lost after an equivalent period without treatment.

CHAPTER 15

THE VALUE OF LASER-DOPPLER MEASUREMENTS IN PREDICTING THE HEALING OF VENOUS ULCERATIONS

15.1 INTRODUCTION

The value of laser Doppler flowmetry measurements in predicting the healing of venous ulceration has been tested in this prospective study.

The aim of the study was to test the hypothesis that a simple scoring system devised on the basis of laser Doppler measurements such as resting flux and the venoarteriolar response may be useful in separating ulcerated legs with a high healing potential from ulcerated legs which heal very slowly or do not heal in a defined period of time (6 months).

15.2 MATERIAL AND METHODS

One hundred and fifty-two ulcerations associated with severe deep venous incompetence in 122 limbs were studied. Laser Doppler resting flux (RF) and the venoarteriolar response (VAR) were measured according to the methods described in Chapter 2 (pages 110-11), placing the laser Doppler probe at least 2 cm from the edge of the ulcerations. A TSI Laserflo, flowmeter (TSI, USA) was used. The treatment for all ulcers during the six-month observation period was elastic compression with below-knee Futuro elastic stockings (Futuro Company, Cincinnati, USA) and ulcer washing and cleaning without using any local or systemic drug treatment.

Patients with peripheral vascular disease, diabetes, obesity or other systemic or limb problems were excluded.

A simple, arbitrary score system (table 15.1) based on RF and VAR was devised. The venous microangiopathy score was defined according to the severity of microangiopathy. The definition of very low (RF or VAR), low, normal, increased, high and very high was decided (Table 15.1) based on data from our previous work using the same methods and instruments (Chapter 2).

Two groups of ulcerations were considered:
ulcerations associated with very low skin flux situated in almost avascular areas as described by Franzeck (1986) and ulcerations associated with normal or increased skin flux.

15.3 RESULTS

The average age of the patients was 65 years (SD 11; range 56-87) and 77 were female.

Results are shown in Table 15.2 and in figures 15.1 and 15.2. In the normal or increased skin flux group 37.62% of the ulcerations healed completely within 6 months. In the low flux group only 3.92% of the ulcerations healed ($p<0.05$). The total number of ulcerations corresponding to each score and the healed ulcers are shown in figure 15.1.

Figure 15.2 shows the percent of healed ulcers in relation to the score in the two categories of ulcerations.

A progressive decrease in the percentage of healing ulcerations was observed with increase in microangiopathy score. This indicated that the microangiopathy score is predictive of the healing power of venous ulcerations (when no other factors such as infection or diabetes are involved).

Table 15.1

A: Microangiopathy score based on resting flux and the venoarteriolar response. RF is expressed in flux units. The arbitrary score (0 to 3) expresses the clinical severity attributed to the microcirculation parameters (0 normal skin; 3 severely impaired microcirculation).

	RF	SCORE	VAR%	SCORE
ABSENT			0	3
VERY LOW	<0.2	3	1-5	2
LOW	0.21-0.4	1	6-15	1
NORMAL	0.41-2.5	0	22-52	0
INCREASED	2.6-6	1	-----	
HIGH	6-10	2	-----	
VERY HIGH	>10	3	-----	

B: Correlation between VAR and RF scores (on the vertical axis the RF score is shown while the VAR score is on the horizontal axis).

		VAR SCALE NORMAL	LOW	VERY LOW	ABSENT
RF SCALE NORMAL		0	1	2	3
INCREASED	1		1+1	1+2	1+3
HIGH	2		2+1	2+2	2+3
VERY HIGH	3		3+1	3+5	3+3

Table 15.2

Total number of ulcerations patients, number of ulceration for each score and number and percent of healed ulcerations in six months.

SCORE	HIGH FLUX		
	n	Healed	%
0	11	11	100
1	16	12	75
2	14	9	64.3
3	16	3	46.1
4	15	2	13.2
5	16	1	6.25
6	13	0	0
Total	101	38	37.62

SCORE	LOW FLUX		
	n	Healed	%
0	--	--	--
1	--	--	--
2	14	1	7.1
3	17	1	5.8
4	7	0	0
5	8	0	0
6	5	0	0
Total	51	2	3.92

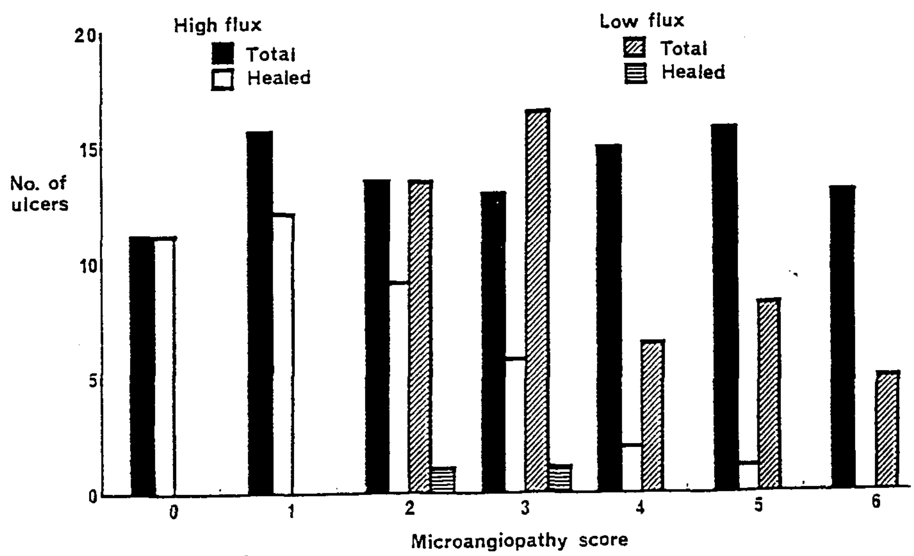


Figure 15.1: The total number of ulcerations relative to each score and the number and percentage of healed ulcers.

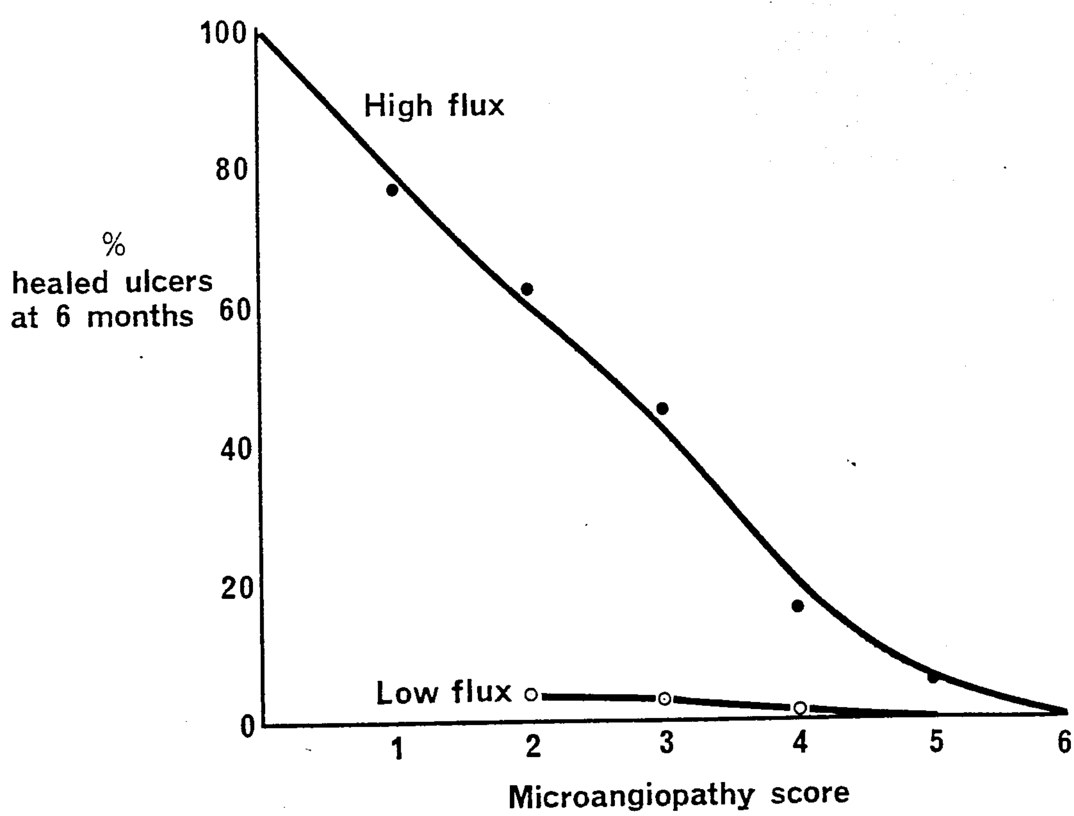


Figure 15.2: The percentage of healed ulcers in relation to the microangiopathy score in the two groups of venous ulcerations.

15.4 DISCUSSION

Results from this study may be useful to decide whether a simple, conservative approach - such as elastic compression - could be taken or whether more radical treatment such as superficial venous surgery, deep venous reconstructive surgery or skin grafting must be undertaken.

The aim of the study - the hypothesis that a simple score system based on laser Doppler parameters - may be useful in separating ulcerations with a high healing power from ulcerations with a low healing power in a defined period of time (6 months) was achieved according to these results.

However these results must be considered preliminary and more prolonged observations in larger groups of patients need to be collected before defining the predictive value of laser Doppler flowmetry parameters in the healing of venous ulcerations.

CHAPTER 16

GENERAL DISCUSSION AND CONCLUSIONS

16.1 INTRODUCTION

Chronic venous insufficiency is generally associated with venous hypertension leading to an abnormal capillary congestion and microcirculatory alterations clinically evident as the skin changes characteristic of venous hypertension (oedema, skin pigmentation, induration, eczema, lipodermatosclerosis and eventually skin ulceration).

The aim of the work described in this thesis was to determine the value of laser Doppler flowmetry in the assessment and quantification of chronic venous insufficiency.

This was achieved by a number of experimental clinical studies. The skin microcirculation (particularly at the internal perimalleolar region, the area most frequently affected by venous hypertensive microangiopathy) was studied by laser Doppler flowmetry (LDF) or by a combination of LDF with other microcirculatory investigative methods.

The studies collected in the thesis were particularly aimed to evaluate the correlation between LDF changes and changes in other physiological parameters such as venous pressure. Also the studies were planned to document the effects produced on venous microangiopathy by different types of treatments commonly used in chronic venous insufficiency.

Initially laser Doppler skin flux at rest (RF) and the venoarteriolar response (VAR) - namely the physiological vasoconstrictory response following postural changes - were compared to ambulatory venous pressure measurements in normal limbs and in limbs of patients with with different degrees of venous hypertension (superficial anr/or deep) also including limbs with venous ulcers (Chapter 3). In comparison with the skin of normal limbs in patients with venous hypertension an increase in RF and a variable decrease in VAR, particularly in severe venous incompetence, were observed. Comparing RF to AVP in normal controls and in patients a linear relationship (r=0.712) between RF and the ambulatory venous pressure was found. This indicates that there is a proportional increase in skin flux with the chronic increase in AVP in patients with venous insufficiency. The venoarteriolar response is unpredictably, variably altered in subjects with venous hypertension with no apparent correlation between the venoarteriolar response and AVP.

In the following study (Chapter 4) it was observed that in subjects with venous hypertension the evaluation of the skin microcirculation by LDF and transcutaneous PO_2 and PCO_2 measurements indicate an increase in RF not directly related to PO_2 or PCO_2 changes.

Capillary filtration measurements (Chapter 5) indicated a linear relationship between RF and capillary filtration (r > 0.7) measured with different methods. This observation revealed the important role of the increased RF in limbs with venous hypertension and its association with the production of oedema which is a very common sign in subjects with chronic venous insufiiciency and hypertension.

In Chapter 6 LDF and skin hystology were compared in order to evaluate the association between the morphological changes seen in venous hypertension and the increased skin flux. The observed findings indicated that the increase in skin flux is associated with clear and consistent histological changes such as an apparent increase in the number of capillary loops, due to the glomerular-like appearance of the convoluted capillaries and to an increased capillary size and thickening of the capillary wall. In most specimens a pericapillary halo was also observed.

Subsequently using the laser Doppler measurements the effects of therapeutic measures on venous microangiopathy were prospectively assessed in a series of clinical studies.

The effects of below-knee elastic stockings (Chapter 7), the effects of sequential compression (Chapter 8) and the effects of graduated compression stockings (Chapter 9) were evaluated in controlled studies. The effects of all these treatments on LDF measurements may be summarised as a generalised decrease of the abnormally high RF and in a general but not consitent, improvement (increase) in the VAR (which was decreased or absent at inclusion). These effects were not only present during or just after the compression period but for some time (days and even weeks) after the treatment period indicating a persistance of the effects of compression.

The effects of two orally administered compounds active in venous hypertension (one flavonoid and the total triterpenic fraction of centella asiatica) were evaluated in Chapters 10 and 11). Both these drugs demonstrated a positive action on RF. The abnormally high skin flux was reduced respectively after 6 weeeks (flavonoid) and 8 weeks (TTFCA) of treatment.

In Chapters 12 and 13 venous surgery and sclerotherapy were evaluated to study the effects of these therapeutic measures on the microcirculation. Both surgery and sclerotherapy were effective in decreasing the abnormally increased skin RF.

In Chapter 14 a 12-month study comparing sclerotherapy and venous surgery (both in combination with compression) with elastic compression alone showed that both treatment methods are equally effective in reducing skin RF and that these effects on RF persist at least 6 months after treatment. Compression alone is useful to reduce skin flux during or just after the treatment period (6-8 weeks), but after 6 months the microcirculation (particularly RF) tends to be as high as it was at the beginning of the study while the effects of sclerotherapy and surgery still persist.

Finally in Chapter 15 a pilot, prospective study is presented. This study indicates that RF and VAR when used in combination to produce a microangiopathy score may be effective in predicting the healing potential of venous ulcerations and to discriminate - on the basis of microcirculatory parameters - those ulcers which are going to heal from those which may require a more careful and active monitoring and treatment.

16.2 RESEARCH THAT NEEDS TO BE DONE

The results described in the clinical studies indicate that there is works that needs to be done particularly in the field of standardisation of microcirculatory measurements so that different centres will be able to study comparable groups of patients. The environmental conditions should be carefully controlled (room temperature, acclimatisation time, site of measurements et cet.) before microcirculatory measurements may be considered for even limited clinical applications.

Also the many different laser Doppler flowmetry standards make laser Doppler mesurements difficult to understand even to laser Doppler users. The increase and decrease in flux, dynamic flux variations due to postural changes or other thermal or physical changes are broadly comparable with any instrument but the scale, variation and range of LDF measurements are different and not quantitatively comparable.

The utilisation of microcirculatory measurements (particularly laser Doppler flowmetry) in the evaluation and quantification of common treatments used in venous disorders as suggested in this thesis should be studied further to confirm their usefulness in analysing the effects of treatment.

The work to be done should consider standard treatments (i.e. elastic compression versus surgery or sclerotherapy) with standard evaluation protocols (i.e. laser Doppler flowmetry) to compare patients' conditions before and after defined treatment periods.

It is also important to compare changes in microcirculatory parameters with changes in medical outcome and patients' quality of life improvement as the final aim of treatment is the improvent they produce on the quality of life.

The microangiopathy score should be used in stratifying patients in prospective, randomised studies testing the efficacy of different therapies.

This use may assess its value further.

* * * * *

GLOSSARY

List of acronyms and abbreviations used in the thesis

APG = air plethysmography

AVP = ambulatory venous pressure

BPM = blood perfusion monitor (Vasamedics, St Paul, Mn, USA)

CF = capillary filtration

DVD = deep venous disease

DF = flux on limb dependency

DVI = deep venous inufficiency

Flux: blood flow component recorded by laser Doppler flowmetry

LD = laser Doppler

LDF = laser Doppler flowmetry

LRR = light reflection rheography

M:F = male:females ratio

PPG = photoplethysmography

RF = resting flux

RT = refilling time

SCD = sequential compression device

SF = flux on standing

Tc PO_2 or PCO_2 = transcutaneous oxigen or carbon dioxide

TED = graduated elastic stockings for venous thrombosis prevention

VAR = venoarteriolar response (postural vasoconstriction)

VSC = vacuum suction chamber

RAS = rate of ankle swelling (measured by straingauge plethysmography)

TTFCA = total triterpenic fration of centella asiatica

r = correlation coefficient

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PUBLICATIONS RELEVANT TO THIS THESIS

Basic Data Underlying Clinical Decision-Making in Vascular Surgery

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5

Lower Extremity Venous Hemodynamics

G. Belcaro, D. Christopoulos, A.N. Nicolaides, *London, England*

Chronic venous insufficiency may be the result of outflow obstruction, reflux or a combination of both. The first question the doctor asks is whether obstruction or reflux are present. The second question is where they are anatomically, if present. The third is how much obstruction or reflux exists (Table I). This last question can be answered in terms of hemodynamics. The tables below list the normal and abnormal hemodynamic values for different anatomically defined conditions.

Ambulatory venous pressure (Table II) is defined as the lowest pressure during a ten tiptoe exercise. It is the oldest diagnostic quantitative test. Ambulatory venous pressure will be high in the presence of popliteal reflux (Table III). For ambulatory venous pressure from 40 to 80 there is a linear relationship with the incidence of ulceration irrespective of what (obstruction or reflux) and where it is (superficial or deep) (Table IV). Ambulatory venous pressure reflects the net effect of all abnormalities that affect hemodynamics.

Photoplethysmographic (PPG) refilling time is similar to ambulatory venous pressure-refilling time. It can identify normal limbs and limbs with superficial and deep venous disease (Table V). However, it is a poor measure of the severity of deep venous disease. Ambulatory venous pressure may be in the range of 45–90 mmHg while the PPG-refilling time is very short (< 10 sec). In this situation a reduction in ambulatory venous pressure (for example, as a result of valve transplantation) will have little effect, if any, on refilling time.

From the Irvine Laboratory for Cardiovascular Investigation and Research, Academic Surgical Unit, St. Mary's Hospital Medical School, London, England.

Reprint requests: Andrew N. Nicolaides, Irvine Laboratory for Cardiovascular Investigation and Research, Academic Surgical Unit, St. Mary's Hospital Medical School, Praed Street, London W2 1PG, England.

Air-plethysmography provides quantitative information about the various components of the calf muscle pump (Table VI): the amount of blood in the reservoir (venous volume), the stroke volume of single step (ejected volume), the ejection fraction, the amount of reflux in ml/sec (VFI) and finally the residual volume (RV) as a result of ten tiptoe movement. The residual volume fraction is linearly related to the ambulatory venous pressure and provides an indirect method to measure ambulatory venous pressure noninvasively.

Tables VII-IX show the relationship between the air-plethysmographic parameters and the incidence of chronic swelling, skin changes and ulceration.

The arm/foot pressure differential (ΔP) with needles in arm and foot veins when the patient is horizontal is the most direct method of assessing the severity of outflow obstruction (Table X). The maximum venous outflow (MVO) using strain gauge plethysmography and one second outflow fraction (OF) using air-plethysmography are noninvasive methods of assessing obstruction (Table XI). The relationship between arm/foot pressure differential (ΔP) and OF is shown in Table XII.

The immediate and long-term effects of elastic compression on venous hemodynamics are shown in Tables XIII and XIV. It appears that graduated elastic compression reduces ambulatory venous pressure by decreasing reflux and increasing the ejection fraction, resulting in a reduced residual volume fraction. The latter is the amount of blood in the calf and determines the ambulatory venous pressure. The improved hemodynamics persist when the compression is removed and the limb retested four weeks later.

Venous hypertensive microangiopathy is the result of chronic venous hypertension. It consists of an increased skin blood flow and a reduction in the venoarteriolar reflex. The latter is a physiological vasoconstrictory response to standing. It prevents high pressure and flow in the capillary bed. In the presence of hypertensive microangiopathy, the high flow is associated with an increased capillary permeability and rate of ankle swelling on standing. Transcutaneous PO_2 measurements are related to the number of nutrient capillary loops open and not to overall blood flow (fibrosis and edema tend to obliterate them). However, because of the high diffusion rate of CO_2, transcutaneous PCO_2 measurements are related to overall skin blood flow. Therapeutic methods that improve venous hemodynamics and venous hypertension, improve the microcirculation. The measurements shown in Table XV are providing a means of studying and understanding the microcirculation and associated skin changes in the gaiter area of the leg.

TABLE I.—**Grades of reflux in the deep veins on descending venography [1,2]**

Grade 0	No reflux below the confluence of the superficial and profunda femoris veins, i.e. the uppermost valve of the superficial femoral vein is competent.
Grade 1	Reflux beyond the uppermost valve of the superficial femoral vein but not below the middle of the thigh.
Grade 2	Reflux into the superficial femoral vein to the level of the knee. Popliteal valves competent.
Grade 3	Reflux to a level just below the knee. Incompetent popliteal valves but competent valves in the axial calf veins.
Grade 4	Reflux through the axial veins (femoral, popliteal and calf veins) to the level of the ankle.

TABLE III.—**Relationship between venographic grades of reflux in the deep veins, ambulatory venous pressure and refilling time [4]**

	AVP* (mmHg)		RT_{90}† (sec)	
	No ankle cuff	Ankle cuff	No ankle cuff	Ankle cuff
Grades 0–2	30–70	10–45	2–15	13–45
Grades 3–4	50–95	40–90	1–8	2–14

*AVP = ambulatory venous pressure
†RT_{90} = refilling time

TABLE IV.—**The incidence of active or healed ulceration in relation to ambulatory venous pressure in 251 limbs [5]**

n	P(mmHg)	Incidence of ulceration (%)
34	<30	0
44	31–40	12
51	41–50	20
45	51–60	38
34	61–70	57
28	71–80	68
15	>80	73

TABLE V.—**Photoplethysmographic refilling time without and with an ankle cuff to occlude the superficial veins [6]**

	Standing		Sitting	
	No ankle cuff	Ankle cuff	No ankle cuff	Ankle cuff
Normal	18–80*	18–80	26–100	26–100
SVI†	5–18	18–50	2–25	18–50
DVI§	3–12	6–18**	2–28	2–30

*RT_{90} > 18 sec without cuff identifies normal limbs.
†SVI = superficial venous insufficiency
§DVI = deep venous insufficiency
**RT_{90} < 18 sec with cuff identifies limbs with deep venous disease

TABLE II.—**Ambulatory venous pressure and refilling time measured with cannulation of the foot vein [3]***

Type of limb	AVP† (mmHg) No ankle cuff	AVP† (mmHg) Ankle cuff	RT_{90}§ (sec) No ankle cuff	RT_{90}§ (sec) Ankle cuff
Normal	15–30	15–30	18–40	18–40
Primary varicose veins with competent performating veins	25–40	15–30	10–18	18–35
Primary varicose veins with incompetent perforating veins	40–70	25–60**	5–15	8–30**
Deep venous reflux (incompetent popliteal valves)	55–85	50–80	3–15	5–15
Popliteal reflux and proximal occlusion	60–110	60–120	—	—
Proximal occlusion and competent popliteal valves	25–60	10–60	—	—

*Standard exercise: 10 tiptoe movements
†Ambulatory venous pressure
§Refilling time
**In one-third of these limbs AVP remained more than 40 mmHg and RT_{90} less than 15 seconds despite the application of the ankle cuff.

TABLE VI.—**Air plethysmography [7–12]**

	Units	Coefficient of variation (%)	Normal limbs	Primary VV*	DVD†
Direct measurements					
Functional venous volume (VV). (The increase in leg volume on standing)	ml	10.8–12.5	100–150	100–350	70–320
Venous filling time (Time taken to reach 90% of VV)	sec	8.0–11.5	70–170	5–70	5–20
Ejected volume (Decrease in leg volume as a result of one tiptoe maneuver)	ml	6.7–9.4	60–150	50–180	8–140
Residual volume Volume of Blood left in the veins after 10 tiptoe maneuvers	ml	6.2–12	2–45	50–150	60–200
Desired movements					
Venous filling index (Average filling rate: 90% VV/VFT 90§)	ml/sec	5.3–8	0.5–1.7	2–25	7–30
Ejection fraction = (EV**/VV)×100	%	2.9–9.5	60–90	25–70	20–50
Residual volume fraction = (RV††/VV)×100	%	4.3–8.2	2–35	25–80	30–100

*VV = varicose vein
†DVD = deep venous disease
§VFT 90 = venous filling time
**EV = ejected volume
††RV = residual volume

TABLE VII.—**Incidence of the sequelae of venous disease in relation to the venous filling index [7–12]**

VFI* (ml/sec)	Chronic swelling (%)	Ulceration (%)	Skin changes with/without ulcers (%)
< 3	0	0	0
3–5	12	0	0
5–10	46	46	61
> 10	76	58	76

*VFI = Venous filling index

TABLE VIII.—**Incidence of ulceration in relation to the residual volume fraction of the calf muscle pump in 175 limbs with venous disease [11]**

Residual volume fraction (%)	Number	Incidence of ulceration (%)
< 30	20	0
31–40	24	8
41–50	48	27
51–60	43	42
61–80	32	72
> 80	8	87

TABLE IX.—**Incidence of ulceration in 175 limbs with venous disease in relation to ejection fraction and venous filling index [11]**

	EF* > 40%		EF< 40%	
	No.	Incidence of ulceration	No.	Incidence of ulceration
VFI† < 5	41	2%	19	32%
VFI 5–10	37	30%	19	63%
VFI > 10	32	41%	27	70%

*EF = ejection fraction
†VFI = venous filling index

TABLE X.—**Arm/foot pressure differential in limbs with outflow obstruction [13]**

Grade	<gkD>P* at rest	Pressure increment during hyperemia
I. Fully compensated	<4	<6
II. Partially compensated	<4	>6
III. Partially decompensated	>4	>6 (often10–15)
IV. Fully decompensated	>>>4 (often15–20)	No further increase

*Arm/foot pressure differential

TABLE XI.—**Maximum venous outflow [14,15]**

Obstruction	Normal	Moderate	Severe
MVO* strain gauge (1 sec) (ml/100ml/mm)	>45	45–30	<30
One second outflow fraction using air plethysmography (percent of varicose vein)	>40	40–30	<30

*MVO = maximum venous outflow

TABLE XII.—**Relationship between arm/foot pressure differential and outflow fraction using air-plethysmography [15]**

	Arm/foot pressure differential (ΔP)	
	>5 mmHg	<5 mmHg
One second outflow fraction using air-plethysmography	14–33%	35–60%

TABLE XIII.—**Effect of applying graduated elastic compression on venous hemodynamics* [16]**

	Mean percentage change	
	Limbs with SVI† (n = 22)	Limbs with DVD§ (n = 9)
Venous pressure		
Ambulatory venous pressure	−48**	−18%**
Refilling time	+114**	+56% NS
Air-Plethysmography		
Venous volume (ml)	−9††	+3
Venous filling time	+24	+57**
Venous filling index	−25**	−28**
Ejected volume	+7 NS	+49††
Ejection fraction	+19**	+49**
Residual volume	−29**	−10 NS
Residual volume fraction	−22**	−14**

*Medium compression. 18 mmHg at ankle for superficial venous incompetence (SVI) and high compression 27 mmHg at ankle for deep venous disease (DVD). Kendall Research Center, Barrington, Illinois.
†superficial venous incompetence
§deep venous disease
** $P < 0.01$ Wilcoxon test for paired samples
†† $P < 0.05$

TABLE XIV.—**Effect of graduated elastic compression for four weeks on venous hemodynamics in 20 limbs with superficial venous incompetence (primary varicose veins)* [17]**

Venous pressure	Mean percentage change
Ambulatory venous pressure (mmHg)	−16†
Air-Plethysmography	
Venous volume (ml)	−5.5†
Venous filling index (ml/sec)	−15†
Ejected volume (ml)	−3
Ejection fraction (%)	+21†
Residual volume (ml)	−30†
Residual volume fraction (%)	−27†

*Limbs tested without the elastic stockings: graduated medium compression thigh length stockings with 30 mmHg ankle compression, manufactured by Kendall Futuro, Cincinnati, Ohio, were worn for four weeks.
† $P < 0.01$ Wilcoxon test for paired samples

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Skin blood flux and the venoarteriolar response in the perimalleolar area in patients with venous hypertension

G. LAURORA*, M. R. CESARONE*, L. INCANDELA and G. BELCARO* #

*From the *Microcirculation Laboratory Cardiovascular Institute (Head: Prof. A. Barsotti) "G. D'Annunzio" University, Chieti, Italy and #Irvine Laboratory for Cardiovascular Research and Investigation St. Mary's Hospital Medical School, London, UK*

In patients with venous hypertension due to postphlebitic syndrome or varicose veins skin changes, liposclerosis and ulcerations are associated with increased skin blood flux at rest, a decreased venoarteriolar response and increased capillary filtration. Using laser-Doppler flowmetry we studied skin flux and the venoarteriolar response in the perimalleolar region in 100 normal limbs, 100 limb with varicose veins and 100 postphlebitic limbs with edema, skin changes and liposclerosis. The venoarteriolar response was studied with the leg on dependency, the foot being 50 cm below heart level. Flux at rest and on dependency were increased and the venoarteriolar response decreased in both groups of patients at a significantly greater extent in postphlebitic limbs. In conclusion laser-Doppler flowmetry measurements differentiate between normal limbs and those with venous hypertension and between postphlebitic limbs and limbs with venous hypertension due to varicose veins. The increase in skin flux and decrease in venoarteriolar response may be useful to define and quantify the degree of microangiopathy and the effects of treatments in venous hypertension.

Key words: **Skin blood flux - Venous hypertension - Postphlebitic syndrome - Liposclerosis - Laser-Doppler - Flowmeters.**

In normal subjects, the increased venous pressure produced by lowering the foot below heart level induces a venoarteriolar response [1, 2] which increases the precapillary resistance,[1, 3] and decreases capillary blood flow thereby preventing an increase in fluid loss as edema.

Skin blood flux and the venoarteriolar response can be noninvasively studied by laser-Doppler flowmetry.[2-5]

In venous hypertension the causes of tissue hypoxia, liposclerosis, and eventually ulceration are postulated to be due to increased chronic fluid filtration with chronic pericapillary deposition of fibrin.[6, 7]

The changes in the microcirculation particularly the increased skin flux and the reduction in efficacy of the venoarteriolar response [5] may be the initial cause of this process.

The aim of our study was to confirm the hypothesis that in patients with chronic venous hypertension due to postphlebitic syndrome or varicose veins there is an increase in skin blood flux with loss of an ef-

Address reprint requests to: Dr. G. Belcaro - Via A. Vespucci, 65 - 65100 Pescara (Italy).

fective venoarteriolar response which can be quantified using laser-Doppler flowmetry.

Patients and methods

Two-hundred patients with chronic venous hypertension (100 due to deep venous incompetence and 100 to superficial incompetence due to varicose veins) were studied together with one-hundred controls matched for age and sex. Deep or superficial incompetence was documented with colour duplex scanning and ambulatory venous pressure (AVP) measurements.[8] Patients had edema, skin changes and liposclerosis but no ulceration.

In 23 limbs there was a history of ulceration healed at least 6 months before. In all subjects foot pulses were palpable and the ankle: brachial systolic pressure index measured by Doppler ultrasound was normal (>1.2). The cardiovascular and renal system in all subjects were normal, there were no diabetics and none was under drug treatment.

Ambulatory venous pressure [8] was measured with a needle inserted in a vein of the dorsum of the foot to record the lowest venous pressure during a standard exercise and the refilling time. Patients with venous hypertension had a significantly higher ambulatory venous pressure and shorter refilling time. Ambulatory venous pressure was significantly higher ($p<0.05$) and the refilling time lower in postphlebitic limbs. Normal limbs had an ambulatory pressure lower than 45 mmHg and refilling time longer than 18 seconds [8, 9] (Table I).

In limbs with superficial incompetence the refilling time was normalised by an ankle tourniquet excluding the superficial veins. This indicated a competent deep venous system.

The maximum venous outflow [9] was normal in all limbs indicating that no obstruction was present.

With the patient resting supine the laser-Doppler flowmeter probe (Laserflo, Vasamedics, St. Paul, MN, USA) was placed on the skin of the internal perimalleolar region, 4 cm proximal to the medial malleolus.

TABLE I.—*AVP (ambulatory venous pressure) and refilling time (RT) in patients with postphlebitic limbs, varicose veins and normal limbs.*

	Postphlebitic limbs	Varicose veins	Normal limbs
No. of limbs	100	100	100
AVP mmHg	63±16	54±11*	33±9.7
RT seconds	11±8	13.5±10*	27±9.2
AGE years	45.4±11	46±10	45.5±10.3
Sex	50:50	50:50	50:50

*) AVP and RT were normalised with an ankle tourniquet (indicating that incompetence was superficial).

Previous studies have shown that this area is the most affected by venous hypertension liposclerosis and ulcerations. [5, 10] After 30 minutes acclimatisation at constant room temperature (22°C), the baseline resting flux (RF) was recorded as the average within four minutes. The limb under examination was then lowered straight to 45 degrees until the foot was 50 cm below heart level. Skin flux on dependency (DF) was recorded after a one minute interval (to avoid motion artifacts) for four minutes.

RF and DF were measured in flux units and expressed as the mean flux during the four minutes of measurement.

The venoarteriolar response was calculated for each subjects as:

$$VAR = [(RF-DF)/RF] * 100.$$

All tests were performed before 10 a.m. to minimise the effects of edema on measurements.

By repeating the laser-Doppler measurements 10 times in 25 normal limbs the coefficient of variation of RF and DF for each limb was found to be 13% and 14% respectively.

The number of years from the initial episode of deep venous thrombosis originating the postphlebitic syndrome was also recorded from the clinical hystory.

In all patients haemoglobin and routine blood test were within the normal range.

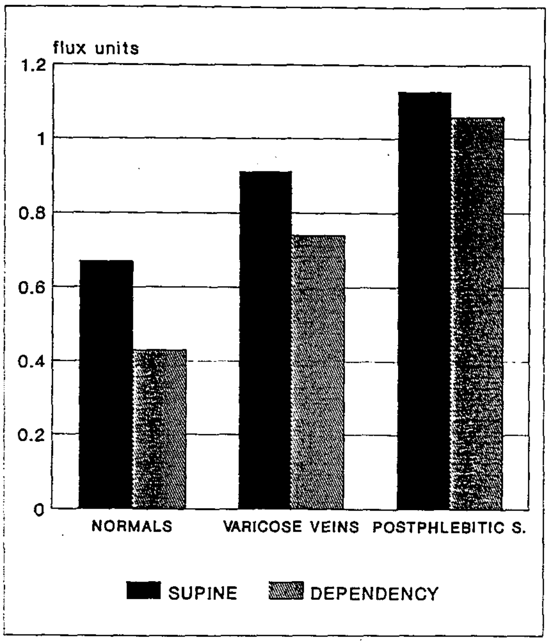

Fig. 1.—Skin flux in the perimalleolar region in the three groups in the supine position and on leg dependency. Skin flux was increased in both groups of patients and significantly higher in the postphlebitic group.

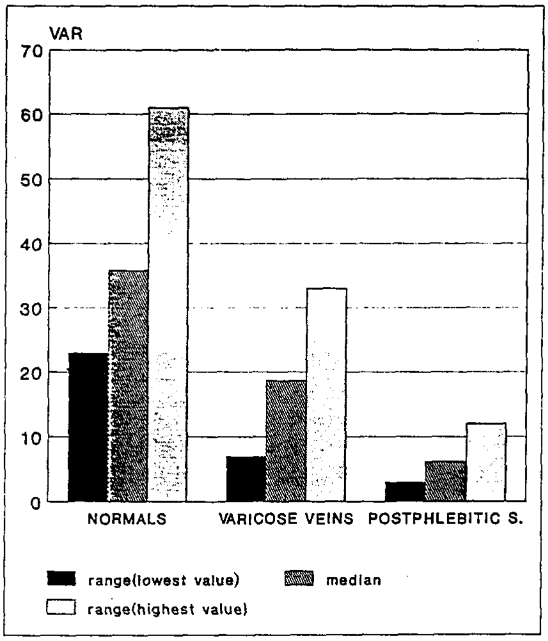

Fig. 2.—The venoarteriolar response in the three groups. The decrease in VAR in the two groups of patients is greater in postphlebitic limbs.

TABLE II.—*Resting (RF) flux, flux on dependency (DF) and the venoarteriolar response (VAR) in 100 normal limbs and in 200 limbs with venous hypertension (100 postphlebitic limbs and 100 limbs with superficial venous incompetence).*

	RF (mean ± sd)	DF (mean ± sd)	VAR (%)	
			Mean	Range
Normals	0.67 ± 0.13	0.43 ± 0.1*	35.8#	23-61#
Postphlebitic limbs	1.13 ± 0.24#+	1.06 ± 0.12#+	6.19#+	3-12#+
Varicose veins	0.91 ± 0.13#	0.74 ± 0.22*#	18.68#	7-33#

*) $p<0.05$ (difference in flux due to postural change). #) $p<0.05$ (difference from normal subjects). +) $p<0.05$ (difference between limbs with varicose veins and postphlebitic limbs).

The differences among groups were statistically evaluated using the Mann-Whitney U-Test.

Results

The age of the patients and of the controls and the male-female ratio were comparable (Table I).

Laser-Doppler measurements are shown in Table II. In normal limbs RF and DF were significantly lower than in patients. DF was significantly lower than RF in normals ($p<0.02$) and limbs with varicose veins ($p<0.05$) as shown in Figure 1.

In normal limbs the VAR was on average 35.8%, higher ($p<0.05$) than in patients ($p<0.05$). In postphlebitic limbs, RF and DF were significantly higher ($p<0.05$) and the VAR was lower ($p<0.05$) than in limbs with varicose veins (Fig. 2).

TABLE III.—*Difference between postphlebitic limbs with and without history of ulcerations.*

	Limbs with history of ulcerations	Limbs without history of ulcerations
RF	1.13±0.1	1.14±0.12
DF	1.08±0.18	1.14±0.1
VAR	6.21%	6.11%
Years after DVT	9.5±2.2*	4.1±1.3

*) $p<0.05$.

No flux differences in SF, DF and VAR were observed between postphlebitic limbs with and without history of ulcerations. However there was a significant difference in the duration of the postphlebitic syndrome in the two groups — longer in the group with previous ulcerations — as shown in Table III.

Discussion

The output from the laser-Doppler flowmeter is proportional to skin blood flow in superficial skin vessels.[2 4] Comparative studies with capillaroscopy indicate that laser-Doppler flowmetry detects flow in subcapillary plexuses and shunts as well as in the capillary loops.[2] The reflex responses observed by the two techniques are comparable.[2] However laser-Doppler flowmetry is a simpler method to study skin flux at the perimalleolar region and to evaluate its variations due to postural changes.

The changes found in patients with venous hypertension are similar to those observed in diabetics with peripheral neuropathy.[2 5] These patients, as those with post-phlebitic limbs often have edema prior to the development of further changes.

In normal limbs the increase in pre- and post-capillary resistance induced by the venoarteriolar response counteracts the increase in capillary hydrostatic pressure.[1] This mecchanism opposes the tendency of increase in fluid filtration out of capillaries during periods of high vascular transmural pressure and it is considered as an edema protection factor.[1]

If the elevation in skin flow persists, with the high hydrostatic pressure, there is increased net fluid loss proportional to the skin flow increase at rest and on postural changes increasing the hydrostatic load. Also capillary filtration is inversely proportional to the venoarteriolar response.[10]

With increased skin flow the accompanying increase in fluid and protein loss, pericapillary fibrin deposition and thickening of the basement membranes [6 7] possibly lead in time to the development of liposclerosis, skin pigmentation and ulceration. Following an increased filtration rate,[10 11] fibrin deposits are formed early in the development of chronic venous hypertension. Fibrin acts as a matrix for the formation of collagen, capillaries are fixed and possibly the stiff capillary walls cannot adjust themselves to changes in hydrostatic load.[11]

The presence of an ulceration when the stage of chronic venous hypertension has been reached seems to be correlated with the duration of the disease more than to further deterioration in the microcirculation.

The finding of the increase in skin flux and decrease in venoarteriolar response and their quantification could be used to define and quantify the degree of venous hypertensive microangiopathy and possibly the risk for ulcerations. Also these simple laser-Doppler measurements may be used to evaluate if it venous hypertension can be improved by physical measures such as elastic compression or pharmacological agents and to quantify the effects of treatments in venous hypertensive microangiopathy.

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Microcirculation Laboratory, Cardiovascular Institute (Dir.: Prof. G. Barsotti), G. D'Annunzio University, Chieti, Italy

Elastic stockings in diabetic microangiopathy

Long term clinical and microcirculatory evaluation

G. Belcaro, G. Laurora, M. R. Cesarone and P. Pomante

In patients with diabetes mellitus microangiopathy and neuropathy cause disabling foot complications often precipitated by minor trauma or injury [1, 2].

New information has been recently obtained on diabetic microangiopathy using laser-Doppler flowmetry (LDF) [3, 4, 5]. In diabetics, laser-Doppler skin flux is related to the transcutaneous PO_2 and PCO_2 and to the increase in capillary filtration which leads to the development of edema [4, 5, 6, 7, 8]. The technique of LDF can be used to monitor the effects of treatment on the microcirculation in groups of diabetics with microangiopathy [9].

Elastic stockings are commonly used to treat and control venous hypertension, lymphatic problems and other conditions related to the development of edema. They are effective in improving the microcirculation and in controlling the abnormally increased capillary permeability [10] in venous hypertensive microangiopathy. In this condition similarities can be found with diabetic microangiopathy namely the increase in skin flux and capillary filtration and the decrease in venoarteriolar response [11, 12]. These alterations are associated with the development of edema and they are positively affected by elastic compression.

In a previous pilot study [4] we have observed that elastic stockings are useful in improving some microcirculatory parameters in patients with diabetic microangiopathy.

The aim of this prospective study was to evaluate prospectively the effects of elastic stockings on the microcirculation and on the development of diabetic ulcerative lesions in patients with diabetic neuropathy and microangiopathy during an observation period of 4 years.

Patients and methods

After having given informed consent 160 patients with diabetic microangiopathy were included in an open study. Patients were under stable control with diet and oral antidiabetic agens.

They were randomly included into two treatment groups: *one group* was treated with elastic compression stockings; the patients of the *second group* were followed-up as controls.

Standard, below knee elastic stockings with compression at the ankle of 25 mmHg were used (Sigvaris 802[1]). Patients were asked to wear the stockings at least 6 hours every day during their usual working or activity hours.

Subjects with severe proteinuria and renal impairment, frequent history of ketosis, poorly controlled diabetes, heavy smokers, hypertension or cardiovascular disease and previous diabetic foot ulcerations were excluded. Also no drugs – excluding drugs used to control diabetes – were used during the study. All patients had altered ankle reflexes and vibration sensory threshold at the toes measured by a biothesiometer [2, 13, 14] as a sign of initial neuropathy.

Ankle to arm systolic blood pressure ratio assessed by Doppler was > 1.1 in all patients.

LDF measurements were performed at constant room temperature (22 ± 1 °C) after 30 minutes acclimatization and supine resting. Skin flux was recorded with the probe placed at the dorsal, distal part of the foot. A Laserflo [VASA-MEDICS – St Paul, MN, USA] was used. Flux measurements were expressed in flux units according to the manufacturer's specifications. *Supine resting flux (RF)* was measured as the average flow in 3 minutes. The patient was then asked to lower one leg at the time until the foot was 50 cm below heart level, with the leg resting at an angle of 45 degree. *Flux on dependency (DF)* was recorded as the lowest flow in 5 minutes after lowering the leg excluding the first minute of recording to avoid motion artifacts. *The venoarteriolar response (VAR)* [1–5] was calculated evaluating the percent flow decrease on dependency: {VAR = [RF-SF]/[RF/100]}.

With this technique the reproducibility of the measurements measured in 20 patients (10 times at each limb) for RF and DF was respectively of 13% and 8%.

Routine blood test, glycosilated haemoglobin and blood sugar levels, hepatic and renal function tests were repeated every three months. After the initial assessment all tests were

[1] Ganzoni, St. Gallen, Switzerland.

Table I: details of patients (M:F = male:female distribution; DD = duration of diabetes [years]).

	No of patients	Drop outs	Age		M:F	DD mean ± sd
			mean ± sd	range		
Stockings	74	6	52.8 ± 11	34–68	36:38	15.4 ± 7
Controls	75	5	53.2 ± 12	33–68	39:36	15.1 ± 8
Total	149	11				

repeated every year. Also 20 normal volunteers were followed up 4 years to evaluate their varation in RF, DF and VAR in 4 years.

Statistical evaluation of the results was made using the Mann-Whitney U-Test and the difference in the number of ulcerative lesions was evaluated with the chi^2 test.

Table II: Variation of laser-Doppler parameters (RF = mean ± sd; Var = median and range) in the 4 year follow up in the two groups. Values in 20 normal controls are also shown.

		Stockings (El. Comp.)	Controls
Year 0		Group	Group
	RF	0.69 ± 0.1	0.68 ± 0.13
	VAR	15.9 (8–38)	17.6 (9–38)
	No. of limbs	148	150
	No. of ulcerations	0	0
Year 1	RF	0.65 ± 0.18	0.69 ± 0.12
	VAR	15.3 (9–40)	8.6 (7–30)*
	No. of limbs	148	149
	No. of ulcerations	0	1
Year 2	RF	0.6 ± 0.13	0.73 ± 0.2
	VAR	11.66 (13–44)	8.2 (6–33)*
	No. of limbs	147	147
	No. of ulcerations	1	2
Year 3	RF	0.62 ± 0.11	0.71 ± 0.21
	VAR	19.3 (14–41)	7.04 (6–29)*
	No. of limbs	145	143
	No. of ulcerations	2	4
Year 4	RF	0.64 ± 0.13	0.78 ± 0.2*
	VAR	20.3 (12–40)	10.2 (6–21)*
	No of limbs	145	140
	No. of ulcerations	0	3*
Ulcerations			
Total:		3	10**
Percent:		2.02%	6.6%

* = p > 0.05 ** = p > 0.02

Normal controls (mean age 52.8 ± 10).

	Initial value	After 4 years
RF	0.57 ± 0.15	0.54 ± 0.12
VAR	38.5 (23–54)	39.2 (24–52)

Results

Out of the 80 admitted patients seventy-four patients completed the study in the treatment group and 75 in the control group. All drop outs were due to difficulty in following the protocol. Table I shows details of the two groups. They were comparable for age, sex distribution and for duration of diabetes. Also RF, DF and the VAR in the two groups were comparable at the beginning of the study. The values observed in patients were significantly different ($p < 0.05$) from those in normals (Table II) which did not significantly change in 4 years.

In the treatment group RF (Fig. 1) and the VAR (Fig. 2) remained unchanged during the follow up period. In the control group RF significantly increased and the VAR significantly decreased ($p < 0.05$) (Fig. 1 and 2) during the follow up period.

The number of ulcerations is shown in Figure 3. The number of ulcerated limbs in the treated group at the end of the study (3 ulcers) was significantly lower than that in the control group (10 ulcers) ($p < 0.02$).

Fasting blood sugar levels were similar in the patients of the two groups at the beginning of the study and during the whole follow up period. No significant variation in blood fasting sugar levels or glycosilated haemoglobin levels were observed during or after the study in both groups (Fig. 4). Also test indicating renal and hepatic functions and routine blood tests did not significantly change during the study and diet, activity and quality of metabolic control were unchanged.

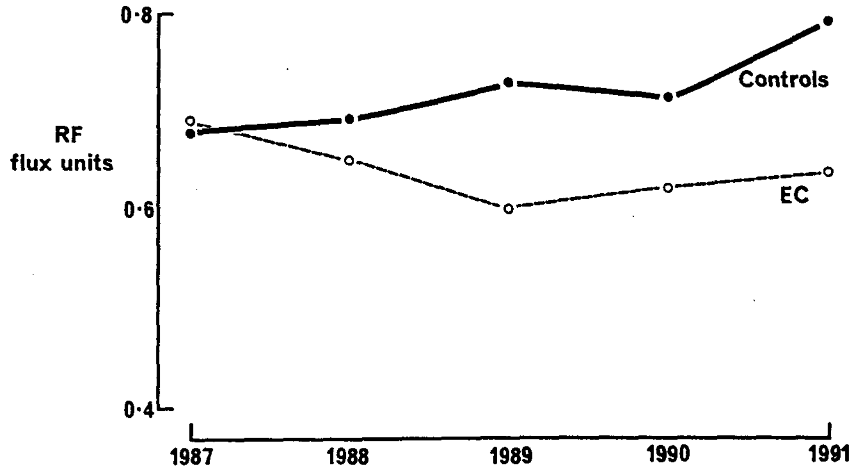

Fig. 1: Variation of the average resting flux in four years in patients treated with elastic stockings (EC) and controls.

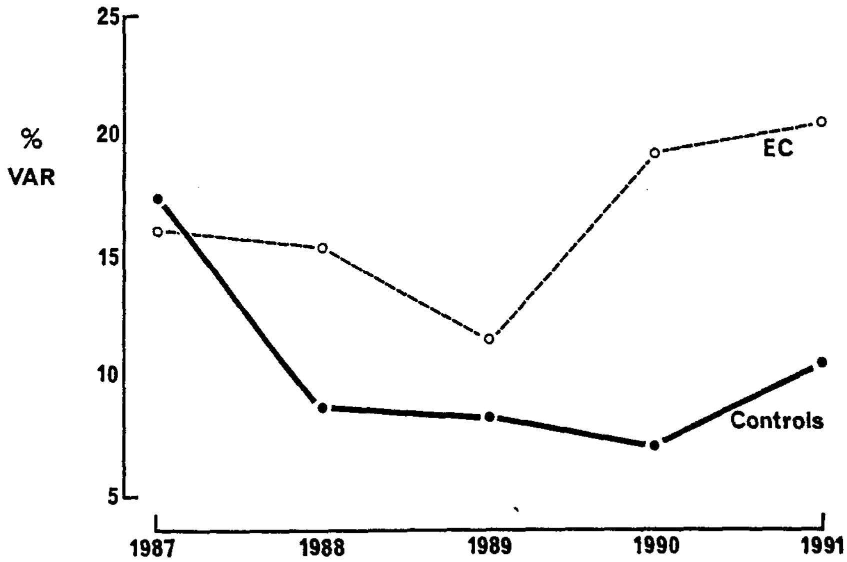

Fig. 2: The venoarteriolar response (median) in patients treated with elastic compression (EC) and in controls.

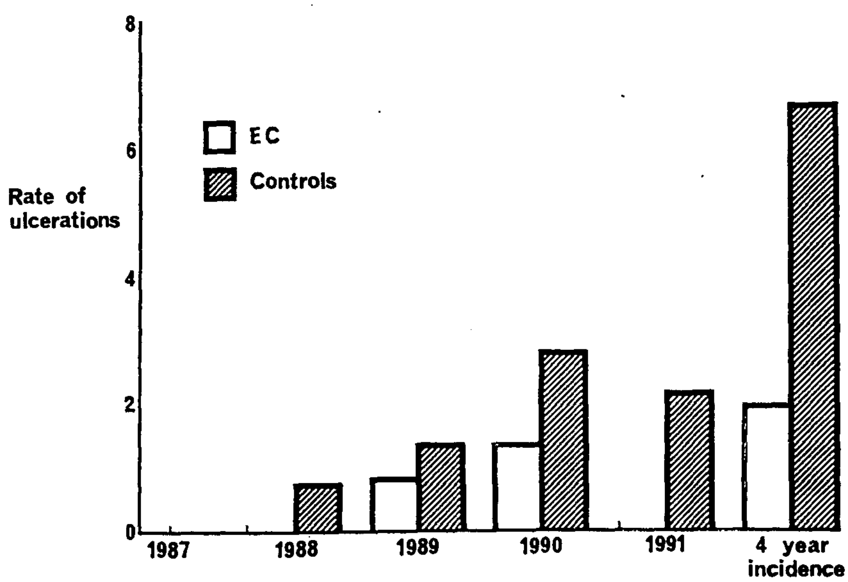

Fig. 3: The rate of ulcerations per year in the four year follow up in patients treated with elastic compression (EC) and controls. The difference in the 4 year incidence is statistically significant.

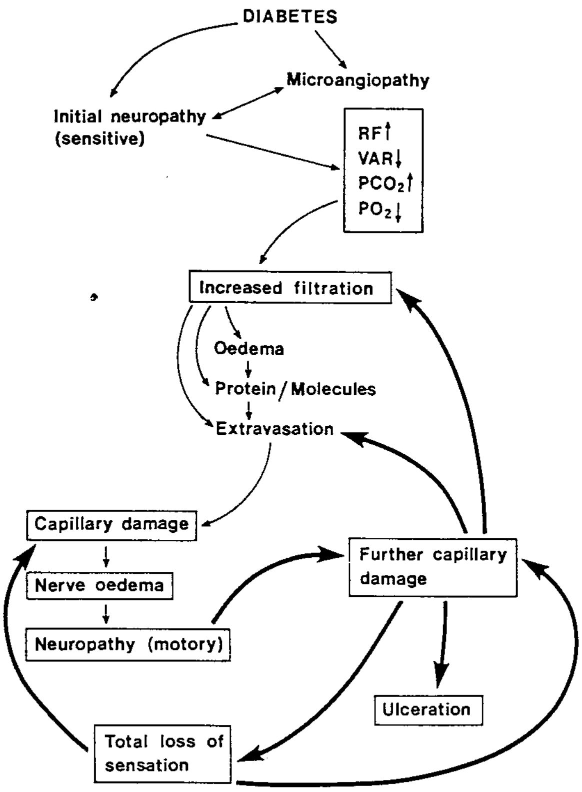

Fig. 4: The presumed sequence of microcirculatory events observed in diabetic microangiopathy. The increased filtration is the key event which may induce further deterioration. On this event elastic compression appear to act effectively slowing down the progression of microangiopathy.

Discussion

An increase in skin blood flow in the foot of patients with diabetic microangiopathy has been shown by different authors [1, 2, 3, 4] in association with a significant decrease in VAR and increase in capillary filtration [7, 8].

The VAR is mediated by a sympathetic axon reflex [5]. In diabetic microangiopathy [4, 13] the reduction in the efficacy of the VAR contributes to edema as a consequence of the failure in limiting the rise in capillary pressure and filtration on standing. The chronic increase in capillary pressure is cause of filtration of fluid and plasma molecules in the pericapillary space [7, 8]. It has been shown, using intravital fluorescence videomicroscopy that capillary permeability is significantly increased in diabetics [7]. The increased penetration of plasma molecules in the interstitial space is an important problem contributing to edema. The increased microvascular protein permeability, leading to enhanced extravasation into the microvascular wall and beyond exists from the very onset in both diabetic and hypertensive microangiopathy [7].

Diabetic microangiopathy is similar to venous hypertension which is characterised by increased skin blood flow and increased capillary filtration [11, 15]. These findings are associated with decreased VAR and an increase in transcutaneous PCO_2 and decrease in PO_2 [15].

It is commonly accepted – and it has been shown by microcirculatory studies [10] – that elastic compression is beneficial in controlling edema and ulceration in venous hypertension.

On the basis of our data elastic compression seems to be useful in improving the microcirculation and in reducing the increased capillary filtration found in patients with diabetic microangiopathy. In this condition increased capillary filtration seems to be a consequence of diabetic microangiopathy and an important cause of further deterioration of the microcirculation. The development of distal, local nerve edema may also impair nerve conduction and alter local reflexes. The presumed sequence of these events is presented in Figure 4.

As ulcerations in diabetics seem to develop as a consequence of the impaired response to minor skin trauma [2] it is also possible that there is a direct protective effect of the stockings on the skin.

In *conclusion* this study indicates a possible application of elastic stockings in diabetic microangiopathy confirming previous observations [4]. However is not clear yet in which stage of microangiopathy compression may be applied.

Further investigations are needed to show long term effect of stockings in improving the microcirculation, in slowing down the evolution of microangiopathy and also to define better the patient who may benefit from elastic compression.

Summary

One hundred and forty nine diabetics with micorangiopathy were followed up for 4 years and studied by laser-Doppler flowmetry – measuring skin blood flux at rest [RF] and the venoarteriolar response [VAR]. Seventy four patients were advised to wear elastic stockings and 75 were kept as controls

with the aim of evalating the effects of stockings on the evolution of diabetic microangiopathy.

After 4 years a significant deterioration was found in RF (increased) and VAR (decreased) in the untreated group in comparison with controls. Also 10 ulcerations developed in the untreated subjects (6.6% of limbs) in comparison with 3 ulcerations (2.02%) in the treated group. The difference was statistically significant.

Therefore elastic stockings appear to be useful in diabetics with microangiopathy as they protect against the deterioration of the microcirculation and reduce the development of ulcerations.

Zusammenfassung

149 Fälle von diabetischer Mikroangiopathie wurden während 4 Jahren mittels Laser-Doppler-Fluxmessung bezüglich Ruheflux der Haut und venoarteriolärem Reflex kontrolliert. 74 wurden mit, 75 ohne Kompressionsstrümpfe behandelt. Nach 4 Jahren zeigte die unbehandelte Gruppe einen signifikant erhöhten Ruheflux der Haut und einen signifikant erniedrigten venoarteriolären Reflex und es entwickelten sich 10 Ulcera cruris (6,6%) gegenüber nur 3 (2,02%) in der bestrumpften Gruppe. Auch dieser Unterschied ist signifikant.

Es scheint daher, dass elastische Kompressionsstrümpfe bei diabetischer Mikroangiopathie gegen die fortschreitende Schädigung der Mikrozirkulation schützen und die Entwicklung von Beinulzera hemmen.

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Dr. G. Belcaro, Via Vespucci 65, I-65 100 Pescara, Italy

Capillary filtration in venous hypertension. Comparison between the vacuum suction chamber (VSC) device and straingauge phlethysmography

G. BELCARO, A. RULO and S. RENTON

*Microcirculation Laboratory, Cardiovascular Institute
G. D'Annunzio University, Chiety (Italy)
and Irvine Cardiovascular Laboratory
for Investigation and Research
St. Mary Hospital Medical School, London (UK)*

To evaluate capillary filtration a group of normal subjects and two groups of subjects with venous incompetence (50 with deep and 50 with superficial incompetence) were studied with the vacuum suction chamber (VSC) device applied onto the internal perimalleolar region. This method was compared with straingauge plethysmography rate of ankle swelling (RAS). By the VSC the time taken for the weal to disappear (VSC time) was considered indicative of capillary filtration. The values obtained with the two methods were well related ($r<0.742$) and there was a good separation between patients and normals.The separation between the two groups of patients was significantly better ($p<0.05$) with the VSC time. In conclusion VSC time is a good indication of capillary filtration in comparison with straingauge plethysmography RAS. It may be used to assess variations in capillary filtration in venous hypertension and possibly to follow up the effects of treatments.

Key words: **Capillary filtration - Capillary permeability - Postphlebitic syndrome - Vascular disorders.**

Local capillary permeability and filtration in patients with peripheral lower limb oedema due to venous hypertension[1-4] or diabetic microangiopathy [5 6] is significantly increased. The increased fluid filtration can be locally assessed with the vacuum suction chamber (VSC) device.[1 3] This system is composed of a flexible (2 cm in diameter) plastic chamber applied to the skin in which a decrease in air pressure is applied for 10 minutes. The pressure decrease (30 mmHg) in the chamber is obtained using a small surgical sucker. A weal (rounded flat-topped, pale-red, evanescent elevation in the skin which disappears in minutes or hours) is determined by the VSC.

Weals are produced by oedema in the upper layer of the dermis due to increased permeability and filtration as a result of local capillary damage. The increased capillary permeability increases the passage of fluid from the intravascular to the extravascular component of the extracellular fluid space. This localized oedema disappears completely in normal skin, in standard environmental conditions, in less than 60 minutes.[1]

The aim of this study was to evaluate local capillary filtration with the VSC in patients with ankle oedema due to venous hypertension and in normal limbs. We also aimed to compare VSC data (expressing local capillary

Address reprint requests to: Dr. G. Belcaro, Via Vespucci 65, 65100 Pescara (Italy).

filtration) with total limb capillary filtration data obtained with venous occlusion straingauge plethysmography used to evaluate the rate of ankle swelling (RAS).[2 4 7 8]

Materials and methods

Fifty patients with moderate venous hypertension due to superficial incompetence, 50 patients with severe venous hypertension due to deep venous incompetence (postphlebitic syndrome) and 20 normal subjects were studied.

Only one limb (the one with the most severe venous hypertension) was evaluated in each patient.

Patients were selected in two groups according to superficial or deep venous incompetence on the basis of ambulatory venous pressure measurements (AVP) performed by the technique described by Nicolaides [9] and according to colour duplex scanning.

Superficial venous incompetence was documented by a shortened refilling time (RT) at the end of the exercise test which could be normalised by a tourniquet excluding the superficial system. In deep incompetence the shortened RT could not be normalised excluding the superficial system. The most important incompetent venous sites (deep and/or superficial venous system) were also detected by colour duplex which confirmed the level of incomptence.

Patients with vascular disease and diabetes were excluded. Doppler ultrasound examination demonstrated normal ankle to arm pressure index (>1.1) in all subjects. Both VSC and straingauge plethysmography were used in a room at constant temperature (212°C). Measurements were recorded after 30 minutes of acclimatisation and resting in the supine position before 10 a.m.

The VSC was used with a negative pressure of 30 mmHg and applied for 10 minutes on the medial perimalleolar region.[2]

Observations and photographs (taken with the same light and angle) were repeated every 5 min up to 120 min or until the weal was not visible on photographs. This was defined as the VSC time.

Straingauge plethysmography capillary filtration rate was measured evaluating the rate of ankle swelling (RAS) with a SPG16 Medasonic straingauge plethysmograph.[3] The straingauge was placed around the ankle and the patient was asked to stand holding on a frame. With this method after an increase in venous volume, the volume changes between the 7th and the 10th minute are considered to correspond to a phase of capillary filtration. The tangent to the curve at the tenth minute was considered to be the rate of ankle swelling (RAS = in ml/100 ml/min).[2 4 10 11]

Statistical evaluation of the differences among groups was performed using the Mann-Whitney U-test.

Results

Details of patients are reported Table 1. The three groups were comparable for age and sex distribution. In patients with deep incompetence, in comparison with those with superficial incompetence, AVP was significantly higher ($p<0.05$) and the refilling time (RT) shorter ($p<0.05$).

VSC time.—The VSC time was shorter in normals than in patients ($p<0.05$) and shorter in those with superficial incompetence in comparison with limbs with deep incompe-

TABLE I.—*Details of normal subjects and patients and AVP measurement data. AVP is the lowest pressure obtained during the exercise test and RT is the refilling time.*

	Venous incompetence		
	Superficial	Deep	Normals
No. of patients	50	50	50
Age (years)	43.7 (7)	44.6 (8)	44.1 (7)
M:F	25:25	25:25	10:10
AVP (mmHg)	45 (10)*	65 (9)* **	27 (9)
RT (s)	12.3 (6)*	8.4 (7)* **	28 (9)

*) $p<0.05$ in comparison with deep incompetence. **) $p<0.02$ in comparison with normals (C).

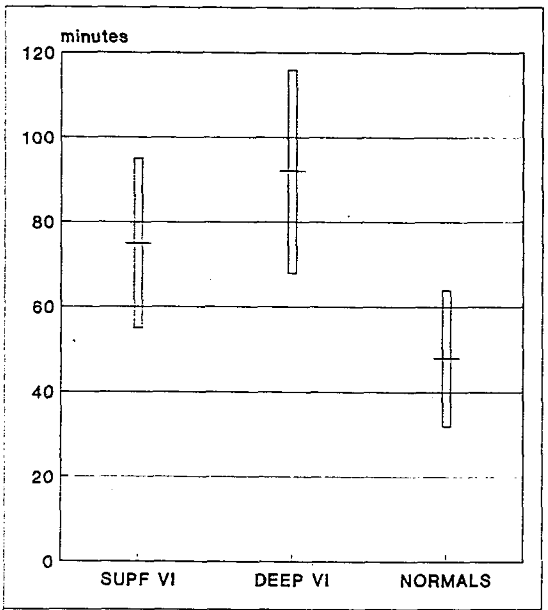

Fig. 1.—VSC time in the three groups (average and 95% confidence limits).

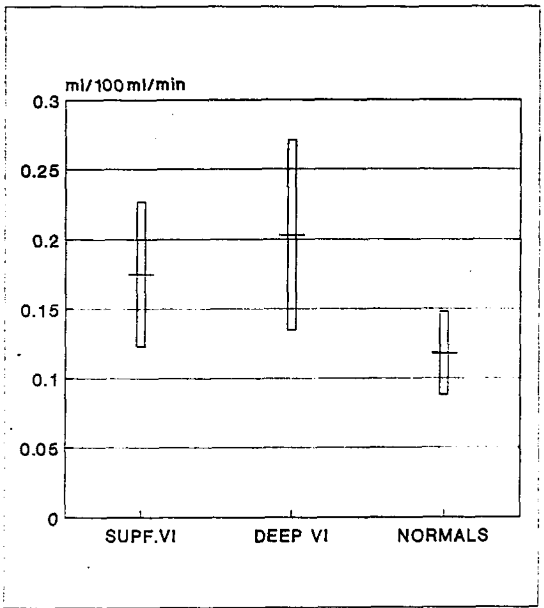

Fig. 2.—Rate of ankle swelling (RAS) in the groups (average and 95% confidence limits).

TABLE II.—*Times taken for the weal to disappear (VSC time in minutes) and rate of ankle swelling (RAS in ml/100 ml/min).*

	Venous incompetence		
	Superficial	Deep	Normals
VSC time			
Average ± S.D.	75 ± 10	92 ± 12	48 ± 8
Range	49-98	48-123	24-63
RAS			
Average ± S.D.	0,175 ± 0,026	0,203 ± 0,34	0,118 ± 0,015
Range	118-233	0,29-0,128	0,08-0,155

tence ($p<0.05$). The 95% confidence limits (average ± 2 sd) are shown in figure 1.

Table II shows the RAS in the three groups. It was significantly lower in normals ($p<0.05$) and higher ($p<0.05$) in the deep incompetence group (95% confidence limits are shown in figure 2) in comparison with limbs with superficial incompetence.

The correlation between VSC time values and RAS values was also good ($r = 0.742$). The separation between normals and patients ($p<0.02$) and between the two groups of patients ($p<0.05$) was significantly better ($p<0.02$) with VSC time than with RAS.

Conclusions

Ankle oedema observed in patients with postphlebitic limbs is due to venous hypertension, increased osmolarity of the extracapillary compartment due to increased level of metabolites and proteins,decreased lymphatic clearance and possibly to micropooling due to increased skin flow and increased PCO_2 levels in the skin.[12 13].

Very little has been reported about capillary permeability and its role in causing chronic peripheral oedema in venous hypertension.

By the VSC method it is possible to evaluate the role of local capillary filtration in venous hypertension directly in the perimalleolar region with a better separation—in comparison with the evaluation of the RAS—between normals and patients and between limbs with different degrees of venous hypertension. The weal produced by the VSC device has a significantly different pattern and evolution in normals, patients with moderate (superficial) venous hypertension and in patients with severe (deep) venous hypertension.

The increased skin flow in the foot and the decrease in venoarteriolar response in patients with diabetic microangiopathy[14-16] has also been shown to be associated with oedema due to increased capillary filtration.[14-16] This early sign is also observed in patients with venous hypertension.[2 12] The venoarteriolar response —the vasoconstrictory response mediated by a sympathetic reflex[15] is impaired in diabetics[15]—and in patients with venous hypertension.[14-16] The reduction in VAR is associated with oedema because of the failure to limit the rise in capillary pressure and capillary filtration on standing. The chronic increase in capillary pressure causes extrafiltration of fluid and large molecules into the pericapillary space. Thickening of the basement membrane,observed in diseased small vessels in diabetic and venous hypertensive microangiopathy is a consequence of chronic hypertension in capillaries.

The new, non-invasive technique of VSC may be used to evaluate the pathophysiology of venous hypertension and to monitor treatments used in venous hypertension.[3]

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Noninvasive tests in venous insufficiency

GIANNI BELCARO [1,2], NICK LABROPOULOS [1], DIMITRIS CHRISTOPOULOS [1], SPIROS VASDEKIS [1], GIUSEPPE LAURORA [2], MARIA ROSARIA CESARONE [2], ANDREW NICOLAIDES [1]

Chronic venous insufficiency (CVI) is the result of out-flow obstruction, reflux or a combination of both. Noninvasive tests detect an quantify obstruction and reflux if present and define the anatomic localisation of the abnormality. In evaluating CVI noninvasive tests combine physiologic and imaging techniques. These tests are widely available, simple, quick and cost-effective and therefore they are the methods of choice for initial objective evaluation. Different tests provide answers to different questions. The optimum clinically useful information can be now obtained using only three instruments: pocket Doppler, duplex or color duplex scanner and air plethysmography. The value of ambulatory venous pressure, photoplethysmography and light reflection reography, air plethysmography, duplex and color duplex scanning to assess reflux and the value of tests to assess out-flow obstruction are presented. Pooled data collected from large studies are also presented for reference. Qualitative and quantitative assessment of CVI are useful both for clinical assessment and to evaluate the effect of treatments.

KEY WORDS: Venous tests, noninvasive - Duplex scanning - Venous incompetence - Venous thrombosis - Varicose veins - Venous insufficiency, chronic.

From the [1] Irvine Laboratory for Cardiovascular Research and Investigation, Academic Surgical Unit, St. Mary's Hospital, London, UK and the [2] Microcirculation Laboratory, G. D'Annunzio University, Chieti, Italy

Chronic venous insufficiency (CVI) may be the result of out-flow obstruction, reflux or a combination of both. The first objective of noninvasive tests is to detect whether obstruction or reflux is present. Second the anatomic localisation of the abnormality must be found, and then the problem of quantification of the reflux or obstruction must be addressed. In evaluating venous stasis, noninvasive tests combine physiologic and imaging techniques. These tests are now widely available, simple, quick and cost-effective. Therefore, noninvasive tests are the methods of choice for initial objective evaluation. It should be noted that different tests provide answers to different questions. Many of these have been established during the past decade. Most recently technologic advances and current thinking indicate that the optimum useful information can be obtained using only three instruments: 1) pocket Doppler; 2) duplex scanning, preferably with colour-flow imaging; 3) air plethysmography.

Authors' address: Dr. Gianni Belcaro, Via Vespucci 65, 65100 Pescara (Italy).

Tests for venous reflux

Venous reflux is the result of gravity drawing the venous blood stream distally. Therefore, reflux testing should be performed with the patient standing. Recent studies have determined that venous reflux detected in the supine position is very often abolished when the patient is standing.[1] This is because valve closure occurs only after reflux exceeds a critical flow velocity which is achieved with the patient standing rather than supine. When the patient is standing, it is important to avoid muscular contractions. Therefore, the patient should be examined holding onto a frame or a table. The leg to be examined should be relaxed with the knee slightly flexed, with the weight on the opposite leg. Studies have shown that during full knee extension, an occlusion of the popliteal vein

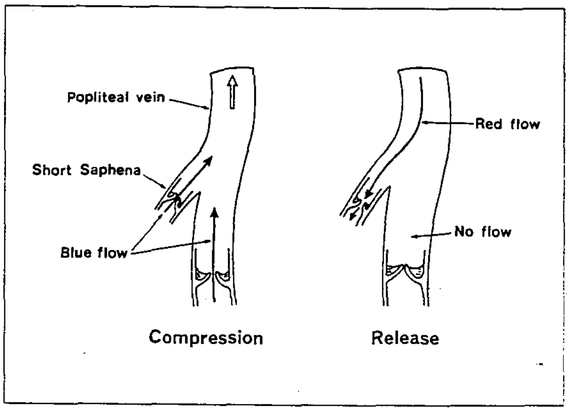

Fig. 1.—Example of sapheno-popliteal reflux. Blue colour on calf compression indicates cephalad flow. Reflux is indicated by red colour on release of the compression.

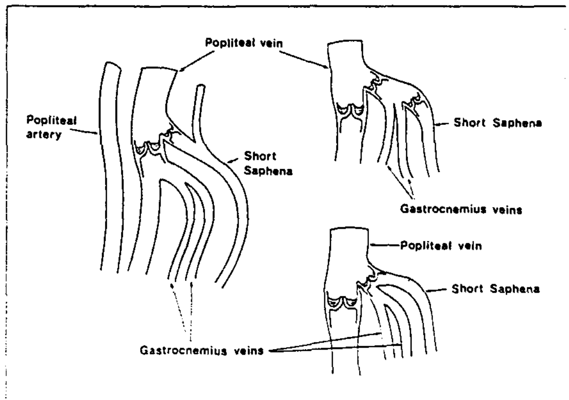

Fig. 2.—Three different but common anatomic variations of the veins in the popliteal fossa. Duplex scanning reveals the anatomy and enables testing of each individual vein for reflux.

occurs in 20% of healthy people.[1] After physical examination, a pocket Doppler instrument is used. The pocket instruments are satisfactory to complement the physical examination as a screening test for outpatients.[2-4] The *continuous-wave instrument* provides information about reflux at the sapheno-femoral and sapheno-popliteal junctions.[2] The knee of the leg to be examined should be slightly flexed to relax the muscles and skin over the popliteal fossa. Manual calf compression produces cephelad flow and reflux may occur when the compression is released. Abolition of the reflux by compression of the superficial veins just below the probe suggests that reflux is confined to the superficial system.

Failure to abolish reflux by compression indicates that the reflux is in the deep system.[5] In experienced hands, a pocket Doppler provides clear answers regarding the presence or absence of reflux at the sapheno-femoral or and sapheno-popliteal junctions in 90% of patients.[6] Abnormal anatomy in the popliteal fossa is responsible for most errors. For example, reflux in the gastrocnemius veins may be interpreted as reflux in the popliteal vein. The continuous-wave Doppler venous examination is not accurate in localising incompetent perforating veins.[7]

Duplex scanning supplements the physical examination and evaluation with the pocket continuous-wave Doppler instrument. The duplex scan provides information about reflux in specific veins. The femoral, popliteal, deep calf veins, and perforating veins can be individually tested. The use of colour has made the duplex evaluation much faster and more accurate. The nonweight-bearing limb is evaluated and the sites to be studied are imaged with a 5 or 7.5 MHz probe. The sapheno-femoral junction, the popliteal venous anatomy, and the perforating veins are visualized. Manual calf compression or, ideally, compression by a rapidly deflatable cuff is used.[8] The cuff inflation produces cephalad flow. Rapid release of the compression is essential to testing for reflux and valve closure can be documented. Figure 1 shows the sapheno-popliteal junction, Figure 2 shows veins in the popliteal fossa, and Figure 3 shows an example of testing for perforating veins. Localisation of calf perforating veins and reflux in them is time-consuming with conventional duplex, but colour-flow imaging has made this examination easy and practical. Colour duplex scanning for localisation of sites of reflux is particularly useful in patients with recurrent varicose veins after previous surgery. Such examination also confirms the normal functioning of deep veins and the extent and site of venous reflux when it is present.

Both localised and generalised reflux (present throughout the deep venous system) can be identified. Although quantification of reflux in individual veins is possible, this is time consuming.[8] Accurate and reproducible results are obtained more easily for

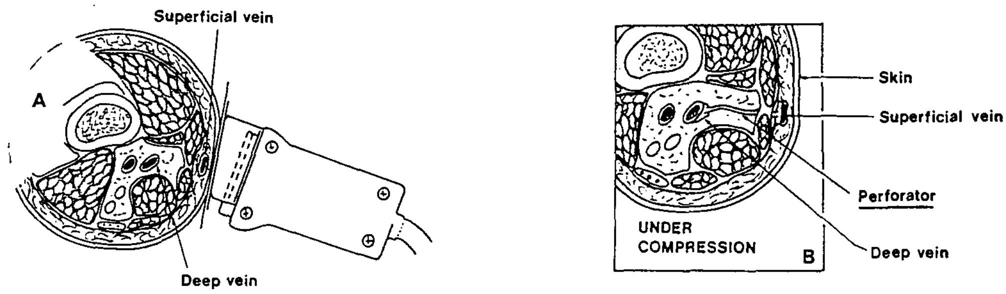

Fig. 3.—Transverse scan of superficial and deep veins (A) by moving the probe up or down the limb with continuous visualisation of the two veins the presence and level of communicating vein is determined (B). The direction of flow with calf compression and release can then be tested.

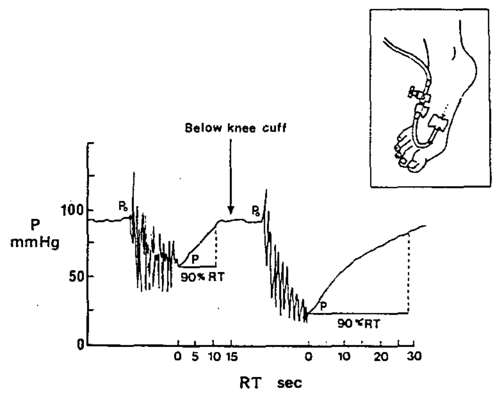

Fig. 4.—Recording of venous pressure during ten tiptoe exercises with and without a below-knee cuff (2.5 cm wide) occluding the superficial veins. Normalisation of ambulatory venous pressure (P) and RT90 indicates that the deep veins are competent.

the whole leg using *air plethysmography*, which has become the test of choice for quantitating reflux.[1]

Ambulatory venous pressure

Although invasive, ambulatory venous pressure examination has remained a standard to which other examinations are compared. Venous pressure is measured by inserting a needle in a vein on the dorsum of the foot with the patient standing (Fig. 4). Pressures are recorded during a ten tiptoe exercise test.[4, 9] The ambulatory venous pressure (AVP) is defined as the lowest pressure reached during the exercise (P in Figure 4). AVP is a function of the calf muscle pump ejecting capacity, the magnitude of reflux, and the outflow resistance. Therefore, it represents the net effect of all the abnormalities that effect venous haemodynamics. In normal limbs, AVP is less than 30

TABLE I.—*Ambulatory venous pressure (AVP) and Refilling Time (RT)**.

Type of limb	AVP (mmHg)		RT_{90} (sec)	
	No ankle cuff	Ankle cuff	No ankle cuff	Ankle cuff
Normal	15-30	15-30	18-40	18-40
Primary varicose veins with competent perforating veins	25-40	15-30	10-18	18-35
Primary varicose veins with incompetent perforating veins	40-70	25-60**	5-15	8-30
Deep venous reflux (incompetent popliteal valves)	55-85	50-80	3-15	5-15
Popliteal reflux and proximal occlusion	60-110	60-120		
Popliteal occlusion and competent popliteal valves	25-60	10-60		

*Standard exercise: 10 tiptoe movements. **In one third of these limbs, AVP remained more than 40 mmHg and RT_{90} less than 15 seconds despite the application of the ankle cuff.

TABLE II.—*Incidence of ulceration in relation to ambulatory venous pressure (AVP) in 222 patients (251 limbs).*

AVP (mmHg)	No.	Incidence of ulceration
<30	34	0
30-40	44	11
41-50	51	22
51-60	45	38
61-70	34	59
71-80	28	68
81-90	10	60
>90	5	100

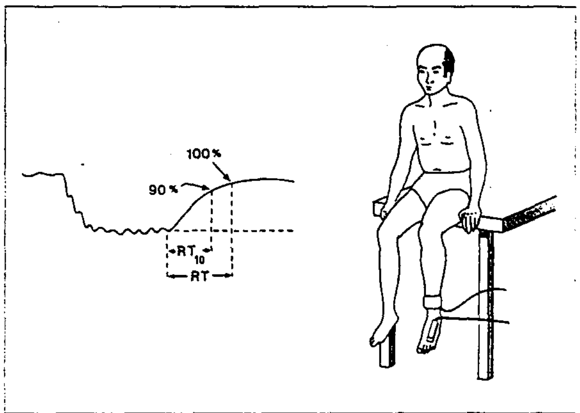

Fig. 5.—Measurement of RT or RT90 using photoplethysmography.

TABLE III.—*Photoplethysmographic Refilling Time (RT_{90}) with and without an Ankle Cuff to Occlude Superficial Veins (10).*

Parameters	Standing (sec)		Sitting (sec)	
	No cuff	Cuff	No cuff	Cuff
Normal	18-80*	18-80	26-100	26-100
SVI	5-18	18-50	2-25	18-50
DVI	3-12	6-18**	2-28	2-30

*RT_{90} >18 seconds without cuff identifies normal limbs.
**RT_{90} <18 seconds with cuff identifies limbs with deep venous incompetence.

mmHg and the refilling time (RT) is greater than 18 seconds. These values are due to filling of the veins from the arterial side. When venous reflux is present, the AVP is higher and the refill time is shortened (Table I). After AVP is obtained, the exercise test can be repeated with narrow tourniquets (2.5 cm wide) applied at the ankle, below knee, or thigh position. These tourniquets control reflux from the superficial veins and if superficial reflux is present, AVP and RT are normalised. In patients with deep venous incompetence, normalisation does not occur. Table I indicates that AVP is elevated in the presence of popliteal reflux. For AVPs from 40-100 mmHg, there is a linear relationship to the incidence of skin ulceration. This is true regardless of the underlying pathology and whether the reflux is in the superficial or the deep system (Table II).

Photoplethysmography and light reflection rheography

To obtain RT noninvasively, photoplethysmography (PPG) and light reflection rheography (LRR) have been developed. In both of these techniques, a photodetector is applied to the skin of the foot or ankle (Fig. 5).[10] These instruments determine whether venous incompetence is in the superficial veins. Table III shows the PPG-RTs with and without an ankle cuff to occlude superficial veins. Results are given for normal controls, patients with superficial reflux, and those with deep venous incompetence. Better reproducibility and better separation of groups can be obtained when the test is performed with the patient standing.[1-11] Figure 6 shows the algorithm used in clinical practice by our groups. It should be emphasised that both RT and RT90 (90% refilling time) are poor measures of severity of deep venous disease.

Figure 7 shows the RT90 plotted against AVP. It can be seen that for a wide range of AVPs between 40 and 100 mmHg, the RT90 is between 5 and 10 seconds. Reduction in AVP from 100 to 60 mmHg by valve substitution or repair (valvuloplasty) thus has little effect on RT90.

Air plethysmography

Air plethysmography using a calibrated air chamber applied to encompass a leg (Fig. 8) provides quan-

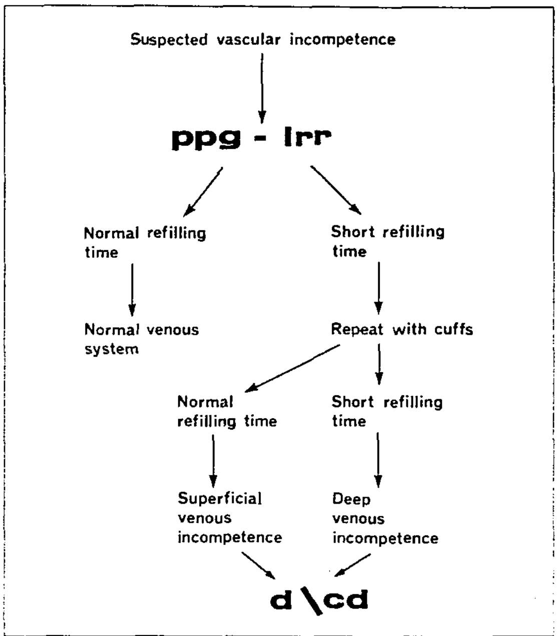

Fig. 6.—Diagnostic flow chart indicating the procedure followed with PPG/LRR for the screening of patients with suspected venous problems (d/cd = duplex or color-duplex scanning).

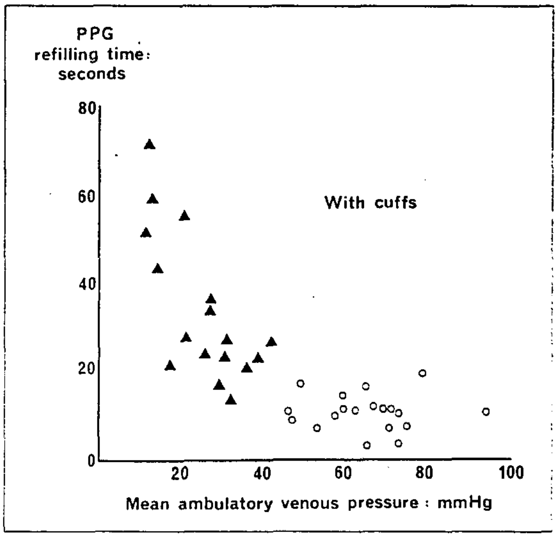

Fig. 7.—Relationship between PPG-RT and AVP with a cuff excluding the superficial system in the standing position (▲ = superficial incompetence only; ○ = deep venous incompetence).

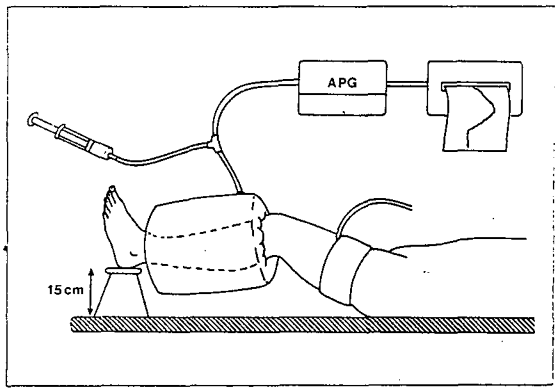

Fig. 8.—Diagrammatic representation of the air plethysmograph. The 100 ml syringe included in the circuit is used for calibration.

titative information about the various components of the calf muscle pump.[11 12] These include the rate of filling of the reservoir (venous filling index [VFI]) as a result of standing; the venous volume (VV), which is the amount of blood in the venous reservoir; the ejected volume (EV), and the ejection fraction (EF = [EV/VV] × 100) as a result of a single step; and the residual volume (RV) and residual volume fraction (RVF = [RV/VV] × 100) as a result of ten tiptoe movements (Fig. 9). The manoeuvers and methods of making these measurements from the recording are shown diagrammatically in Figure 9. There is a high reproducibility of measurements expressed as ratios: VFI, EF, and RVF (coefficient of variation less than 10%) (Table IV).[1 11-13] VFI is a measurement of reflux and is expressed in millilitres per second. Volume measurements are in absolute units (millilitres). The median and 90% range of the various measurements in different groups of patients are shown in Figures 10A, B, C and in Table IV.

The linear correlations that exists between RVF and the AVP (Fig. 11) means that an estimate of the AVP can be obtained from the RVF in a noninvasive fashion. The incidence of cutaneous ulceration increases with increase in the amount of reflux (VFI) and a decrease in the efficiency of the calf muscle pump ejection (EF). Thus, the RFV provides information on the overall effect of all the venous abnormal-

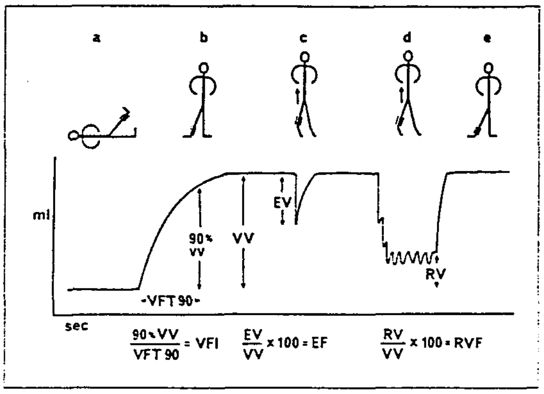

Fig. 9.—The manoeuvres and methods of deriving the air plethysmographic measurements.

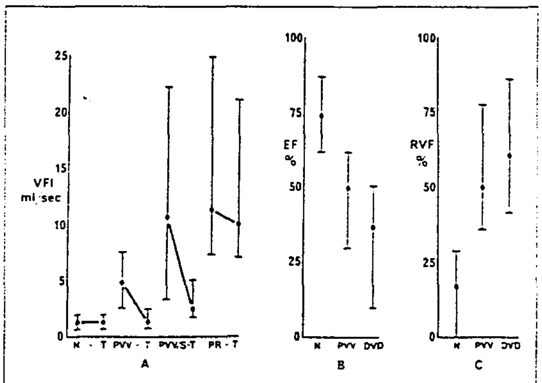

Fig. 10.—A) Venous filling index (VFI) in normal controls (N), limbs with primary varicose veins without (PVV) and with skin changes (PVV/S), and limbs with popliteal reflux (PR). The results are presented as median and 90% range without and with a 2.5 cm tourniquet (T) at the knee occluding the superficial veins. The application of this tourniquet can differentiate between reflux in the superficial and deep veins. B) Ejection fraction (EF) in normal controls (N), limbs with primary varicose veins (PVV) and deep venous disease (DVD). The results are presented as median and 90% range. C) Residual volume fraction (RVF) in the same group of patients.

ities. In addition, the abnormalities are dissected out and measured in terms of the EF (ejection) and the VFI (reflux) components.

Tests for outflow obstruction

Ascending venography remains the standard morphological method of delineating persistent venous

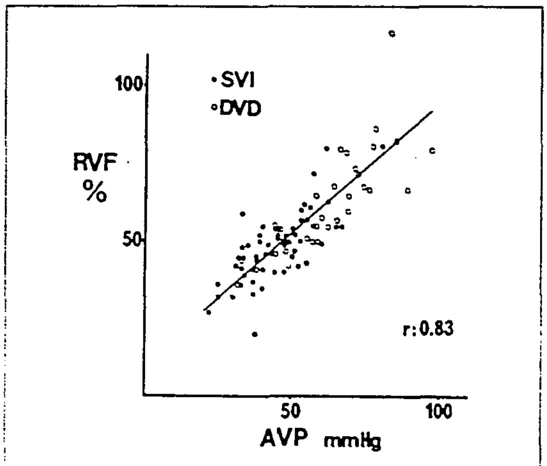

Fig. 11.—Correlation between AVF and RVF (SVI, superficial incompetence; DVD, deep venous disease).

obstruction. There are several noninvasive tests that determine the presence and quantify the degree of outflow obstruction. The simple continuous-wave Doppler measurement can be used as a screening device in outpatients. A history of deep venous thrombosis or persistent leg and ankle swelling suggests the need for such an examination [14]. Although not in general worldwide use, the best test to evaluate obstruction is the arm-foot pressure differential developed by Raju.[15] Other noninvasive tests are based on the measurements of venous outflow by various techniques using different instrumentation. These methods include strain-gauge impedance and air plethysmography. In our opinion the high reproducibility and simplicity of air plethysmography has made this technique the method of choice.

However, the other methods are stil in more general and worldwide use.

Ultrasound techniques: continuous wave Doppler, B-mode, duplex and color duplex scanning.—The patient is examined with the legs horizontal and the knee slightly flexed. The trunk should be at 45 degrees and the ultrasound probe is held over the femoral vein.[16] In normal subjects Doppler flow velocity is phasic with respiration. If this is found, it indicates a normal iliocaval segment. Absence of phasic flow or the finding of flow that is continuous and not affected

TABLE IV.—*Air plethysmography.*

	Coefficient of variation	Normal limbs	Primary DVD	VV's
Direct measurements				
Functional venous volume (VV) increase in leg volume on standing) (ml)	10.8-12.5	100-150	100-350	70-320
Venous filling time (VFT90) (time taken to reach 90% of VV) (sec)	8.0-11.5	70-170	5-70	5-20
Ejected volume (EJ) (decrease in leg volume as a result of one tiptoe) (ml)	6.7-9.4	60-150	50-180	8-140
Residual volume (RV) (volume of blood left in veins after ten tiptoes) (ml)	6.2-12	2-45	50-150	60-200
Derived measurements				
Venous filling index (VFI) (average filling rate: 90% VF/VFT90 (ml/sec)	5.3-8	0.5-1.7	2-25	7-30
Ejection fraction (EF = [EV/VV] × 100) (%)	2.9-9.5	60-90	25-70	20-50
Residual volume fraction (RVF = [RV/VV] × 100 (%)	4.3-8.2	2-35	25-80	30-100

VV's = varicose veins. DVD = Deep venous disease.

TABLE V.—*Arm foot differential (p mmHg) in limbs with outflow obstruction.*

Grade	Pressure at rest	Pressure increment during hyperaemia
I Fully compensated	<5	<6
II Partially compensated	<5	<6
III Partially decompensated	>5	>6 (often 10-15)
IV Fully decompensated	≫5 (often 15-20)	No further increase

TABLE VI.—*Maximum venous outflow (MVO).*

Obstruction	Normal	Moderate	Severe
MVO strain gauge (1 sec) (ml/100 ml/min)	45	45-30	30
1 sec outflow fraction (OF) Air plethysmography (% of venous volume)	38	38-30	30

by respirations suggests obstructions. If flow is diminished or abolished by compression of the contralateral groin or suprapubic area, the presence of obstruction and collateral circulation is established. Augmentation of the velocity in the common femoral vein by calf compression indicates absence of popliteal and femoral venous obstruction.

This maneuver can be repeated with occlusion of the long saphenous vein at the knee by external pressure. This double-checks the patency of the popliteal vein. Augmentation of the velocity in the popliteal vein produced by digital compression of each venous compartment in the leg suggests patent axial deep calf vein flow.[17]

B-mode imaging, duplex scanning and colour flow imaging detect with great accuracy the particular veins containing organised thrombi that are not compressible by probe pressure.

The visualisation of the deep veins may also reveal irregular vein walls with abnormal echo and partially recanalised lumens.[18 19] In experienced hands colour duplex scanning is as effective as venography in detecting deep venous thrombosis [20] and possibly

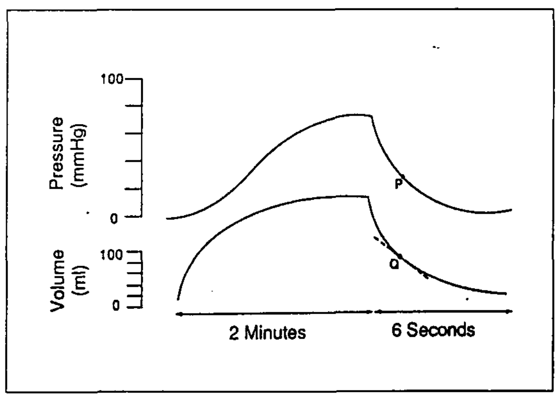

Fig. 12.—Pressure and volume inflow and outflow curves obtained simultaneously using air plethysmograph and cannulation of a vein on the dorsum of the foot.

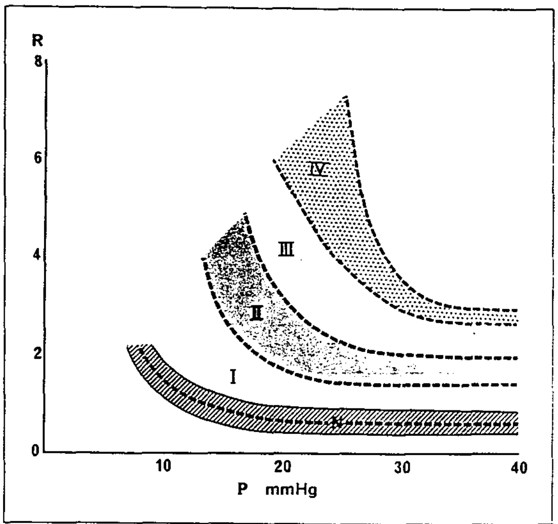

Fig. 13.—Relation between outflow resistance curves and Raju classification of outflow obstruction (grades I to IV) (N, normal limbs).

more effective than venography in diagnosis recurrent deep venous thrombosis.[21]

Arm-foot pressure differential (Raju).—The arm-foot pressure differential measurement is considered to be an excellent method of quantitating outflow obstruction. This technique consists of recording the venous pressure in the veins of the foot and hand simultaneously after venous cannulation.

The measurements are made with the patient supine and are repeated after inducing reactive hyperaemia in the leg. In normal limbs, the arm-foot pressure differential is less than 5 mmHg with a rise of 1 to 6 mmHg (ie, 5 may rise by 1 to 6 mmHg, to become 6 to 11 mmHg) during reactive hyperaemia. Patients with venographically proven evidence of obstruction have been classified into four grades according to the criteria shown in Table V.

Outflow measurements.—The degree of venous obstruction can be assessed from outflow measurements using mercury strain gauge or air plethysmography. In both techniques, a proximal thigh cuff is inflated with the patient supine and the limb elevated 10 degrees with external rotation and 10 degrees knee flexion. The veins are allowed to fill for at least 2 minutes and the cuff is suddenly deflated. Measurements are calculated from the outflow curves. Maximum venous outflow, 1-second outflow, and 3-second outflow fractions are all valid measurements used and advocated by different authors.

The outflow fraction is expressed as $OF = (V_1/VV) \times 100$.[1]

Table VI shows the range of values for limbs with normal veins, moderate, and also severe obstruction for strain gauge plethysmography (MVO) and air plethysmography (OF). The correlation between outflow fraction using air plethysmography and arm-foot pressure differentials is good ($r = 0.7$). Outflow resistance can be also calculated from the air plethysmographic and direct venous pressure outflow curves obtained simultaneously (Fig. 12). Actual flow (Q) can be calculated from the tangent at any point on the volume outflow curve. Resistance ($R = P/Q$) is calculated by dividing the corresponding pressure (P) by the flow (Q). This can be done for a series of points on the outflow curves. By plotting the resistance against pressure, as shown in Fig. 13, it has been shown that the relation between these is not linear. At low pressures when the veins are collapsed, the resistance is high. The resistance decreases at higher pressures when the veins, and presumably the veins of the collateral circulation, are distended. Figure 13 also demonstrates the relationship between the resistance and the four grades of arm-foot pressure differential described by Raju (Table V).

Conclusions

It is now possible to detect the presence or absence or reflux or obstruction in venous circulation noninvasively. It is also possible to determine the anatomic site of each and obtain quantitative measurements of the severity of both. Many types of investigations have been developed during the past decades. However it is possible to obtain clinically relevant information using simple and standardised methods such as the pocket Doppler, the duplex scanner (with or without colour flow imaging), and the air plethysmograph.

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ORAL COMMUNICATIONS

OC1 IMPAIRED CUTANEOUS MICROVASCULAR PERFUSION IN PATIENTS WITH CHRONIC VENOUS HYPERTENSION (CVH).

R.H. Bull, O. Luetolf, P.S. Mortimer
Department of Dermatology, St. George's Hospital, London SW17, U.K.

Venous hypertension causes leg ulceration by an unknown mechanism. Microcirculatory changes were assessed in the skin of the lower leg of patients at risk of venous ulceration using intra-vital video-capillaroscopy.
The dermal capillaries were examined with the leg supine and dependent in 13 subjects with CVH (7 female, 6 male; mean age 60.8 ± 11.1 years) and in 13 normal controls (6 female, 7 male; mean age 51.7 ± 15.1 years) under native light and during fluorescence angiography (FA).

	SUBJECTS WITH CVH		NORMAL CONTROLS	
	SUPINE	DEPENDENT	SUPINE	DEPENDENT
NATIVE	13.1 ± 7.4	12.9 ± 6.9	28.5 ± 4.9	26.8 ± 5.0
FA	15.4 ± 8.1	15.9 ± 8.2	30.7 ± 5.8	28.9 ± 5.3

Table I. Capillary density (mean ± s.d. /mm^2).

Capillary density was significantly lower in the subjects with CVH compared to the normal controls both in the supine and dependent positions ($p<0.01$). During fluorescence angiography in normal controls fewer capillaries were filled during dependency compared to the supine position ($p<0.01$) but there was no reduction in the CVI subjects.
Fluorescence angiography only highlights perfused capillaries; these results indicate that capillary underperfusion in the gaiter skin of subjects with CVI may be important in the pathogenesis of leg ulceration.

OC2 SKIN FLUX AND RATE OF FOOT SWELLING (RFS) IN VENOUS HYPERTENSION

G.Belcaro, G.Laurora, M.R.Cesarone, M. Leon, A.N. Nicolaides
Microcirculation Laboratory, Chieti University, Italy and Irvine Cardiovascular Laboratory, St.Mary's Hospital, London,U.K.

The rate of foot swelling (RFS) with straingauge plethysmography and laser-Doppler (LDF) skin flux (internal, perimalleolar region) were studied in subjects with venous hypertension (selected by color duplex and ambulatory venous pressure measurements). We evaluated 350 normal subjects (mean age 48.5±10) and 475 patients [259 with superficial (47.7±9) and 216 with deep venous incompetence (47.1±6)] using a Laserflo (Vasamedics-USA) LDF. The strain gauge was placed around the maximum circumference of the foot. After 30 minutes of supine rest patients were asked to stand (10 minutes). The RFS - the tangent to plethysmography curve between the 8th and 10th minute - was measured. Skin flux in normals was on average 0.68±0.19 units, lower [p<0.05] than in patients with superficial (0.93±0.17) or deep venous incompetence (1.01±0.2). The RFS was 1.201 ml/min per 100 ml of tissue (±0.215) in normals, 1.989 (±0.212) (p<0.02) in superficial incompetence and 2.215 (±0.24) in deep incompetence. There were no differences in flux between the two groups of patients. However the RFS was significantly higher in deep incompetence (p<0.02%). The correlation between skin flux and RFS was good (r=0.67).
In conclusion this work indicates that in venous hypertensive microangiopathy there is an increased skin flux and in that RFS is also proportionally increased.

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FINAL PROGRAM

34. ACUTE EFFECTS OF INTERMITTENT SEQUENTIAL COMPRESSION IN VENOUS HYPERTENSION

Giovanni Belcaro, M.D. and Andrew N. Nicolaides, M.D., Pescara, Italy and London, England

Discussant: Thomas W. Wakefield, M.D., Ann Arbor, Michigan

It has been observed that intermittent sequential compression (ISC) produces an increase in the rate of healing of venous leg ulcers possibly improving the microcirculation. The aim of our study was to determine the effect of ISC on the microcirculation of the skin at the gaiter area in patients with venous hypertension and skin changes without and with venous ulcerations. Two treatment protocols were used in two separate studies in comparable group of patients.

STUDY ONE (UK): sixteen limbs in 11 patients (mean age 43±9; M:F=5:6) with chronic venous hypertension and perimalleolar skin changes (8 with ulcers) have been studied. Skin flux using laser Doppler flowmetry (LDF), was measured at rest in the supine resting position (RF) and on standing (SF). The venoarteriolar response (VAR=the vasoconstrictory response on standing) was calculated from (RF-SF)/(RF:100). Previous work had shown that in patients with venous hypertensive microangiopathy the VAR is markedly reduced and RF is increased. ISC was applied for 30 minutes (maximum pressure 50 mmHg) and the measurements were repeated at 0, 30, 60 and 90 minutes after cessation of compression. The LDF probe was placed at least 1 cm from the edge of the ulceration on the internal perimalleolar region.

STUDY TWO (Italy): 18 limbs in 15 patients (mean age 45±8; M:F=7:8) with chronic venous hypertension and perimalleolar skin changes (9 with ulcers) have been studied. RF, SF and VAR were calculated with the same technique and LDF (Laserflo, Vasamedics, USA). ISC was applied for one hour and the tests were repeated after 2 and 3 hours.

In both centers 10 normal subjects (mean age 44±8; M:F=5:5) were also evaluated with the same tests for comparison.

RESULTS:

STUDY ONE: RF in patients was increased (Table) and the VAR was significantly decreased. At the end of the ISC session there was a change towards normality ($p<0.01$) as RF decreased and the VAR increased. The positive changes in RF and VAR were still present at 30 and 60 minutes.

STUDY TWO: RF in patients was increased and the VAR decreased. At the end of the ISC session there was a significant change towards normality in RF (decreased) and in VAR (increased). These improvements in RF and VAR were still present after 2 and 3 hours. Treatment used in study one produced a decrease in RF of 41.4% and an increase in VAR of 16%, while in study two the decrease in RF was of 54.1% and the increase in the VAR of 20.3%. These differences are significant (Table) and therefore it appears that the effects of ISC are 'dose-related'.

CONCLUSIONS: These microcirculatory observations offer an explanation on the remarkable effect of ISC on the healing of venous ulceration.

	RF	VAR		RF	VAR
ST.1 NOR	0.56±0.2	35 (28-63)	ST.2	0.68±0.21	35 (27-60)
PAT bef	1.45±0.8*	7 (2-23)*		1.59±0.4*	9 (3.3-21)*
aft	0.85±0.5#	23 (9-34)#		0.73±0.2#	29.3 (13-36)#
variat.	41.4%	16%		54.1%**	20.3%**

* = p<0.05 difference from normal values; # p<0.02 difference before/after.
** = p<0.05 difference between the two treatment protocols (Nor = normals; Pat = patients; bef = before; aft = after; variat = variation).

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Skin Flux and Histology in Venous Hypertension

Giuseppe Laurora, M.D.*
Giuseppe Pizzicannella, M.D.*
Maria Rosaria Cesarone, M.D.*
C. Fisher, M.D.†
Giovanni Belcaro, M.D.*†
and
A. N. Nicolaides, M.S.†

CHIETI, ITALY and LONDON, ENGLAND

Abstract

Skin blood flux and the venoarteriolar response have been studied by laser-Doppler flowmetry (LDF) in 20 postphlebitic limbs and in 20 normal limbs. Histology was also studied with punch biopsy specimens in postphlebitic limbs and in 4 randomly selected, normal volunteers.

Skin flux was increased and the venoarteriolar response decreased in all postphlebitic limbs. Also in all patients an apparent increase in the number of capillaries was observed. They appeared dilated and tortuous, and the thickened capillary wall was surrounded by a pericapillary halo composed of protein, neutral polysaccharides, hemosiderin, and fibrin.

In conclusion, measurements with LDF differentiate between normal and postphlebitic limbs, corresponding to the histologic finding of an altered capillary system. Therefore, LDF is useful for defining the degree of microangiopathy due to venous hypertension.

Introduction

In normal subjects, the increased venous pressure produced by lowering the foot below heart level induces a venoarteriolar response (VAR)[1-4] that increases the precapillary resistance, decreasing capillary blood flow and preventing an increase in fluid loss as edema.

Skin blood flux and the VAR can be noninvasively studied by laser-Doppler flowmetry.[2,4] With this technique, it has been observed that the resting skin blood flux increases and the VAR is reduced in patients with diabetic neuropathy and microangiopathy.[2]

From the *Microcirculation Laboratory, Cardiovascular Institute, G. D'Annunzio University, Chieti, Italy; and †Irvine Laboratory for Cardiovascular Research and Investigation, St. Mary's Hospital, London, England

In chronic venous hypertension (CVH) the causes of tissue hypoxia, liposclerosis, and eventually ulceration are postulated to be chronic increase in fluid filtration with pericapillary deposition of fibrin.[5] It has been suggested that the collagen IV layer becomes thicker, leading to a decreased capillary function.[6] Another explanation is that the production of collagen IV is induced by high capillary pressure in CVH.[6] The changes in the microcirculation, particularly the reduction in the efficacy of the VAR,[4,7] may be the initial cause of this process.

The aim of our study was to test the hypothesis that in patients with CVH the increase in skin blood flux and the alteration of an effective VAR are at first associated with edema[7,8] and then with histologic changes typical of venous hypertensive microangiopathy.[9]

Patients and Methods

Selection of Patients

Twenty limbs with CVH due to deep venous incompetence confirmed on color duplex flow imaging and with no ulceration were studied and compared with 20 normal limbs (with normal veins confirmed on color duplex scanning). In all subjects foot pulses were palpable and ankle:brachial systolic pressure ratio measured by Doppler ultrasound was normal (>1.0). Ambulatory venous pressure (AVP)[10] was measured with a needle inserted into a vein of the foot to determine the lowest AVP and the refilling time (RT). Patients with deep incompetence, an AVP higher than 55 mmHg (66 ± 12), and an RT shorter than 14 seconds (12 ± 8) were included. Normal limbs had an AVP lower than 45 mmHg (mean 33 ± 10) and an RT longer than 18 seconds[10] (mean 28 ± 9).

The laser-Doppler flowmeter probe was placed on the skin of the internal perimalleolar region, 4-6 cm proximal to the medial malleolus. After thirty minutes' acclimatization at constant room temperature (22°C), the baseline resting flux (RF) was recorded as the average over two minutes. The subject was then asked to stand. Standing flux (SF) was recorded after a one-minute interval for four minutes. The RF and SF were measured in flux units and expressed as the average during the four minutes of measurement.

The VAR was measured as:

$$(RF-SF)/(RF{:}100) \qquad (1)$$

By repeating the test ten times in 10 normal limbs and ten times in 10 postphlebitic limbs, the coefficient of variation of RF and SF for each limb was found to be between 14% and 12.5% (normal limbs) and between 12% and 16% (postphlebitic limbs).

After informed consent in all patients a punch biopsy of the skin was taken under local anesthetic. The biopsies were from liposclerotic skin of the internal perimalleolar region at least 2 cm from scars of previous ulcerations. A hematoxylin-eosin stain was used. Also, commercially available stains for collagen IV deposits (anticollagen IV serum) and fibrinogen were used. Fibrin deposits were detected with immunofluorescence.[8,9] Four randomly selected, normal volunteers had a perimalleolar punch biopsy in the same region.

In all normal subjects and in patients routine blood test results were within the normal range.

The differences between the two groups were statistically evaluated by the Mann-Whitney U-test.

Results

Details of the two groups are shown in Table I. Results are shown in Table II. In postphlebitic limbs the mean resting and standing flux were significantly increased ($p < 0.05$) in comparison with normal limbs. Also the VAR, which was (median) 41% in normal limbs, was significantly ($p < 0.05$) decreased to 15% in postphlebitic limbs.

TABLE I
Details of the Two Groups of Patients

	Normal Limbs	Postphlebitic Limbs
No.	20	20
Age (mean ± sd)	46.5±10	45±11
M:F	10:10	10:10
Punch biopsy	20	4*

*Randomly selected.

TABLE II
Resting (RF) and Standing (SF) Flux and the Venoarteriolar Response (VAR) in Normal Limbs and in Limbs with Venous Hypertension Due to Postphlebitic Syndrome

		RF	SF	VAR
Normal limbs	Mean	0.67	0.4*	(median) 41
	SD	0.13	0.1	(range) 26-63#
Postphlebitic limbs	Mean	1.13#	0.96#	(median) 15#
	SD	0.2	0.22	(range) 3-24#

*$p < 0.05$ difference in flux due to the postural change.
#$p < 0.05$ difference from normal limbs.

Histopathology

In all specimens three major features were constantly observed in comparison with normal skin:

1. There was an apparent increased number of capillaries (Figure 1).
2. The capillaries were dilated and tortuous (Figure 2).
3. The capillary wall was thickened and surrounded by a pericapillary halo composed of protein, neutral polysaccharides, hemosiderin, and fibrin (Figure 2).

Also, in 16 specimens, collagen IV layers were observed on the basal membrane and around capillary walls. Collagen IV deposits were less clear in normal limbs. Fibrin deposits were detected with immunofluorescence only in 4 (20%) of specimens. They were not seen in normal limbs.

Hemosiderin and histiocytes were observed in liposclerotic skin only.

FIG. 1. Biopsy of the skin in the internal perimalleolar region. The apparent number of capillaries is increased.

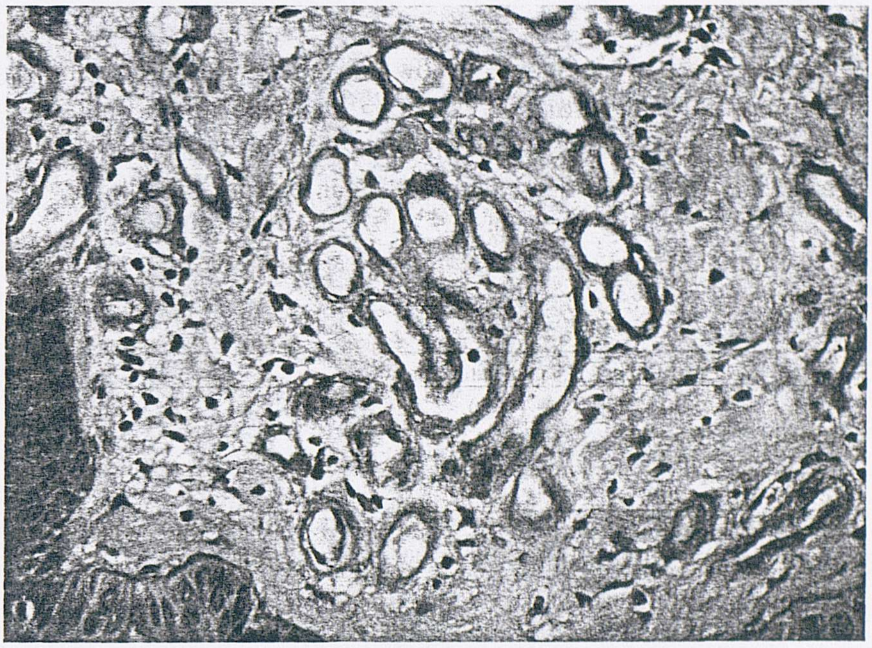

FIG. 2. Skin biopsy. The increased size of the capillaries and of the capillary wall is visible in this section.

Discussion

The output from the laser-Doppler flowmeter is proportional to skin blood flux in superficial skin vessels. Comparative studies with capillaroscopy indicate that the laser-Doppler flowmeter detects flow in subcapillary plexuses and shunts as well as in the capillary loops.[2] The reflex responses observed by the two techniques are comparable.[2] The changes observed by laser-Doppler flowmetry in patients with venous hypertension are similar to those previously observed in diabetics with peripheral neuropathy.[2] It appears that the reduced VAR results in the loss of tone in the precapillary sphincters. In the resting (supine) state, although the blood flow through the individual capillary may not be increased, the total number of capillaries open at any time increases, thus increasing the net blood flow. If the net increase in flow persists with the increased hydrostatic pressure, there is increased net fluid loss as edema.[7] The accompanying increased protein loss leads to pericapillary fibrin deposition and the thickening of the basement membrane[5] and eventually to the development of liposclerosis, skin pigmentation, and ulceration. In liposclerotic areas an increase of capillaries as compared with normal skin in transversal sections has been documented.[8,9] It has been found that the increase in fibrin deposits was seen in 80% of specimens of liposclerotic skin.[8,9]

In our study, however, we observed collagen IV deposits in almost all patients while fibrin was documented in only 36% of the specimens. As a consequence of an increased filtration rate,[5,8] fibrin deposits are formed early in the development of CVH. Fibrin acts as a matrix for the formation of collagen, and when collagen is formed, the capillaries become fixed. The stiff capillary walls cannot adjust themselves to postural changes in hydrostatic load, and this increases capillary leakage.[7]

Another explanation can be a reactive hyperplasia of the normal collagen IV as a result of the high capillary pressure in CVH.[8,9]

Conclusions

The laser-Doppler findings of an increased skin flux and of a reduced VAR are almost constantly associated with the histologic findings of venous hypertension and venous hypertensive microangiopathy. Therefore, these measurements can be used to quantify and follow up the degree of microangiopathy and venous hypertensive microangiopathy in venous hypertension and the effects of treatments in this condition.

G. Belcaro, M.D.
Via Vespucci 65
65100 Pescara, Italy

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Capillary Filtration and Ankle Edema in Patients with Venous Hypertension: Effects of Daflon

Maria Rosaria Cesarone, M.D.*
Giuseppe Laurora, M.D.*
Maria Teresa De Sanctis, M.D.*
and
Giovanni Belcaro, M.D.**

CHIETI, ITALY

Abstract

Capillary filtration (CF) was assessed in 43 patients with venous hypertension and in 10 normal subjects by means of strain gauge plethysmography. The patients were then divided into two treatment groups; 22 were treated with Daflon, 500 mg tid, and 21 with Daflon, 500 mg bid. The normal subjects were also treated (500 mg tid).

After four weeks CF was significantly decreased in all subjects, the decrease being higher in the high-dose groups. CF did not significantly change in normal subjects. In conclusion Daflon decreases CF in subjects with venous hypertension and the CF decrease is dose related.

Introduction

Two of the most common complaints of patients with venous diseases are ankle edema and foot swelling. For this reason evaluation of the effects of treatment of venous disease and particularly of venous hypertension must consider the effects of treatment on the development of edema.

Laser-Doppler also shows that microcirculatory parameters, namely, increased skin flow and decrease in venoarteriolar response (the vasoconstriction observed on standing and lowering the foot below the heart level,[1] are associated with marked increase in capillary filtration.[2]

Therefore, drugs decreasing capillary filtration are useful in venous hypertension by decreasing the severity of symptoms and by slowing the progressive changes in the skin and subcutaneous tissue possibly due to chronic fluid and protein leak.

From the *Laboratorio di Microcircolazione and the **Clinica Cardiovascolare, Università G. D'Annunzio, Chieti, Italy

Daflon, a drug used in the treatment of venous hypertension, has recently been used in patients with venous disorders with good clinical results.[3] This compound has also demonstrated good activity on experimentally increased permeability[4,5] in animal models.

This pilot study was undertaken to evaluate the effects of Daflon 500 on capillary filtration (CF) in patients with venous hypertension and on the correlation between CF reduction and the improvement in ankle and foot edema.

Patients and Methods

Ten normal subjects and 43 patients with venous hypertension were studied in the early morning (8:30-9:30 AM) to avoid the effects of a day of standing on ankle and foot edema. The study was performed in a room at constant temperature (22°C). Patients were evaluated after resting supine for thirty minutes. Only one lower extremity was studied in each patient.

Selection of Patients

Patients with venous hypertension due to severe superficial venous incompetence with a normal deep venous system were selected. Venous hypertension was diagnosed by color duplex scanning and quantified by ambulatory venous pressure measurements (AVP) performed with an intravenous needle according to the technique described by Nicolaides.[6]

Subjects with peripheral arterial disease and diabetes were excluded. Also the MVO (maximum venous outflow) evaluated by strain-gauge plethysmography was studied to exclude patients with venous obstruction or occlusion of the deep venous system. Elastic compression was not used during this study.

Capillary filtration rate (CFR) was studied by venous occlusion plethysmography (VOP) with use of 22-cm-wide cuff inflated at 70 mmHg, which was placed above the knee and applied for five minutes according to the technique described by Thulesius.[7] A strain-gauge plethysmograph was used to record volume changes. The strain gauge was placed around the calf's maximum circumference.

Figure 1 shows how VOP was used to evaluate CFR and Figure 2 shows two typical curves (normal and abnormal). The test was repeated three times at intervals of twenty minutes. The mean of three test reads from the tangent drawn to the plethysmographic curve during the fifth minute of occlusion was taken as the capillary filtration rate (CFR) (mL/min).

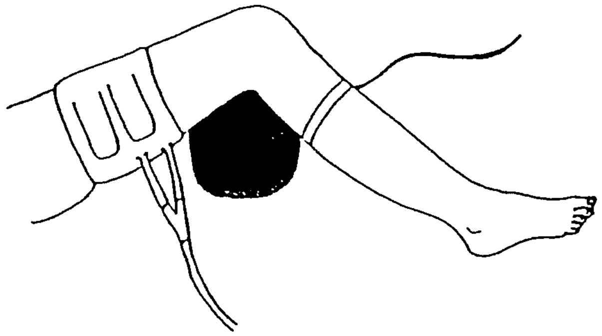

Fig. 1. Evaluation of capillary filtration rate (CFR) by VOP (venous occlusion plethysmography).

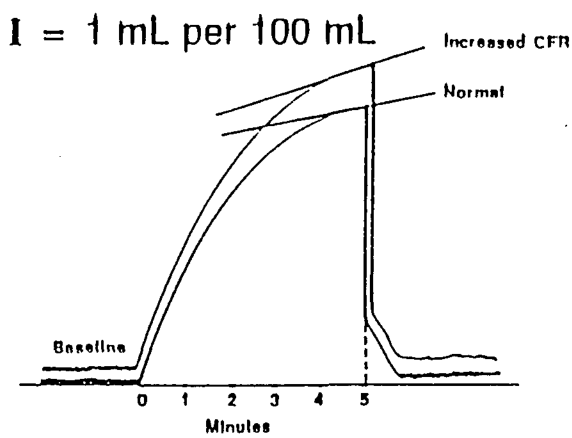

Fig. 2. Two typical curves of CFR (normal and abnormal) obtained by VOP.

Ankle Edema

The presence of ankle edema was a criterion for inclusion. To evaluate the presence of ankle edema we developed a technique called the ankle edema coin test (AECT).[8] This test is shown in Figure 3. A metal plate with two rows of three (2 cm) round circles (Figure 3A) is applied under a sphygmomanometer at the internal perimalleolar region. The three circles in one row were of increasing height (3, 6, and 9 mm) while in the other row they were of decreasing height. A pressure of 70 mmHg was applied to the sphygmomanometer cuff for ten minutes. The resulting "coin signs" on the skin indicated (Figure 3B) the presence of edema. Serial photos were taken every five minutes (with the same angle of light incidence) until the signs disappeared. The "coin signs" disappeared in a variable time according to different degrees of edema and venous hypertension. Using AECT we selected patients with AECT compression marks lasting more than forty-five minutes. According to this technique, in normal limbs, the AECT produces small, superficial marks that disappear completely in less than thirty minutes. All tests were repeated after four weeks of treatment.

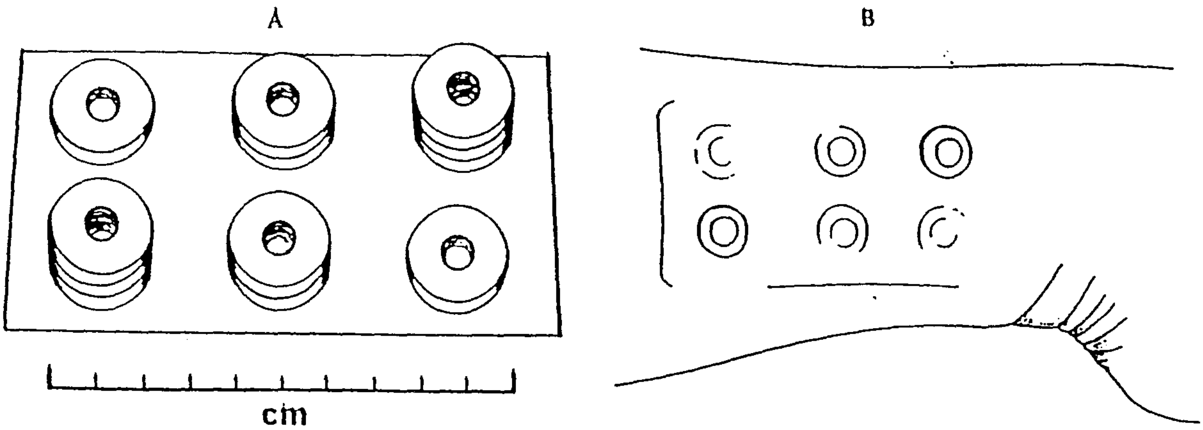

FIG. 3. Ankle edema coin test (AECT). A. the metal plate used for AECT. B. The "coin signs" on the skin after the test.

Groups of Treatment

Subjects were divided into three groups:

Group A (22 limbs) was treated with Daflon 500 at the dosage of 500 mg tid

Group B (21 limbs) was treated with Daflon 500 bid

Group C (10 normal limbs) were studied during the same period to evaluate the effect of the drug (500 mg tid) on their CFR.

The duration of treatment was four weeks.

Symptoms and Signs

An analogue scale line ranging from 1 to 10 was used to evaluate the following subjective signs/symptoms:

1 = swelling
2 = restless lower extremity
3 = pain and cramps
4 = tiredness

An average score was taken from the results of these four symptoms.

Informed consent was obtained by all patients and normal subjects. The statistical evaluation was performed using the Mann Whitney U-test.

Results

Details of the three groups are shown in Table I (mean ± sd). There were no significant differences for sex and age distribution among the three groups. There was, however, a significant difference ($p < 0.05$) in AVP and RT between normal subjects and patients. The CFR

TABLE I
Patient Data

No. Subjects	Group	Treatment	Age (Years)	Male: Female	AVP (mmHg)	RT (sec)
22	A	500 mg tid	46±6	11:11	44±9 (25±9)	13±6
21	B	500 mg bid	44±6	11:10	47±7 (24±8)	14±6
10	C	500 mg tid	42±7	6:4	20±7 (21±8)	18±4

AVP (=ambulatory venous pressure measurements) and RT (=refilling time) obtained without and with (in brackets) an ankle tourniquet to exclude the superficial venous system.
The normalization of AVP and RT values with exclusion of superficial veins indicates a normal deep venous system.

(Table II) was significantly increased in patients ($p < 0.05$). It significantly decreased ($p < 0.02$) after treatment and the decrease was significantly higher in patients treated with the higher dosage ($p < 0.05$). There was a small, nonsignificant CFR decrease in normal subjects.

Table III shows the variation of the signs/symptoms score. It was significantly decreased in both groups ($p < 0.05$). The score decrease was significantly higher ($p < 0.05$) in the group with the higher dosages.

The treatments were well tolerated and patients did not report any unwanted effect.

TABLE II
Capillary Filtration Rate (CFR) in ml/100 per Minute

Group	Before mean	sd	After Treatment mean	sd
A	1.990 ± 0.11 ##		1.213 ± ** #	0.19
B	2.016 ± 0.10 ##		1.672 ± *	0.17
C	0.976 ± 0.07		0.830 ± ns	0.084

Differences before-after: * = $p < 0.05$; ** = $p < 0.01$; ns = not significant
Differences from normals' values: # = $p < 0.05$; ## = $p < 0.01$.

TABLE III
Average Score Obtained Considering Four Major Symptoms: (1) Swelling, (2) Restless Leg, (3) Pain and Cramps, (4) Tiredness. The Analogue Scale Line Ranged from 1 to 10

Group	Before	After Treatment
A	7.7±1.1	4.6±1.3**
B	7.7±1.5	6.2±1.7*

* = $p < 0.05$
** = $p < 0.01$

Discussion

Ankle and foot edema in patients with venous insufficiency due to severe superficial incompetence are associated with an increased capillary filtration rate, an increase in skin blood flow and swelling, and a failure in the venoarteriolar response.[1,2] The increased capillary filtration in association with the microcirculatory findings[3] observed in venous hypertension lead to skin alterations, pigmentation, lipodermatosclerosis, and eventually ulcerations.

According to the results observed in this study, Daflon appears to decrease ankle swelling and edema in venous hypertension by reduction of the capillary filtration rate. The decrease of CFR appears to be dose-related, the higher dose producing a proportionally higher decrease.

These results are consistent with the results of previous studies showing the activity of Daflon on capillary filtration in venous hypertension.[3]

Conclusions

According to these preliminary data, Daflon seems to be useful for reducing the abnormally increased capillary filtration in patients with venous hypertension and is effective in diminishing signs and symptoms of venous hypertension.

The treatment in these subjects is generally surgery or sclerotherapy aiming to reduce the number of incompetent veins. Daflon is useful in subjects awaiting definitive treatment and seems effective in controlling signs and symptoms of venous hypertension.

These data need to be confirmed by a longer study involving a larger number of patients.

Giovanni Belcaro, M.D.
Via Vespucci 65
65100 Pescara, Italy

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Microcirculatory effects of elastic stockings in diabetic microangiopathy: A 24-week study

G. BELCARO, G. LAURORA, M. R. CESARONE, M. T. DE SANCTIS, L. INCANDELA

From the Microlab, Cardiovascular Institute "G. D'Annunzio" University, Chieti, Italy and Angiology and Vascular Surgery "Pierangeli Clinic", Pescara, Italy

Patients with diabetic microangiopathy were studied by laser-Doppler flowmetry—measuring skin blood flux at rest (RF) and the venoarteriolar response (VAR) and evaluating the rate of ankle swelling (RAS) to study capillary filtration. After randomisation, 38 patients were treated for 24 weeks with below-knee elastic stockings, and 36—acting as controls—were left without elastic compression.
After 12 and 24 weeks, there were no significant changes in the control group, while there was a significant improvement of the microcirculatory parameters in patients using stockings. RF (increased at the beginning of the study) was significantly decreased, the VAR (impaired at the beginning of the study) improved significantly and the abnormally increased capillary filtration decreased. Elastic stockings seem to be useful in diabetic microangiopathy improving microcirculatory parameters and decreasing capillary filtration and oedema. These effects may improve diabetic microangiopathy and possibly slow down its rate of progression.

KEY WORDS: Elastic stockings - Diabetic microangiopathy - Microcirculation - Edema - Laser-Doppler flowmetry - Capillary permeability.

In patients with diabetes mellitus, microangiopathy and neuropathy cause of disabling foot complications are often precipitated by minor trauma or injury.[1 2] New information has been recently gained on the microcirculation in diabetics using laser-Doppler flowmetry (LDF).[1-4] LDF allows the evaluation of superficial skin blood flow of the foot both in resting condition and after dynamic (i.e postural) changes.[1-4]

The increase in skin flux observed in diabetic microangiopathy by LDF appears to be related to the increase in capillary filtration and to the development of foot and ankle oedema [1-4] which are important early clinical signs of diabetic microangiopathy.[5 6]

In subjects with diabetic microangiopathy the impairment in venoarteriolar response (VAR), namely the reflex vasoconstrictory response observed on standing [7 8] may also contribute to the development of oedema. The chronic presence of oedema and filtration of fluid and proteins into the extracapillary compartment may contribute to the alterations of the basement membrane of capillaries in diabetic microangiopathy.[4-9]

Elastic stockings are used to treat and control venous hypertension, lymphatic problems and other conditions related to the development of oedema. A recent study has shown that it is possible to improve the microcirculation and reduce oedema using elastic stockings in diabetic microangiopathy.[9]

The aim of this study was to evaluate in a randomised study patients with diabetic microangiopathy to assess the effect of elastic stockings used for 24 weeks on microcirculatory parameters.

Materials and methods

Patients

After giving informed consent, patients with diabetic microangiopathy were included in an open ran-

Authors' address: G. Belcaro, Via Vespucci 65, 65100 Pescara, Italy.

TABLE I.—*Laser-Doppler parameters (RF = resting flux in flux units as mean and SD; and VAR as median and range) after 12 and 24 weeks in the two groups.*

Parameters	Before inclusion	12 weeks	24 weeks	% variation
Compression:				
RF	0.94±0.2*	0.62±0.1**	0.69±0.12**	26.6**
VAR	13 (10-28)*	30.1 (11-34)**	28.3 (23.45)**	150.4**
Controls:				
RF	0.93±0.16*	0.98±0.11	1.02±0.2	9.6
VAR	13 (11-27)*	15 (7=23)	12 (7-33)	9.2
Normal values:				
RF	0.57±0.15		0.54±0.17	5.3
VAR	42.5 (26-64)		44 (23-61)	3.5

*p<0.05 in comparison with normal values: **p<0.05 difference before-after.

domised trial. On the basis of previous findings [1-6] we only included subjects with diabetic microangiopathy. This condition was characterised at microcirculatory level by: 1) increased RF; 2) decreased VAR; 3) increased capillary filtration (as indicated by the rate of ankle swelling obtained with strain-gauge plethysmography).

All subjects included were under good stable diabetic control with diet and oral antidiabetic agents.

Criteria of exclusion: Patients with proteinuria or any subclinical or clinical renal impairment or those with history of ketosis and poorly controlled diabetes were excluded. Smokers, patients with systemic hypertension or vascular disease were excluded (ankle to arm systolic blood pressure ratio assessed by Doppler was >1.1 in all patients). There was no previous history of foot ulceration. Also, all patients had normal ankle reflexes. Vibration sensory threshold at the toes measured with a biothesiometer [1 2] was within the normal centiles for age on the basis of centile charts.

Methods

After randomisation, 50% of these patients were treated with below-knee elastic compression stockings for 24 weeks. Elastic compression at the ankle was 26 to 36 mmHg. The stockings were made of fibre (67% nylon and 33% lycra spandex/elastane). The patients were asked to wear the stockings for at least 6 to 8 hours daily during their usual working or activity hours. Stockings were changed every four weeks to assure optimal compression.

Microcirculatory evaluation: Measurements were made at constant room temperature (23°C) after 30 minutes acclimatization and resting in the supine position. LDF measurements were recorded with the probe placed at the dorsal, distal part of the foot. A Laserflo (Vasamedics - USA) laser-Doppler flowmeter was used. LDF skin flow measurements were expressed in flux units. Skin blood resting flux (RF) in the supine position was measured as the average flow in 5 minutes. The patient was then asked to stand, keeping still and holding onto a frame and the standing flux (SF) was recorded as the average flux within 5 minutes of standing, excluding the first minute to avoid motion artifacts. The venoarteriolar response (VAR) namely the skin flow decrease on standing was calculated using the formula:

$$[VAR = (RF-SF)/(RF/100)].$$

The rate of ankle swelling (RAS) was measured using a SPG16 MedaSonic strain-gauge plethysmograph. After resting supine for 20 minutes, patients were asked to stand for 10 minutes. The venous volume increase curve was recorded and the tangent to the curve was taken between the 8th and 10th minute.

After the initial assessment, all tests were repeated after 12 and 24 weeks. Data obtained from a group of 25 normal subjects, comparable with the two groups of patients studied are presented for comparison as normal values (Table I).

Statistical evaluation of the results was made using the Mann-Whitney U-test.

TABLE II.—*Details of the two groups of patients, the number of patients completing the 24-week follow-up, the number and percentage of dropouts and the total number of patients included. Also details of the normal subjects group are included.*

Parameters	N. of patients	Age mean ± SD	M:F	DD mean ± SD	Drop outs	Included
Compression	38 (70.3%)	46.5 ± 12	18:20	7.4 ± 6	16 (29.6%)	54
Controls	36 (64.3%)	46.8 ± 10	17:19	7.2 ± 5	20 (35.7%)	56
Normal subjects	20	46.3 ± 11	10:10	—	0	20

DD = duration of diabetes (years).

TABLE III.—*Strain-gauge plethysmography rate of ankle swelling (ml per 100 ml/min).*

Parameters	At inclusion	12 weeks	24 weeks	% variation
Compression	1.982 ± 0.21	1.72 ± 0.2	1.731 ± 0.18	12.66
Controls	1.932 ± 0.26	1.98 ± 0.18	2.01 ± 0.21	4.03
Normal values	1.022 ± 0.18		1.024 ± 0.2	1.9

TABLE IV.—*Fasting blood glucose and glycosilated haemoglobin in the two groups of patients (as mean ± standard deviations).*

Groups	Fasting glucose	Glycosilated haemoglobin
Compression:		
Inclusion	123 ± 28	6.37 ± 0.23
12 weeks	125 ± 25	6.68 ± 0.29
24 weeks	127 ± 31	6.43 ± 0.31
Controls:		
Inclusion	128 ± 22	6.37 ± 0.26
12 weeks	119 ± 23	6.38 ± 0.3
24 weeks	128 ± 19	6.43 ± 0.31

Results

Details of two groups of patients completing the study, the number of drop-outs and the mean duration of diabetes is presented in Table II. Details of the normal subjects are also reported. All drop-outs were due to social causes, none was caused by intolerance to stockings.

At the beginning of the study microcirculatory parameters (Tables I, III) were not significantly different in the two groups of patients. Both laser-Doppler parameters and RAS in both groups of patients were significantly different ($p<0.05$) from those recorded in normal subjects as in patients RF and RAS were increased and the VAR decreased.

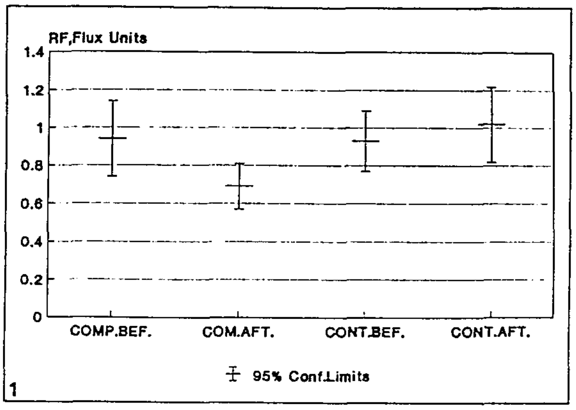
The variations in laser-Doppler parameters in treated patients after 12 and 24 weeks indicated a significant increase in VAR ($p<0.05$) decrease in RF (Fig. 1) and a significant increase in VAR ($p<0.05$) (Fig. 2). No significant variations were observed in the control group and in normal subjects. The RAS in the treatment group was significantly decreased with a median 12.6% decrease after 24 weeks (Table I, Fig. 3).

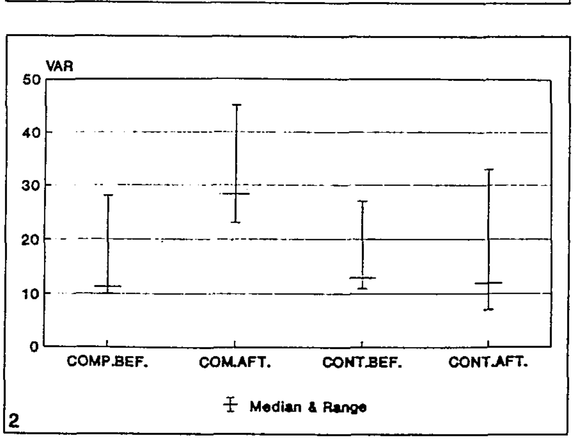
The variations in fasting glucose and glycosilated haemoglobin (Table IV) were not significant during the study indicating that the changes in microcirculatory parameters were not due to metabolic causes.

Conclusions

An increase in skin blood flux in the foot in patients with diabetic microangiopathy has been recently documented.[1-4] The increased skin flux is associated with significant decrease in the efficacy of the venoarteriolar response. In diabetics the reduced efficacy of the VAR may be an important cause of oedema which indicates failure in limiting the rise in capillary pressure and filtration on standing. The constant, prolonged increase in capillary pressure causes chronic extrafiltration of fluid and plasma molecules in the pericapillary space.[5 6 9]

Bollinger *et al.*[5] have also demonstrated, using intravital fluorescence microscopy, that capillary permeability is significantly increased in diabetics. The increased penetration of plasma molecules in the interstitial space is an important cause of oedema. Parving [6] has reported that increased microvascular protein permeability, leading to enhanced extravasation into the microvascular wall and beyond exists from the very onset in both diabetic and hypertensive





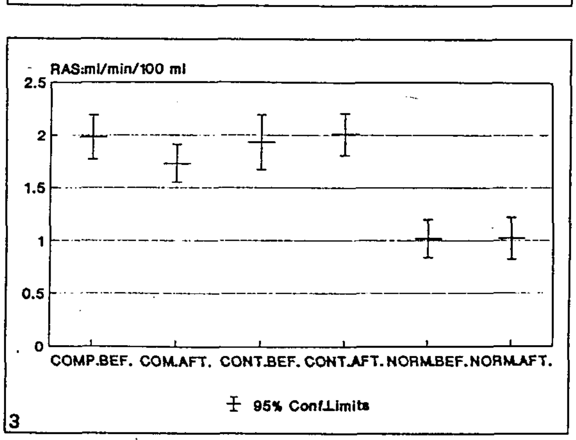


Fig. 1, 2, 3.—Variations in laser-Doppler parameters in treated patients after 12 and 24 weeks. Significant increase in VAR ($p<0.05$), decrease in RF (Fig. 1), significant increase in VAR ($p<0.05$) (Fig. 2). Decrease after 24 weeks of RAS (Fig. 3). COMP: compression group; CONT: controls; NORM: normal subjects.

microangiopathy. Several plasma proteins have been identified in the deposits in the microvascular wall in patients with microangiopathy due to diabetes or hypertension. The thickening of the arterial wall further impairs the possibility of capillaries of having to vasoconstrictory response on standing or to increased capillary pressure.[9]

Elastic compression appears to be useful in improving the microcirculation and in reducing the abnormally increased capillary filtration present in diabetic microangiopathy. Below-knee elastic stockings are well tolerated by patients and according to the results of the present study may be effective in reducing complications due to microangiopathy and possibly the number of amputations.

In conclusion, in diabetic microangiopathy, increased skin flux, increased capillary filtration appear to be both consequences of diabetic microangiopathy and an important cause of further deterioration of the microcirculation.

Controlling and reducing by elastic compression oedema it is possible to observe an improvement in the microcirculation and possibly a slower evolution of diabetic microangiopathy and its consequences.

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Acute effects of intermittent sequential compression in venous hypertension

GIOVANNI V. BELCARO, M.D.*, ANDREW N. NICOLAIDES, M.D.**

From the Irvine Laboratory, Academic Surgical Unit
St Mary's Hospital Medical School
Queen Elizabeth the Queen Mother Wing
London, England

Chronic venous hypertension produces microangiopathy which often progresses to ulceration. It has been recently observed that intermittent sequential compression (ISC) increases the rate of healing of venous ulcers. The aim of this study was to investigate the effect of this form of therapy on the microcirculation in limbs with venous hypertension.

Skin blood flow at rest (RF) was measured by laser Doppler flowmetry at the perimalleolar region at rest (horizontal position) and on standing in 34 limbs with chronic venous hypertension (17 with ulcerations) and 20 limbs of healthy volunteers. The venoarteriolar response (VAR = the vasoconstrictory response on standing) was also measured. Also 8 limbs with venous hypertension not treated with ISC were studied to evaluate the effects of supine resting alone on the microcirculation.

Two treatment protocols were used. In *Study 1* intermittent sequential compression was applied for 30 minutes. Laser-Doppler measurements were performed at time 0 (before intermittent sequential compression) and after 30, 60 and 90 minutes. In *Study 2* intermittent sequential compression was applied for 60 minutes and measurements were performed at time 0 and after 60 and 120 and 180 minutes.

In patients of *Study 1* RF was 1.45±0.8, significantly higher than in normals ($p<0.05$) and the venoarteriolar response only 7%, significantly lower than in normals. At the end of the compression period there was a marked change towards normality as RF decreased (1.1±0.2) while the change in venoarteriolar response was not significant. At 60 and 90 minutes the changes in RF were still significant ($p<0.05$) and the VAR was significantly increased ($p<0.05$).

In *Study 2* RF was 1.59±0.4, higher than in normals ($p<0.05$) and the venoarteriolar response 9%, significantly lower than in normals. At the end of the compression period there was a marked change towards normality as RF decreased (0.73±0.2) and the venoarteriolar response was significantly higher ($p<0.05$). At 120 and 180 minutes the decrease in RF and increase in venoarteriolar response were still significant ($p<0.05$). No significant changes were observed in normals and in control patients in both studies.

***Conclusions*: The findings offer an explanation on the remarkable effect of sequential compression on the healing of leg ulcers. The improvement in RF and in venoarteriolar response towards normality appears to be dose-related to the period of intermittent sequential compression used and it persists well after the end of the intermittent sequential compression session.**

KEY WORDS: Intermittent sequential compression - Venous hypertension - Laser-Doppler flowmeters - Microcirculation.

In limbs with venous hypertension due to postthrombotic syndrome there are marked changes in the microcirculation of the perimalleolar skin. They consist of a chronic high level of skin blood flow (red cell flux) [1] as shown by laser-Doppler flowmetry [1,2] and a decreased venoarteriolar response (VAR). The latter is expressed as the percentage decrease of red cell flux on standing. The VAR is the vasoconstrictory reflex induced by changes in posture from the supine to the standing position.[2,3] This physiologic response reduces the number of capillaries exposed

*Research Fellow.
**Professor of Vascular Surgery.

Authors' address: Andrew N. Nicolaides, Irvine Laboratory for Cardiovascular Investigation and Research, Academic Surgical Unit, St Mary's Hospital Medical School, Queen Elizabeth the Queen Mother Wing, South Wharf Road, London W2 1NY, England.

to a high pressure and flow in the standing position, minimising the amount of capillary leakage and ankle oedema.[2 3]

It has been observed that in limbs with venous hypertension, elastic compression applied during the day for several weeks improves the venoarteriolar response, reduces the abnormally increased skin blood flow [4] and promotes the healing of leg ulcers. More recently, it has been shown that intermittent pneumatic sequential compression produces a tenfold increase in the rate of healing of venous ulcers [5-7] but little is known about its mode of action on the microcirculation.

The aim of our study was to investigate the effects of intermittent pneumatic sequential compression (intermittent sequential compression) on the microcirculation of the skin of the gaiter area in patients with venous hypertension and skin changes (pigmentation, lipodermatosclerosis) without and with and ulceration. Two treatment protocols were used (30 minutes versus 60 minutes of intermittent sequential compression), in two separate studies in two comparable groups of patients to evaluate if the microcirculatory effects of intermittent sequential compression were dose-related.

Materials and methods

Criteria of inclusion. Patients with post-thrombotic limbs with skin changes (lipodermatosclerosis and ulceration) as a result of long standing venous hypertension were included. All patients had popliteal vein incompetence demonstrated by colour duplex scanning,[8] ambulatory venous pressure (AVP) greater than 54 mmHg and refilling time (RT) shorter than 9 seconds. The AVP and RT were not modified by the application of an ankle tourniquet excluding the superficial venous system (indicating deep venous incompetence).

Patients were studied after informed consent and after a wash-out period of one week during which no treatment had been used. Subjects with orthopaedic problems, diabetes, vascular or other microcirculatory of systemic cardiovascular disease or under any treatment were excluded.

Study 1 (UK): Sixteen limbs (11 patients) with chronic venous hypertension and perimalleolar lipodermatosclerosis (8 with venous ulcers < 1.5 cm at the maximum diameter) have been included. Laser-Doppler red cell flux was measured at the perimalleolar region initially in the supine position after aclimatisation and resting (30 minutes) in a room at constant temperature (21 ± 1 °C). The patient was asked to stand holding onto a frame and the standing flux (SF) (mean between the second and minute after standing) was measured. The first minute of recording was excluded to avoid motion artifacts.

The venoarteriolar response (namely the vasoconstrictory response on standing) was measured as venoarteriolar response = [(RF-SF)/(RF)]100. The probe of the laser-Doppler was attached to the skin of the perimalleolar region using a double-adhesive tape, to avoid local microcirculatory compression. In the presence of ulceration, the probe was placed at least 1 cm from the edge of the ulcer.

Previous work using this method has shown that in patients with chronic venous hypertension and venous hypertensive microangiopathy RF and SF are generally increased and the venoarteriolar response is reduced.[1 2 4] Intermittent sequential compression was applied for 30 minutes, with the patient supine. The Kendall sequential compression device 5315 (SCD) was used. The plastic legging was applied over a light, non-compressive fine paper bandage to avoid excessive transpiration due to the contact between the plastic surface and the skin. The compression period was set at 11 seconds with a deflation period of 60 seconds. The maximum pressure during the cycle was 50 mmHg (minimum pressure = 0).

Laser-Doppler measurements were recorded before the onset of compression and at 0, 30, 60 and 90 minutes after cessation of intermittent sequential compression. The mean of 5 minutes recording was considered as the RF.

Study 2 (Italy): Eighteen limbs (in 15 patients) with CVH and perimalleolar lipodermatosclerosis (9 with ulcers) have been studied. RF, SF and venoarteriolar response were measured with the same method and instrument (Laserflo, Vasamedics, St. Paul, USA) intermittent sequential compression was applied for one hour using the same pressure and cycles and the microcirculatory tests were repeated at 60, 20 and 180 minutes.

In both centres 10 normal subjects were also evaluated for comparison.

Finally, 8 patients with venous hypertension (4 with ulcerations) comparable to the other two groups of

TABLE I.—*Details of the two groups (age. AVP and RT are expressed as means and 1 sd).*

	N. of subjects	Number of limbs	Mean age	M:F	AVP mean (sd)	AVP range	RT mean (sd)
Study 1							
Patients	11	16 (8)*	43 (9)	5:6	66 (7)	54-75	6.5 (1.2)
Normal vols	10	10	44 (8)	5:5	34 (9)	21-44	24 (6)
Study 2							
Patients	15	18 (9)*	45 (8)	7:8	65 (9)	54-72	6.6 (8)
Normal vols	10	10	43 (9.5)	6:4	32 (10)	23-47	23.3 (9)
Controls	8	8 (4)*	44 (9)	5:3	63 (8)	55-70	6.5 (9)

*In brackets: limbs with ulcerations.

patients were included. The laser-Doppler measurements were recorded at time 0. 30. 60. 90, 120 and 180 minutes to exclude that the microcirculatory changes were a consequence of supine resting. The Mann-Whitney U-test was used to test the statistical significance of the results.

Results

The groups of both normal volunteers and patients studied in the two centers were comparable for age and sex distribution, and ambulatory venous pressure. Also, they all had popliteal reflux on colour flow duplex. The control patients were comparable for age and sex distribution and for AVP to the two other groups of patients (Table I).

RF and VAR were not significantly different in the two groups of treated patients and in the control (untreated) group. Also, there were no significant differences in RF and venoarteriolar response between limbs with ulceration and those without ulceration.

In patients the RF was increased in comparison to normal subjects in both studies. In both studies, at the end of the intermittent sequential compression session there was a significant decrease in RF. The a increase in venoarteriolar response (Table II) was significant only in study 2. Also in study 2, after 60 minutes of intermittent pneumatic compression, the RF was lower (0.73 ± 2) than after 30 minutes of compression (1.1 ± 0.2) in study 1. A significant decrease in RF and increase in VAR were present even at one hour in study 1 and at two hours in study 2 after the cessation of the compression (Table II).

No significant variations in RF and venoarteriolar response were observed in normal subjects and in control patients. No side effects were observed, patients tolerated well the intermittent sequential compression session and no drop-outs due to intolerance to intermittent sequential compression were observed.

Discussion

In limbs with chronic venous insufficiency, ankle swelling, skin changes (eczema, lipodermatosclerosis) and eventually ulceration are the result of venous hypertension consequent to superficial and/or deep venous reflux, or a combination of reflux and outflow obstruction. The chronic effect of venous hypertension on the skin of the perimalleolar region causes microcirculatory disturbances and venous hypertensive microangiopathy whose significance has only recently been understood.[1 2 9 10] The quantitative measurement of the microcirculatory disturbances has become possible with the development and application of noninvasive techniques such as laser-Doppler flowmetry, transcutaneous PO_2 and PCO_2 [1] measurements, strain-gauge plethysmography and leg volumetry.

Laser-Doppler flowmetry can measure skin blood flux at rest in the horizontal position, and on standing and also evaluate the venoarteriolar response from the decrease in skin flux relative to the resting flux on standing.[1-3] The venoarteriolar response consists of a physiological arteriolar vasoconstriction which occurs on standing and which protects the skin capillaries from being exposed to high pressure.[3] It has

TABLE II.—*Mean (and 1 sd) resting flux (RF) and the venoarteriolar response (venoarteriolar response; median and range) in patients and normal subjects and in comparable control patients (resting supine).*

	Time (min)	Study 1		Study 2	
		RF	VAR	RF	VAR
Normals	before (0)	0.56 (0.2)	35 (28-63)	0.68 (0.21)	35 (27-60)
	30 after	0.53 (0.12)	35 (23-56)	—	—
	60 after	0.5 (0.14)	37 (22-72)	0.56 (0.12)	32 (25-60)
	90 after	0.54 (0.2)	35 (21-65)	—	—
	120 after	—	—	0.58 (0.14)	33 (21-56)
	180 after	—	—	0.55 (0.16)	34 (26-63)
Patients	before (0)	1.45 (0.18)*	7 (2-23)*	1.59 (0.4)*	9 (3.3-21)*
	30 after	1.1 (0.2)	9 (3-43)	—	—
	60 after	0.85 (0.2)***	23 (9-34)***	0.73 (0.2)***	29.3 (13-36)***
	90 after	0.87 (0.15)***	21 (8-30)***	—	—**
	120 after	—	—	0.92 (0.18)***	18 (7-33)***
	180 after	—	—	0.91 (0.2)***	21 (12-45)***
Controls	before (0)	—	—	1.55 (0.2)*	11 (7-25)*
	30 after	—	—	1.4 (0.18)*	9 (4-35)*
	60 after	—	—	1.34 (0.2)*	11.3 (12-30)*
	90 after	—	—	1.39 (0.18)*	12 (7-22)*
	120 after	—	—	1.44 (0.14)*	18.5 (12-23)*
	180 after	—	—	1.52 (0.11)*	9.3 (12-45)*

*$p<0.05$ difference from normals; **$p<0.02$ difference between the two treatment protocols; ***$p<0.05$ difference before-after.

recently been demonstrated that in limbs with venous hypertension, both RF and SF are increased and that the venoarteriolar reflex is impaired [1-4] allowing a large number of capillaries to become exposed to high pressure on standing and result in an increased fluid leakage as demonstrated by the increased rate of ankle swelling using strain-gauge plethysmography.[10] The chronic increase in skin blood flow and fluid leakage are associated with venous lesions (pre-ulceration red appearance of skin with interstitial fluid loss and edema) and eventually ulceration.[9] There is a linear relationship between the RF, SF, ambulatory venous pressure, PCO_2 and the rate of ankle swelling.[1-9]

Elastic compression applied for several weeks tends to normalise all these measurements.[4] This can explain the beneficial effects of elastic compression on the rate of healing of leg ulcers.[4]

However, the changes obtained with elastic compression require some weeks (in a previous study, significant changes were observed only after 4 weeks of treatment [4]).

Although under stable experimental conditions normal skin may appear to have a constant blood flow over a relatively large area (e.g., 1 cm^2) periodical changes in blood flow in small areas (e.g., 1 mm^2) exist as a result of vasomotor activity. Thus, while there is vasoconstriction in one area there is simultaneous vasodilatation in an adjacent area. This cyclical vasomotor activity is detected with laser-Doppler flowmetry.[2] Paralysis of the vasomotor activity in patients with venous hypertension results in a permanent, maximum vasodilatation. Possibly the induction of vasomotor activity by stimulating the limb with intermittent sequential compression results in a decreased skin blood flow since some areas vasoconstrict. A decrease in skin blood flow is itself a stimulus to further vasomotion and tends to perpetuate this phenomenon. It appears that elastic compression [4] and, as shown in our study, sequential compression induces a decrease in skin flux and an increase in venoarteriolar response which persists well after the cessation of intermittent sequential compression.

Our data suggest that the decrease in RF may be related as 60 minutes of intermittent sequential compression produce a greater change (Table II). Further studies are required to substantiate this.

The intermittent sequential compression device consists of 6 chambers, 4 in the leg and 2 in the thigh, which inflate sequentially from ankle to thigh over a period of 11 seconds. The deflation period is 60 seconds. The pressure applied on the limb is graduated because each chamber has a pressure that is always lower than the most adjacent distal chamber. This device was designed to prevent venous stasis and was found to be effective in preventing post-operative deep venous thrombosis.[10]

The reduction in skin flux by intermittent sequential compression indicates a return of local blood flow regulation towards normal. Another possible explanation of the microcirculatory response to sequential compression is that compression enhances the washout of metabolic or inflammatory mediators that cause the chronic vasodilatation seen in these patients.

Recent work has demonstrated that the addition of sequential compression devices to low compression graduated elastic stockings used intermittently (3 hours per day) accelerates the rate of healing of venous ulcers by more than 10 times.

Our findings offer a possible explanation for the above. The persistence of a decreased flux after the intermittent sequential compression has been stopped, is an important finding which needs further investigation in order to determine the "dose" of such treatment, i.e., what is the optimum compression (pressure and cycle), duration and frequency of treatment.

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BERGAN and KISTNER

Atlas of VENOUS SURGERY

2

Venous Insufficiency: Noninvasive Testing

GIANNI BELCARO, DIMITRIS CHRISTOPOULOS,
and ANDREW NICOLAIDES

Chronic venous insufficiency (CVI) may be the result of outflow obstruction, reflux, or a combination of both. The objective of examination is to detect whether obstruction or reflux is present. Second, the anatomic localization of the abnormality must be found, and then the problem of quantification of the reflux or obstruction must be addressed.

In evaluating venous stasis, noninvasive tests combine physiologic and imaging techniques. For the most part, these tests are widely available, simple, quick, and cost-effective. Therefore, these are the methods of choice for initial objective evaluation.

It should be noted that different tests provide answers to different questions. It is not surprising to see a plethora of investigations done. Many of these have been established during the past decade. Most recently, however, technologic advances and current thinking indicate that the optimum useful information can be obtained using only three tools or instruments. These are the continuous-wave pocket Doppler; the duplex scanning device, preferably with color-flow imaging; and air plethysmography.

TESTS FOR VENOUS REFLUX

Venous reflux is the result of gravity inexorably drawing the venous blood stream distally. Therefore, reflux testing should be performed with the patient standing. Recent studies have determined that venous reflux detected in the supine position is frequently abolished when the patient is standing. This is because valve closure occurs only after reflux exceeds a critical flow velocity. This is achieved with the patient standing rather than supine.

When the patient is standing, it is important that muscular contractions be avoided. Therefore, the patient should be examined holding onto a frame or table. The leg to be examined should be relaxed with the knee slightly flexed and most of the weight on the opposite leg. Studies have shown that during full knee extension, an occlusion of the popliteal vein occurs in 20% of healthy people.

After physical examination, the continuous-wave Doppler ultrasound instrument is used. The pocket instruments are eminently satisfactory and these complement the physical examination in performing a screening test for outpatients.[1-3] The continuous-wave instrument provides information about reflux at the saphenofemoral and saphenopopliteal junctions.[2] As indicated above, the patient is examined standing, holding onto an orthopedic frame or table with the weight mainly on the opposite lower extremity. The knee of the leg to be examined should be slightly flexed to relax the muscles and skin over the popliteal fossa. Manual calf compression produces cephalad flow and reflux may occur when the compression is released. Abolition of the reflux by compression of the superficial veins just below the probe suggests that reflux is confined to the superficial system. Failure to abolish reflux by such a maneuver indicates that the reflux is in the deep system.[4]

In experienced hands, a pocket Doppler instrument provides clear answers regarding the presence or absence of reflux at the saphenofemoral and saphenopopliteal junctions in 90% of patients.[5] Abnormal anatomy in the popliteal fossa is responsible for most of the errors (8%). For example, reflux in the gastrocnemius veins may be interpreted as reflux in the popliteal vein. The continuous-wave Doppler venous examination is not accurate in localizing incompetent perforating veins.

Duplex scanning supplements the physical examination and evaluation with the pocket continuous-wave Doppler instrument. The duplex scan provides information about reflux in specific veins the examiner wants to interrogate. For example, the femoral, popliteal, deep calf veins, and perforating veins can be individually interrogated. The use of color has made the duplex evaluation much faster and more accurate. Color Doppler examination is precise because repeated sampling in the various veins is avoided.

As in examination of a patient with the continuous-wave instrument, the patient is examined standing. The nonweight-bearing lower extremity is evaluated and the sites to be interrogated are imaged with the 5 or 7.5 MHz probe. Thus, the saphenofemoral junction, the popliteal venous anatomy, and the perforating veins may be visualized. Manual calf compression or, ideally, compression by a rapidly deflatable cuff is used. The cuff inflation produces cephalad flow. Rapid release of the compression is essential to testing for reflux and valve closure can be documented. Figure 2–1 shows the saphenofemoral junction, Fig. 2–2 shows the popliteal fossa, and Fig. 2–3 shows an example of testing for perforating veins. Localization of calf perforating veins and reflux in them is

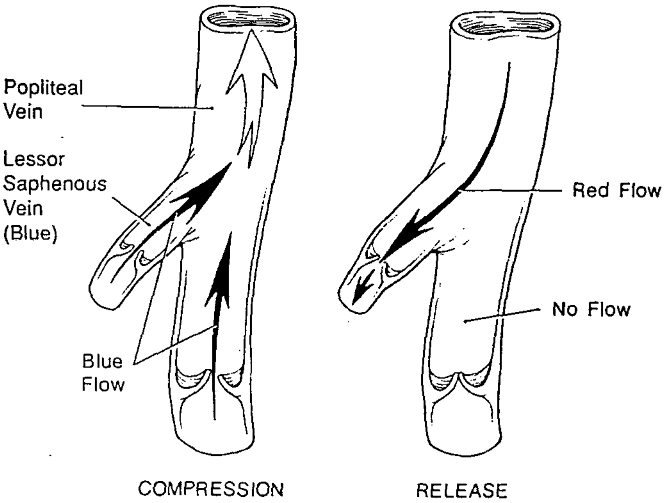

FIGURE 2–1. Example of saphenopopliteal reflux. Blue color on calf compression indicates cephalad flow. Reflux is indicated by red color in the long saphenous on release of the compression.

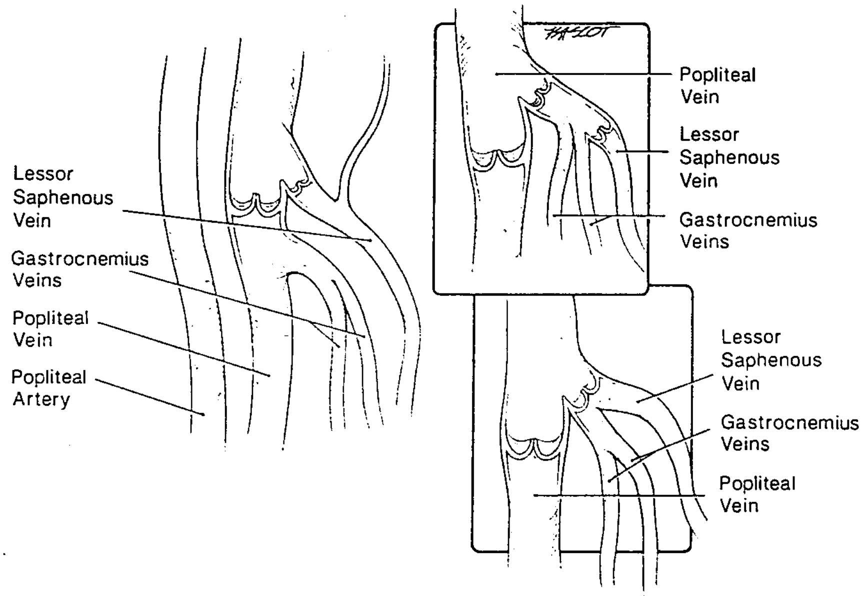

FIGURE 2–2. Three different but common anatomic variations of the veins in the popliteal fossa. Duplex scanning not only reveals the anatomy but also enables the examiner to test each individual vein for reflux.

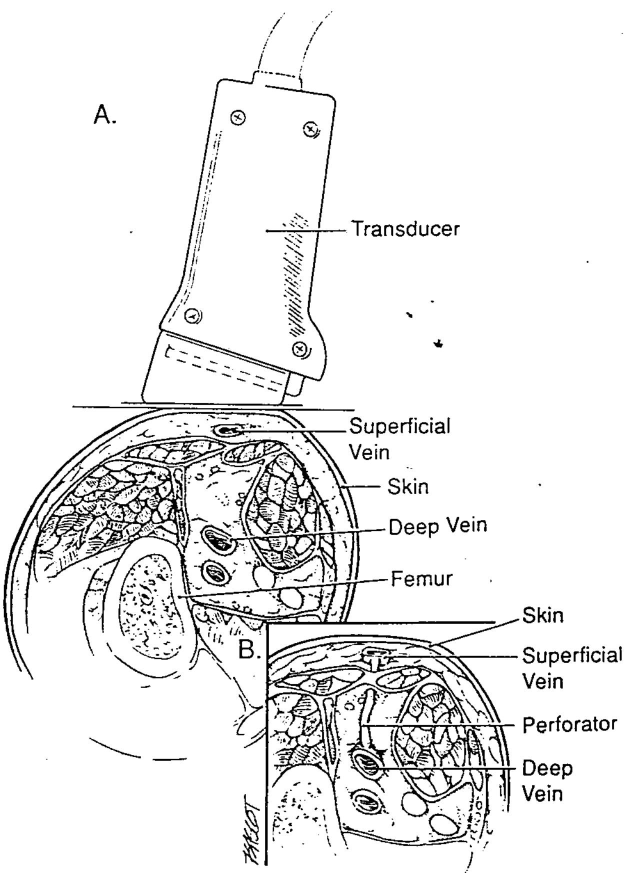

FIGURE 2–3. Transverse scan of superficial and deep vein (*A*). By moving the probe up or down the limb with continuous visualization of the two veins the presence and level of communicating vein is determined (*B*). The direction of flow with calf compression and release can then be tested.

tedious with conventional duplex, but color-flow imaging has brought this examination into the realm of practicality.

Duplex scanning for localization of sites of reflux is particularly useful in patients with recurrent varicose veins after previous surgery. Such examination also confirms the normal functioning of deep veins and the extent and site of venous reflux when it is present. Both localized and generalized reflux (eg, whether it is present throughout the deep venous system) can be identified.

Although quantification of reflux in individual veins is possible, this is a tedious examination.[6] Accurate and reproducible results are obtained more easily for the whole leg using air plethysmography. Air plethysmography has become the test of choice for quantitating reflux.

AMBULATORY VENOUS PRESSURE

Although invasive, the venous pressure examination has remained a standard to which other examinations are compared. Venous pressure is measured by inserting a needle in a vein on the dorsum of the foot with the patient standing (Fig. 2–4). Pressures are recorded during ten tiptoe movements.[3,7] The ambulatory venous pressure (AVP) is defined as the lowest pressure reached during the exercise (Fig. 2–5). The ambulatory venous pressure is a function of the calf muscle pump ejecting capacity, the magnitude of reflux, and the outflow resistance. Therefore, it represents the net effect of all the abnormalities that affect venous hemodynamics. In normal limbs, the AVP is less than 30 mmHg and the refill time (RT) is greater than 18 seconds. These values are due to filling of the veins from the arterial side. When venous reflux is present, the AVP is higher and the refill time is markedly shortened (Table 2–1).[8,9]

After AVP is obtained, the exercise test can be repeated with narrow tourniquets (2.5 cm wide) applied at the ankle, below knee, or thigh position. These tourniquets control reflux from the superficial system and if superficial reflux is present, the AVP and RT are normalized. In patients with deep venous incompetence, normalization does not occur. Table 2–1 indicates that AVP is elevated

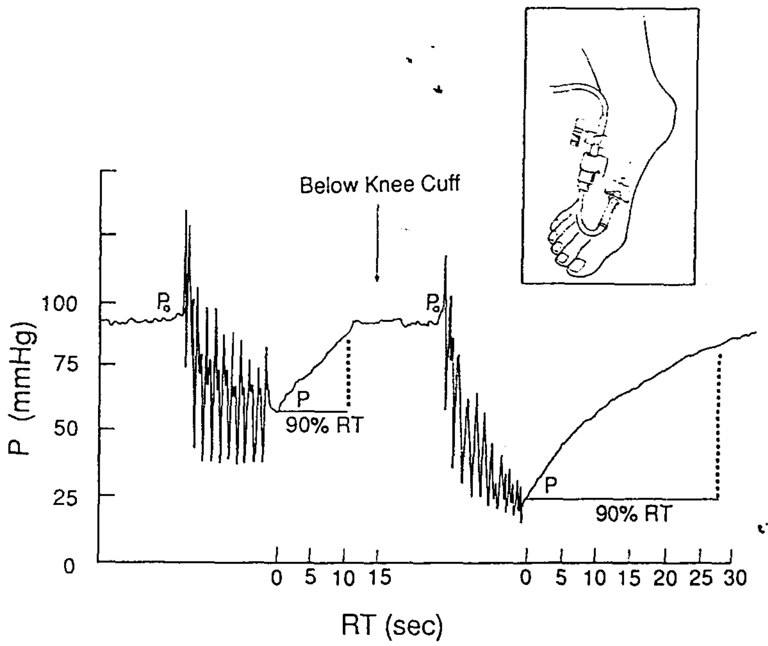

FIGURE 2–4. Recording of venous pressure during ten tiptoe movements without and with a below-knee cuff (2.5 cm wide) that occluded the superficial vein. Normalization of ambulatory venous pressure (P) and RT_{90} indicates that the deep veins are competent.

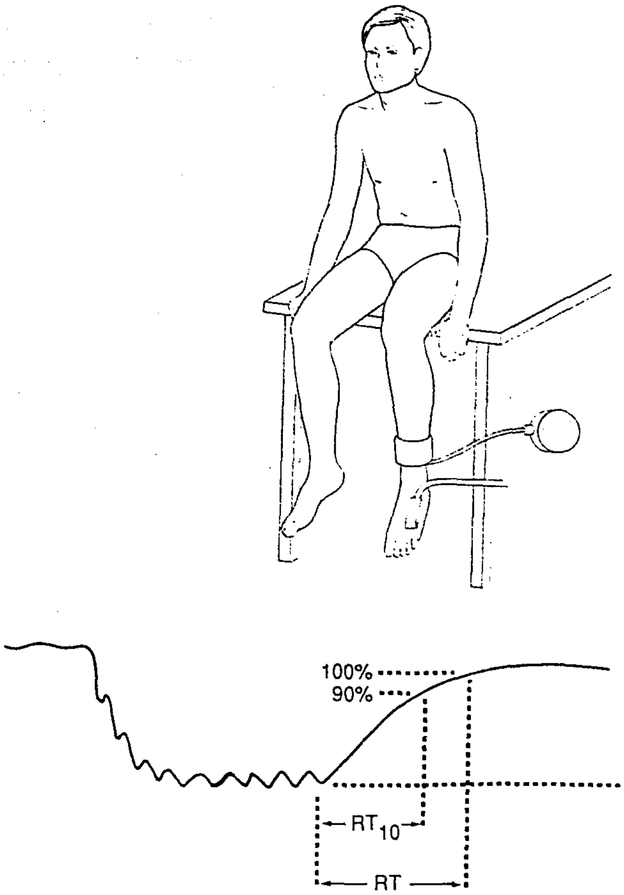

FIGURE 2-5. Measurement of RT or RT_{90} using photoplethysmography.

TABLE 2-1. Ambulatory Venous Pressure (AVP) and Refilling Time (RT_{90}) Measured with Cannulation of Foot Vein*[9]

TYPE OF LIMB	AVP (mmHg)		RT_{90} (sec)	
	No Ankle Cuff	Ankle Cuff	No Ankle Cuff	Ankle Cuff
Normal	15–30	15–30	18–40	18–40
Primary varicose veins with competent perforating veins	25–40	15–30	10–18	18–35
Primary varicose veins with incompetent perforating veins	40–70	25–60†	5–15	8–30
Deep venous reflux (Incompetent popliteal valves)	55–85	50–80	3–15	5–15
Popliteal reflux and proximal occlusion	60–110	60–120		
Popliteal occlusion and competent popliteal valves	25–60	10–60		

*Standard exercise: 10 tiptoe movements.

†In one third of these limbs, AVP remained more than 40 mmHg and RT_{90} less than 15 seconds despite the application of the ankle cuff.

TABLE 2–2. Incidence of Ulceration in Relation to Ambulatory Venous Pressure (AVP) in 222 Patients (251 Limbs)

AVP (mmHg)	N	INCIDENCE OF ULCERATION (%)
< 30	34	0
30–40	44	11
41–50	51	22
51–60	45	38
61–70	34	59
71–80	28	68
81–90	10	60
> 90	5	100

in the presence of popliteal reflux. For AVPs from 40 to 100 mmHg, there is a linear relationship to the incidence of skin ulceration. This is true regardless of the underlying pathology and whether the reflux is in the superficial or the deep system (Table 2–2).

PHOTOPLETHYSMOGRAPHY AND LIGHT REFLECTION RHEOGRAPHY

In an attempt to obtain RT without bodily invasion, photoplethysmography (PPG) and light reflection rheography (LRR) tests were devised. In both of these techniques, a photodetector is applied to the skin of the foot or ankle (Fig. 2–5).[10] These instruments determine whether venous incompetence is in the superficial veins. Table 2–3 shows the PPG refill times with and without an ankle cuff to occlude superficial veins. Results are given for normal controls, patients with superficial reflux, and those with deep venous incompetence. Our laboratory has found better reproducibility and better separation of groups when the test was performed with the patient standing.[10] Figure 2–6 shows the algorithm used in clinical practice by our group. It should be emphasized that both RT and RT_{90} (90% refilling time) are poor measures of severity of deep venous disease. This is obvious in Fig. 2–7, which illustrates the RT_{90} plotted against AVP. It can be seen that for a wide range of AVPs between 40 and 100 mmHg, the RT_{90} is between 5 and 10 seconds. Reduction in AVP from 100 to 60 mmHg by valve repair (valve plasty) thus has little effect on RT_{90}.

Air Plethysmography

Air plethysmography using a calibrated air chamber applied to encompass a leg (Fig. 2–8) provides quantitative information about the various components of the calf muscle pump.[11-13] These include the rate of filling of the reservoir

TABLE 2–3. Photoplethysmographic Refilling Time (RT_{90}) with and without an Ankle Cuff to Occlude Superficial Veins[10]

	STANDING (sec)		SITTING (sec)	
	NO CUFF	CUFF	NO CUFF	CUFF
Normal	18–80*	18–80	26–100	26–100
SVI	5–18	18–50	2–25	18–50
DVI	3–12	6–18†	2–28	2–30

*RT_{90} > 18 seconds without cuff identifies normal limbs.
†RT_{90} < 18 seconds with cuff identifies limbs with deep venous incompetence.

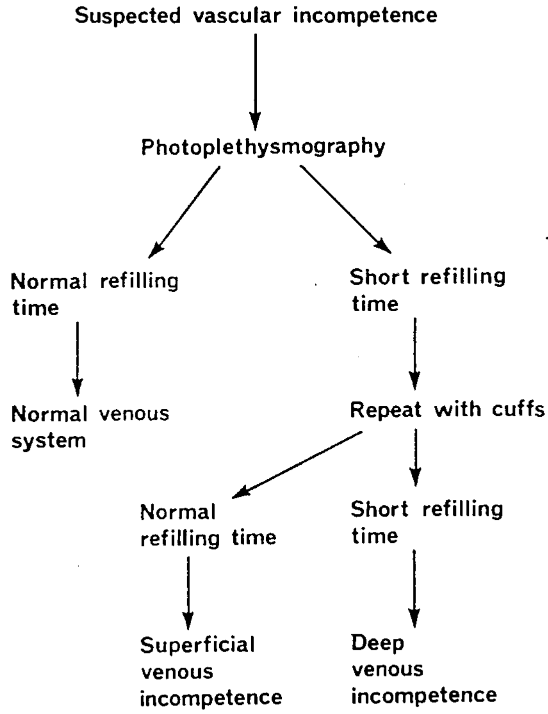

FIGURE 2–6. Diagnostic flow chart indicating the procedure followed with PPG for the screening of patients with suspected venous problems.

(venous filling index [VFI]) as a result of standing; the venous volume (VV), which is the amount of blood in the venous reservoir; the ejected volume (EV), and the ejection fraction (EF = [EV/VV] × 100) as a result of a single step; and the residual volume (RV) and residual volume fraction (RVF = [RV/VV] × 100) as a result of ten tiptoe movements (Fig. 2–9). The maneuvers and methods of making these measurements from the recording are shown diagrammatically in Fig. 2–9. There is a high reproducibility of the desired measurements that are expressed as ratios: VFI, EF, and RVF (coefficient of variation less than 10%) (Table 2–4).

VFI is a measurement of reflux and is expressed in milliliters per second. Volume measurements are in absolute units (milliliters). The median and 90% range of the various measurements in different groups of patients are shown in Figs. 2–10 to 2–12 and summarized in Table 2–4. The linear correlation that exists between RVF and the AVP (Fig. 2–13) means that an estimate of the AVP can be obtained from the RVF in a noninvasive fashion. The incidence of cutaneous ulceration increases with increase in the amount of reflux (VFI) and a decrease

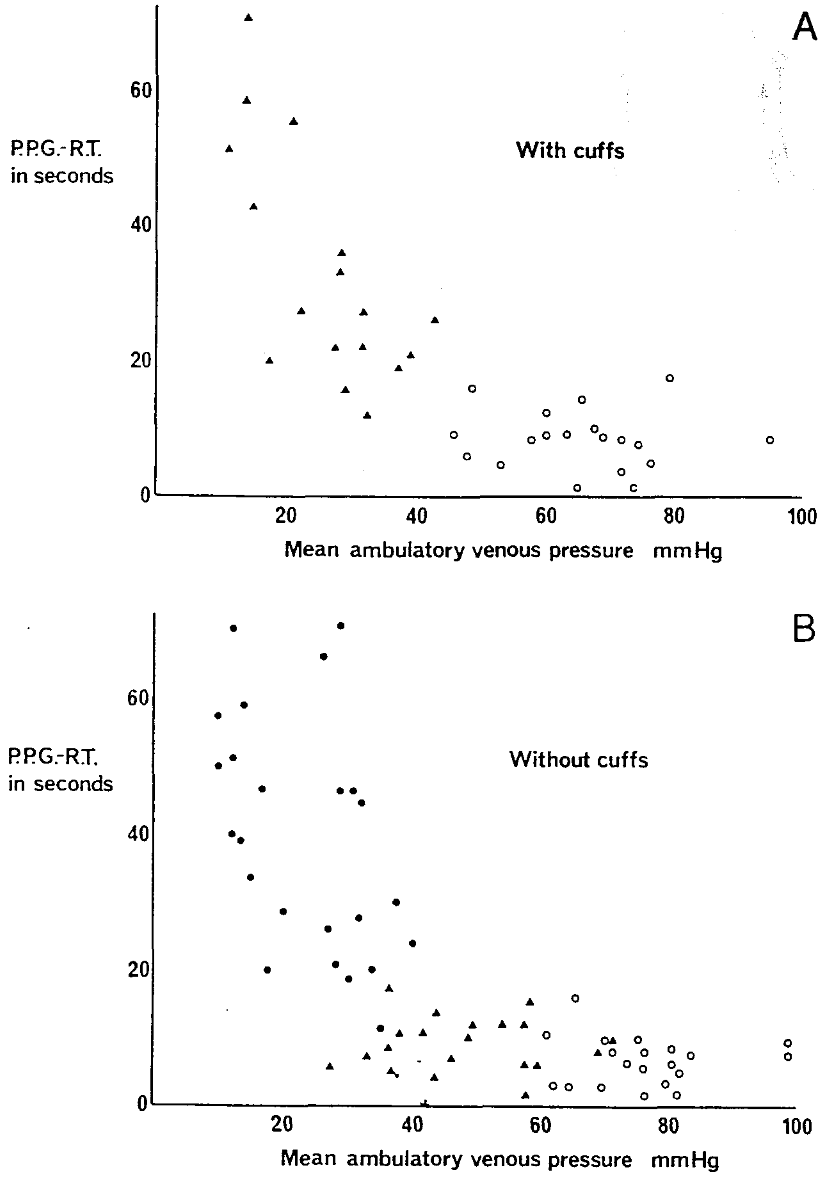

FIGURE 2–7. Relationship between PPG-RT and AVP with (*A*) and without (*B*) a cuff excluding the superficial system in the standing position. (●, normal limbs; ▲, superficial incompetence only; O, deep venous incompetence.)

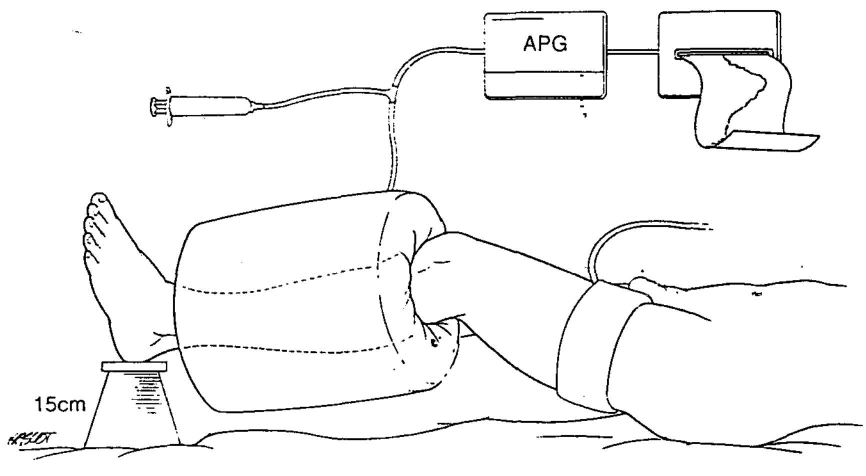

FIGURE 2–8. Diagrammatic representation of the air plethysmograph. The 100 mL syringe included in the circuit is used for calibration.

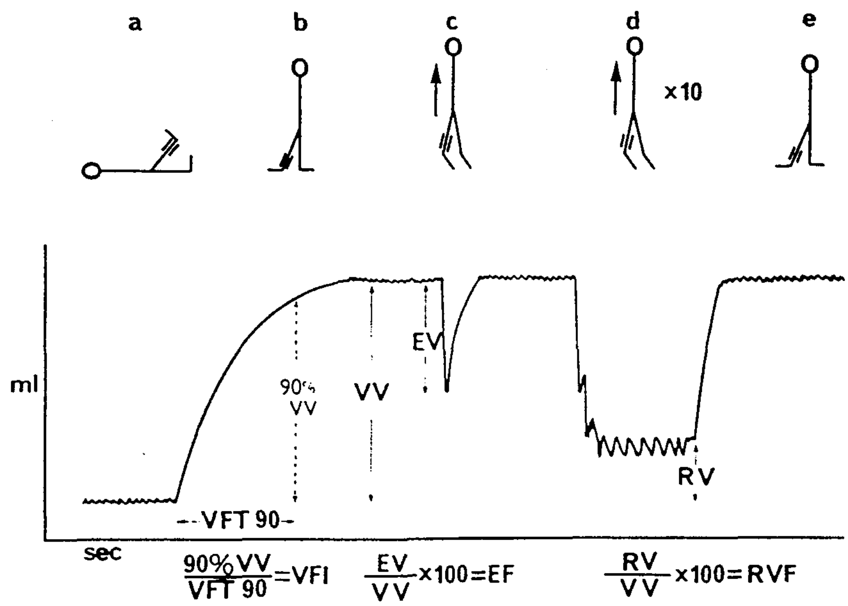

FIGURE 2–9. The maneuvers and methods of deriving the air plethysmographic measurements.

TABLE 2–4. Air Plethysmography[1–3,5,14,17]

DIRECT MEASUREMENTS	UNITS	COEFFICIENT OF VARIATION (%)	NORMAL LIMBS	PRIMARY VVs	DVD
Functional venous volume (VV) (increase in leg volume on standing)	mL	10.8–12.5	100–150	100–350	70–320
Venous filling time (VFT 90) (time taken to reach 90% of VV)	sec	8.0–11.5	70–170	5–70	5–20
Ejected volume (EJ) (decrease in leg volume as a result of one tiptoe)	mL	6.7–9.4	60–150	50–180	8–140
Residual volume (RV) (volume of blood left in veins after ten tiptoes)	mL	6.2–12	2–45	50–150	60–200
DERIVED MEASUREMENTS					
Venous filling index (VFI) (Average filling rate: 90% VV/VFT 90)	mL/sec	5.3–8	0.5–1.7	2–25	7–30
Ejection fraction (EF = [EV/VV] × 100)	%	2.9–9.5	60–90	25–70	20–50
Residual volume fraction (RVF = [RV/VV] × 100)	%	4.3–8.2	2–35	25–80	30–100

VVs, varicose veins; DVD, deep venous disease.

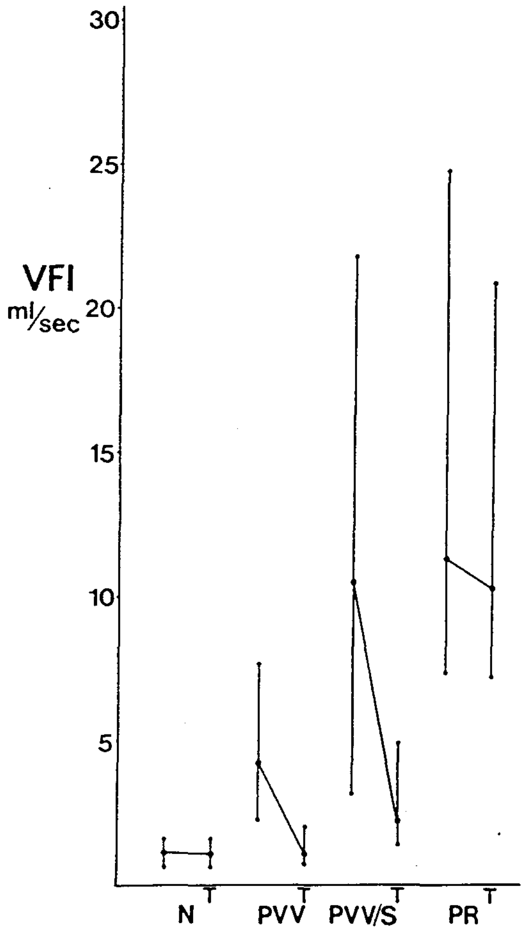

FIGURE 2–10. Venous filling time (VFI) in normal controls, limbs with primary varicose veins without (PVV) and with skin changes (PPV/S), and limbs with popliteal reflux (PR). The results are presented as median and 90% range without and with a 2.5 cm tourniquet (T) at the knee that occluded the superficial veins. The application of this tourniquet can differentiate between reflux in the superficial and deep veins.

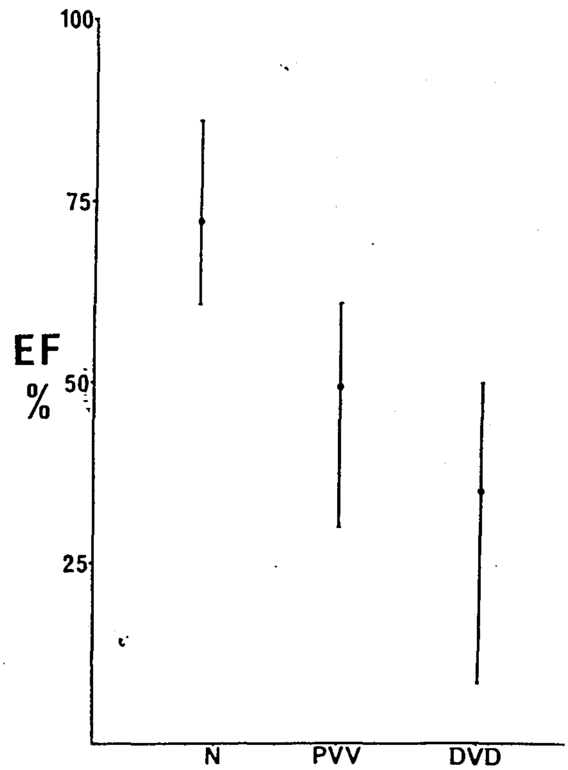

FIGURE 2–11. Ejection fraction (EF) in normal controls, limbs with primary varicose veins (PVV), and deep venous disease (DVD). The results are presented as median and 90% range.

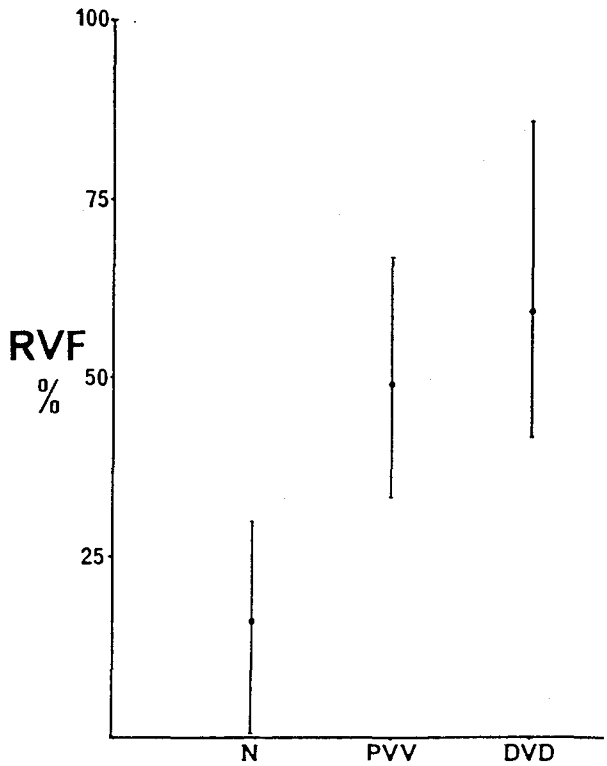

FIGURE 2–12. Residual volume fraction (RVF) in the same group of patients as in Fig. 2–11.

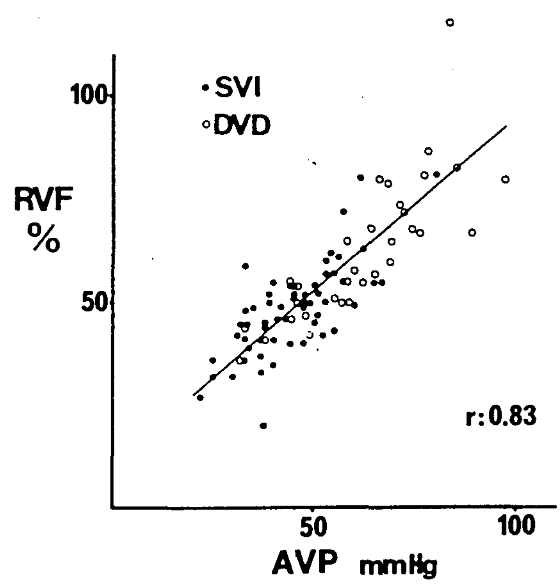

FIGURE 2–13. Correlation between AVP and RVF. (SV1, superficial incompetence; DVD, deep venous disease.)

in the efficiency of the calf muscle pump ejection (EF). Thus, the RVF provides information on the overall effect of all of the venous abnormalities. In addition, the abnormalities are dissected out and measured in terms of the EF (ejection) and the VFI (reflux) components.

TESTS FOR OUTFLOW OBSTRUCTION

When evaluating venous stasis, ascending phlebography remains the standard method of delineating persistent venous obstruction. There are several noninvasive tests that determine the presence and quantify the degree of outflow obstruction. The simple continuous-wave Doppler instrument can be used as a screening device in outpatients. A history of deep venous thrombosis or persistent leg and ankle swelling suggests the need for such an examination.[14]

Although not in general worldwide use, the best test to evaluate obstruction is the arm–foot pressure differential developed by Raju.[15] Other noninvasive tests are based on the measurements of venous outflow by various techniques using different instrumentation. These methods include the strain-gauge, impedance, and air-plethysmography modalities. Our opinion is that the high reproducibility and simplicity of air plethysmography has made this technique the method of choice; however, the other methods are in more general worldwide use.

Ultrasound Techniques: Continuous-Wave Doppler and Duplex Scanning

The patient is examined with the legs horizontal and the knee slightly flexed. The trunk should be at 45 degrees and the ultrasound probe is held over the femoral vein.[16] Flow velocity is phasic with respiration. If this is found, this indicates a normal iliocaval segment. Absence of phasic flow or the finding of flow that is continuous and not affected by respirations suggests obstruction. If flow is diminished or abolished by compression of the contralateral groin or suprapubic area, the presence of obstruction and collateral circulation is established. Augmentation of the velocity in the common femoral vein by calf compression indicates absence of popliteal and femoral venous obstruction. This maneuver can be repeated with occlusion of the long saphenous vein at the knee by external pressure. This double-checks the patency of the popliteal vein. Augmentation of the velocity in the popliteal vein produced by digital compression of each venous compartment in the leg suggests patent axial deep calf vein flow.[17]

Duplex scanning and color flow imaging detect with great accuracy the particular veins containing organized thrombus that are not compressible by probe pressure. Such duplex visualization of the deep veins may reveal irregular vein walls with abnormal echo and partially recannalized lumens.[18,19]

Arm–Foot Pressure Differential (Raju)

The arm–foot pressure differential measurement is considered to be an excellent method of quantitating outflow obstruction. This technique consists of recording the venous pressure in the veins of the foot and hand simultaneously after appropriate venous cannulation. The measurements are made with the patient supine and are repeated after inducing reactive hyperemia in the leg. In normal limbs, the arm–foot pressure differential is less than 5 mmHg with a rise of 1 to 6 mmHg (ie, 5 may rise by 1 to 6 mmHg, to become 6 to 11 mmHg) is observed during reactive hyperemia. Patients with venographically proven evi-

TABLE 2–5. **Arm–Foot Differential (P mmHg) in Limbs with Outflow Obstruction[10]**

GRADE	PRESSURE AT REST	PRESSURE INCREMENT DURING HYPERAEMIA
I: fully compensated	< 5	< 6
II: partially compensated	< 5	> 6
III: partially decompensated	> 5	> 6 (often 10–15)
IV: fully decompensated	>>> 5 (often 15–20)	No further increase

dence of obstruction have been classified into four grades according to the criteria shown in Table 2–5.

Outflow Measurements

The degree of venous obstruction can be assessed from outflow measurements using mercury strain-gauge or air plethysmography. In both techniques, a proximal thigh cuff is inflated with the patient supine and the limb elevated 10 degrees with external rotation and 10 degrees knee flexion. The veins are allowed to fill for at least 2 minutes and the cuff is suddenly deflated. Measurements are made from the outflow curves. Maximum venous outflow, 1-second outflow, and 3-second outflow fractions are all valid measurements used and advocated by different authors. Figure 2–14 shows the tangent used for calculating maximum venous outflow and the measurement for 1-second outflow using strain-gauge plethysmography. Figure 2–15 shows the venous volume (VV) and 1-second decrease in volume (V_1) measurements using air plethysmography. The outflow fraction is expressed as $OF = (V_1/VV) \times 100$.

Table 2–6 shows the range of values for limbs with normal veins, moderate, and also severe obstruction for strain-gauge plethysmography (MVO) and air plethysmography (OF). The relation between outflow fraction using air plethysmography and arm–foot pressure differentials is shown in Fig. 2–16.

Outflow resistance can be calculated from the air plethysmographic and direct venous pressure outflow curves obtained simultaneously (Fig. 2–17). Actual flow (Q) can be calculated from the tangent at any point on the volume outflow curve. Resistance ($R = P/Q$) is calculated by dividing the corresponding pressure (P) by the flow (Q). This can be done for a series of points on the

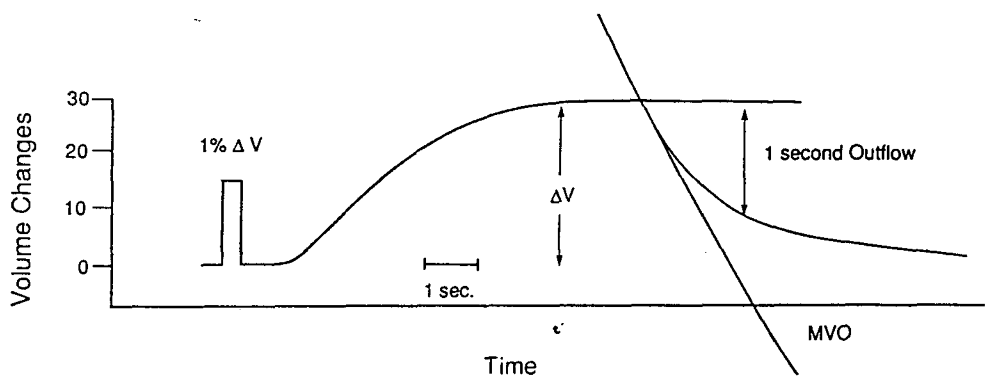

FIGURE 2–14. The outflow curve obtained by strain-gauge plethysmography. A tangent at the initial part of the outflow curve is used for calculating maximum venous outflow (MVO).

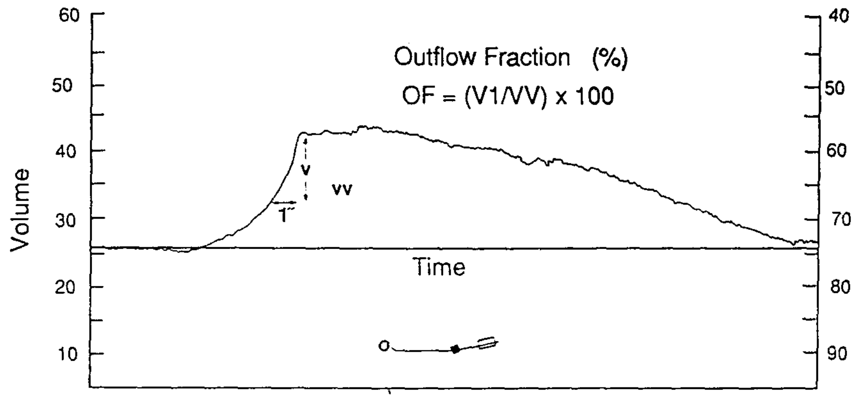

FIGURE 2–15. The calculation of outflow fraction (1 sec) from the air plethysmographic outflow curve.

TABLE 2–6. Maximum Venous Outflow (MVO)

OBSTRUCTION	NORMAL	MODERATE	SEVERE
MVO strain-gauge (1 sec) (mL/100 mL/mm)	45	45–30	30
1 sec outflow fraction (OF) Air plethysmography (% of VV)	38	38–30	30

VV, venous volume.

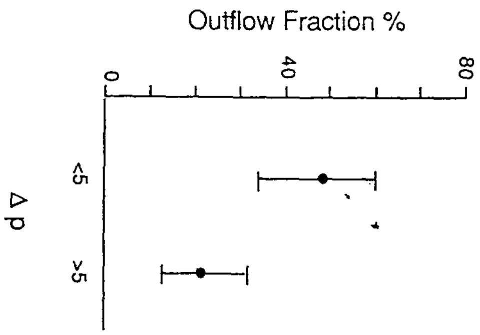

FIGURE 2–16. Outflow fraction (OF) in 15 limbs with deep venous reflux but no obstruction and arm–foot pressure differential (ΔP) less than 5 mm Hg, and 8 limbs with venographic deep venous obstruction and ΔP greater than 5 mm Hg.

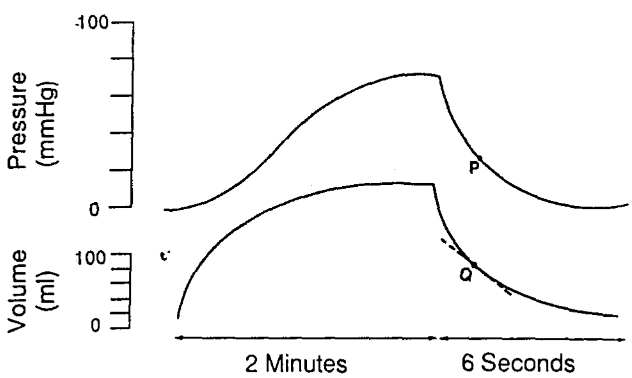

FIGURE 2–17. Pressure and volume inflow and outflow curves obtained simultaneously using an air plethysmograph and cannulation of a vein on the dorsum of the foot.

outflow curves. By plotting the resistance against pressure, as shown in Fig. 2–18, it has been shown that the relation between these is not linear. At low pressures when the veins are collapsed, the resistance is high. The resistance decreases at higher pressures when the veins, and presumably the veins of the collateral circulation, are distended. Figure 2–18 also demonstrates the relationship between resistance and the four grades of arm–foot pressure differential described by Raju.

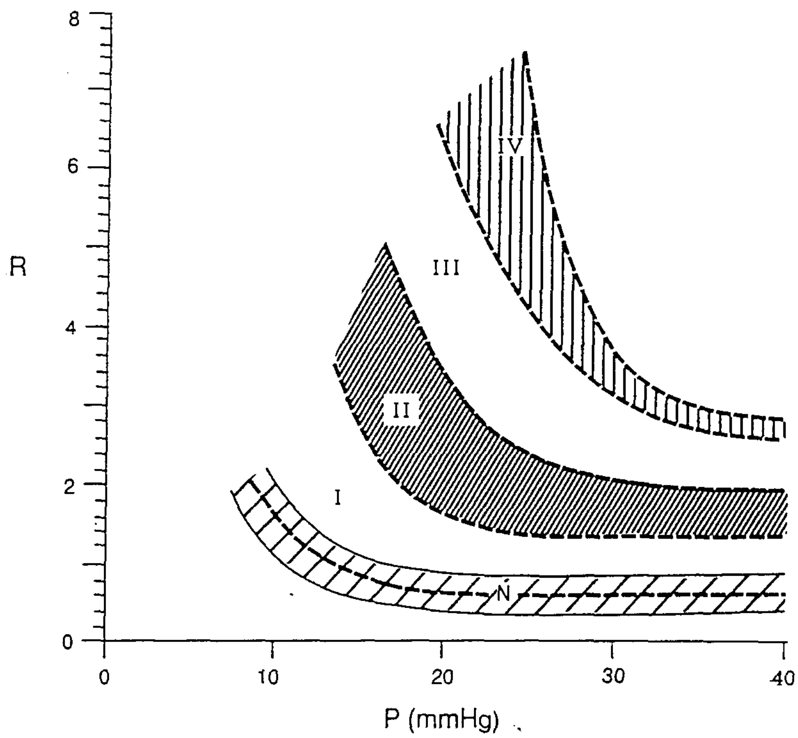

FIGURE 2–18. Relation between outflow resistance curves and Raju classification of outflow obstruction (Grades I to IV). (N, normal limbs.)

CONCLUSION

It is now possible to detect the presence or absence of reflux or obstruction in venous circulation noninvasively. It is also possible to determine the anatomic site of each and obtain quantitative measurements of the severity of both. Despite the plethora of investigations that have emerged during the past 10 years, it is possible to obtain optimum information using simple tools such as the pocket Doppler, the duplex scanner (with or without color flow imaging), and the air-plethysmograph.

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RECOMMENDED FURTHER READING

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Director, Microcirculation Laboratory, Cardiovascular Institute, Chieti University, Italy, and Senior Research Fellow, Irvine Laboratory, Academic Surgical Unit, St Mary's Hospital Medical School, London, UK.

ULRICH HOFFMANN MD

Angiology Division, Department of Internal Medicine, University Hospital, Zurich, Switzerland.

ALFRED BOLLINGER MD

Professor and Head of the Angiology Division, Department of Internal Medicine, University Hospital, Zurich,
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PREVENTION OF VENOUS THROMBOEMBOLISM
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INVESTIGATION OF PATIENTS WITH DEEP VEIN THROMBOSIS AND CHRONIC VENOUS INSUFFICIENCY

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This volume provides a short but comprehensive overview of the progress made in the last few years in the investigation of patients suspected of having deep vein thrombosis or chronic venous disease; also, a foundation for embarking on further studies on clinical investigations. Part I addresses the diagnosis of deep vein thrombosis and Part II the diagnosis of chronic venous insufficiency. In each section, both invasive and non-invasive tests are described and their advantages, disadvantages, limitations, applications and interpretation are discussed.

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The effect of hydroxyethylrutosides on capillary filtration in moderate venous hypertension: a double blind study

S. RENTON, M. LEON, G. BELCARO, A. N. NICOLAIDES,

From the Irvine Laboratory for Cardiovascular Investigation and Research, St. Mary's Hospital Medical School, London W1, England

The aim of this study was to evaluate the effect of hydroxyethylrutosides on capillary filtration in subjects with mild to moderate venous incompetence—superficial varicose veins and/or deep venous disease and ankle oedema—using the vacuum suction chamber (VSC) device applied to the internal perimalleolar region and the wheal vanishing (WV) time. Subjects entered in to the study were randomised to receive either hydroxyethylrutosides (1 g twice daily for 4 weeks) or placebo for four weeks. The two groups entering and completing the study were comparable. Microcirculatory parameters (laser-Doppler resting flux, the venoarteriolar response, transcutaneous PO_2 and PCO_2) remained constant during the four week study in both groups. The WV time, which was comparable in the two groups at the beginning of the study decreased significantly [from a median 55 min (interquartile 955 min), to a median 45 minutes (interquartile 65-40 min) in the treated group, $p<0.01$]. No change was observed in the WV time in the placebo group. Subjective symptoms measured with an analogue scale improved following treatment with hydroxyethylrutosides [foot oedema ($p<0.005$), ankle oedema ($p<0.001$), and paraesthesia ($p<0.01$)]; only night cramps were reported less in patients receiving the placebo ($p<0.05$). In conclusion, the WV time can be used to assess the beneficial effect of therapy on capillary filtration in subjects with mild-moderate venous hypertension, even after a short period of treatment, and before other microcirculatory parameters change. Furthermore, the changes observed in WV time correlate well with an improvement in patients symptoms.
[Int Angiol 1994;13:259-62].

Key words: **Capillary filtration - Capillary permeability - Postphlebitic syndrome - Venous disorders - Vascular investigations, non invasive - Hydroxyethylrutoside.**

Local capillary permeability and filtration are increased in patients with venous hypertension [1-4] or diabetic microangiopathy.[5 6] This manifests itself as ankle and foot oedema on standing and at the end of the day. Local oedema can be assessed with the vacuum suction chamber (VSC).[1 3] The VSC is composed of a flexible (2 cm in diameter) plastic chamber, applied to the skin, to which a negative pressure of 30 mmHg is applied for 10 minutes. A wheal (rounded flat-topped, pale-red, evanescent elevation in the skin which disappears in minutes or hours) is provoked by the VSC. Wheals are produced by oedema in the upper layer of the dermis due to increased permeability and filtration as a result of local capillary damage. As a result, fluid accumulates in the extracellular space, in response to the applied negative pressure. This local oedema disappears completely in normal skin, in standard environmental conditions, in less than 60 minutes (the wheal vanishing WV time).[1 3]

A recent study [7] has shown that the WV time in healthy individuals and patients with ankle oedema is well correlated ($r=0.74$) with the rate of ankle swelling (RAS) measured by venous occlusion strain gauge plethysmography (RAS) [2 4 7-10]

Hydroxyethylrutosides* have been used to treat ankle oedema in patients with venous hypertension [3 4 11 12] and, more recently, diabetic patients.[11 13] These studies have shown that microcirculation parameters (resting skin flow, the venoarteriolar response, transcutaneous PO_2 and pCO_2) improve significantly after a few weeks of treatment with hydroxyethylrutosides.

It has been also shown that the capillary filtration is improved within hours of treatment.[4 11]

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*Venoruton/Paroven, Zyma Healthcare, Mill Road. Holmwood, Surrey, UK.

The aim of this study was to the assess the effect of four weeks treatment with oral hydroxyethylrutosides (HR) on capillary filtration in venous hypertension; in a randomised double blind trial, comparing HR to placebo.

Materials and methods

Patients

Forty patients with ankle oedema due to mild to moderate venous hypertension due to deep or superficial incompetence were recruited. In all cases, the limb with the most severe venous hypertension was studied. All patients included in the study had ambulatory venous pressures (AVP) of at least 45 mmHg [14] and venous incompetence documented on colour duplex scanning.

Patients with peripheral arterial disease or diabetes were excluded and Doppler ultrasound examination demonstrated a normal ankle to arm pressure index (>1.1) in all subjects. Elastic stockins were not worn for two weeks prior to the study, and throughout the study period.

Methods

All microcirculatory measurements were recorded in a room at constant temperature (21±2°C).

Patients were examined at the same time on each visit (before 10 a.m.) after 30 minutes acclimatisation, lying supine on a couch with the limb exposed. After acclimatisation the VSC was applied to the medial perimalleolar region, and a negative pressure of 30 mmHg applied for 10 min,[1 3] the suction was then released and the time to disappearance of the wheal recorded (the WV time).

The microcirculatory parameters: resting flux (RF), standing flux, and the venoarteriolar response (VAR), were measured with a laser-Doppler flow meter, and transcutaneous PO_2 and PCO_2 were recorded.[1 12 13 15-17]

Patients were also asked to evaluate subjectively six symptoms: foot oedema, ankle oedema, night cramps, paraesthesia, ache or pain on prolonged standing, and sensation of restless legs.

Symptoms were scored on an analogue line scale (score 0-10) before and after treatment.

Treatment

After the initial examination, the patients were randomised to receive either 2 tablets of 500 mg HR twice daily or a placebo of identical appearance. After 4 weeks treatment, WV time, laser Doppler studies and transcutaneous pCO_2, and PO_2 measurements were repeated along with the symptom severity assessment.

The study was approved by the St. Mary's Hospital Ethics Committee and informed written consent was obtained from all patients.

Statistics

Differences between the 2 groups for the initial patients characteristics were tested with the Wilcoxon Rank Sum test. Changes following treatment were tested using the 2-tailed Wilcoxon Signed Ranks (matched pairs) test.

Results

The 2 groups of patients were comparable for age and sex distribution (Table I) and characteristics of venous disease. Fifteen patients (77%) completed the study in the treatment group and 16 (75%) in the placebo group. There were no unwanted side-effects. The drop-outs were due to causes unrelated to treatment.

No differences were observed between the two treatment groups in the microcirculatory parameters before or after the 4 week treatment (Table I). The WVT time was significantly longer ($p<0.05$) than the normal range in both groups at entry in to the study. After 4 weeks treatment with HR, the WVT time was significantly reduced [from a median 55 min (interquartile 95-45 min), to a median 45 minutes (interquartile 65-40 min $p<0.01$)]. No change occurred in the WVT time in the placebo group (Fig. 1).

Subjective symptoms measured with an analogue scale improved following treatment with HR [foot oedema ($p<0.005$), ankle oedema $p<0.001$, and paraesthesia ($p<0.01$)], only night cramps were reported less in patients receiving the placebo ($p<0.05$) (Table II).

TABLE I.—*Microcirculation parameters for the patients completing the trial (median and interquartile range).*

Parameters	HR group		Placebo group	
	Before treatment	After treatment	Before treatment	After treatment
RF (flux units)	1.27 (0.8-2.55)	——	1.24 (0.96-2.91)	1.35 (0.84-2.82)
VAR (RF-SF/RF%)	50% (36-82%)	77% (71-83%)	59% (45-80%)	75% (58-78%)
pO_2 (mmHg)	48.5 (34.5-79.3)	52 (46-68)	54.5 (46.5-59.8)	57.5 (58.5-60)
pCO_2 (mmHg)	40 (32.8-46)	43 (40-46)	45 (42.3-46.8)	43 (39-47)
WVT (min)	55 (45-95)	45 (40-65)*	72.5 (40-108)	72.5 (45-82.5)

*p (two tailed) <0.01 compared with pre-treatment values in the HR group (Wilcoxon's signed ranks (matched pairs) test.
HR: hydroxyethylrutosides.

TABLE II.—*Subjective symptom scores (analogue scale) (median and interquartile range).*

Symptoms	HR group		Placebo group	
	Before treatment	After treatment	Before treatment	After treatment
Foot oedema	1.5 (0.8-3.9)	0.5 (0.2-3)**	2.7 (0.6-8.5)	1 (0.5-3.5)
Ankle oedema	1.2 (0.8-5.2)	1 (0.2-5)**	2.8 (1.1-5.1)	1.5 (0.5-3.7)
Ache on standing	4.5 (1.4-7)	3.2 (0.5-7)	2.3 (0.9-6.3)	1.9 (0.8-4)
Night cramps	2.5 (0.2-3.5)	0.7 (0.2-2.1)	3.1 (0.9-6.2)	1 (0.5-1.9)***
Paraesthesia	4.1 (1.5-7.2)	2 (1.2-4.8)*	2.7 (0.6-8.5)	0.7 (0.5-3.4)
Restless legs	4 (1.6-8.2)	3.2 (0.8-6.9)	3 (0.6-4.6)	2.5 (0.8-4.5)

Using Wilcoxon signed ranks (matched pairs) test. *p<0.01; **p (two tailed) <0.005; ***p<0.05.

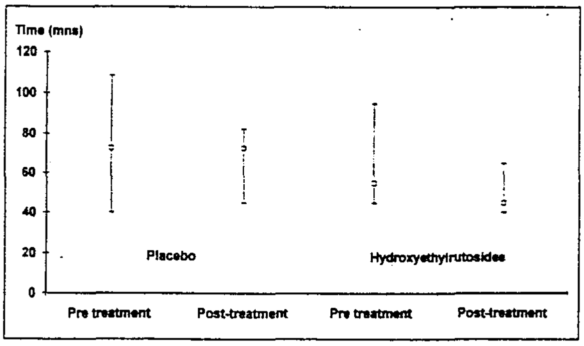

Fig. 1.—The wheal vanishing time before and after treatment with HR or placebo (median and interquartile range).

Conclusions

The ankle oedema of venous hypertension is due to the increased osmolarity of the extracapillary compartment as a result of the accumulation of metabolites and proteins in the tissues, a decreased lymphatic clearance, micropooling, and an increased skin blood flow.[3 15]

In patients with venous hypertension [16] and in diabetics,[18 19] the venoarteriolar response (VAR)—the vasoconstrictory response to standing mediated by a sympathetic axon reflex—is impaired. This reduction in VAR is associated with ankle and foot oedema due to an inability to limit the rise in capillary pressure and hence, capillary filtration, on standing. This chronic increase in capillary pressure results in the accumulation of fluid and large molecules into the pericapillary space.[5 6] Thickening of the basement membrane, observed in diseased smal vessels in diabetic and venous hypertensive microangiopathy is a consequence of chronic capillary hypertension.

Both in venous hypertension and in diabetic microangiopathy administration of HR has been shown to improve capillary leakage [11 13] and reduce oedema formation.[3 12] Using the VSC and measurement of the WV time, it is possible to evaluate the local capillary filtration in the perimalleolar region directly, with a better separation—in comparison with the evaluation of the rate of ankle swelling on venous occlusion strain gauge plethysmography—between healthy individuals and patients, and between limbs with different degrees of venous hypertension.[7]

This study confirms that HR acts by modifying capillary filtration even after a short period of treatment and this response can be detected with the WV time prior to the detection of changes in other microcirculation parameters. Furthermore, changes in the WV time correlate well with significant improvement in symptoms following treatment with HR.

The effects of HR on WV time observed in mild/moderate venous hypertension are consistent with the microcirculatory results previously reported in patients with severe venous hypertension [3 12] and diabetic microangiopathy.[13]

In conclusion, HR improves the capillary filtration in venous hypertension with an associated improvement in symptoms. Furthermore, changes in the capillary filtration can be detected by the VSC technique prior to significant changes in other microcirculation parameters.

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Address reprint requests to: G. Belcaro - Irvine Laboratory for Cardiovascular Investigation and Research, St. Mary's Hospital Medical School - London W1 (England).

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Microcirculation in high perfusion microangiopathy

G. BELCARO, G. LAURORA, M.R. CESARONE, M.T. DE SANCTIS, L. INCANDELA

Using laser-Doppler flowmetry in association with other noninvasive microcirculatory techniques such as transcutaneous PO_2 and PCO_2 and capillary filtration measurements it is possible to define two major types of microangiopathy. *Low perfusion microangiopathy* (LPM) is observed in peripheral vascular disease, essential hypertension, Raynaud's disease etc. *High perfusion microangiopathy* (HPM) is observed in venous hypertensive microangiopathy and diabetic microangiopathy. In both these conditions there is an increased skin flux, decreased venoarteriolar response and increased capillary filtration leading to edema formation. In HPM elastic compression and drugs acting on capillary filtration effectively reduce skin flux and the increased capillary leakage and edema formation.

KEY WORDS: Diabetic microangiopathy - Laser-Doppler flowmetry - Microcirculation - Postphlebitic syndrome - Venous hypertension - Capillary permeability.

From the Microcirculation Laboratory, Cardiovascular Institute, G. D'Annunzio University, Chieti and ACV Pierangeli Clinic, Pescara, Italy and Irvine Laboratory, St. Mary's Hospital, London, UK

In the last few years the application of noninvasive microcirculatory techniques such as laser-Doppler flowmetry (LDF) has given us a better picture of venous hypertensive microangiopathy (VHM).

VHM can be both a consequence of deep or superficial incompetence or a combination of the two, possibly in association with some degree of obstruction. The result is a chronic increase in venous pressure which is progressively transmitted to the more distal capillary bed.

In the skin of the perimalleolar region of subjects with VHM it is possible to observe (Fig. 1) an apparent increase in the number of capillaries. This aspect is due to the convoluted and elongated capillaries in the skin. Also there is an increase in the average size of capillaries (Fig. 2) with thickening of the capillary wall (Fig. 3).

These histology findings are related to an increased skin flux (when measured by laser-Doppler flowmetry=LDF) in areas of venous hypertension such as the perimalleolar region. This observation is often found in association with a decreased efficacy in the venoarteriolar res-ponse (VAR) namely the skin flow reduction observed

Fig. 1.—Skin biopsy (internal perimalleolar region) in a limb with venous hypertension. The apparent number and size of the capillaries is increased.

Address reprint request to: G. Belcaro, Via Vespucci, 65, 65100 Pescara, Italy.

Fig. 2.—Skin biopsy: the convoluted capillary in the biopsy section.

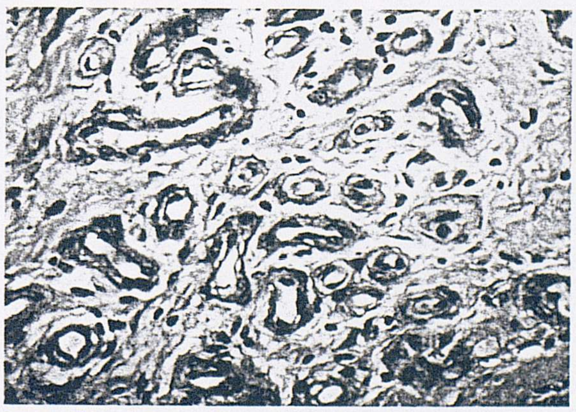

Fig. 3.—The capillary wall appears thickened. In some specimens fibrin deposition within the capillary wall may be observed.

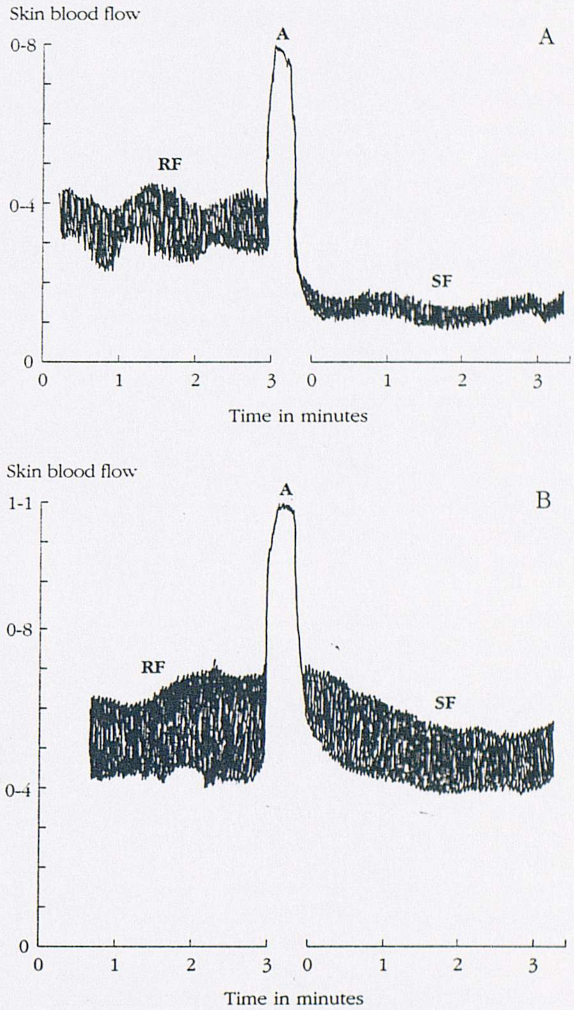

Fig. 4.—*Above*: an example of the venoarteriolar response in a normal limb (perimalleolar region). SF (flow on standing) is significantly lower than RF (resting flow in the supine position). *Below*: the venoarteriolar response (abolished) in the perimalleolar skin of a subjects with severe venous hypertensive microangiopathy. A: indicates the motion artifact.

with the passage from the supine to the standing position.

This reflex response — due to a sympathetic axon reflex — limits skin flow on standing [1-3] and appears to control the filtration of fluid and proteins into the interstitial tissue, preventing the formation of edema [4] (Fig. 4).

TABLE I.—*Microcirculatory parameters in 8 normal volunteers before and after inhalation of an athmosphere with 3% of CO_2 (20 minutes). All measurements (mean±sd) were taken from the internal perimalleolar region. RF=resting flux; RAS=rate of ankle swelling by straingauge plethysmography.*[2] *The VAR is expressed as median and range. Excluding PO_2 (ns=not significant) all differences are significant.*

Parameter	Before	After CO_2 inhalation
RF (flux units)	0.51±01	0.87±0.02
VAR (percent skin flux decrease)	39 (28-48)	21 (11-23)
PO_2 (mmHg)	67±11	65±10 ns
PCO_2 (mmHg)	27±8	35±12
RAS (ml/100 ml)	1.009±0.12	1.235±0.15

Firstly documented in diabetic microangiopathy [1-5] the increased skin flux and decrease in VAR has been also documented in the perimalleolar region in some subjects with venous hypertension.[6] The increase in skin flux and decrease in VAR are proportional to the increased rate of ankle swelling and capillary filtration which are important in the development of edema.[2] In previous studies we have observed that in VHM the increase in skin flux is often related to a significant increase in transcutaneous PCO_2 and, only very late in the evolution of microangiopathy, to a decrease in PO_2.[7]

The role of PCO_2 is not clear but it seems to be constantly increased in conditions of high skin flux. It is possible that the increase in local level of catabolic products in the skin — particularly in venous hypertension — may increase PCO_2 levels possibly leading to local vasodilatation.[7*]

It has been observed in healthy volunteers that it is possible to reproduce an experimental VHM by CO_2 (3%) inhalation for 20 minutes. This situation increases skin PCO_2. An increase in skin flux follows associated with a decreased venoarteriolar response and an increase in capillary filtration (observed studying the rate of ankle swelling by straingauge plethysmography; Table I).

*) *Flow and flux:* flow indicates the actual skin flow while flux is a term used to express skin flow measurements obtained by LDF which are proportional but not exactly corresponding to skin blood flow. While in some situations (like VHM) an increase in flux corresponds to an increase in skin flow this is not true in all conditions. LDF measures skin flux within a depth of 0.75 to 1.5 mm (some variations are due to different probes and LDF technology) which is not the global flow in the skin. According to some authors,[8] the nutritional flow (5% of the global flow) and the termoregulatory flow (95%) are not separately measured by LDF.[8]

Low and high perfusion microangiopathy

Two major types of microangiopathy may be observed and defined by laser-Doppler flowmetry. The first kind of microangiopathy which may be defined as low perfusion microangiopathy (LPM) is present in subjects with severe peripheral vascular disease,[5, 8] Raynaud's disease and essential hypertension.[9]

Low perfusion microangiopathy (LPM) is characterised by severe decrease in skin flux and VAR and low capillary filtration. The second type of microangiopathy (*high perfusion microangiopathy*) is characterised by elevated skin flux, decreased VAR, a marked increase in capillary permeability and filtration.[1, 4] HPM is specifically observed in diabetic microangiopathy and in venous hypertension. In reperfusion injury, in high altitude (mountain) sickness (above 3500 m) and in some other physiological and clinical situation — including some calcium-antagonists treatment — HPM can be also observed.

Both low and high perfusion microangiopathy lead to skin and tissue necrosis but this happens through different mechanisms. In HPM the increased capillary filtration possibly following the increase in skin flux leads to compression and obstruction of the nutrient capillaries. Also the edema present in the interstitial tissue slows down the diffusion of nutrients and gasses in the affected areas. In LPM the total LDF skin flux does not always represent the nutritional flow (which is more superficial and only 5% of the total flow). Therefore in this condition it is difficult to evaluate only by LDF the nutritional changes induced in the skin by drugs or treatment.

On the contrary in HPM the measurements of skin flux and the venoarteriolar response may be often used to monitor the efficacy of treatments especially in groups of patients [10].

Monitoring LDF parameters to monitor the microcirculatory effects of treatments

By LDF it is possible to observe an increase in skin flux in patients with venous hypertension: i. e. as a consequence of postphlebitic syndrome.

Figure 5 shows the increased skin flux in 20 subjects with VHM in comparison with 25 normal sub-

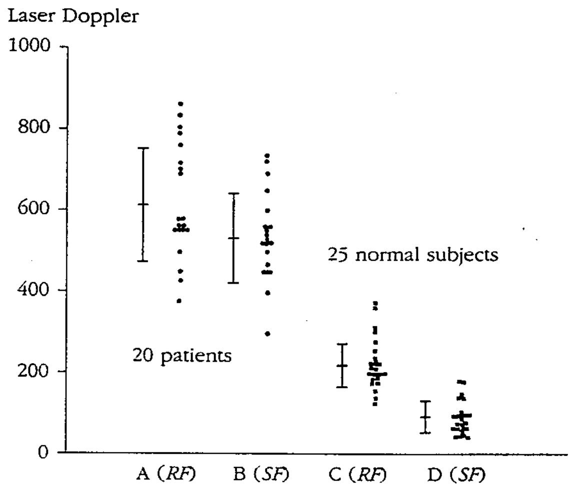

Fig. 5.—Skin flux at supine rest (RF) and on standing (SF) in 25 normal subjects and in 20 patients with severe venous hypertension. In patients both RF and SF are higher and the VAR is decreased.

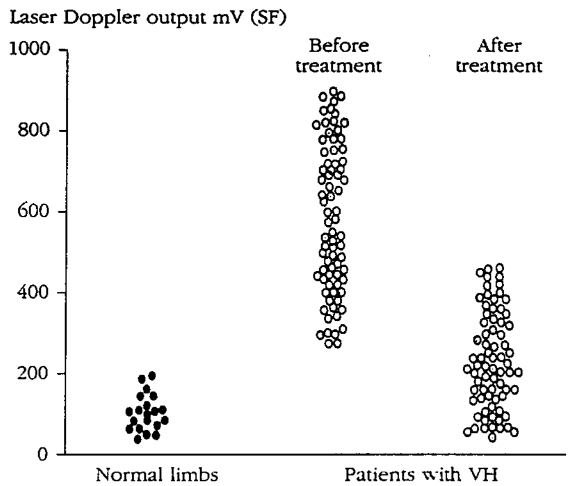

Fig. 7.—Significant decrease in skin flux after 4 weeks of elastic compression (stockings) in patients with venous hypertension. Skin flux in normal limbs is shown for comparison.

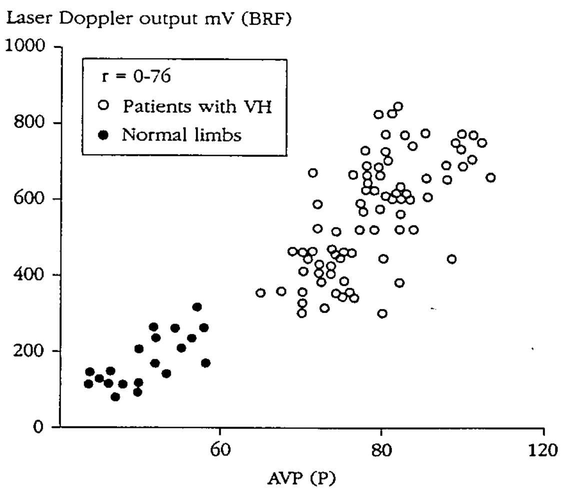

Fig. 6.—The correlation between ambulatory venous pressure (AVP=pressure at the end of the ten tiptoe exercise test) and laser-Doppler output. The correlation between skin flux and AVP is good (r= 0.76) and there is a good separation between patients (severe postphlebitic syndrome) and normal subjects (VH=venous hypertension).

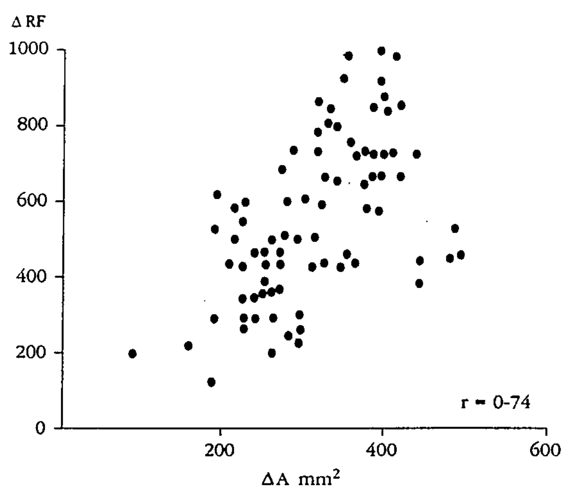

Fig. 8.—The correlation between the decrease in skin flux at rest (RF) and the decrease in the ulcerated area in patients with postphlebitic limbs. The decrease in the ulcerated area is proportional to the decrease in RF obtained with elastic compression (four weeks).

jects. Both supine resting flow (RF) and the standing flow (SF) are increased and the VAR is decreased in patients. It is possible to show that the increase in skin flux is well correlated with ambulatory venous pressure measurements [11] as observed in Figure 6. The measurement of ambulatory pressure in the venous system, at the end of a ten tiptoe exercise, by an intravenous needle is considered to be the gold standard in the dynamic evaluation of venous hypertension.[11] Both LDF and

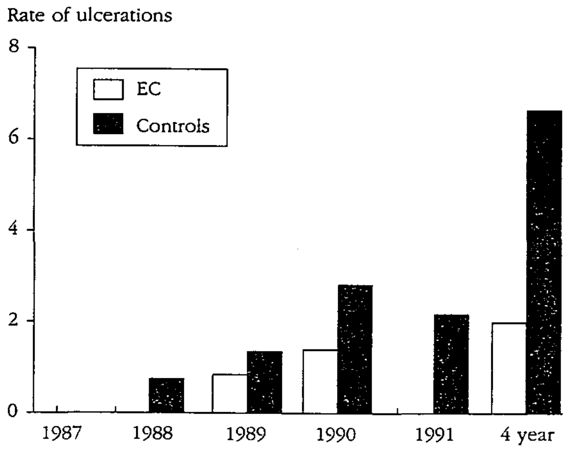

Fig. 9.—The incidence *of ulcerations in four years* in 150 limbs (75 patients) treated (EC) with elastic compression (stockings) and untreated (148 limbs) (controls). The four year incidence decrease in the treated subjects is significant ($p<0.05$).

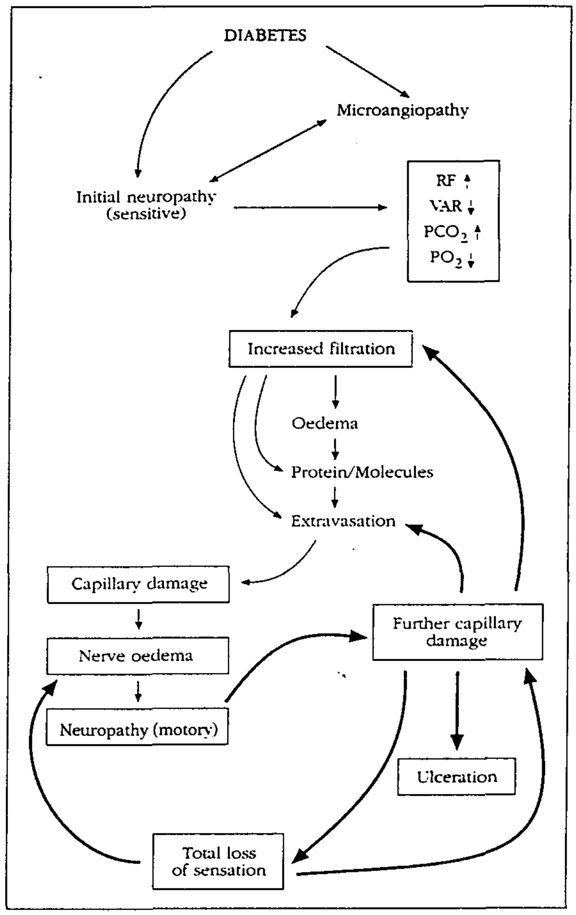

Fig. 10.—Microcirculatory events in diabetic microangiopathy leading to increased fluid filtration and eventually to ulceration (VAR=venoarteriolar response; RF=resting flux).

venous pressure measurements separate normals and patients with severe VHM.

LDF measurements indicate the degree of ve-nous hypertension and have been used to monitor the effects of elastic compression on the microcirculation.[10] Figure 7 shows the effects of elastic compression stockings on skin flux before and after 4 weeks of treatment in patients with VHM (postphlebitic syndrome).[10] Normal values (subjects comparable for age and sex distribution) are also shown for comparison. It appears that elastic compression improves the microcirculation by decreasing skin flux, and proportionally improving the VAR.[10] It is also possible to observe that in patients with venous ulcerations due to postphlebitic syndrome the average decrease in the ulcerated areas (Δ in Fig. 8) is correlated with the decrease in skin resting flux (Δ RF in Fig. 8).

The effects of elastic compression on diabetic microangiopathy has also been shown [12] in a previous study by a quantitative evaluation using LDF, PO_2-PCO_2 measurements and capillary filtration evaluation. The study has shown that it is possible to improve the microcirculation in diabetics with microangiopathy — both with and without neuropathy — by a reduction of the abnormally increased skin flux and capillary filtration which lead to ankle and foot edema. In diabetics with microangiopathy, during periods of elastic compression, the VAR improved and a proportional improvement in skin flux and capillary filtration was observed.[13]

In a more prolonged study it was observed that the improvement in the microcirculation produced by elastic stockings in diabetics is also clinically very relevant as it leads to a reduced rate of ulceration. *Figure 9 shows the number of diabetic foot ulcerations* in 4 years observed in two groups of patients with diabetic microangiopathy. In this study one group (75 patients, 150 limbs) was treated with elastic stockings. The control group was comparable for age, sex distribution and average duration of diabetes (74 patients, 148 limbs). After four years only 3 ulcerations were observed in the treated group in comparison with 10 ulcerations in the untreated controls. Also the ulcerations were smaller and healed faster then those in the control group.

Figure 10 shows in a diagram the events and microcirculatory changes in diabetic microangiopathy which lead to skin necrosis and ulcerations. A very similar sequence of events is observed in VHM.

Therefore the role of any treatment able to reduce and control edema appears to be extremely important and effective considering the very early findings of increased capillary permeability in diabetic microangiopathy.[15 16] This also seems to be the most important characteristic of VHM that responds very rapidly to any compression or antiedema treatment.

Conclusions

The use of noninvasive microcirculatory techniques, particularly of LDF, to evaluate HPM gives us a better understanding of this complex and common microcirculation syndrome. The measurements of skin flux and VAR — particularly in diabetics — may be effectively used to monitor and quantify changes in the microcirculation produced by treatments.

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VENOUS DISORDERS

A Manual of Diagnosis and Treatment

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SAUNDERS

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G. Belcaro

Cardiovascular Institute, Chieti University, Italy; and
Academic Vascular Surgery and Irvine Laboratory, St Mary's Hospital, London, UK

A. N. Nicolaides

Academic Vascular Surgery and Irvine Laboratory, St Mary's Hospital, London, UK

M. Veller

University of Witwatersrand, Johannesburg, South Africa

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MESURES DU FLUX DOPPLER LASER *IN VIVO* ET RÉACTIVITÉ DE LA PAROI VEINEUSE NORMALE ET ANORMALE

G. BELCARO (1, 2), G. LAURORA (1), M.R. CESARONE (1), M.T. DE SANCTIS (1), L. INCANDELA (1), A. TACCOEN (3), A.N. NICOLAIDES (2)

(1) Microcirculation Laboratory, Cardiovascular Institute, Chieti University, Chieti, Angiology and Vascular Surgery, Pierangeli Clinic, Pescara, Italie. (2) Irvine Laboratory, St Mary's Hospital Medical School, Londres, Royaume-Uni. (3) Laboratoires Negma, Immeuble Strasbourg, avenue de l'Europe, 78117 Toussus-le-Noble

RÉSUMÉ :

Mesures du flux Doppler laser *in vivo* et réactivité de la paroi veineuse normale et anormale.

Le flux sanguin a été mesuré au niveau des parois veineuses par vélocimétrie laser Doppler à la surface externe de 24 veines normales, partiellement disséquées au cours de leur préparation pour pontage aorto-coronarien par greffe. Les mesures ont été réalisées avant la dissection finale de la veine, alors qu'au moins 3/4 des tissus de l'adventice et de la périadventice étaient encore intacts sur une longueur de 3 cm. Le segment proximal de veine (10 cm), à la jonction saphéno-fémorale, a été étudié. Des mesures ont été également réalisées sur 22 veines variqueuses avant stripping ou ligature de la jonction saphéno-fémorale.

Le flux a été mesuré en utilisant un vélocimètre Laserflo (Vasamedics). Une pièce en Delrin (polycarbonate) a été placée entre la sonde et la surface de la paroi veineuse. Les mesures présentées sont les valeurs moyennes de trois minutes d'enregistrement. L'analyse préliminaire indique que le flux apparaît plus faible dans la paroi des veines variqueuses que dans celle des veines normales.

Cependant, compte tenu de la variabilité des résultats et des problèmes techniques posés par les mesures de flux, il est nécessaire de réaliser des mesures sur un plus grand nombre d'échantillons avant de confirmer la diminution de perfusion dans la paroi de la veine variqueuse. *(J Mal Vasc* 1996 ; *21, suppl. C* : pages *253-258).*

Mots-clés : Perfusion de la paroi veineuse. Laser Doppler. Vasa vasorum. Veines variqueuses.

ABSTRACT :

Laser Doppler flux in normal and varicose veins wall.

Venous wall flux was measured using laser-Doppler flowmetry on the external surface of 24 normal veins, partially dissected during the preparation of the vein for aortocoronary bypass grafting. Measurements were performed before the final dissection of the vein when at least 3/4 of the adventitia and periadventitia tissue was still intact for a lenght of 3 cm. The segment of vein (10 cm) proximal to the sapheno-femoral junction was studied. Measurements were repeated on 22 varicose veins before stripping or ligation of the sapheno-femoral junction.

Flux was measured with a Laserflo (Vasamedics) flowmeter. A Delrin (polycarbonate) spacer was placed between the probe and the vein wall surface. Measurements shown are the average of three minutes recording. Preliminary analysis indicates that flux appears to be lower in varicose veins in comparison with flux in the normal vein wall.

However the variability of results and technical problems in flux measurements indicate the need of a larger measurement sample before confirming the observation of a decreased perfusion of the varicose venous wall. *(J Mal Vasc* 1996 ; *21, suppl. C* : pages *253-258).*

Key-words : Perfusion of venous wall. Laser Doppler. Vasa vasorum. Varicose veins.

INTRODUCTION

La perfusion de la paroi veineuse et le rôle des altérations des vasa vasorum dans la production des lésions de la paroi veineuse et artérielle restent mal élucidés à ce jour. L'hypoxie de la paroi artérielle entraînée par l'hypoperfusion des vasa vasorum a été considérée comme étant une cause concomitante importante des altérations de la paroi artérielle chez les sujets atteints d'athérosclérose précoce (1). Il a été suggéré que les altérations et la déformation des vasa vasorum jouent un rôle important dans le développement des modifications artérielles observées chez les sujets hypertendus (2). De même, des altérations sévères de la perfusion pariétale (y compris une nécrose de la média) ont été observées après une lésion ou une ablation expérimentale des vasa vasorum (3, 4). Sottiurai a récemment indiqué que l'occlusion des vasa vasorum pourrait induire une fibrodysplasie de la média artérielle (5). La modification des cellules musculaires lisses en myofibroblastes primitifs semble être une caractéristique pathologique majeure, sinon la principale, de cette maladie fibroproliférative. Avec l'aide de la microangiographie, de la micrographie fluorescente et de l'histologie, Nakata et Shionova ont également démontré que les perturbations de la microcirculation et, par suite, du méta-

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Tirés à part : G. BELCARO, Via Vespucci 65, 65100 Pescara, Italie.

bolisme de la paroi vasculaire entraînent des lésions vasculaires (6). Une hypoxie artérielle intraluminale aiguë expérimentale semble induire une dilatation des vasa vasorum (7), ce qui indique une réponse rapide et importante du système vasa vasorum aux variations métaboliques. Le rôle des modifications du flux sanguin des vasa vasorum de la paroi veineuse a également été envisagé dans les modifications endothéliales initiales pouvant conduire à la thrombose veineuse (8). Des lésions thermiques expérimentales des vasa vasorum ont entraîné l'apparition de lésions intimales, en particulier une hypertrophie, un dépôt de lipides et une augmentation de la production des fibres élastiques et collagènes (9).

Il existe donc des éléments indiquant que les modifications observées au niveau de la paroi des veines variqueuses pourraient être liées à des altérations de la perfusion de la paroi veineuse (10).

Il est difficile de définir si les anomalies de la perfusion entraînent, sont associées à, ou sont une conséquence des varicosités, de la dilatation ou de l'incompétence veineuse, en raison du faible volume de données dont on dispose.

Le *but de notre étude* était d'évaluer *in vivo* la perfusion de la paroi veineuse au niveau des veines normales, des veines variqueuses, et des veines fémorales post-phlébitiques par débitmétrie laser Doppler (DLD). Etant donné les éléments en faveur d'un changement de la structure et de la réponse hémodynamique microcirculatoire, ce travail avait également pour intention d'étudier les modifications de la perfusion de la paroi veineuse consécutives à une vasodilatation locale induite par injection de papavérine.

PATIENTS ET MÉTHODES

Le flux de la paroi veineuse a été mesuré par DLD au niveau de la paroi externe antérieure de 24 veines saphènes internes normales, partiellement disséquées lors de la préparation de la veine pour un pontage aorto-coronaire, ainsi qu'au niveau de la paroi antérieure de veines fémorales communes. Les mesures ont été réalisées avant la dissection complète de la veine saphène interne – et seulement après une dissection antérieure très limitée de la veine fémorale – alors qu'au moins les 3/4 du tissu adventitiel et périadventiel étaient encore intacts sur une longueur de 3 cm. Les mesures ont été également effectuées sur 42 veines variqueuses avant ligature de la jonction saphéno-fémorale, ainsi qu'au niveau de la paroi antérieure de la veine fémorale commune de patients présentant une insuffisance veineuse sévère dans le cadre d'un syndrome post-phlébitique.

Les indications de la chirurgie veineuse étaient une hypertension veineuse sévère, et des veines variqueuses associées à des signes et des symptômes d'insuffisance veineuse chronique. La ligature des veines superficielles incompétentes était également indiquée pour une insuffisance veineuse sévère tant superficielle que profonde, liée à un syndrome postphlébitique.

Les critères d'exclusion étaient le diabète et l'hypertension ainsi que toute pathologie rénale ou cardiovasculaire (à l'exclusion de la coronaropathie ischémique).

Un consentement éclairé a été obtenu de tous les patients recrutés.

Site des mesures. Au niveau de la veine fémorale commune, le segment de veine (10 cm) proximal à la jonction saphéno-fémorale

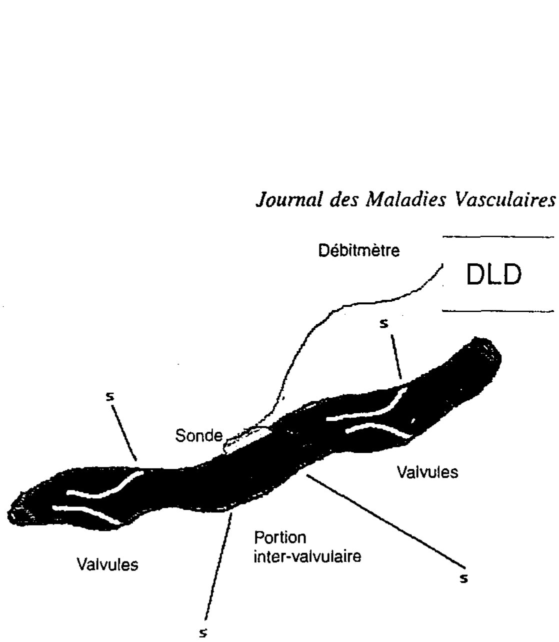


FIG. 1. – Système laser Doppler de mesure du flux de la paroi veineuse. S = site des mesures.
Laser Doppler system for flux measurements of the venous wall.

a été étudié *(fig. 1)*. Un Laser Doppler Laserflo (Vasamedics, St. Paul, Minnesota, USA) muni d'une sonde à système optique latéral (d'une section de 3 mm) a été utilisé. Une pièce d'espacement en polycarbonate (« spacer » *Delrin*®) a été insérée dans l'espace séparant le système optique de la sonde de la paroi veineuse, afin de limiter la pénétration du faisceau laser. La pénétration théorique du laser de cette sonde spécifique étant d'environ 1 mm, l'épaisseur de la pièce d'espacement étant d'environ 0.5 mm, et, la paroi veineuse étant d'une section inférieure à 1 mm, l'application de la pièce d'espacement optique a permis de prendre des mesures pariétales sans inclure (ni minimiser) le signal ni le bruit provenant du sang de la lumière veineuse. Les pièces d'espacement *Delrin*® en polycarbonate ont les mêmes caractéristiques de densité optique et de phototransmission que le tissu humain (c'est-à-dire la peau). Pour les mesures de la veine fémorale, la sonde a été appliquée immédiatement au-dessus de la jonction saphéno-fémorale.

Technique de mesure. Le flux sanguin a été interrompu afin d'éviter le bruit provenant de l'écoulement sanguin dans l'espace intraluminal. Après application de la sonde et des pièces d'espacement, la veine saphène interne a été délicatement occluse à l'aide d'une pince atraumatique (un tube en caoutchouc ayant été placé sur les deux branches d'un clamp vasculaire) au moins 10 cm en distalité et proximalement aussi près que possible de la jonction saphéno-fémorale. La sonde a été appliquée à 4 cm de distance de la jonction saphéno-fémorale. Au bout de deux minutes de stabilisation, le flux a été défini comme étant la moyenne de trois minutes d'enregistrement. La veine fémorale n'a pas été occluse au cours des mesures. Le traumatisme chirurgical et lié aux manipulations veineuses a été limité autant que possible, et une technique chirurgicale strictement « sans toucher » a été utilisée afin de minimiser les réactions de la paroi veineuse et les altérations de son flux. Les pinces veineuses atraumatiques ont été appliquées à cause d'une élévation du niveau du bruit liée aux mouvements tels que les mouvements respiratoires, le flux veineux intraluminal, la manipulation distale ou les contractions musculaires spontanées. Ces facteurs ont également été responsables d'une tendance à la variabilité des mesures du flux (de 10 à 18 %).

Test à la papavérine. Après les mesures du flux de base effectuées sur un sous-groupe de 8 veines saphènes normales et de 8 veines saphènes variqueuses, une solution de papavérine (7,5 mg) a été injectée dans la veine (sans l'étirer) au niveau du segment distal. La papavérine a été injectée distalement au matériel de mesure, à l'aide d'une aiguille fine (24 G). Le flux pariétal a été mesuré après 4 minutes de stabilisation. Le flux a été défini comme étant la moyenne de trois minutes d'enregistrement.

Flux au niveau des différentes composantes de la paroi veineuse. Le flux a été mesuré au niveau d'une paroi veineuse située entre deux valves (veines normales), au niveau des valvules (veines normales) et au niveau d'une dilatation anévrismale (veines variqueuses).

Statistiques. Un logiciel Statgraphics (STSC. USA) a été utilisé. Des tests non paramétriques de Wilcoxon ont été appliqués en vue de comparer le flux des veines normales à celui des veines variqueuses, tant avant qu'après l'administration de papavérine.

RÉSULTATS

Le *tableau I* montre les caractéristiques démographiques des sujets étudiés. Les différents groupes de patients étaient comparables en termes de distribution des âges et des sexes. Le *tableau II* et la *figure 2* montrent les valeurs du flux DLD (en unités de flux) dans les différents groupes de veines. Le flux mesuré au niveau de la paroi des veines saphènes et fémorales normales était significativement plus élevé ($p < 0.05$) que celui des veines variqueuses et des veines post-phlébitiques. Aucune différence de flux n'a été observée entre les veines variqueuses et les veines post-phlébitiques. Le *tableau III* et la *figure 3* montrent le flux de la paroi veineuse avant et après injection intraveineuse de papavérine dans des veines saphènes normales et des veines saphènes variqueuses. Ces sous-groupes de sujets étaient également comparables en termes de distribution des âges et des sexes. Dans les veines normales, une élévation

TABLEAU I. – Caractéristiques démographiques des patients par types de veines étudiées par débitmétrie laser Doppler.
Demographic data of the patients by type of vein studied by laser Doppler flux.

	Nb	Age moyenne	Age écart-type	H/F
Veines normales				
J. S. fémorale	24	43,4	7,2	19/5
V. fémorale	11	44,1	8	8/3
Total	35			27/8
Veines variqueuses	42	44,3	7,6	26/16
Veines post-phlébitiques	11	44,1	6,9	6/4

TABLEAU II. – Valeurs du flux DLD (en unités DLD arbitraires).
Laser Doppler flux (in arbitrary units).

	Nb	moyenne	écart-type	extrêmes
Veines normales (VN)				
J.S. fémorale (JSF)	24	9,87	4,7	2-18
V. fémorale (VF)	11	12,8	5,3	4-16
Total	35	10,8	5,03	2-20
Veines variqueuses (VV)	42	4,9	3,6	1-19
Veines post-phlébitiques (VP)	11	6	4,1	1-12

VN = veines normales ; VV = veines variqueuses ; VP = veines post-phlébitiques ; JSF = jonction saphéno-fémorale ; VF = veines fémorales ; ns = non significatif.
VN versus (VV, VP) $p < 0,05$; VV versus VP ns ; VN versus VP $p < 0,05$; JSF versus VF ns.

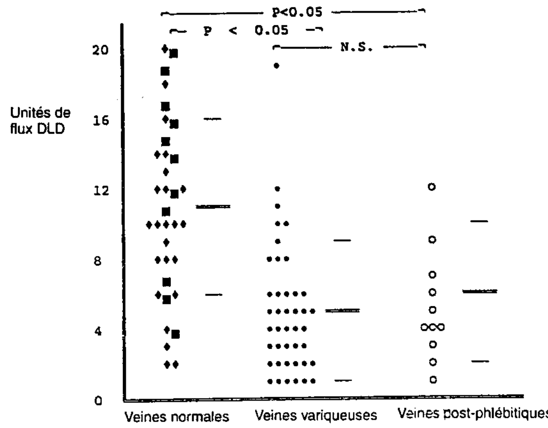


FIG. 2. – Flux DLD au niveau des veines normales et pathologiques. Veines normales : ◆ = jonction saphéno-fémorale ; ■ = veine fémorale. Moyenne (==). Ecart type (--).
Laser Doppler flux in normal and pathological veins.

TABLEAU III. – Flux avant et après injection de papavérine, au niveau des veines normales et variqueuses.
Flux before and after injection of papaverine in normal and varicose veins.

	Veines normales Avant	Veines normales Après	Veines variqueuses Avant	Veines variqueuses Après
Moyenne ± écart-type	8,5 ± 5,1	13,25 ± 3,8	6,25 ± 4	6,12 ± 4,2
Extrêmes	1-16	7-20	1-12	1-12
p	$p < 0,05$		ns	
Nb	8 (H/F = 3/5)		8 (H/F = 4/4)	
Age	44 ± 3		44 ± 6	

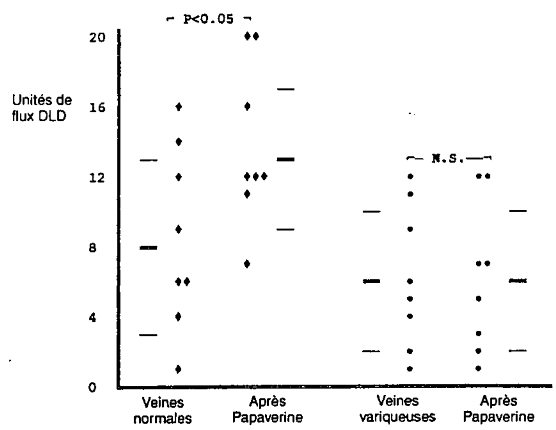


FIG. 3. – Variations du flux veineux avant et après perfusion intraluminale de papavérine dans des veines normales et variqueuses. Après administration de la papavérine, l'augmentation du flux de la paroi des veines normales est significative. Moyenne (==) et écart-type (--).
Variations in venous flux before and after intraluminal infusion of papaverine in normal and varicose veins. After administration of papaverine, there is a significant increase in the wall flux in normal veins.

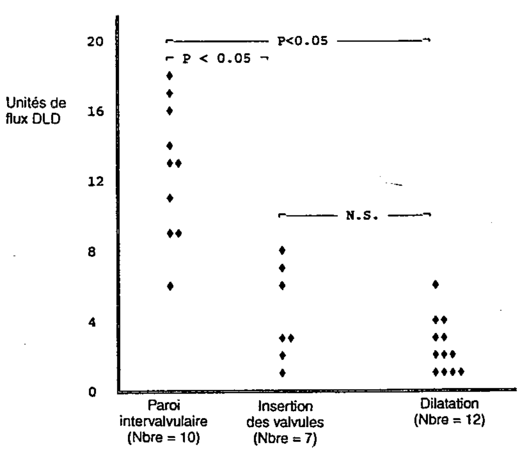
significative du flux (de 8,5 ± 5,1 unités de flux à 13,2 ± 3,8 ; $p < 0,05$) a été constatée après injection de papavérine, ce qui n'a pas été le cas des veines variqueuses.

Ceci semble indiquer une meilleure réactivité vasculaire de la paroi des veines normales à un agent vasodilatateur intraluminal, par rapport aux veines pathologiques.

La *figure 4* montre les valeurs du flux mesuré au niveau des parois veineuses situées entre deux valves, au niveau des valvules, et au niveau d'une dilatation anévrismale de veines variqueuses. Le flux était supérieur au niveau de la paroi veineuse située entre deux valves ($p < 0,05$) qu'au niveau des valvules ou des dilatations.

DISCUSSION ET CONCLUSION

Les vasa vasorum et la perfusion de la paroi veineuse sont liés, sans toutefois être synonymes. Par conséquent, l'hémodynamique de perfusion microcirculatoire et la distribution des vasa vasorum doivent être évaluées par des études menées en parallèle. La micrographie de la plus grande partie de la veine saphène montre un réseau capillaire correspondant au tissu conjonctif et aux structures musculaires, alors que les vasa vasorum semblent absents des veines de diamètre inférieur à 1 mm (11). Deux types de vasa vasorum ont été décrits. Les vaisseaux du premier type courent le long de la veine, souvent en groupes de deux ou trois. Les vasa vasorum du second type sont plus fins et pénètrent dans la média, presque jusqu'à l'intima. Il est possible que ces vaisseaux communiquent directement avec la lumière veineuse (12). Dans notre étude, l'injection intraluminale de papavérine révèle



	Paroi intervalvulaire	Insertion des valvules	Dilatation
Moyenne	12.6	4.2	2.5
Ecart-type	3.8	2.6	1.5
Extrêmes	6-18	1-8	1-6

FIG. 4. – Valeur du flux de la paroi veineuse située entre deux valves, au niveau des valvules, et au niveau des dilatations (veines variqueuses).

Flux measured in a venous wall between two valves, at the valves and at dilatations (varicose veins).

une réponse rapide à une injection intraluminale et ainsi qu'une meilleure réactivité vasculaire à la papavérine de la paroi des veines normales comparées aux veines variqueuses.

La perfusion de la paroi veineuse et la distribution, la structure et la fonction des vasa vasorum sont importantes non seulement du point de vue étiologique mais également en raison du nombre croissant de méthodes chirurgicales de reconstruction veineuse (13-15) et de l'intérêt grandissant pour la correction chirurgicale de l'incompétence veineuse. Ces méthodes tendent à respecter autant que possible la structure de la veine et la perfusion de la paroi (16), allant même jusqu'à utiliser l'angioscopie et une dissection très limitée (17). Les veines de plus gros calibre tendent à se dilater en post-opératoire (transplantation ou valvuloplastie externe) et le recours aux manchons veineux pour limiter la dilatation a été suggéré (18, 19). La dilatation semble survenir plus fréquemment après une dissection veineuse poussée, laquelle peut détruire tant les vasa vasorum que l'innervation (18). Les nouvelles techniques chirurgicales de reconstruction veineuse avec dissection limitée semblent être plus efficaces, et ont de bons résultats à moyen terme (20-22), peut-être parce que le respect de la perfusion et de l'innervation de la paroi veineuse lors de la restauration de la compétence permet d'éviter la dilatation veineuse.

La DLD est une méthode relativement récente d'évaluation de la microcirculation. Plusieurs types d'instruments sont proposés. La technologie, le type de laser, les normes des mesures, le type de sonde et la pénétration tissulaire du laser varient d'un instrument à l'autre, chacun produisant son faisceau caractéristique (23). Toutefois, les altérations de la microcirculation tissulaire détectées par les différents instruments sont comparables. Les divers types de faisceaux laser ont une pénétration tissulaire différente (23-25). Ce point est essentiel, car la couche nutritionnelle la plus importante (au niveau de la peau), est considérée comme très superficielle (à 0,5 mm de profondeur). Le faisceau laser Doppler, pénétrant plus profondément (en moyenne à 1-1,5 mm), inclut également le flux de la couche thermorégulatrice, laquelle pourrait n'avoir qu'une importance marginale en termes de nutrition et de cicatrisation tissulaires (de la peau) (26). La pénétration tissulaire au niveau des parois veineuses semble comparable à la pénétration observée au niveau de la peau.

Des niveaux différents de pénétration et de mesures de perfusion tissulaire peuvent être obtenus sans modifier les caractéristiques de la lumière laser, en utilisant des pièces d'espacement en polycarbonate d'épaisseur connue (0,2 à 1 mm), lesquelles, en augmentant la distance séparant l'extrémité de la sonde du tissu, permettent de détecter un flux au niveau de la couche la plus superficielle du tissu étudié (27). Ceci est obtenu au prix d'une élévation modérée du niveau de bruit en raison d'une perte limitée de cohérence (élargissement du faisceau laser) au point de sortie du faisceau laser de la structure en fibres optiques (la sonde). Des pièces d'espacement de différentes épaisseurs diminuent proportionnellement le signal du flux, et détectent théoriquement le flux au niveau de couches tissulaires proportionnellement plus superficielles. Les pièces d'espacement utilisées dans cette étude avaient pour but d'exclure le bruit produit par le flux veineux intraluminal du signal de la paroi veineuse. Des pinces veineuses atraumatiques ont été appliquées à cause d'une élévation modérée du niveau du bruit liée aux mouvements tels que les mouvements respiratoires, le flux veineux intraluminal ou les manipulations distales, ce qui augmentait la variabilité des mesures du flux. Au niveau de l'ensemble des veines normales non clampées, les limites (1 à 27) et la moyenne (13,9 ± 7) du flux étaient augmentées par rapport aux mesures obtenues au cours du clampage et indiquées au *tableau II*. La composante « flux luminal » n'a pas été directement prise en compte dans les mesures, mais, au niveau des veines non clampées, de fins artefacts de mouvement provenaient de cette composante (en raison de mouvements passifs de la paroi).

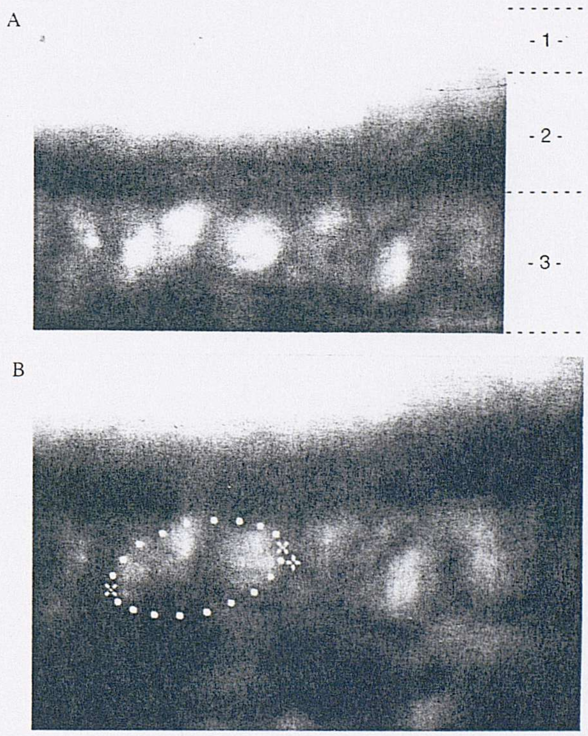


FIG. 5. – A : Imagerie à haute résolution de la paroi artérielle montrant les unités « glomérule-like » des vasa vasorum, régulièrement espacées le long de la paroi artérielle. 1 : lumière artérielle (en blanc) ; 2 : complexe intima-média ; 3 : couche adventitielle-périadventitielle contenant les unités « glomérule-like » des vasa vasorum. B : Dans la figure du bas, trois unités sont montrées, leurs vaisseaux individuels étant visualisés par le Doppler de puissance.

A : High-resolution imaging of the arterial wall showing glomerula-like units of the vasa vasorum, regularly located along the arterial wall. Top to bottom : 1) arterial lumen (white) ; 2) intima-media complex ; 3) adventitia-periadventitia layer containing glomerula-like units of the vasa vasorum. B) Three units are shown in the lower panel with their individual vessels visualized by high-resolution Doppler.

Les résultats d'une étude préliminaire antérieure, utilisant le laser Doppler au niveau de la paroi des veines normales et variqueuses, sont comparables à ceux obtenus par la présente étude (28). De même, la mesure par Laser Doppler du flux de la paroi d'artères carotides normales et athéromateuses, à l'aide d'une technologie comparable, a révélé des altérations (à savoir une réduction) du flux au niveau des portions athéromateuses de l'artère (29), par rapport aux vasa vasorum de la paroi d'une artère carotide normale. Récemment, le réseau des vasa vasorum de la paroi artérielle a été mis en images, et la vitesse du flux a été enregistrée à l'aide de sondes à haute résolution ayant recours à un Doppler de puissance (30) *(fig. 5)*. Les résultats préliminaires indiquent que comparées aux portions normales de l'artère, les portions athéromateuses ont une distribution différente et une vitesse de flux différente des *unités de perfusion « glomérule-like »* des vasa vasorum. En effet, dans la paroi normale, ces unités sont régulièrement espacées le long de l'artère et dans l'espace adventiel-périadventitiel *(fig. 5)*.

Des résultats comparables ont été obtenus lors de l'évaluation de la perfusion de la paroi des veines fémorales (Belcaro et coll., à paraître).

D'après les résultats de la présente étude, la paroi des veines variqueuses et des veines post-phlébitiques semble avoir une perfusion réduite. La réponse microvasculaire des veines variqueuses était également réduite, voire abolie. Outre son importance sur le plan étiologique, le fait que la perfusion des veines variqueuses et post-phlébitiques est déjà altérée doit être pris en compte lors d'une chirurgie de reconstruction veineuse. Les nouvelles méthodes chirurgicales doivent respecter l'innervation et les vasa vasorum de la veine, et avoir recours à une dissection très limitée, afin d'éviter de détériorer davantage la perfusion pariétale veineuse.

En conclusion, cette étude préliminaire indique que le flux de la paroi veineuse semble être plus faible au niveau des veines variqueuses que des veines normales. Après injection de papavérine, une augmentation significative du flux pariétal a été observée au niveau des veines normales, alors que la variation du flux au niveau des veines variqueuses était limitée et non significative. Il apparaît donc que la réponse de la paroi d'une veine variqueuse à un agent vasodilatateur est plus faible.

Dans notre étude, le traumatisme chirurgical et lié aux manipulations veineuses a été limité autant que possible, et une technique chirurgicale « sans toucher » a été utilisée afin de minimiser les réactions de la paroi veineuse et les altérations de son flux. Toutefois, la variabilité des résultats et les problèmes techniques liés aux mesures du flux pariétal veineux indiquent qu'il est nécessaire de répéter ces mesures sur un échantillon plus large avant de confirmer nos observations d'une perfusion diminuée et d'une réactivité microvasculaire réduite de la paroi des veines variqueuses.

Il pourrait être important de prendre ces observations en compte lors de la planification de nouvelles procédures de reconstruction veineuse visant à restaurer la compétence des veines. Par ailleurs, la possibilité d'améliorer (en cas d'anomalie) le flux de la paroi veineuse et la perfusion des vasa vasorum par physiothérapie ou traitement médical pourrait être envisagée.

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PHLEBOLOGY

Original Article

Laser Doppler Flux in the Venous Wall

G. Belcaro, A. N. Nicolaides, G. Laurora, M. R. Cesarone, M. T. De Sanctis, L. Incande and A. Ricci

Microcirculation Laboratory, Chieti University, Chieti, Italy and Irvine Laboratory, St Mary's Hospital Medical School, London UK

ABSTRACT

Objectives: To evaluate in vivo the perfusion of the venous wall in normal veins, varicose veins and in femoral veins of post-phlebitic limbs recording wall flux with laser Doppler flowmetry. As there is some evidence that both structure and microcirculatory dynamic responses are altered in the abnormal vein wall, we also aimed to study the response of vein wall perfusion to locally induced vasodilatation following papaverine infusion.

Design: Open prospective study in patients with venous insufficiency and in patients undergoing coronary revascularization with a normal venous system.

Setting: Cardiovascular Institute, Chieti University, Pierangeli Clinic, Italy and Irvine Laboratory, St Mary's Hospital, London, UK.

Patients: Twenty-four normal long saphenous veins and 11 common femoral veins (35 normal veins, 35 subjects) and 42 varicose veins (42 patients).

Measurements: Venous wall flux was measured on the external surface of normal long saphenous veins and common femoral veins. Measurements were also made on varicose veins before ligation of the sapheno-femoral junction. All measurements were made when at least three-quarters of the adventitia and periadventitia tissue were still intact for a length of 3 cm.

Results: Flux in the normal vein wall was higher (t = 5.88; $p<0.05$) than in varicose veins and in veins of post-phlebitic limbs. There was no difference in flux between varicose veins and post-phlebitic veins. After intravenous papaverine injection in a subgroup of eight normal and eight varicose veins, in the wall of normal veins there was a significant increase in flux (from 8.5 (SD 5.1) units to 13.2 (SD 3.8) units; $p<0.05$) which was not observed in varicose veins.

Conclusions: A higher vein wall perfusion was observed in normal veins compared with varicose veins and post-phlebitic limb veins. Greater vascular reactivity to intraluminal papaverine injection was observed in normal veins.

Keywords: External valvuloplasty; Laser Doppler; Microcirculation; Post-phlebitic limbs; Varicose veins; Vasa vasorum; Vein walls

Introduction

Venous wall perfusion and the role of vasa vasorum in causing venous and arterial wall lesions are still poorly understood. Arterial wall hypoxia following hypoperfusion at the vasa vasorum level has been considered an important concomitant cause of arterial wall alterations in subjects with early atherosclerosis [1]. It has been suggested that alterations and deformation of vasa vasorum may play an important role in the development of arterial changes observed in hypertensive subjects [2]. Severe arterial wall perfusion alterations (including medial necrosis) have been observed after experimental damage or removal of the vasa vasorum [3,4].

Sottiurai et al. [5] have indicated that vasa vasorum occlusion may induce arterial medial fibrodysplasia.

Correspondence and offprint requests to: G. Belcaro, Via Vespucci 65, 65100 Pescara, Italy.

Modification of smooth muscle cells to more primitive myofibroblasts appears to be a major, if not the primary, pathological feature of this fibroproliferative disease. Using microangiograms, fluorescent micrography and histology, Nakata and Shionova also demonstrated that disturbances of the microcirculation and therefore of the metabolism of the vascular wall cause vascular lesions [6].

Experimentally induced acute, intraluminal arterial hypoxia appears to produce dilatation of the vasa vasorum [7] and therefore indicates a fast, important response of the vasa vasorum system to metabolic changes. The role of blood flow alteration in the vasa vasorum of the vein wall has also been considered responsible for initial endothelial alterations possibly leading to venous thrombosis [8].

Experimental, thermally induced lesions of the vasa vasorum have caused intimal lesions, particularly thickening, lipid deposition and an increase in the production of elastic and collagen fibres with an increase in the substance stained by metachrome [9]. There is therefore an indication that the alterations observed in the venous wall in varicose veins may be associated with modifications of vein wall perfusion [10]. Whether perfusion alterations cause, are associated with, or are a consequence of varicosity, vein dilatation and incompetence is very difficult to define as only a limited amount of information is available.

The aim of our study was to investigate in vivo the perfusion of the venous wall in normal veins, varicose veins and femoral veins of post-phlebitic limbs evaluating wall flux using a non-destructive test (laser Doppler flowmetry). As there is some evidence that both structure and microcirculatory dynamic responses are altered, we also aimed to evaluate the response of vein wall perfusion to vasodilatation locally induced with papaverine.

Patients and Methods

Venous wall flux was measured using laser Doppler flowmetry on the external, anterior surface of 24 normal long saphenous veins partially dissected during preparation of the vein for aortocoronary bypass grafting and on the anterior wall of the common femoral veins. Measurements were performed before the complete dissection of the long saphenous vein – and only after very limited anterior dissection of the femoral vein – when at least three-quarters of the adventitia and periadventitia tissue were still intact for a length of 3 cm. Measurements were also made in 42 varicose veins before ligation of the sapheno-femoral junction and on the anterior wall of the common femoral vein of patients with severe venous insufficiency resulting from post-phlebitic syndrome.

Indications for vein surgery were severe venous hypertension or varicose veins associated with signs and symptoms of chronic venous insufficiency. Ligation of incompetent superficial veins was also indicated for severe deep and superficial venous insufficiency resulting from post-phlebitic syndrome.

Exclusion criteria included diabetes and hypertension and any renal or cardiovascular disease (excluding coronary ischaemic disease). Informed consent was obtained from all patients.

Site of Measurements

The segment of vein (10 cm) proximal to the sapheno-femoral junction was studied on the common femoral vein segment proximal to the sapheno-femoral junction. The measurement set-up is shown in Fig. 1. A Laserflo (Vasamedics, St Paul, Minnesota, USA) lateral optic system probe (3 mm in section) was used as shown in Fig. 1. In the space between the probe optic system and the vein wall, a polycarbonate spacer (Delrin spacer) was applied to limit the penetration of the laser beam. As the theoretical laser penetration of this specific probe was about 1 mm, the spacer was 0.5 mm in thickness and the vein wall less than 1 mm in section, the application of the optic spacer allowed wall measurements without including (or minimizing) signal and noise from the blood within the vein lumen. Delrin polycarbonate spacers have the same optic density and light transmission characteristics of human tissue (particularly skin). The contact spaces between spacer and probe and vein wall and probe were filled with a small amount of acoustic (Aquasonic) gel to facilitate the transmission of the laser light beam. For femoral vein measurements the probe was applied just above the sapheno-femoral junction.

Measurement Technique

Blood flow was stopped in the saphenous vein during measurements to avoid interference from moving blood in the vein lumen. After application of the probe and spacers, the long saphenous vein was gently occluded with a soft clamp (a rubber tube was applied to both arms of a vascular clamp) at least 10 cm distally and as proximally as possible at the sapheno-femoral junction. The probe was applied 4 cm distally to the sapheno-femoral junction. After 2 min of stabilization, flux was defined as the average of 3 min of recording. The femoral vein was not occluded during measurements.

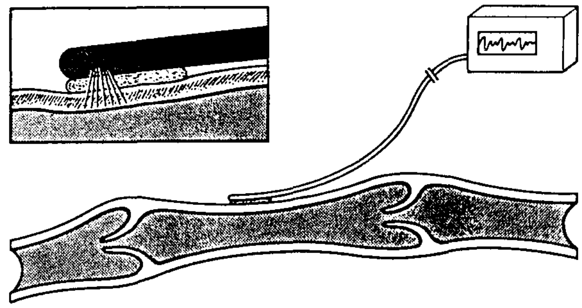


Fig. 1. The laser Doppler set-up to measure the vein wall flux.

Surgical trauma and trauma caused by vein manipulation were maintained to a minimum and a strict no-touch surgical technique was used in order to minimize vein wall reactions and flow alterations.

The soft venous clamps were applied as motion produced by components such as respiratory movements, venous flow within the lumen, distal manipulation or spontaneous muscular contraction all contributed to an increase in noise level (decreasing the signal/noise ratio). These factors also tended to increase the variability of flux measurements (between 2% and 18%) considering all measurements recorded in normal veins before the application of clamps (10 measurements, repeated three times) in comparison with measurements recorded in clamped veins (10 measurement repeated three times).

Papaverine Test

After basal flux measurement in a subgroup of eight normal saphenous veins and in eight varicose saphenous veins, a papaverine solution (7.5 mg) was injected into the vein (avoiding stretching of the vein), in the occluded segment. Papaverine was injected distally to the measurement set-up, with a fine (24 gauge) needle. Wall flux was measured after 4 min of stabilization. Flux was defined as the average of 3 min of recording.

Statistics

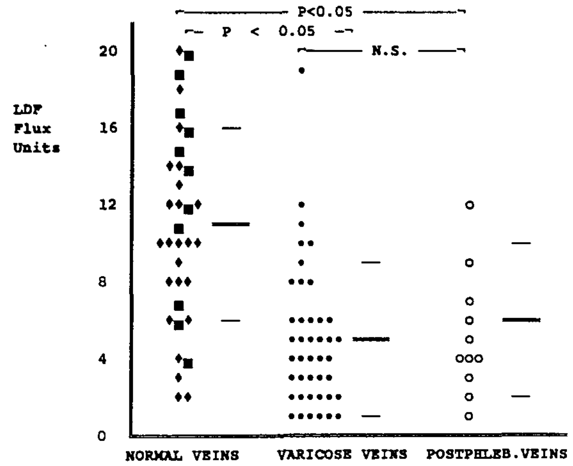
A Stratgraphics (STSC, USA) software package was used. Student's t-test for unpaired data was applied to compare flux between normal and varicose veins and in the veins before and after papaverine.

Results

Table 1 shows details of the subjects studied. The different groups of patients were comparable for age and sex distribution. Figure 2 shows the laser Doppler flux values (in flux units) for the different groups of veins. Flux in normal saphenous and femoral vein wall was significantly higher ($t = 5.88$; $p<0.05$) than flux in varicose veins and in veins of post-phlebitic limbs.

Table 1. Details of the groups of veins studied with laser Doppler flowmetry

	No.	Age (years)		M:F
		Mean	SD	
Normal veins				
Sapheno-femoral junction	24	43.4	7.2	19:5
Femoral vein	11	44.1	8.0	8:3
Total	35	–	–	27:8
Varicose veins	42	44.3	7.6	26:16
Post-phlebitic limbs	10	44.1	6.9	6:4



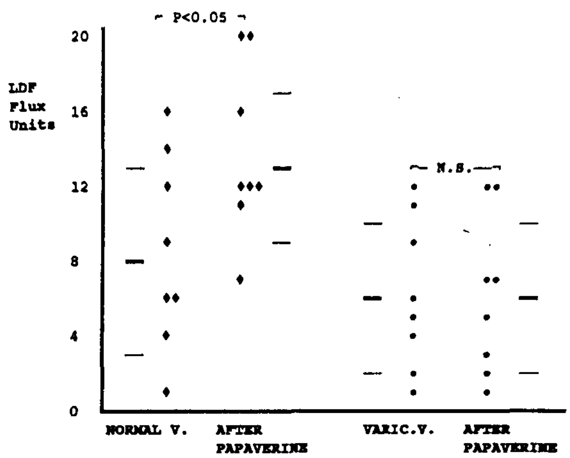
NORMAL VEINS: ♦ = SAPHENOFEMORAL JUNCTION; ■ = FEMORAL VEIN

Mean (═) and SD (—)

Fig. 2. Flux in normal and pathological veins.

There was no difference in flux between varicose veins and post-phlebitic veins.

Figure 3 shows vein wall flux before and after intravenous papaverine injection into normal saphenous veins and in varicose saphenous veins. These subgroups of subjects were also comparable for age and sex distribution. In normal veins there was a significant increase in flux (from 8.5 (SD 5.1) flux units to 13.2 (SD 3.8); $p<0.05$) after papaverine, which was not observed in varicose veins. This appears to indicate greater vein



Mean (▬) and SD (—)

Fig. 3. Vein flux variations before and after intraluminal papaverine infusion in normal and varicose veins. The flux increase after papaverine is significant in normal vein wall.

wall vascular reactivity to an intraluminal vasodilating agent in normal veins.

Discussion and Conclusions

Vasa vasorum and vein wall perfusion are associated but are not synonymous and therefore dynamic microcirculatory perfusion and the distribution of vasa vasorum should be evaluated in parallel studies.

Microscopy of the larger part of the saphenous vein shows a capillary network corresponding to connective tissue and muscle structures while no vasa vasorum appear to be present in veins less than 1 mm in diameter [11]. Two types of vasa vasorum have been described. The first type of vasa vasorum appears to be running longitudinally, often in groups of two or three. A second type of vasa vasorum constituted by smaller vessels penetrates the media almost to the intima. It is possible that these vasa vasorum communicate directly with the vein lumen [12].

Intraluminal papaverine injection in our study indicates a fast response to intraluminal injection and greater vein wall vascular reactivity to papaverine in normal veins compared with varicose veins.

The perfusion of the vein wall and the distribution, structure and function of the vasa vasorum are important not only aetiologically but also because there is an increase in the number of venous reconstructive surgical methods [13–15] and a growing interest in surgical correction of venous incompetence. These methods tend to respect as much as possible the vein structure and wall perfusion [16], even using angioscopy and very limited dissection [17]. Larger veins tend to dilate after surgery (transplant or external valvuloplasty) and the use of venous cuffs to control di-ilatation has been suggested [18,19]. Dilatation appears to occur more often after large vein dissection, which may destroy both vasa vasorum and innervation [18]. New reconstructive venous surgery with limited dissection appears to be effective with good medium-term results [20–22], possibly because respecting perfusion and innervation of the vein wall when restoring competence avoids vein dilatation.

Laser Doppler flowmetry is a relatively new method to evaluate microcirculation. Several instruments are available. Technology, laser type, standards of measurements, types of probes and laser tissue penetration are variable and each instrument produces its characteristic output [23]. However, tissue microcirculation alterations detected with different instruments are broadly comparable [23]. Different types of laser beams have different tissue penetration [23–25]. This is significant because the most important nutritional layer (i.e. in the skin) is considered to be very superficial (within 0.5 mm) while the laser Doppler beam, having a deeper penetration (1.0 to 1.5 mm on average), also includes flux in the thermoregulatory layer which may be only marginally important in tissue (namely skin) nutrition and healing [26]. Tissue penetration of the laser Doppler light in vein walls appears to be similar to the penetration observed in skin. A different level of penetration and tissue perfusion measurement may be obtained without changing laser light characteristics using polycarbonate spacers with a known thickness (0.2 to 1.0 mm) which, increasing the distance between probe ending and tissue, may detect flux mainly in the more superficial layer of the tissue under evaluation. This is obtained at the expense of a moderate increase in the level of noise due to the limited loss of coherence (enlargement of the laser beam) when the beam leaves the optic fibre structure (probe). Spacers with different thickness (from 0.2 to 1.0 mm) proportionally decrease the flux signal (theoretically detecting flux in proportionally more superficial tissue layers) [27].

The spacers used in this study had the aim of excluding noise produced by venous flow present in the lumen from vein wall flux. Soft venous clamps were applied as motion produced by respiratory movements, venous flow within the lumen or distal manipulation all contributed to a moderate increase in noise level, increasing the variability of flux measurements. Flux range in all unclamped normal veins (1 to 27) and mean flux (13.9, SD 7) were increased compared with the measurements obtained during clamping (Fig. 2). The luminal flow component was not directly included in the measurement but fine motion artefacts were present from this component (due to passive wall motion) in unclamped veins.

According to results from this study, varicose veins and post-phlebitic limb veins appear to have a decreased wall perfusion. The microvascular response is also reduced or abolished in varicose veins. This may be important for aetiological considerations, and also in reconstructive venous surgery it is useful to consider that perfusion is already altered in varicose and post-phlebitic veins. Therefore new surgical methods must respect the innervation and vasa vasorum using very limited dissection to avoid further vein wall perfusion damage.

In conclusion, this preliminary study indicates that vein wall flux appears to be lower in varicose veins compared with flux in the normal vein wall. After papaverine injection there is a significant increase in wall flux in normal veins while the variation in flux observed in varicose veins is limited and not significant. Therefore it appears that in the varicose vein wall the response to a vasodilating agent is lower.

In our study, surgical trauma and trauma caused by vein manipulation were maintained to a minimum and a no-touch surgical technique was used to minimize vein wall reactions and flux alteration. However, the variability of results and technical problems in vein wall flux measurements indicate the need of a larger measurement sample before confirming the observations of decreased perfusion and reduced microvascular reactivity of the varicose vein wall. These observations may be important when planning new reconstructive venous procedures aiming at restoring vein competence.

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Efficacy of Troxerutin in Patients With Chronic Venous Insufficiency: A Double-Blind, Placebo-Controlled Study

L. Incandela, M.D.
M. T. De Sanctis, M.D.
M. R. Cesarone, M.D.
G. Laurora, M.D.
G. Belcaro, M.D.
Angiology and Vascular Surgery
Pierangeli Clinic, Pescara
Microcirculation Laboratory
Chieti University
Chieti, Italy

A. Taccoen, M.D.
I. Gerentes, M.D.
Laboratoires Negma
Toussus-le-noble, France

ABSTRACT

Chronic venous insufficiency (CVI) is associated with microcirculatory changes that can be investigated with laser Doppler flowmetry, transcutaneous oximetry, and capillaroscopy. Disturbances in blood flow and red cell properties have also been described in patients with hypertensive venous microangiopathy. This double-blind, placebo-controlled, 8-week study investigated the effects of troxerutin on microcirculatory changes in 30 patients with the skin changes of CVI who were enrolled after undergoing color duplex and light-reflection rheography. A venous refilling time of less than 15 seconds indicated significant reflux. Perimalleolar resting flow of greater than 1.5 U and altered venoarteriolar response were assessed by laser Doppler flowmetry. At study end, a nonsignificant reduction in resting flow (11.9%) and improved venoarteriolar response (21.8%) were observed in the patients who received troxerutin but not in those given placebo. In addition, significant improvements were noted in transcutaneous PO_2 and red blood cell aggregation in the troxerutin-treated patients. Additional studies with more patients are needed to confirm our results.

Keywords: chronic venous insufficiency; microcirculation; red blood cell aggregation; rheology; troxerutin; varicose veins

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Address reprint requests to
L. Incandela, M.D.
Angiology and Vascular Surgery
Pierangeli Clinic
65100 Pescara, Italy

INTRODUCTION

Venous incompetence and venous hypertension leading to chronic venous insufficiency (CVI) are characterized by microcirculatory alterations that cause high-perfusion microangiopathy.[1]

Hypertensive venous microangiopathy, in turn, involves changes in the microcirculation. Recently, a number of functional physiologic tests have been developed to better evaluate the microcirculation of patients with CVI. These noninvasive microcirculatory techniques show (1) increased skin flow (the laser Doppler–detected component of flow) in the perimalleolar region, as evaluated with laser Doppler flowmetry; (2) decreased dynamic responses to postural or thermal stimulation and to reactive hyperemia; (3) decreased transcutaneous PO_2 and concomitant increases in PCO_2; (4) increased capillary filtration and permeability, clinically evident as peripheral edema; and (5) increased blood viscosity, red blood cell aggregation,[2] and alterations in white blood cell function.

These microcirculatory alterations constitute a complex, self-perpetuating, and chronically worsening microangiopathy leading to edema, skin changes, discoloration and thickening, lipodermatosclerosis, and ultimately, venous ulcerations.[3] Treatment of patients with CVI and venous microangiopathy has centered on surgical correction of reflux and diseased venous segments, control of edema with elastic compression,[4] and pharmacotherapy. Venous incompetence and CVI are common in industrialized countries, and effective treatment is needed.

Troxerutin has interesting clinical and pharmacologic activity: it improves some symptoms and signs of CVI and increases venous tone.[5-11] Troxerutin also reduces capillary permeability and edema, and its rheologic effects on red blood cell aggregation may help correct altered blood flow.

This investigation of a new formulation of troxerutin, Veinamitol 3500 mg®*, was undertaken to evaluate drug effects on the microcirculation of patients with CVI.

PATIENTS AND METHODS

Thirty patients 30 to 80 years of age with CVI presenting as skin changes (edema, lipodermatosclerosis, discoloration) gave informed consent to participate in a double-blind, 8-week study. CVI was confirmed by color duplex testing and light-reflection rheography (LRR). Patients with a venous refilling time of less than 15 seconds, which indicates significant venous reflux,[4] were included, as were those demonstrating abnormal laser Doppler flowmetry parameters (ie, perimalleolar resting flow >1.5 U and altered venoarteriolar response). Exclusion criteria were cigarette use; pregnancy; active venous ulceration or peripheral vascular disease, as detected by noninvasive methods; clinical or subclinical diabetes; medication use; deep venous thrombosis within 2 years; or history of bone or joint surgery of the legs.

All patients received placebo or troxerutin 3500 mg. Microcirculatory and blood tests were performed at the beginning and end of the study.

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Laser Doppler flowmetry was performed with a Vasamedics BPM Laser Doppler Flowmeter (Vasamedics, St. Paul, Minn.) in a room at constant temperature (22.5°C). Skin flow was recorded after 20 minutes with patients undressed and resting supine. The following parameters were measured:

1. Resting flow (RF), expressed as the average of a 4-minute recording.
2. Standing flow (SF), expressed as the average after 4 minutes.
3. Venoarteriolar reflex (VAR), the response of the skin microcirculation, observed when the patient stood after being supine. VAR was expressed as $(RF - SF / RF) \times 100$.

Transcutaneous Po_2 and Pco_2 were evaluated with a Kontron (United Kingdom) analyzer and a Combi-Sensor probe. The probe was heated at 44°C, and readings were taken after 20 minutes of skin heating. Red blood cell aggregation was also determined (RBC Aggregometer, Affibio, France), as were aggregation velocity (aggregation time [AT] and aggregation index [AI]) and aggregation resistance with the partial dissociation threshold (PDT). Red blood cell count, hematocrit, and fibrinogen level were measured.

The results were analyzed by means of nonparametric Wilcoxon and χ^2 tests.

RESULTS

At baseline, the two groups were comparable in age, sex, and type of venous incompetence. No significant differences were observed in LRR or laser Doppler parameters, transcutaneous Po_2 and Pco_2, or red blood cell aggregation (AT, AI, PDT) (Table 1).

All 30 patients completed the study. After 8 weeks, laser Doppler parameters did not differ significantly between groups; RF, however, was reduced in the troxerutin-treated group (-11.9%), whereas no change was demonstrated in the placebo group (Table 2; Fig 1). In addition, the within-subject differences in VAR improved more in the drug-treated patients than in those who received placebo (+21.8% vs +8.8%). At study end, a significant difference ($P<.05$) in transcutaneous Po_2 was observed between groups (Fig 1).

Red blood cell aggregation also differed significantly after 8 weeks of treatment: between-group differences were demonstrated for AT ($P<.05$), AI ($P<.01$), and PDT ($P<.05$). These differences resulted from improvements in the troxerutin-treated group (AT +10.0%, AI -7.7%, PDT -4.6%); no changes were observed in the placebo group (-2%, 0.3%, and 0%, respectively) (Fig 2).

No side effects occurred during the study or within 6 months after study end.

DISCUSSION

An earlier double-blind trial that evaluated the efficacy of troxerutin versus placebo in patients with CVI indicated significant reductions in signs and symptoms. This previous study noted improvements in ankle circumference.[5] Comparable results were obtained in another placebo-controlled troxerutin study[6] and in a recent study in which clinical signs and symptoms were evaluated by plethysmography.[7] Significant increases in venous tone were observed in two separate clinical studies.[7,8]

Table 1. Demographic Characteristics at Baseline

	Troxerutin	Placebo
No. of patients	15	15
Age, y	46.5±13.9	47.7±13.2
No. with saphenofemoral incompetence	15	15
Venous refill time, s	12.2±1.4	12.5±1.2
Resting flow, U	4.2±2.3	4.4±1.9
Venoarteriolar response, %	44.5±15.9	46.5±13.0
PO_2, mm Hg	64.8±3.6	62.5±3.6
PCO_2, mm Hg	37.6±1.5	38.5±1.9
Aggregation time, s	2.51±1.06	2.02±0.57
Aggregation index	27.4±6.6	30.7±5.1
Partial dissociation threshold, s	65.3±15	74.8±17.3

Table 2. Characteristics of the Two Groups After 8 Weeks of Treatment

	Troxerutin	Placebo	*P* Value
Resting flow, U	3.7±1.8	4.4±2.6	NS
Venoarteriolar response, %	54.2±18.5	50.6±17.5	NS
PO_2, mm Hg	66.8±2.4	64.5±4.0	<.05
PCO_2, mm Hg	36.1±1.2	36.5±1.7	NS
Aggregation time, s	2.76±0.92	1.98±0.49	<.05
Aggregation index	25.3±5.4	30.8±4.4	<.01
Partial dissociation threshold, s	62.3±14.7	74.8±15.5	<.05

NS = not significant.

Earlier studies also showed improved blood flow parameters; specifically, compared with placebo, significant reductions in PDT[5] and in AI[5-7,8] have been documented. Moreover, reduced erythrocyte aggregation has been demonstrated in other studies.[9-10] In the experimental rat model, capillary density and arteriolar velocity had improved in troxerutin-treated animals compared with controls. Finally, troxerutin significantly affects euglobulin lysis time and plasminogen activator inhibitor, with a significant increase in tissue plasminogen activator.[7]

Fig 1. Percentage variation in resting flux and venoarteriolar response.

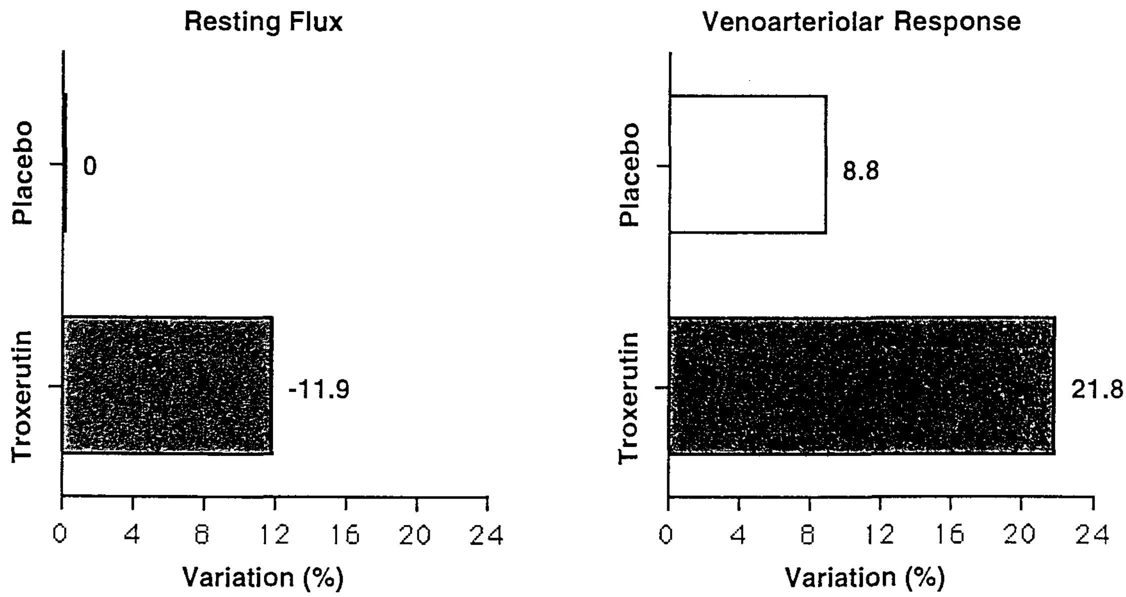
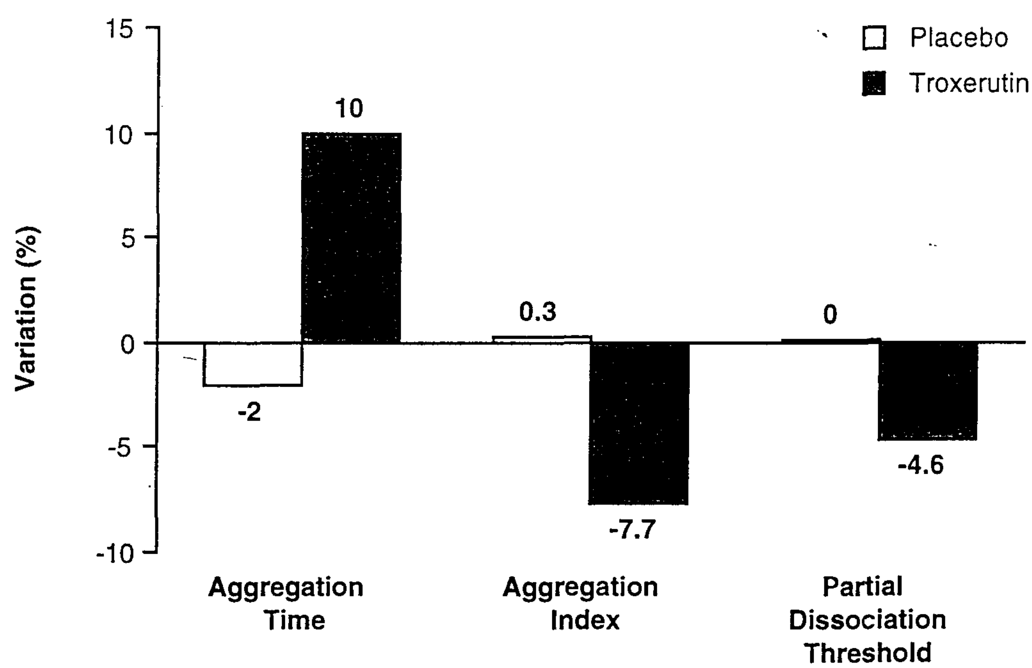


Fig 2. Variations in erythrocyte aggregation parameters.



Because of the limited number of patients and the short duration of our study, the only microcirculatory parameter that improved was Po_2. A favorable trend was observed, however, in laser Doppler flowmetry, with reduced RF and increased VAR. These findings and the improvements in AT, AI, and PDT indicate that troxerutin, by acting on altered microcirculation and red blood cell aggregation and viscosity, may help correct abnormalities found in individuals with hypertensive venous microangiopathy. In addition, it is feasible that erythrocyte aggregation parameters may show greater improvement if measured in areas of venous hypertension rather than in systemic blood.

CONCLUSION

It is important to treat patients with longstanding venous disorders to avoid ulcerations and their consequent high personal and economic cost. Ongoing treatment with compression and an appropriate drug regimen[12] may help stop the progressive degeneration of the venous system, thus reducing morbidity in a cost-effective manner. A long-term study is needed to evaluate the effects of troxerutin, a safe and very well tolerated agent, on the venous system, microcirculation, and blood flow (with and without compression) and to observe the pharmacologic effect on the progressive evolution of CVI.

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Microcirculation Laboratory, Cardiovascular Institute (Director: Prof. A. Barsotti),
Chieti University, Italy and
Irvine Laboratory, St Mary's Hospital Medical School, London, U.K.

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Laser Doppler Flux in normal and arterio-sclerotic carotid artery wall

G. Belcaro, A. N. Nicolaides, G. Laurora, M. R. Cesarone, M. T. De Sanctis, L. Incandela and N. Labropoulos

Arterial wall perfusion and vasa vasorum alterations may be the initial cause of venous and arterial wall lesions, but the pathways and correlations between vessel wall blood perfusion and vascular diseases are not clear. Hypoxia of the arterial wall following blood hypoperfusion in the vasa vasorum network has been considered an important concomitant cause of arterial wall alterations in subjects with early wall lesion and initial atheroma [11]. Also it has been proposed that malformations, alterations or deformation of vasa vasorum play a very important role in the development of arterial changes observed in subjects with systemic hypertension [16]. Severe arterial wall perfusion alterations (i.e. medial necrosis) have been observed after experimental damage or surgical removal of the vasa vasorum [1, 18]. It has also been suggested that experimental vasa vasorum occlusion induces localised arterial medial fibrodisplasia [17]. The modification of smooth muscle cells to primitive myofibroblast appears to be a major, if not the primary, pathologic feature of this fibroproliferative disorder. Different methods of investigations (i.e. microangiograms, fluorescent micrography and histology) have shown that vascular wall disturbances, alterations of the arterial wall microcirculation and of the vasa vasorum system and consequently of the metabolism of the vascular wall are cause of vascular lesions [12].

Experimentally induced acute, intra-luminal arterial hypoxia produces vasa vasorum dilatation [8]. This indicates an important, fast response of the vasa vasorum system to metabolic changes. Even in the venous system the role of blood flow alterations in the vasa vasorum of veins has been considered responsible for initial endothelial alterations possibly leading to severe problems including venous thrombosis [14].

It has been observed that experimental lesions of the vasa vasorum – induced by thermal coagulation – cause intimal lesions such as thickening, lipid deposition and increase in the production of elastic and collagen fibres with an increase in the substance stained by metachrome [13].

There is, therefore, at least an indication that the alterations observed in the arterial wall may be associated with alterations in vessel wall perfusion [10]. Arterial wall perfusion alterations are possibly a cause of thickening, plaque formation and calcifications. Often they are associated with plaques and atheroma but they may also be a consequence of atherosclerosis and it is difficult at this stage to define the role of vasa vasorum alterations in atherogenesis as only limited information is available.

The aim of our study was to evaluate *in vivo* the perfusion of the carotid wall in normal arterial sections, in sections with fibrotic plaques and in sections with plaques associated with diffuse calcifications using a non-destructive test (laser-Doppler flowmetry).

Patients and methods

Informed consent was obtained from all involved patients. Indications for carotid surgery were signs and symptoms associated with severe stenosis and CT scanning evidence of ipsilateral infarctions. Carotid wall flux (namely the flow components measured by laser Doppler flowmetry) was measured using laser Doppler flowmetry on the external, anterior surface of the common carotid artery partially dissected during the preparation of the carotid for endarterectomy. Measurements were performed before complete dissection of the artery (after very limited anterior dissection of the common carotid, for a length of 3 cm) when at least ¾ of the adventitia tissue (around the artery circumference) was intact. Measurements were made on normal carotid artery wall, on sections with fibrotic plaques without calcification and on carotid sections with diffusely calcified plaques [4, 6]. A strict no-touch surgical technique was used in order to minimise arterial wall reactions and flow alterations due to arterial manipulation.

Criteria of exclusion were diabetes and hypertension and any renal or cardiovascular disease (excluding coronary ischemic disease).

Intra-operative Ultrasound. An ATL (ATL, Bothell, Washington, USA) 10 Mhz probe was used to define the carotid sections as sections with a normal wall, sections with fibrotic plaques without calcification and sections with heavily calcified arterial wall and plaques [4, 6]. Previous work has indicated [6] that the ultrasound images of echogenic plaques are well related to histology. The segment of artery (4 cm) proximal to the bifurcation (flow divider) was studied (Fig. 1).

The laser Doppler measurement set-up is shown in Figure 2. A Laserflo (Vasamedics, St. Paul, Minnesota, USA) lateral optic system probe (3 mm in section) was used. In the space between the probe optic system and the arterial wall a polycarbonate spacer (*Delrin*® spacer) was applied to limit the penetration of the laser beam. As the theoretical tissue laser penetration of this specific probe is about 1 mm, the spacer is 0.5 mm in thickness and the arterial wall thickness is about 2 mm the application of the optic spacer allowed wall flux measurements without including (or minimising and attenuating) signal and noise from the moving blood within the arterial lumen. *Delrin*® polycarbonate spacers have the same optic density and light transmission characteristic of human tissue (particularly skin) [2, 3, 9]. The probe was applied on the anterior surface of the artery. Blood flow blockage was not used during measurements. Surgical trauma and trauma due to artery manipulation was maintained to a minimum. Flux was defined as the average laser Doppler recording of 3 minutes (the first minute after placing the probe was considered for stabilisation and excluded from the average).

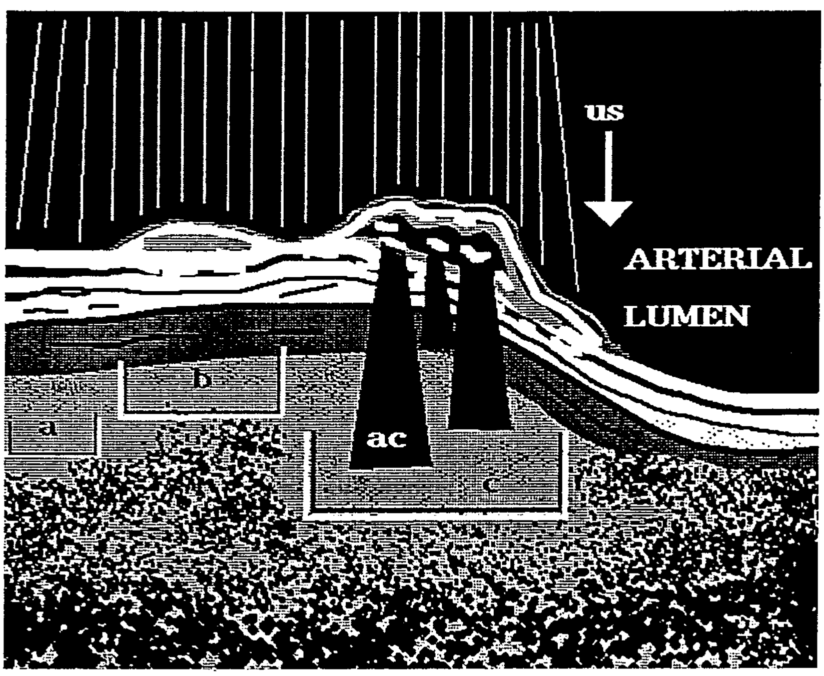


Fig. 1: Different sections of the arterial wall where measurements of wall flux were recorded (diagram). US indicates the ultrasound beam.

a: normal wall;
b: fibrotic plaques without calcifications;
c: calcified – predominantly echogenic – plaque with calcifications and acoustic shadows (ac).

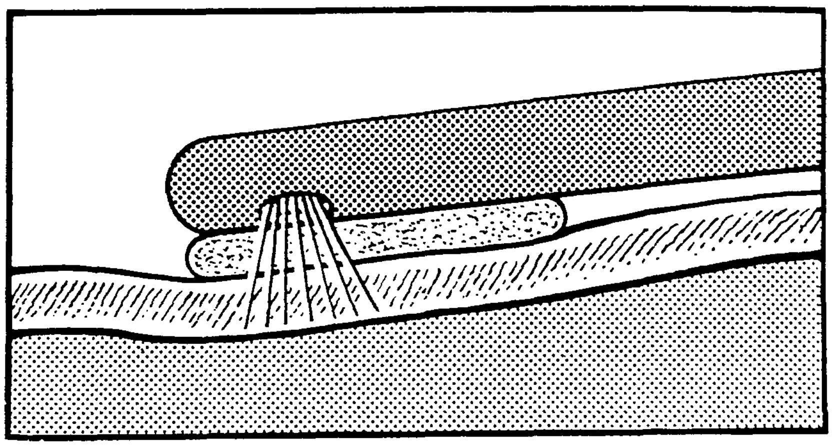


Fig. 2: The laser-Doppler system used to measure arterial wall flux.

Statistics. A Statgraphics (STSC, USA) software was used. T statistic was used to compare flux between normal and altered arterial wall.

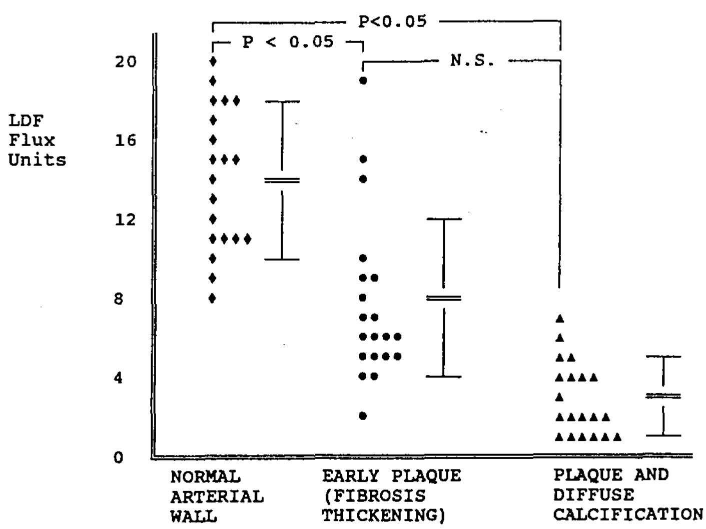
Results

Flux measurements were possible in 20 (mean age 65.3; SD 12; range 58–73; 6 females) out of 29 subjects. In 9 subjects very diffuse calcifications, arterial abnormalities, extended surgical dissection needed for exposure, or bleeding made measurements impossible and/or unreliable. Figure 3 shows flux values in the different arterial wall sections.

Flux in normal carotid wall was significantly higher ($p < 0.05$) than flux in sections with plaques. There was also a significant difference in flux between wall with fibrotic plaques and calcified carotid sections with larger plaques ($p < 0.05$).

Discussion

This preliminary research indicates that arterial wall flux appears to be lower in the atherosclerotic wall in comparison with flux in normal wall. Large plaques and severe calcifications are asso-



	NORMAL ARTERIAL WALL	EARLY PLAQUE (FIBROSIS THICKENING)	PLAQUE AND DIFFUSE CALCIFICATION
AVERAGE	14.05	7.6	2.9
VARIANCE	12.78	17.04	3.4
SD	3.57	4.17	1.8
RANGE	8-20	1-19	1-6

Fig. 3: Flux in normal arterial sections and in section with fibrotic and diffusely calcified plaques [mean (=) and SD (—)].

	T Stat.	P
NORMAL vs EARLY PLAQUE	5.24	< 0.05
NORMAL vs CALCIFICATION	12.36	< 0.05
EARLY PLAQUE vs CALCIFICATION	4.6	< 0.05

ciated with a very low intra-wall flux. In the present study surgical trauma and trauma due to vessel manipulation were maintained to a minimum to reduce arterial wall reactions and flux alteration. However, the variability of results and technical problems in arterial wall flux measurements indicate the need of a larger measurement sample before confirming the observation of decreased perfusion in the altered wall.

Vasa vasorum and arterial wall perfusion are associated, but are not synonymous. Therefore, dynamic microcirculatory perfusion and the distribution of vasa vasorum should be evaluated in parallel studies. Micrografy of the larger part of arteries and veins shows a capillary network corresponding to connective tissue and muscle structures [5, 15].

LDF is a relatively new method to evaluate microcirculation. Several instruments are available. Technology, laser type, standards of measurements, types of probes and laser tissue penetration are variable and each instrument produces its characteristic output [2, 7]. However tissue microcirculation alterations detected with different instruments are comparable [7]. Different types of laser beams have different tissue penetration [2]. This is important because the most important nutritional layer (i.e. in the skin) is considered to be very superficial (within 0.5 mm) while the laser Doppler beam, having a deeper penetration (1 to 1.5 mm on average), includes also flux in the thermoregulatory layer which may be only marginally important in tissue (namely skin) nutrition and healing [7, 9]. Tissue penetration in vein walls appears to be similar to the penetration observed in skin. A different level of penetration and tissue perfusion measurements may be obtained without changing laser light characteristics using polycarbonate spacers with a known thickness (0.2 to 1 mm) which, increasing the distance between probe ending and tissue, may detect flux in the more superficial layer of the tissue under evaluation [9]. This is obtained at the expense of a moderate increase in the level of noise due to the limited loss of coherence (enlargement of the laser beam) when the beam leaves the optic fibre structure (probe). Spacers with different thickness proportionally decrease the flux signal theoretically detecting flux in proportionally more superficial tissue layers [9]. The spacers used in this study had the aim of excluding noise produced by flow present in the lumen from arterial wall flux. The luminal flow component was not directly included in the measurements but fine motion artifacts were possibly present from this component (due to passive wall motion).

In a previous preliminary study using laser Doppler in normal and varicose veins wall differences in flux between normal veins and varicose veins were detected [3].

Arterial wall perfusion and distribution, structure and function of vasa vasorum are possibly important both aetiologically (in the genesis of early lesions linked to atherosclerosis) and in the evolution of atherosclerotic changes in the arterial wall.

Whether in arterioslcerosis wall perfusion alterations cause or follow arterial wall thickening, plaque formation and calcifications it is very difficult to understand since, at present, only limited information is available.

Summary

The perfusion of the arterial wall was evaluated in vivo in normal sections of the carotid artery, in sections with fibrotic plaques and in sections with plaques and diffuse calcifications using laser Doppler flowmetry. Patients with carotid plaques undergoing carotid endarterectomy were studied. Using intraoperative ultrasound three different levels of atherosclerosis involvement of the arterial wall were defined: normal arterial wall where all components (intima, media and adventitia) were clearly separated and intact; wall with intima-media thickening and fibrotic plaques (without calcifications); sections with diffusely calcified plaques. In 20 patients 20 normal sections, 20 sections with fibrotic plaques and 20 sections with large plaques and diffuse calcifications were studied. Diabetic and hypertensive patients were excluded. Wall flux was measured on the external surface of the common carotid artery before complete dissection for endarterectomy. Measurements were recorded when at least ¾ of the adventitia was intact for a length of at least 4 cm. The average flux in normal sections was higher ($p < 0.05$) than in sections with fibrotic plaques and in sections with calcified plaques. A significant difference in flux ($p < 0.05$) between fibrotic (decreased flux) and calcified areas (very low flux) was recorded. In conclusion a higher wall perfusion was observed in normal arterial sections in comparison with sections with plaques. Sections with diffuse calcifications and larger plaques had a very low flux.

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Zusammenfassung

Die Perfusion in der Arterienwand in vivo wurde mittels Doppler Fluxmetrie in gesunden Karotiden und in Regionen mit Plaques und diffuser Verkalkung ermittelt. Bei Patienten mit Plaques in der A. carotis wurden bei der Endarteriektomie mit intraoperativem Ultraschall drei verschiedene Grade von arteriosklerotischen Wandveränderungen festgestellt: 1) Normaler Arterienwandregion mit Intima, Media und Adventitia intakt und klar getrennt, 2) Wandung mit Intima-Media-Verdickung und fibrotischen Plaques ohne Verkalkungen 3) Regionen mit diffus verkalkten Plaques. Total wurden bei 20 Patienten 20 normale Wandregionen, 20 mit fibrösen und 20 mit großen Plaques und diffuser Verkalkung untersucht. Diabetiker und Hypertoniker unter den Patienten wurden ausgeschlossen. Der Wandflux wurde auf der äußeren Oberfläche der A. carotis communis vor der Dissektion zwecks Endarteriektomie gemessen. Die Meßergebnisse wurden aufgezeichnet, wenn mindestens ¾ der Adventitia auf einer Länge von wenigstens 4 cm intakt waren. Es zeigte sich, daß der durchschnittliche Flux in normalen Regionen signifikant höher war als in den beiden veränderten Regionen. Auch zwischen fibrotischen Abschnitten (herabgesetzter Flux) und verkalkten Regionen (sehr geringer Flux) bestanden signifikante Unterschiede. Es wurde demnach festgestellt, daß in normalen Arterionabschnitten eine höhere Wandperfusion besteht als in solchen mit Arteriosklerose. Abschnitte mit diffuser Verkalkung und großen Plaques wiesen einen sehr geringen Flux auf.

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G. Belcaro, Via Vespucci 65, I-65100 Pescara

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CHAPTER 96

Chronic Deep Venous Insufficiency

Andrew Nicolaides, Gianni Belcaro, and Philip Chan

It is estimated that 10% to 20% of the population in the developed world have varicose veins or some degree of superficial or deep venous insufficiency in the lower extremities (1). Chronic venous insufficiency may be due to incompetence localized to the superficial system (varicose veins) or to both superficial and deep venous incompetence. Primary varicose veins are usually associated with a normal deep venous system, while secondary varicose veins are often a complication of chronic deep venous insufficiency (DVI) or arteriovenous fistulas. Both primary and secondary varicose veins, if untreated, lead to chronic venous hypertension and ulcerations.

It has been postulated that in both superficial and deep venous incompetence sequential incompetence of the valves in proximal venous segments may cause higher pressure at the level of the distal valves and produce localized dilatation of the more distal venous segment.

An alternative hypothesis considers a congenital weakness of the vein wall, chronically associated with venous dilatation even when venous pressure is normal. The valvular ring is slowly but progressively dilated with secondary failure of valvular competence. Although there is often a positive family history, the vein wall weakness is probably not entirely inherited but due to both congenital and postnatal factors.

The role that the low-roughage diet consumed in many developed countries plays in increasing the incidence of varicose veins and deep chronic venous insufficiency is still not completely defined. Some other aggravating factors—female sex, parity, constricting clothing, prolonged standing, obesity, professional or strenuous physical training, and chronic use of estrogens such as oral contraceptives (1)—seem to be associated with both an increased incidence of varicosity and deep venous disease.

Secondary varicosities associated with chronic venous disease originally develop after damage or obstruction to the deep venous systems. Recanalization of the thrombosed deep veins leaves the superficial valves incompetent and this leads to reflux. Secondary varicosities progressively develop as a consequence of the increased venous pressure and flow transmitted from the deep to the superficial veins mainly by communicating veins. Severe obstruction of the deep venous system, such as inferior vena cava or iliac vein blockage, may cause secondary varicosities in the lower extremities following chronically increased venous pressure. Suprapubic varicosities may be due to residual collateral veins that develop after obstructing iliofemoral thrombosis.

Arteriovenous malformations and fistulas may also lead to increased venous pressure and localized varicosity with associated dilatation of the deep venous system and chronic incompetence. Klippel-Trenaunay syndrome, a form of congenital arteriovenous malformation, is also associated with diffuse varicosities of the lower extremities and absence or malformation of the deep veins.

Introduction to Chronic Deep Venous Insufficiency

Chronic venous insufficiency is a widespread, serious, and often underestimated problem. Chronic DVI affects some 0.5% of the population in the United Kingdom and United States (2). Female patients appear to be affected twice as much as males. The mean age of presentation for females is 55, and 10% of patients are hospitalized once or more for recurrent thrombosis, cellulitis, lipodermatosclerosis, venous ulcerations, or different forms of surgical treatment (3). It has been calculated that two million work days are lost in the United States each year for complications caused by chronic DVI (4).

The majority of cases possibly are—or are considered to be—late sequelae of deep venous thrombosis, hence the term *postphlebitic syndrome*, which is generally used to define, although not always correctly, chronic DVI. Other factors such as congenital absence or incompetence of the valves and congenital or chronic dilatation of the deep venous system may be the initial cause of chronic DVI.

Ferris and Kistner have identified a population with primary vein valvular incompetence (5). It may be that some of the patients thought to have silent deep venous thrombosis suffer instead from this syndrome. It is possible that this abnormal anatomic situation is associated with a venous stasis and higher incidence of deep venous thrombosis.

The specific morphological causes of chronic DVI in a particular patient may not be determinant when medical or conservative management is successful. However, when direct reconstruction of the deep venous system is planned (as discussed in other chapters), surgery must be proposed on the basis of a clear understanding of the particular disease process and its anatomy.

The acute onset of DVI associated with signs of obstruction in previously healthy patients, particularly the elderly, suggests the need to search for extrinsic causes of compression such as pelvic tumors or aneurysms.

Pathophysiology

The venous system of the lower extremities may be divided into four subsystems: 1) the deep system; 2) the superficial system; 3) the perforating, communicating system; and 4) the microcirculation and the venular system. The problem causing DVI may be localized in one or more than one of these systems.

The *deep system* includes veins lying within the muscular compartments, beneath the deep fascia; it returns approximately 85% of the blood delivered to the lower extremities.

The *superficial system* includes the greater saphenous and lesser saphenous vein systems with their tributaries in the subcutaneous tissue, superficial to the deep fascia.

The *perforating, communicating system* includes veins traversing the fascia and connecting the deep to the superficial system. Perforating veins have valves designed normally to direct flow from the superficial to the deep veins in the extremity proximal to the foot level. The valves present in the lower extremity are bicuspid. They are more numerous distally, with many fewer valve stations in the thigh than in the leg. The valves are often absent in the iliac veins (6).

In humans, when the body is erect, the effective zero level of venous pressure is in the right atrium. The hydrostatic pressure in a vein on the dorsum of the foot is equal to the distance from the right atrium to the foot, approximately 100 cm H_2O. In more distal, dependent veins the hydrostatic pressure is higher and the vein walls tend to be proportionally thicker in consideration of the caliber of the vein. The valves in the veins of the leg by themselves are not effective enough to break down completely the hydrostatic pressure of the column of blood between heart and foot.

Muscular contractions compressing the deep veins tend to continuously force blood toward the heart as the valves prevent retrograde flow. With muscular relaxation, the pressure in the deep venous systems decreases and the veins fill passively with blood. Frequent and efficient muscular action helps maintain low levels of venous pressure. In a normal limb, during walking, venous pressure decreases to about 30 mm H_2O from a resting venous pressure of approximately 100 to 120 mm H_2O (Fig. 96.1). The decrease in venous pressure is maintained until the end of the exercise, after which the intravenous pressure returns slowly to the pre-exercise level.

Iliofemoral venous thrombosis is considered to be possibly the most common precursor of DVI. A clear history of iliofemoral thrombosis is found in 20% to 87% of patients with DVI (7), and many patients may have had silent episodes in the past. However, patients with chronic venous disease due to primary valvular incompetence, agenesis, or dysfunction have been identified (5,8), although the percentage of such patients is unknown. It has been observed that up to 86% of patients with a previous, documented deep venous thrombosis may be expected to develop a venous ulcer if followed for 10 years (9). The evolution of the sequelae of deep venous thrombosis is still unclear and confusing. It has been observed that one-fourth of patients with thrombosis extending above the knee level may not develop symptoms for 5 to 15 years (10). In the months that follow thrombosis, recanalization of the veins restores patency, but competency is often lost as thrombosis and the healing process partially or totally alter or destroy the valves involved. Venous valves distal to the thrombus are thought to dilate sequentially as the

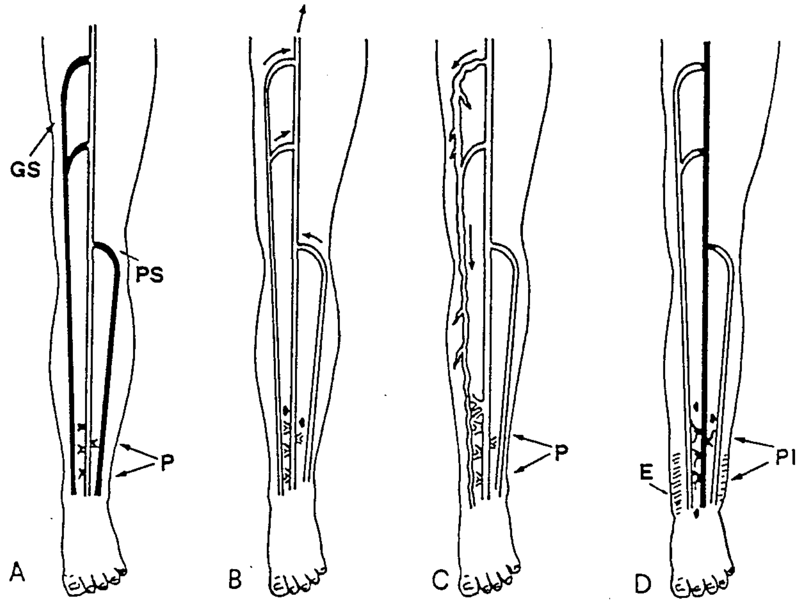


FIGURE 96.1 Normal venous physiology during standing (A) and walking (B) and abnormalities during exercise (C, D). Pressure in the superficial veins is decreased during exercise if the valves are competent. The action of the muscles promotes venous return from the superficial to the deep system and to the central proximal veins toward the heart (B). When the superficial proximal valves are incompetent, the superficial system becomes varicose (C). In initial superficial venous incompetence, competence of the distal communicating veins maintains venous flow from superficial to deep and venous return during exercise. The efficacy of the calf muscle pump is essentially maintained and the ambulatory venous pressure is only slightly elevated. If the valves of the deep system are incompetent and the distal valves in the communicating veins are also incompetent, severe chronic venous hypertension develops, leading to edema, swelling, and eventually to ulceration (D). GS, greater saphenous system; PS, posterior system; P, perforators; PI, perforator incompetence.

proximal incompetent venous segment transmits an abnormally high hydrostatic pressure to the next distal valve. The increase in intravenous pressure is eventually transmitted to the perforating veins, which dilate with loss of competency and reversal of venous flow. This combination of progressive deep and perforating venous incompetence often leads to the syndrome of chronic DVI. Schanzer and Peirce (11) found incompetent perforators to be the most important pathologic factor in 60% of their patients and incompetent deep veins in 27%.

Szendro et al. found that deep venous incompetence correlates well with symptomatic chronic venous insufficiency (12). Yao et al. believe that deep and perforating valve incompetence together are the most important factors in symptomatic DVI (13). Also it has been observed that popliteal vein incompetence correlates best with symptoms and signs of DVI (14).

As a consequence of chronic DVI determining chronic venous hypertension, the increased venous pressure is transmitted to *the venules and the microcirculation* and the pathologic process affects the skin and subcutaneous tissues. In chronic venous insufficiency the capillary network is altered. The increased exchange surface is due to elongation and dilatation of the capillaries, which assume a glomerular-like appearance with thickening of the capillary wall (Plates 63 and 64).

In association with the morphological changes in the microcirculation, increased skin flux may be observed by laser Doppler flowmetry in the perimalleolar region, and this is associated with an increase in capillary filtration (15). The increased hydrostatic pressure in the microcirculation transmitted to these tissues causes increased chronic leakage of fluid and proteins into the interstitial space with resultant edema, which is often the first clinical manifestation of chronic DVI. Venous edema initially appears in the evening, involving the ankle and lower leg, and recedes at night. It may progress with time so that the involved leg does not return to normal size after a night's rest. In some patients it may progress up the thigh. Massive swelling of the entire extremity or both legs may be seen with iliac or inferior vena cava occlusion.

Other signs of chronic DVI are dermatitis, induration, local pain, and ulceration usually localized at the perimalleolar region. Associated with the edema are often congestion and cyanosis of the skin chronically leading to hemosiderin deposition and causing brown pigmentation. Stasis dermatitis and eczema are frequently associated problems. Chronic edema and dermatitis lead to fibrosis of the subcutaneous tissue and induration of the involved skin. These changes are usually seen at the internal perimalleolar area, most commonly over the medial malleolus. Ulcerations tend to develop mostly in these areas. Perforating veins here arise directly from the subcutaneous tissues, and the incompetence of these valves transmits the pressure in the deep veins directly to the microcirculation and subcutaneous tissue (16). An increased escape of fibrin through the microvascular network in these areas has been postulated (17). This excess filtration of fibrin and fibrin degradation products *filtration* constitutes a dense, pericapillary "cuff" of fibrin, which an inadequate fibrinolytic system cannot clear, and some patients with chronic venous insufficiency possibly have inadequate local fibrinolysis (17). This fibrin wall around the more distal capillaries possibly acts as a barrier to diffusion of gas, nutrients, and metabolites, leading to cellular ischemia and ultimately to necrosis (18). However, the fibrin cuff theory has not been confirmed by other authors (15). Fibrin is also an inflammatory protein present in many pathological processes, not necessarily specific to venous microangiopathy. Therefore multiple factors appear to be in action in determining the microcirculatory changes observed in venous hypertensive microangiopathy (15), and more research is needed in this field.

Skin oxygen tensions have been shown by some researchers to be decreased in patients with chronic venous stasis, but this has not been substantiated by others (19,20). The effects on the increased skin PCO_2, in association with increased skin flux, in promoting and maintaining local vasodilatation are still not fully understood (20).

Ulcerations due to chronic DVI are slow to heal and generally recurrent if the underlying cause of venous hypertension is not removed. Some patients complain of pain in the muscles of the leg after standing for some time. Supine resting or leg elevation generally relieves aching and fatigue.

Venous claudication, a severe, bursting pain, usually of the thigh, may occur in some subjects with DVI and severe obstruction. This symptom is more common in subjects with long-standing iliofemoral obstruction, absence of collaterals, and a patent distal venous system (21). Pain is the result of venous congestion, made worse with exercise because the increased arterial and venous flow associated with muscle activity cannot be returned to the heart at the same rate as it is delivered. It has been observed that an increased intramuscular pressure in the anterior and deep posterior compartments and increased water content are present in the leg muscles ipsilateral to iliac vein occlusion (21). Therefore the pain of venous claudication appears to be mainly secondary to the acute increase in intramuscular pressure during exercise.

Diagnosis

The clinical diagnosis of chronic venous insufficiency, with edema, induration, and ulceration, is usually made easily on history and physical examination. The differential diagnoses include congestive heart failure, chronic glomerulonephritis (generally bilateral) chronic lymphedema, and lipedema (15). Probably the most difficult differential diagnosis is between chronic venous insufficiency and chronic lymphedema. In chronic DVI edema does not generally involve the foot, and the skin and subcutaneous tissues do not show the diffuse thickening of lymphedema with its characteristic firm pitting edema.

Ulceration may result from a combination of arterial and venous disease. Distal localization of the lesion at the toes and feet, their pale appearance, and the pain associated with them, as well as the other sings of arterial insufficiency, are useful in distinguishing between the two entities.

Edema and chronic skin changes and thickening may be obstacles to accurate pulse examination; therefore vascular laboratory studies, both arterial and venous, are critical in such situations. Whereas physical examination may reveal the presence of chronic venous insufficiency, it is not sufficient to localize and quantify the underlying anatomic and functional defects. Szendro and colleagues (12) and Moore, Himmel, and Sumner (6) have shown that in some limbs valvular incompetence may be a localized disease. Femoral veins may reflux separately, as may popliteal veins, while in some limbs incompetence may be generalized.

Popliteal vein incompetence is believed to correlate most directly with the classic signs of chronic DVI (6,13,14), although Ferris and Kistner suggest that femoral incompetence is the most important causal factor and reported that 5% of their patients had proximal incompetence either localized or in conjunction with distal incompetence (5).

If there is no apparent cause for venous thrombosis or deep venous insufficiency, other possibilities may be evaluated. Pelvic tumors, hemangiomas, and arteriovenous fistulas may give rise to chronic, rapidly progressive venous insufficiency, as may primary valvular agenesis or postthrombotic incompetence. Ascending phlebography has been for years the standard against which new diagnostic tests have been compared. The patency and competence of the deep venous system and perforators can be easily demonstrated as can postphlebitic changes and chronic obstructions. Ascending phlebography can be also performed so as to define the valves' incompetence (22).

If deep venous reconstructive surgery is considered, a clear definition of the state of the venous valves usually requires descending phlebography. This method is considered by some to be controversial because of differences in technique and appraisal (23). Kistner has developed a grading system for evaluating descending phlebography (Table 96.1) (24). Decisions concerning deep venous valvular replacement or reconstruction are dependent on the results of such anatomic and functional assessment. Descending phlebography is a fluoroscopic, dynamic study and as such provides functional as well as anatomic data.

Ambulatory venous pressure (AVP) determination is a very useful diagnostic measurement and a good method of follow-up for reconstructive procedures

TABLE 96.1 Interpretation of descending phlebography

Complete competence	
	Does not leak during full Valsalva maneuver
Satisfactory incompetence	
	Mild leakage limited to thigh during Valsalva maneuver
Moderate incompetence	
	Prominent leakage into calf during Valsalva maneuver
	Retains prograde flow in iliac vein
Severe incompetence	
	Cascading retrograde flow during Valsalva maneuver
	Reflux into calf perforators

although it is a minimally invasive and moderately complex procedure (25–29). These factors have prevented its wider application. A small-gauge needle or catheter is placed in a dorsal vein of the foot, and resting supine and standing venous pressures and exercise pressures are obtained. In a patient with chronic DVI without obstruction, the supine pressure is normal. Upon standing, the rise in venous pressure occurs in less than normal time. The standing resting (baseline) pressure is usually normal. With exercise the decrease in pressure often does not achieve the 50% level, and in severe obstruction it may exceed standing baseline. The quantitative value of AVP is discussed in the following section.

Noninvasive laboratory examination of the deep veins has become the most important method of venous evaluation. Impedance plethysmography (IPG) may be useful in the diagnosis of acute deep venous obstruction but is of little help in the diagnosis and quantification of chronic DVI.

Photoplethysmography (25,30–33), *Doppler ultrasound* venous examination (34), *duplex* and *color duplex scanning*, and *air plethysmography* are currently considered the most useful noninvasive tests available to assess chronic DVI.

The clinical diagnosis value and the value in the quantification of chronic venous insufficiency of the most important noninvasive tests are discussed in the following section.

Noninvasive Diagnosis

Localization and Quantification of Incompetence

As previously observed, chronic DVI may be the result of outflow obstruction, reflux, or a combination of both. The objective of any noninvasive examination is to detect whether obstruction or reflux is present. Second, the anatomic localization of the abnormality must be found, and then the problem of quantification of the reflux or obstruction must be addressed.

In evaluating venous stasis, noninvasive tests combine physiologic and imaging techniques. For the most part, these tests are widely available, simple, quick, and cost-effective. Therefore these are the methods of choice for initial objective evaluation.

It should be noted that different tests provide answers to different questions. Many of these have been established during the past decade. Most recently, however, technologic advances and current thinking indicate that the optimum useful information can be obtained using only three test modalities: 1) pocket Doppler ultrasound instrument; 2) duplex scanning, preferably with color flow imaging; and 3) air plethysmography.

Tests for Venous Reflux

Venous reflux is the result of gravity drawing the venous bloodstream distally. Therefore reflux testing should be performed always with the patient standing. Recent studies have determined that venous reflux detected in the supine position may be abolished when the patient is standing. This is because valve closure occurs only after reflux exceeds a critical flow velocity. This is better achieved with the patient standing rather than supine. When the patient is standing, it is also very important to avoid muscular contractions. Therefore the patient should be examined holding onto a frame or table. The leg to be examined should be relaxed with the knee slightly flexed, with the weight on the opposite leg. Studies have shown that during full knee extension, an occlusion of the popliteal vein occurs in 20% of healthy people.

Pocket Doppler Instrument

After physical examination, a pocket Doppler instrument is used. The pocket instruments are satisfactory to complement the physical examination as a screening test for outpatients (35–37). The continuous wave instrument provides information about reflux at the saphenofemoral and saphenopopliteal junctions (36). The knee of the leg to be examined should be slightly flexed to relax the muscles and skin over the popliteal fossa. Manual calf compression produces cephalad flow and reflux may occur when the compression is released. Abolition of the reflux by compression of the superficial veins just below the probe suggests that reflux is confined to the superficial system. Failure to abolish reflux by such a maneuver indicates that in the reflux is in the deep system (38).

In experienced hands, a pocket Doppler instrument provides clear answers regarding the presence or absence of reflux at the saphenofemoral and saphenopopliteal junctions in 90% of patients (39). Abnormal anatomy in the popliteal fossa is responsible for most of the errors (8%). For example, reflux in the gastrocnemius veins may be interpreted as reflux in the popliteal vein. Also the continuous wave Doppler venous examination is not accurate in localizing incompetent perforating veins.

Duplex Scanning

Duplex scanning supplements the physical examination and evaluation with the pocket continuous wave Doppler instrument. The duplex scan provides information about reflux in specific veins the examiner wants to interrogate. For example, the femoral, popliteal, deep calf, and perforating veins can be individually tested. The use of color has made the duplex evaluation much faster and more accurate.

As in the examination of a patient with the continuous wave instrument, the patient is examined standing. The non-weight-bearing lower extremity is evaluated, and the sites to be interrogated are imaged with the 5- or 7.5-MHz probe. Thus the saphenofemoral junction, the popliteal venous anatomy, and the perforating veins may be visualized. Manual calf compression or, ideally, compression by a rapidly deflatable cuff is used. The cuff inflation produces cephalad flow. Rapid release of the compression is essential to testing for reflux, and valve closure can be documented. Figure 96.2 shows the saphenopopliteal junction, Figure 96.3 shows the anatomy of veins in the popliteal fossa, and Figure 96.4 and Plate 65 show an example of testing for perforating veins.

Localization of calf perforating veins and reflux in them is time-consuming with conventional duplex, but color flow imaging has brought this examination into the realm of practicality. Duplex scanning for localization of sites of reflux is particularly useful in patients with recurrent varicose veins after previous surgery. Such examination also confirms the normal functioning of deep veins and the extent and site of venous reflux when it is present. Both localized and generalized reflux (e.g., whether it is present throughout the deep venous system) can be identified. Although quantification of reflux in individual veins is possible, this is very time-consuming (40). Accurate and reproducible results are obtained more easily for the whole leg using air plethysmography, which has become the test of choice for quantitating reflux.

Ambulatory Venous Pressure Measurements

The venous pressure examination, although invasive, has remained a standard to which other examinations are compared. Venous pressure is measured by inserting a needle in a vein on the dorsum of the foot with the patient standing (Fig. 96.5). Pressures are recorded during 10 tiptoe exercises (41). The ambulatory venous pressure (AVP) is defined as the lowest pressure reached during the exercise (Fig. 96.5). The AVP is a function of the calf muscle pump's ejecting capacity, the magnitude of reflux, and the outflow resistance. Therefore it represents the total effect of all the abnormalities that affect venous hemodynamics. In normal limbs, the AVP is less than 30 mm Hg and the refilling time is greater than 18 seconds. These values result from filling of the veins from the arterial side. When venous reflux is present, the AVP is higher and the refilling time is shortened (Table 96.2).

After AVP is obtained, the exercise test can be repeated with narrow tourniquets (2.5 cm wide) applied at the ankle, below-knee, or thigh position. These tourniquets control reflux from the superficial veins, and if pure superficial reflux is present, the AVP and refilling time are normalized. In patients with deep venous incompetence, normalization does not occur. Table 96.2 indicates that AVP is elevated in the presence of popliteal reflux. For AVPs from 40 to 100 mm Hg, there is a linear relation to the incidence of skin ulceration. This is true regardless of the underlying pathology and whether the reflux is in the superficial or the deep system (Table 96.3).

Photoplethysmography and Light Reflection Rheography

In an attempt to obtain the refilling time noninvasively, photoplethysmography and light reflection rheography tests were developed. In both of these techniques, a photodetector is applied to the skin of the foot or ankle (Fig. 96.6) (42). These instruments determine whether

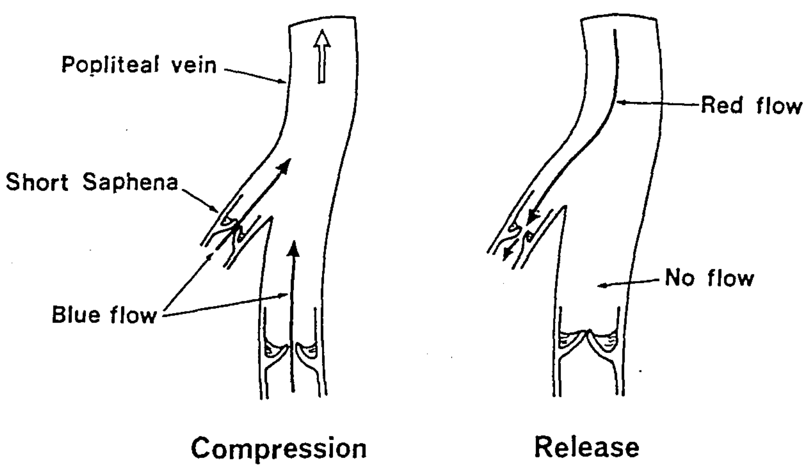
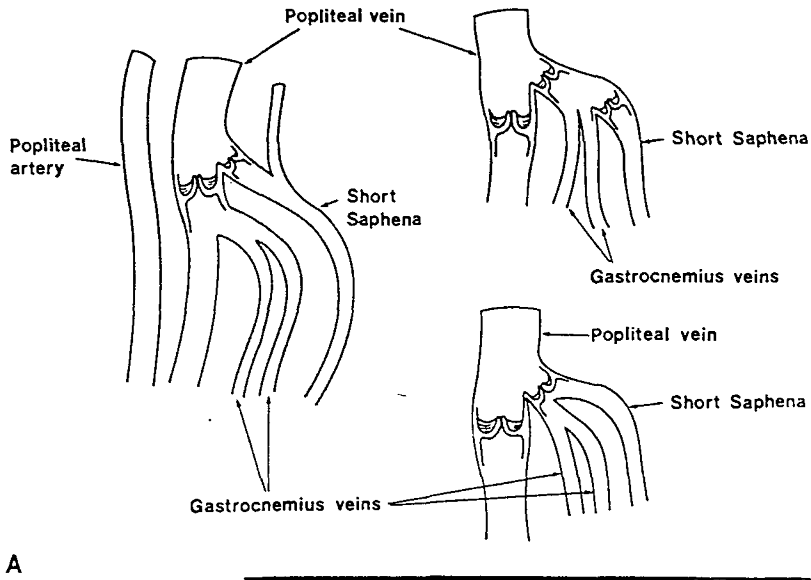


FIGURE 96.2 Example of saphenopopliteal reflux. On calf compression flow is cephalad (*blue flow*). Reflux is indicated (*red flow*) on release of the compression.



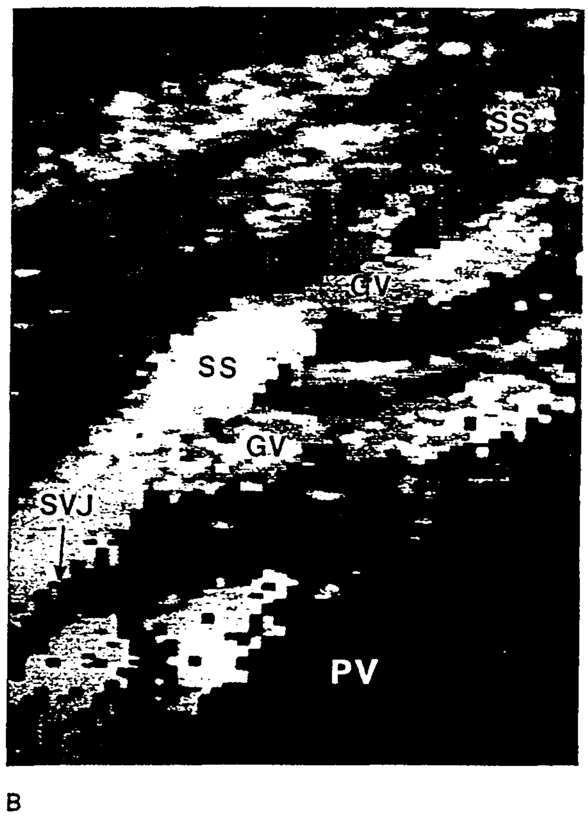


FIGURE 96.3 (A) Three different but common anatomic variations of the veins in the popliteal fossa. Duplex scanning reveals the anatomy and enables testing of each vein for reflux. The use of color duplex scanning shows simultaneously the veins in the region and the presence of reflux in them, avoiding the need of testing for reflux in individual veins. (B) At 3 seconds after a calf compression-release maneuver, the two gastrocnemius veins are shown joining the short saphenous vein, and in all three veins reflux is visible. There is no significant reflux in the underlying popliteal vein.

venous incompetence is in the deep or superficial veins. Table 96.4 shows the photoplethysmography refilling times with and without an ankle cuff to occlude superficial veins. Results are given for normal subjects, patients with superficial reflux, and patients with deep venous incompetence. Better reproducibility and better separation of groups can be obtained when the test is performed with the patient standing (42). An algorithm including photoplethysmography and light reflection rheography may be used in clinical practice (Fig. 96.7). These techniques are practical screening methods because the instruments can be easily used by staff not experienced in venous disease. As an example, in a diabetic clinic photoplethysmography or light reflection rheography could be used to evaluate whether edema—frequent in subjects with microangiopathy and neuropathy—is associated with significant venous disease. In case of a shortened refilling time the subject can be sent, according to the algorithm in Figure 96.7, for a more specialized assessment.

It should be emphasized that both photoplethysmography and light reflection rheography refilling time and 90% filling time (RT_{90}) are poor quantitative measures of severity of deep venous disease. Figure 96.8 illustrates the RT_{90} plotted against AVP. The tests have been performed with a tourniquet excluding the superficial system. It can be seen that for a wide range of AVPs from 40 to 100 mm Hg the RT_{90} is between 5 and 10 seconds. With a reduction in AVP from 100 to 60 mm Hg, the RT_{90} is between 5 and 10 seconds. With a reduction in AVP from 100 to 60 mm Hg by deep venous reconstruction (i.e., valve substitution or valvuloplasty), there would be only a little effect on RT_{90}.

Air Plethysmography

The air plethysmograph consists of a calibrated air chamber applied to encompass a leg (Fig. 96.9) and provides quantitative information about the various components of the calf muscle pump (43–45).

This information includes the rate of filling of the venous system (venous filling index [*VFI*]) as a result of standing; the venous volume (*VV*), which is the amount of blood in the venous reservoir; the ejected volume

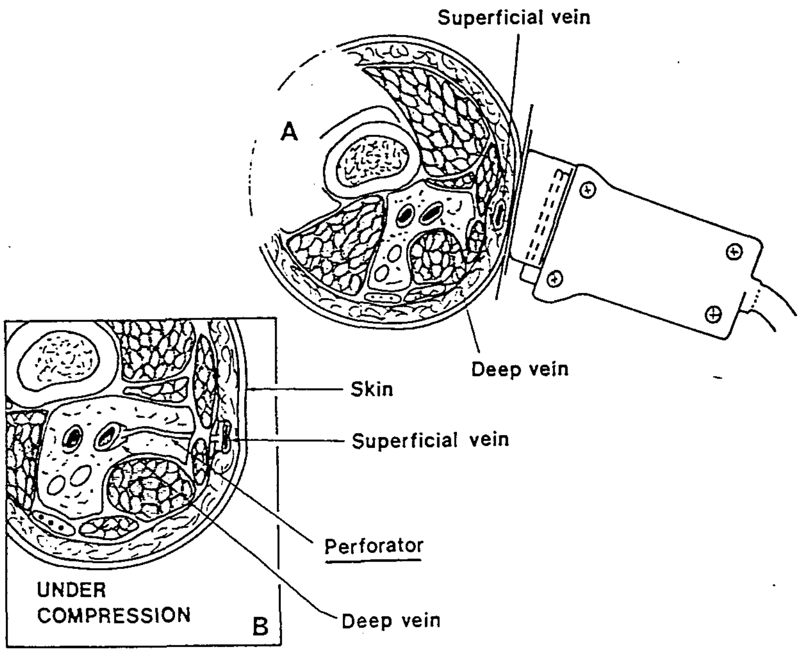


FIGURE 96.4 Transverse scan of superficial and deep veins. (A) The probe is moved up or down the limb with continuous visualization of the two veins. (B) The presence and level of a communicating vein is determined. The direction of flow with calf compression-release can then be tested.

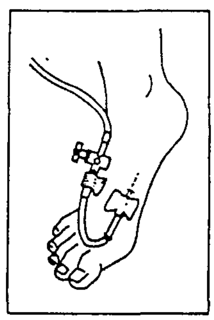


FIGURE 96.5 Recording of venous pressure during 10 tiptoe exercises without (*left*) and with (*right*) a below-knee cuff (2.5 cm wide) occluding the superficial veins. The patient has reflux in the long and short saphenous veins. Normalization of ambulatory venous pressure (P) and 90% refilling time (RT) indicates that the deep veins are competent.

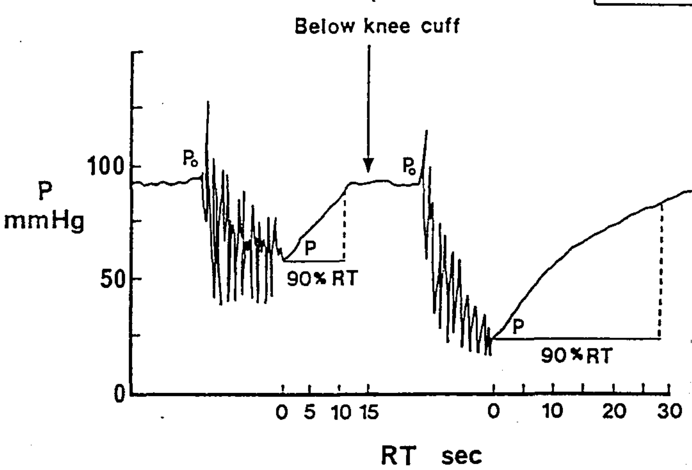


TABLE 96.2 Ambulatory venous pressure and refilling time

	AVP (mm Hg)		RT_{90} (sec)	
Type of Limb Cuff	No Ankle Cuff	Ankle Cuff	No Ankle Cuff	Ankle Cuff
Normal	15–30	15–30	18–40	18–40
Primary varicose veins with competent perforating veins	25–40	15–30	10–18	18–35
Primary varicose veins with incompetent perforating veins	40–70	25–60*	5–15	8–30
Deep venous reflux (incompetent popliteal valves)	55–85	50–80	3–15	5–15
Popliteal reflux and proximal occlusion	60–110	60–120		
Popliteal occlusion and competent popliteal valves	25–60	10–60		

The standard exercise is 10 tiptoe movements.

*In one-third of these limbs, AVP remained more than 40 mm Hg and 90% refilling time (RT_{90}) less than 15 seconds despite the application of the ankle cuff.

TABLE 96.3 Incidence of ulceration in relation to ambulatory venous pressure in 222 patients (251 limbs)

AVP (mm Hg)	n	Incidence of ulceration (%)
< 30	34	0
30–40	44	11
41–50	51	22
51–60	45	38
61–70	34	59
71–80	28	68
81–90	10	60
> 90	5	100

TABLE 96.4 Photoplethysmographic refilling time with and without an ankle cuff to occlude superficial veins

	Standing (sec)		Sitting (sec)	
No. of limbs	No Cuff	Cuff	No Cuff	Cuff
Normal 100	18–80*	18–80	26–100	26
SVI 50	5–18	18–50	2–25	18
DVI 30	3–12	6–18†	2–28	2

RT_{90}, 90% refilling time; SVI, superficial venous incompetence; DVI, deep venous incompetence.

*RT_{90} > 18 seconds without cuff identifies normal limbs.

†RT_{90} < 18 seconds with cuff identifies limbs with deep venous incompetence.

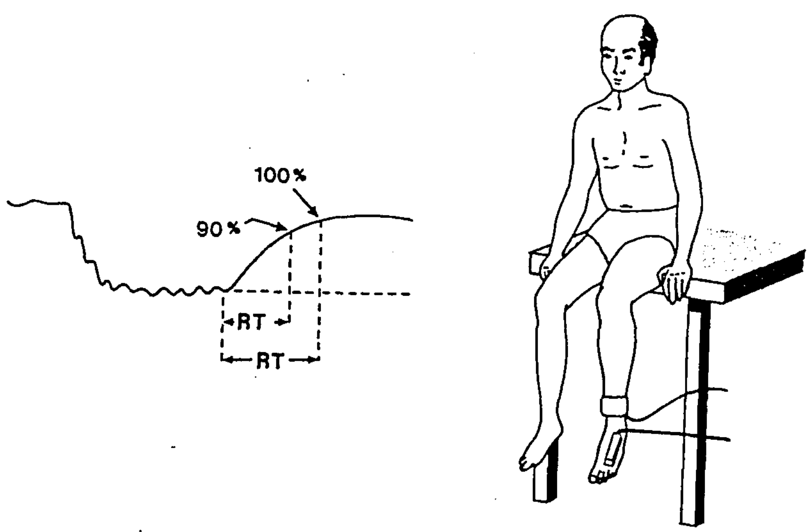


FIGURE 96.6 Measurement of the refilling time or 90% refilling time (RT or RT_{90}) after exercise using photoplethysmography.

(*EV*), and the ejection fraction ($EF = [EV/VV] \times 100$) as a result of a single step; and the residual volume (*RV*) and residual volume fraction ($RVF = [RV/VV] \times 100$) as a result of 10 tiptoe movements (Fig. 96.10). The maneuvers and methods of making these measurements from the recording are shown diagrammatically in Figure 96.10. There is a high reproducibility of measurements expressed as ratios: *VFI*, *EF*, and *RVF* (coefficient of variation less than 10%) (Table 96.5).

Venous filling index (*VFI*) is a measurement of reflux and is expressed in milliliters per second. Volume measurements are in absolute units (milliliters). The median and 90% range of the various measurements in different groups of patients are shown in Figure 96.11 and in Table 96.5. The linear correlation that exists between residual volume fraction (*RVF*) and the AVP (Fig. 96.12) means that an accurate estimate of the AVP can be obtained from the residual volume fraction noninvasively. The incidence of cutaneous ulceration increases with increase in the amount of reflux (*VFI*) and a decrease in the efficiency of the calf muscle pump ejection (*EF*) (45,46). Thus the residual volume fraction provides information on the overall effect of all the venous abnormalities. In addition, the abnormalities are dissected out and measured in terms of the ejection (*EF*) and the reflux (*VFI*) components.

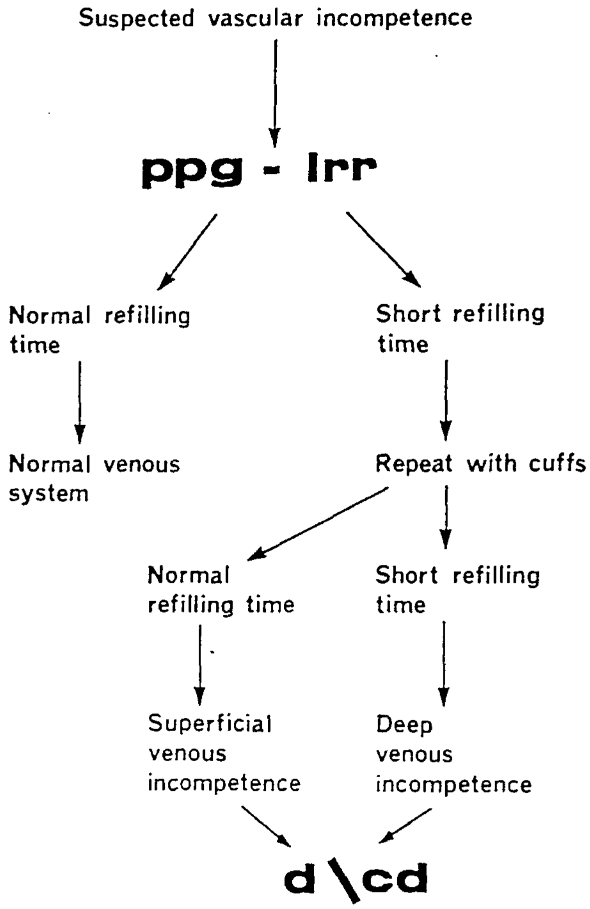


FIGURE 96.7 Diagnostic flow chart indicating the procedure followed with photoplethysmography (ppg) or light reflection rheography (lrr) for the screening of patients with suspected venous problems (d/cd = duplex or color duplex scanning).

FIGURE 96.8 Relation between photoplethysmographic filling time and ambulatory venous pressure with a cuff excluding the superficial system in the standing position (▲ = superficial incompetence only; ○ = deep venous incompetence).

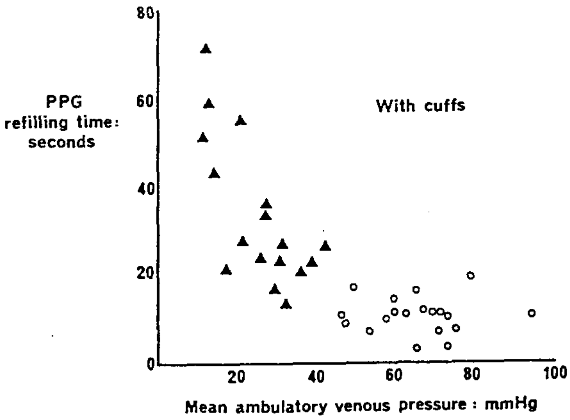


FIGURE 96.9 The air plethysmograph (APG). The 10-ml syringe included in the circuit is used for calibration.

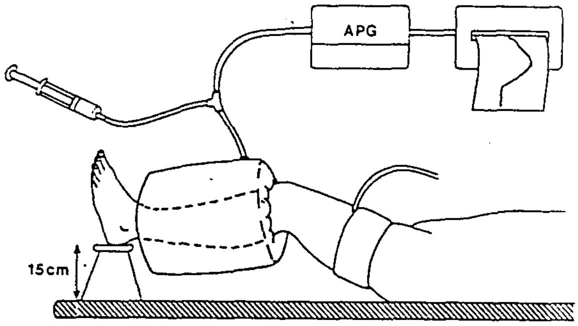


FIGURE 96.10 The maneuvers and methods of deriving the standard air plethysmography measurements.

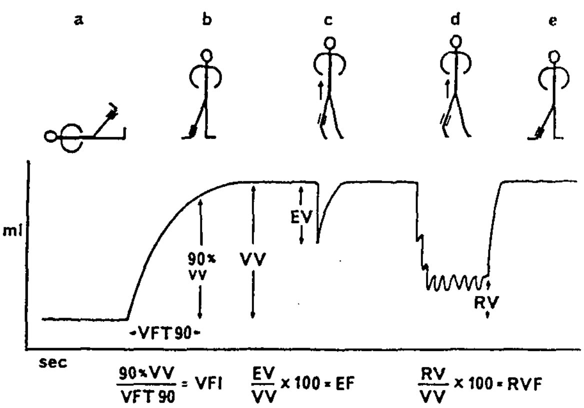


TABLE 96.5 Air plethysmography

Direct Measurements	Unit	Coefficient of Variation	Normal Limbs	Primary DVD Varicose Veins
Functional venous volume (*VV*) (increase in leg volume on standing) 70–320	ml	10.8–12.5	100–150	100–350
Venous filling time (VFT_{90}) (time taken to reach 90% of *VV*) 5–20	sec	8.0–11.5	70–170	5–70
Ejected volume (*EJ*) (decrease in leg volume as a result of one tiptoe) 8–140	ml	6.7–9.4	60–150	50–180
Residual volume (*RV*) (volume of blood left in veins after ten tiptoes) 60–200	ml	6.2–12	2–45	50–150
Derived measurements				
Venous filling index (*VFI*) (average filling rate: 90% VF/VFT_{90}) 7–30	ml/sec	5.3–8	0.5–1.7	2–25
Ejection fraction ($EF = [EV/VV] \times 100$) 20–50	%	2.9–9.5	60–90	25–70
Residual volume fraction ($RFV = [RF/VV] \times 100$) 30–100	%	4.3–8.2	2–35	25–80

DVD, deep venous disease.

FIGURE 96.11 (A) Venous filling time (VFI) in normal controls, limbs with primary varicose veins without skin changes (PVV) and with skin changes (PVV/S), and limbs with popliteal reflux (PR). The results are presented as median and 90% range without and with a 2.5-cm tourniquet (T) at the knee that occluded the superficial veins. The application of this tourniquet can differentiate between reflux in the superficial and deep veins. (B) Ejection fraction (EF) in normal controls, limbs with primary varicose veins (PVV), and deep venous disease (DVD). The results are presented as median and 90% range. (C) Residual volume fraction (RVF).

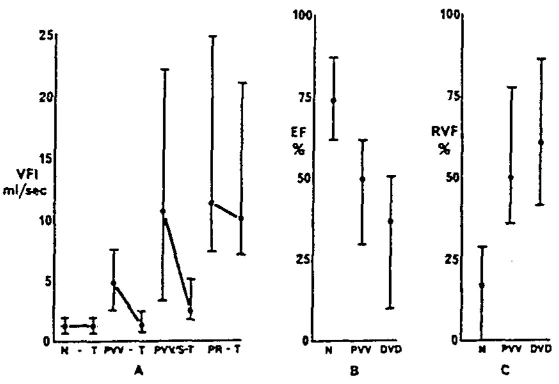
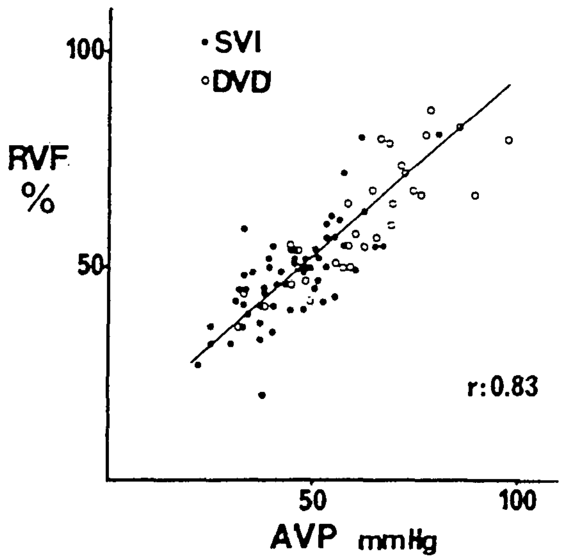


FIGURE 96.12 Correlation between ambulatory venous pressure (AVP) and residual volume fraction (RVF) (SVI, superficial venous incompetence; DVD, deep venous disease).



Tests for Outflow Obstruction

Ascending venography remains the standard method of delineating persistent venous obstruction. There are several noninvasive tests that determine the presence and quantify the degree of outflow obstruction. The simple continuous wave Doppler measurement can be used as a screening device in outpatients. A history of deep venous thrombosis or persistent leg and ankle swelling suggests the continuous need for such an examination.

Although not in general use worldwide, the best test to evaluate obstruction is the arm–foot pressure differential developed by Raju (47). Other noninvasive tests are based on the measurements of venous outflow by various techniques using different instrumentation. These methods include the strain-gauge, impedance, and air plethysmography modalities. Our opinion is that the high reproducibility and simplicity of air plethysmography has made this technique the method of choice; however, the other methods are in more general and worldwide clinical use.

Ultrasound Techniques: Continuous Wave Doppler and Duplex Scanning

The patient is examined with the legs horizontal and the knee slightly flexed. The trunk should be at 45° and the ultrasound probe is held over the femoral vein (48). Flow velocity is phasic with respiration. If this is found, it indicates a normal iliocaval segment. Absence of phasic flow or the finding of flow that is continuous and not affected by respirations suggests obstruction. If flow is diminished or abolished by compression of the contralateral groin or suprapubic area, the presence of obstruction and collateral circulation is established. Augmentation of the velocity in the common femoral vein by calf compression indicates absence of popliteal and femoral venous obstruction. This maneuver can be repeated with occlusion of the long saphenous vein at the knee by external pressure. This double-checks the patency of the popliteal vein. Augmentation of the velocity in the popliteal vein produced by digital compression of each venous compartment in the leg suggests patent axial deep calf vein flow (48,49).

Duplex scanning and color flow imaging detect with great accuracy the particular veins containing organized thrombus that are not compressible by probe pressure. Such duplex visualization of the deep veins may reveal irregular vein walls with abnormal echo and partially recanalized lumens (49–51).

Arm-Foot Pressure Differential

The arm-foot pressure differential measurement is considered to be an excellent method of quantitating outflow obstruction (47,52). This technique consists of recording the venous pressure in the veins of the foot and hand simultaneously after venous cannulation. The measurements are made with the patient supine and are repeated after inducing reactive hyperemia in the leg. In normal limbs, the arm-foot pressure differential is less than 5 mm Hg with a rise of 1 to 6 mm Hg (i.e., it may rise from 5 mm Hg, to become 6 to 11 mm Hg) during reactive hyperemia. Patients with venographic evidence of obstruction have been classified into four grades according to the criteria shown in Table 96.6.

Outflow Measurements

The degree of venous obstruction can be assessed from outflow measurements using mercury strain-gauge or air plethysmography. In both techniques, a proximal thigh cuff is inflated with the patient supine and the limb elevated 10° with external rotation and 10° knee flexion. The veins are allowed to fill for at least 2 minutes, and the cuff is suddenly deflated. Measurements are made from the outflow curves. Maximum venous outflow (Table 96.7), 1-second outflow, and 3-second outflow fractions are all valid measurements used and advocated by different authors.

The outflow fraction is expressed as $OF = V_1/VV) \times 100$.

Table 96.7 shows the range of values for limbs with normal veins, moderate obstruction, and also severe obstruction for strain-gauge plethysmography (*MVO*) and air plethysmography (*OF*). The correlation between the outflow fractions obtained using air plethysmography and arm-foot pressure differentials is good ($r > .7$).

TABLE 96.6 Arm-foot differential in limbs with outflow obstruction

Grade	Description	Pressure at Rest (mm Hg)	Pressure Increment During Hyperemia (mm Hg)
I	Fully compensated	< 5	< 6
II	Partially compensated	< 5	< 6
III	Partially decompensated	> 5	> 6 (often 10–15)
IV	Fully decompensated	>>>5	15–20
		(often no further increase)	

Outflow resistance can be calculated from the air plethysmograph and direct venous pressure outflow curves can be obtained simultaneously (Fig. 96.13). Actual flow (Q) can be calculated from the tangent at any point on the volume outflow curve. Resistance ($R = P/Q$) is calculated by dividing the corresponding pressure (P) by the flow (Q). This can be done for a series of points on the outflow curves.

By plotting the resistance against pressure, as shown in Figure 96.14, it has been shown that the relation between these is not linear. At low pressures when the veins are collapsed, the resistance is high. The resistance decreases at higher pressures when the veins, and presumably the veins of the collateral circulation, are distended. Figure 96.13 also demonstrates the relation between the resistance and the four grades of arm-foot pressure differential described by Raju (51,52).

In conclusion, it is now possible to detect the presence or absence of reflux or obstruction in venous circulation noninvasively. It is also possible to determine the anatomic site of each and obtain quantitative measurements of their severity. Despite the plethora of investigations that have emerged during the past 10 years, it is possible to obtain optimum information using simple tools such as the pocket Doppler instrument, the duplex scanner (with or without color flow imaging), and the air plethysmograph.

TABLE 96.7 Maximum venous outflow

Obstruction	Normal	Moderate	Severe
Strain gauge *MVO* (1 sec) (mL/100 ml/min)	45	45–30	30
Air plethysmography *OF* (1 sec) (% of *VV*)	38	38–30	30

MVO, maximum venous outflow; *OF*, outflow fraction; *VV*, venous volume

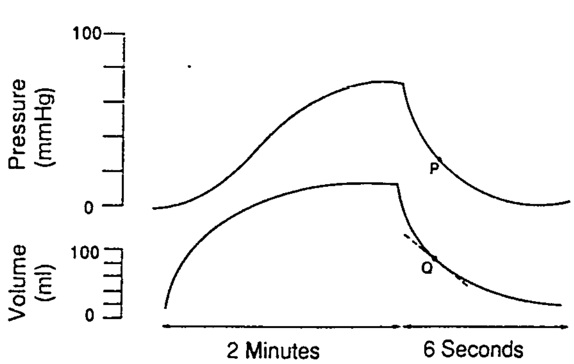


FIGURE 96.13 Pressure and volume inflow and outflow curves obtained simultaneously using an air plethysmograph and by direct venous pressure measurement by cannulation of a vein on the dorsum of the foot.

Nonoperative Treatment

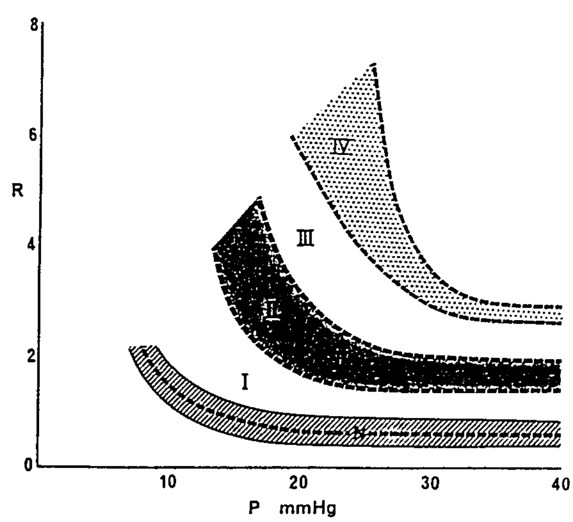
Medical management continues to be the pillar of treatment for the majority of patients with chronic DVI. Education of patients is a difficult but essential basis of care. Venous disease is chronic and insidious, causing permanent damage and invalidity over years. Many physicians fail to understand the slow, progressive evolution of DVI, and often patients do not appreciate the necessity of protracted care.

Graduated elastic support is a lifelong necessity for most patients. At the moment, graduated-compression elastic stockings appear to provide the best support. Strict adherence to the use of these stockings often prevents the consequences of chronic venous hypertension and may alleviate signs and symptoms. Knee-length stockings are usually sufficient as most of the muscular action causing venous return is in the calf and the highest venous pressure is below the knee. Stockings producing 30 to 40 mm of compression at the ankle level are generally very effective in reducing edema and other signs of venous insufficiency. Heavier stockings are advisable for patients with associated lymphedema or refractory venous edema.

Ulcerations are conservatively treated with elevation, medication, and compressive therapy, usually on an outpatient basis. Unna's boots are still used extensively.

Selective antibiotics or antibacterial solutions are indicated only in patients with documented bacterial contamination. If cellulitis intervenes, the most appropriate

FIGURE 96.14 Relation between outflow resistance curves and Raju classification of outflow obstruction (grades I to IV) (N, normal limbs).



antibiotics are used either locally or systemically after isolating the predominant bacteria causing infection.

Patients' allergies to local treatment must be noted and prevented because local allergic reactions can turn small ulcerations into larger skin defects more difficult to heal. Eczema and dermatitis are treated when appropriate with lanolin solutions, aluminum subacetate, steroid preparations, or antibiotics whenever indicated.

Extensive ulcerations with associated cellulitis may require hospitalization with elevation of the leg. Skin grafting may be a necessity for some patients. Large, recurrent ulcerations are an indication for more aggressive management.

The application of microcirculation techniques to evaluate venous hypertensive microangiopathy has made it possible to understand and evaluate the qualitative and quantitative changes in the microcirculation produced by elastic compression (53), intermittent sequential compression, and some "venoactive" drugs.

Elastic compression reduces the abnormally high skin flux observed by laser Doppler flowmetry in the perimalleolar region. The decrease in perimalleolar skin flux is proportionally correlated to the decrease in the area of ulceration observed in 4 weeks of treatment using below-knee graduated compression stockings. A decrease in skin flux with improved vasomotion is acutely observed after the application of intermittent sequential compression for 30 to 60 minutes.

Also a decrease in skin flux toward normal values, associated with a decrease in the abnormally increased capillary filtration causing edema, has been observed in patients with chronic DVI and venous microangiopathy treated with flavonoids (54) and other venoactive drugs such as centellase used in Europe.

Surgical Management

Long-term results of direct surgical correction of chronic venous insufficiency is still undergoing evolution, and evaluation and must be reserved for well-defined patients in specialized centers. A detailed analysis of treatment is outside the scope of this chapter and is discussed elsewhere in the book. A few comments, nonetheless, are useful. Classic operations, such as the Linton procedure, which interrupts incompetent perforators, may still have their place when incompetent communicating veins, documented and possibly localized by phlebography or noninvasive tests, are the major problem. Extensive dissection can be now avoided as it is possible to localize with precision incompetent perforators particularly with the use of color duplex scanning (Fig. 96.4).

The important role of incompetent perforators in aggravating DVI when performing direct deep venous reconstruction may be overlooked. With regard to distal deep venous reconstruction, different authors point out the necessity of treating incompetent perforators at the same time (5,55,56). Deep venous reconstruction, leaving incompetent perforators uncorrected, leads to unsatisfactory results.

Controversies concerning femoral valve reconstruction are still unresolved. It seems that symptomatic incompetent communicating veins should also be corrected whether or not deep venous disease is treated surgically. It is common to find significant reflux in incompetent perforators in the presence of an incompetent deep system, and the incompetence at this level definitely contributes to increasing the level of chronic venous hypertension.

At the moment, newer procedures have been and are being developed on the basis of a better understanding of venous pathophysiology and following criteria based on reconstructive, rather than destructive, surgical procedures on the deep veins.

There is controversy about the role of a single, competent valve at the superficial femoral vein level and about the importance of femoral incompetence versus popliteal incompetence. These controversies are still open as it will require years of prospective studies, in selected patients, to prove the efficacy and superiority of this one treatment in comparison with others. Also the cost of chronic medical treatment must be balanced against the cost and benefits of selective surgical procedures.

Surgery for chronic deep venous insufficiency may be divided into two categories of operative procedures: 1) operations to restore patency and 2) operations to restore venous competency.

Patency

At present three types of operations are performed to restore patency: 1) the Husni operation, 2) the Palma-Dale operation and its variants, and 3) direct reconstructions of the iliac vein and the inferior vena cava.

The Husni operation, or in situ saphenopopliteal venovenous bypass, is designed to relieve obstruction of the femoral and popliteal veins by use of the ipsilateral saphenous vein anastomosed end-to-side to the most proximal patent deep vein, usually the popliteal. Free vein grafts can be used if the ipsilateral saphenous vein is not suitable and if the other extremity is not involved (57) (Fig. 96.15).

In the Palma-Dale operation, iliac obstruction is bypassed by use of the contralateral saphenous vein (58,59). Many patients treated with a Palma-Dale operation had malignancies obstructing the iliac vein (43%), and many of the patients over 50 had obstruction by pelvic cancer (65%). It would appear from this experience that the best results occur with extrinsic compression in which the veins themselves are structurally intact.

Before surgery dynamic tests should indicate an outflow obstruction. If patency of collaterals is of a degree that distal venous pressures, even after exercise, are only mildly elevated, bypass grafting cannot be expected to be either necessary or successful. Some surgeons have used externally reinforced polytetrafluoroethylene

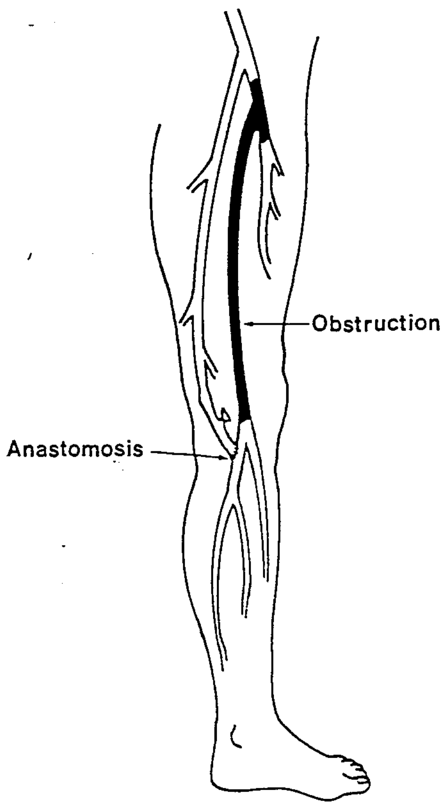


FIGURE 96.15 Saphenopopliteal anastomosis (*arrow*) to relieve superficial femoral obstruction (*arrow*).

(PTFE) as their crossover component, citing better patency rates (60). Arteriovenous fistulas are often created at the time of operation to increase flow rates through the graft in the first postoperative days. They are usually temporary and ligated or occluded after 6 to 12 weeks. Distinct from extra-anatomic or cross pubic grafting are direct reconstructions of the iliac veins and the superior and inferior vena cavae, which have been performed with spiral vein grafts and with externally supported (ringed) PTFE grafts (61–63). Results are promising, and it may be that direct reconstructions will prove superior to extra-anatomic grafts. Gloviczki and Hollier have recommended temporary arteriovenous fistulas and anticoagulation as adjuvant therapy (64,65). Dale, Harris, and Terry did not use arteriovenous fistulas in their clinical placement of grafts (63). Operations to restore patency are applicable to only a small minority of patients with chronic DVI. Schanzer and Peirce found that only 7.6% of cases of chronic venous disease are based on true venous obstruction (11).

Competency

There are different operations aimed to restore venous competency. They include valvuloplasty, both direct (5) and indirect through the use of a gracilis muscle or Silastic band (66), transplants of valve-containing segments of brachial vein to the femoral and popliteal levels (5), and vein-segment transpositions (5). Results in highly specialized centers are satisfactory (5,67,68), but patient selection is still controversial. The majority of patients probably continue to be treated best by elastic compression. The 14-year results reported by Ferris and Kistner (5) are encouraging, and surgeons continue to perform these difficult venous reconstructions in selected subjects when medical management is unsatisfactory.

The diffusion of new methods of investigation and a better understanding of venous problems and of the effects of venous reconstruction and nondestructive treatment are relatively new subjects for research. They indicate an increased and more scientific interest in venous disorders and particularly in chronic DVI.

The Future

The recognition and localization of regional or segmental reflux by duplex scanning and its exact quantification are now an obtainable objective in most patients with chronic DVI (51,52). The advent of direct operations on the venous system offers new, exciting prospects for the treatment of venous disease. As methods of diagnosis become more precise and quantitative, diagnosis itself is more precise, and the generic term of *chronic deep venous insufficiency* may be now better defined. Specific diagnoses such as superficial femoral venous incompetence or popliteal venous incompetence with associated perforator incompetence are now made noninvasively. Surgeons may expect that, with more precision in diagnostic methods, operations will be tailored for particular and individual disease states just as they are for the arterial system.

The definition and localization of incompetence may contribute to diffuse new forms of surgery limited exclusively to the affected venous segment (69,70). Limiting and localizing venous dissection before restoring competency by valvuloplasty may preserve vasa vasorum and vein wall innervation, preventing the vein segment dilatation that is often observed some time after valvuloplasty (70). New methods of clinical investigation, new applications, better definition of standards, new noninvasive tests (71), or the evolution of simple screening methods (72) will transform the assessment of chronic DVI and as a consequence its treatment.

In the coming years exciting developments will take place as chronic venous disease becomes better understood, diagnosed, localized, quantified, and selectively managed.

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The microcirculatory effects of intermittent sequential compression in chronic venous hypertension

G.V. BELCARO, M.D. A.N. NICOLAIDES, M.S.

Academic Surgical Unit, St. Mary's Hospital Medical School, London, UK, Microcirculation Lab, Chieti University and Angiology and Vascular Surgery, Pierangeli Clinic, Pescara, Italy

It has been observed that intermittent sequential compression (ISC) produces an increase in the healing rate of venous leg ulcers. We assessed the effects of ISC on the microcirculation of the skin in the medial perimalleolar region of patients with chronic venous hypertension (CVH) and skin changes (lipodermatosclerosis), and compared them to normal control.

***Methods*. Five groups of patients (total 72 patients, 78 limbs; mean age 46.2±5.0 (SEM)) with CVH and perimalleolar lipodermatosclerosis were studied. All had deep venous incompetence diagnosed with high ambulatory venous pressure (AVP >46 mmHg, mean: 63.6±1.9) and short refilling time (RT <12 seconds, mean: 6.7±0.3). Resting skin flux (RF) was measured using a laser Doppler fluxmeter (LDF), in the supine position, and then while standing (SF) for 5 minutes. The venoarteriolar response — the vasoconstrictor response on standing — was calculated as VAR=100×(RF–SF)/(RF). Previous work has shown that in patients with CVH and venous hypertensive microangiopathy RF is generally increased and the VAR may be altered. Four of the 5 patient groups were treated with ISC, which was applied for 30 to 60 minutes with the patient supine, using a sequential compression device (Kendall SCD™ 5315). LDF was recorded before ISC, immediately after and up to 2 hours after cessation of ISC. The probe was placed at the perimalleolar region. Four comparable groups of normal subjects were similarly treated, and the remaining patient group served as untreated controls.**

***Results*. In all patients, baseline RF was increased and VAR was significantly diminished in comparison with normals. In treated patients, there was a significant decrease in RF with ISC ($p<0.02$), which became evident after 10 minutes. The change in RF was still present and significant ($p<0.02$) up to 2 hours after the cessation of ISC. There was no change in RF or VAR in normal subjects or untreated patient controls.**

***Conclusions*. ISC produces a significant improvement of the microcirculation in venous hypertensive microangiopathy. These observations offer an explanation for the clinical effects of ISC on the healing of venous ulcers.**

Key words: **Chronic venous hypertension - Intermittent pneumatic compression - Laser Doppler fluxmetry - Microcirculation.**

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Limbs that suffer from chronic venous hypertension, often the result of post-thrombotic syndrome, experience marked changes in the microcirculation of the skin, particularly in the perimalleolar region. In the extreme, these changes can lead to venous stasis ulcers, whose treatment imposes significantly on the health care resources of any community, and in particular, on those with an ever-ageing population. Among the techniques that have been used to treat venous ulcers, graded elastic compression [1 2] and intermittent sequential pneumatic compression [3-7] have enjoyed moderate to great success, but the reasons for these successes are not well understood.

Laser Doppler flowmetry is a useful tool for the study of the microcirculation,[8] providing a signal that is related to the concentration and velocity of red blood cells. LDF, in general, is proportional to the perfusion (systemic) pressure, and is strongly influenced by local (auto)s' regulatory mechanisms commonly identified as vasomotion and vascular tone. In the specific region of the lower leg, such autoregulation can take the form of the venoarteriolar response (VAR), which is the reflex vasoconstriction induced by changes in posture from the supine to the standing position.[8] This physiological response reduces the number of capillaries exposed to high pressure and prevents an increase in capillary flow while standing, thereby minimizing the ankle edema that is associated with capillary leakage.

Measurements of LDF may be an indication of the relative health of the microcirculation of the lower leg. In patients with venous hypertension, for example, the resting flux (RF; measured with the patient in the supine position) is significantly

TABLE I.—*Description of patient groups.*

Group	Patients	Limbs	Ulcers	Compression time (min)	M:F	Age	AVP	Range	RT
1	11	16	8	30	5:6	43±9	66±7	54-75	6.5±1.2
2	15	18	9	60	7:8	45±8	65±9	54-72	6.6±0.8
3	8	8	4	0	5:3	44±9	63±8	55-70	6.5±0.9
4	16	16	6	30	5:7	55±9	61±11	46-78	—
5	20	20	0	30	12:8	44±6	63±5	>59	7.1±2.6

AVP = ambulatory venous pressure, mmHg; RT = refill time, sec.

raised, while the VAR is markedly lower than in normals. The wearing of graduated elastic compression stockings, which has been shown to promote the healing of venous ulcers and then help maintain an ulcer-free condition, also tends to normalize the RF and VAR, but only after the stockings have been worn consistently over a period of several weeks to months.[8] Intermittent sequential pneumatic compression (ISC) has also been shown to promote ulcer healing, but it is not known to what extent this compression treatment must be used in order for the patient's microcirculation to derive some benefit. The following studies were conducted to determine the acute effects of ISC on the microcirculatory parameters measured with the LDF, and whether such changes can persist once the compression device is discontinued.

Materials and Methods

Studies were conducted on 5 groups of patients and 4 groups of normal volunteers. All patients had legs with significant skin changes (lipodermatosclerosis) including ulceration, in some cases, as a consequence of long standing post-thrombotic venous hypertension. When perimalleolar ulcers were present, these were at most 2 cm in diameter. The patients all had popliteal vein incompetence as demonstrated by color duplex imaging, elevated ambulatory venous pressures (mean±SEM: 63.6±1.9 mmHg), measured with the use of a tourniquet at the ankle to exclude the superficial venous system, and short refilling times (6.7±0.3 sec., all less than 12 seconds). Patients with diabetes, peripheral vascular and cardiac disease, renal and other systemic pathology were excluded. All subjects were studied after giving their informed consent. Table I lists some relevant details of these subjects.

A laser Doppler fluxmeter (LDF: Vasomedics) was used to measure the subjects' resting flux (RF) and venoarteriolar response to standing (VAR). The LDF probe was attached to the skin with double adhesive tape, avoiding local compression of the skin. When an ulcer was present, the probe was positioned at least 1 cm from the ulcer's edge. Attempts were made to perform the study at a consistent time in the morning, to minimize the effects of daily changes in edema on the microcirculation. LDF measurements were recorded only while pneumatic compression was turned off, and are reported in arbitrary flux units.

RF was measured in the supine position after each subject experienced a 30 minute period of acclimatization in a room of constant temperature (21 °C). An average of 5 minutes' recording was used. To measure VAR, the subjects were asked to stand, holding on to a frame, and the standing flux (SF) was recorded for another 5 minutes. To avoid motion artifact, however, the first 1-2 minutes' recording were discarded, taking the average calculated over a stable period of 3-4 minutes. VAR was then calculated as the percentage change in flux on standing: VAR = [(RF-SF)/RF] ×100.

Intermittent sequential compression was applied using the SCD™ Model 5315 sequential compression device (Kendall). The device compresses first the ankle, then the calf and finally the thigh, by means of a pneumatic sleeve, maintaining a gradient of pressures, *e.g.* 45, 35 and 30 mmHg, respectively. Compression is developed and maintained during an interval of 11 seconds, and is followed by a 60 second period of venting to zero pressure. Compression was applied with the subjects supine for periods of 30 or 60 minutes, as indicated below. When LDF was monitored during the compression interval, the probe was mounted outside the region being compressed. After measuring the VAR, the

TABLE II.—*LDF measurements in response to intermittent compression.*

Groups	Time (min)	Patients		Normals	
		RF	VAR (%)	RF	VAR (%)
1	0	1.45±0.18	7 (2-23)	0.56±0.20	35 (28-63)
	30*	1.10±0.20	9 (3-43)	0.53±0.12	35 (23-56)
	60	0.85±0.20	23 (9-34)	0.50±0.14	37 (22-72)
	90	0.87±0.15	21 (8-30)	0.54±0.20	35 (21-65)
2	0	1.59±0.40	9 (3-21)	0.68±0.21	35 (27-60)
	60*	0.73±0.20	29 (13-36)	0.56±0.12	32 (25-60)
	120	0.92±0.18	18 (7-23)	0.58±0.14	33 (21-56)
	180	0.91±0.20	21 (12-45)	0.55±0.16	34 (26-63)
3	0	1.55±0.20	11 (7-25)	—	—
	30	1.40±0.18	9 (4-35)	—	—
	60	1.34±0.20	11 (12-30)	—	—
	90	1.39±0.18	12 (7-22)	—	—
	120	1.44±0.14	19 (12-23)	—	—
	180	1.52±0.11	9 (12-45)	—	—
4	0	1/45±0.80	7 (2-11)	0.56±0.30	35 (15-38)
	10*	1.10±0.60	—	0.59±0.30	—
	30*	0.90±0.50	—	0.67±0.30	—
	60	0.85±0.50	23 (9-29)	0.47±0.20	38 (15-36)
	90	1.10±0.60	14 (7-27)	0.44±0.29	38 (14-38)
5	0	1.66±0.30	19 (13-49)	0.67±0.20	38 (27-66)
	30*	0.91±0.20	21 (12-48)	0.63±0.20	37 (24-57)
	60	0.56±0.20	21 (13-46)	0.62±0.10	39 (22-61)
	90	0.75±0.50	23 (15-47)	0.64±0.10	38 (24-66)

* Measurements made immediately after compression was discontinued.

subjects were again asked to lie down, and LDF was recorded for up to 2 more hours.

The following groups were studied on different occasions and in different settings. Group 1 consisted of 11 patients who presented 16 limbs. Compression was carried out for 30 minutes, beginning at time = 0. LDF measurements were made at 0, 30, 60 and 90 minutes, i.e. just before and just after compression, and up to 60 minutes after compression was stopped. Group 2 included 15 patients who presented 18 limbs. Their legs were compressed for 60 minutes, and LDF measured at 0, 60, 120 and 180 minutes. Group 3 consisted of 8 patients who served as controls. They were measured at 0, 30, 60, 90, 120, and 180 minutes, but were never exposed to compression. Group 4 were 16 patients presenting 16 limbs. Their legs were compressed for 30 minutes, and LDF was mesasured at 0, 10, 30, 60 and 90 minutes. The measurements of RF and VAR after 10 minutes of compression, however, were obtained with the SCD temporarily turned off. Group 5 consisted of 20 patients, who followed a protocol similar to that of Group 1. In addition there were 4 groups of normal subjects, associated with Groups 1 (n=10), 2 (n=10), 4 (n=12) and 5 (n=20).

Results

Measurements of RF and VAR as a function of time and in response to compression are summarized in Table II and in Figures 1 and 2. The normal subjects consistently exhibited RF in the range of 0.4 to 0.7 flux units, and demonstrated substantial vasoconstriction upon standing, with an average VAR of 35%. In contrast, all patients exhibited an abnormally high RF, which was significantly greater than measured in their age matched normal controls. This is consistent with the presence of high perfusion microangiopathy that often accompanies chronic venous hypertension. The patients' VAR was also significantly different, averaging only 10% overall before compression.

The effect of intermittent sequential compression on the resting flux was almost immediate. After

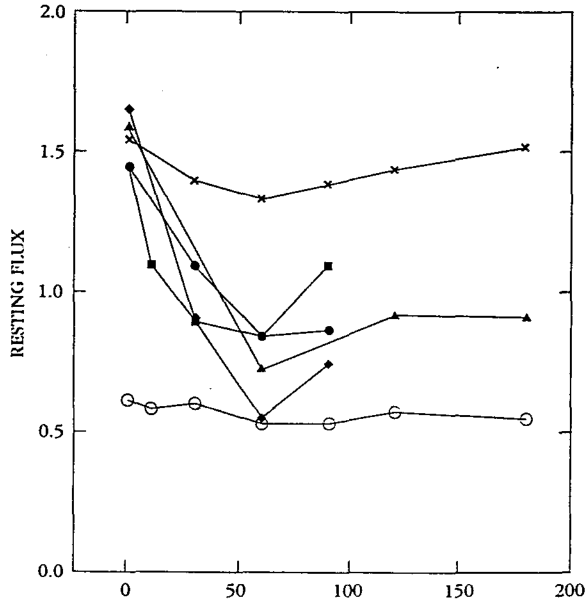

Fig. 1.—Average resting flux vs. time for the patients in Groups 1 (●), 2 (▲), 4 (■), and 5 (◆), for the average of corresponding normal (O), and for untreated controls (Group 3: ×). RF is in arbitrary flux units. Group 2 was subjected to intermittent compression for one hour, all others for 30 minutes.

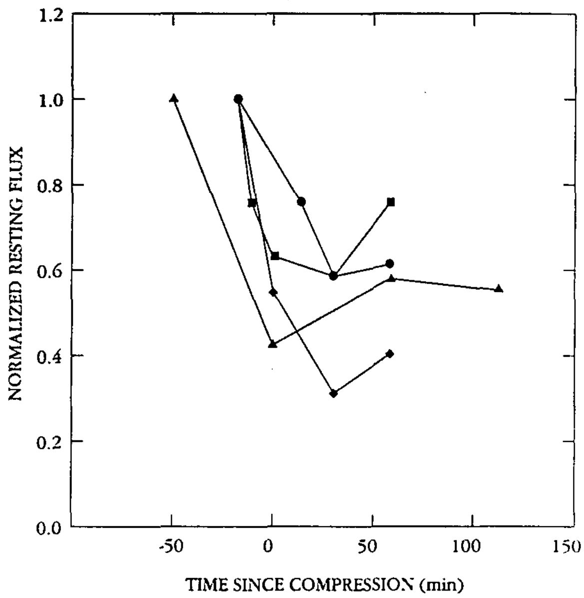

Fig. 2.—Average resting flux normalized to initial values, vs. time after compression was stopped. Symbols as in Figure 1.

only 10 minutes, RF decreased by 24% (from 1.45 to 1.10 flux units), and the decrease continued to an average of 36%±11% at 30 minutes (mean±SEM; Fig. 1) and 51%±12% at 60 minutes of compression. The effect on VAR was not as immediate, becoming evident only after 60 minutes with an increase from 9% to 29%. Nor was it as consistent, showing little change in Group 5. These responses are in contrast to the completely unchanging values obtained with normals and the control group who did not undergo compression.

RF and VAR continue to change towards normal values after compression is terminated, and the changes that occur as a result of compression seem to persist for at least 2 hours. This is best seen in Figure 2 which shows the changes in RF referenced to the time compression was stopped.

Discussion and conclusions

It is known that gratuated compression, whether in the form of elastic stockings or intermittent pneumatic compression, helps to promote the healing of venous ulcers. For example, Mayberry *et al.* [1] obtained more consistent healing faster with graduated compression stockings, while others used intermittent pneumatic compression to obtain improved healing of new [3 6 7] or previously intractable ulcers.[4 5] The combination of elastic stockings plus a limited regimen of intermittent compression is more effective than use of the stockings alone.[6]

But the mechanism by which compression works to heal ulcers is not known. Given that skin changes and ulceration ultimately depend on the condition of the microvasculature, it would seem that the benefits of compression will become evident at the level of the capillaries. We, therefore, used laser Doppler fluxmetry (LDF) to monitor acute changes in the microcirculation that occur in response to intermittent compression of the legs. LDF has the advantage of being totally noninvasive, allowing it to be used repeatedly as needed, with a small enough probe to make meaningful measurements near the edge of an ulcer.

Using LDF, we measured 2 parameters that describe the physiological state of the microcirculation, the resting flux (RF) and the venoarteriolar response to standing (VAR). The RF is known to be markedly increased, compared to normal legs, in the high perfusion microangiopathy that is associated with chronic venous hypertension. This increase may be related to the dilatation and/or proliferation of nutritional capillaries that occurs in response to local ischemia. These, in turn, provide a greatly increased exchange surface which, together with the increased hydrostatic pressure of hypertension, promotes increased fluid filtration out of the capillaries leading to edema. On the other hand, the VAR represents the tissue's ability, through arteriolar vasoconstriction, to protect the skin capillaries from being exposed to the hypertension. Both the RF and VAR, therefore, may be useful physiological markers by which to monitor the benefits of compression.

Wearing graduated compression stockings tends to normalize the values of RF and VAR, but only after 3 or 4 weeks.[8] In a study of 80 patients similar to the ones reported here, RF and LDF were measured before and after compression with below-knee stockings. After 3 weeks, the average RF was reduced by 36% and the VAR increased from 14% to 34%. This was accompanied by a 57% decrease in the average area of the patients' ulcers.

The current study demonstrates that just a brief period of intermittent compression can result in similar changes in RF and VAR, and that these changes can persist for at least an hour or two after compression is stopped. Measurements of changes in ulcer area were not a part of this study. Whether a longer period of intermittent compression would result in greater changes, or more persistent changes is not known. Nor is it known whether the equivalence of RF and VAR changes, following graduated elastic and intermittent pneumatic compression, implies an equivalence in the ability of these two modes of compression to promote healing.

The normal microvasculature experiences cyclic vasomotor activity, so that areas of vasoconstriction coexist with adjacent areas of vasodilation. Based on LDF measurements, this cyclic activity appears to be absent in many limbs that have had long exposure to venous hypertension, rendering them at greater risk of ulceration. It may be that the acute local decrease in skin blood flow (measured in the RF) that accompanies external compression stimulates the tissue's attempt to increase capillary perfusion by vasodilation, which in time stimulates a return to more normal vasomotion. This is consistent with the more rapid decrease in RF, compared to the increase in VAR, in response to intermittent compression.

In closing, RF and VAR measurements provide only a small glimpse of a very complex, multifactorial process that occurs during healing. It is too soon to determine the importance of these parameters or the physiological phenomena they represent in the pathology and healing of skin changes that accompany chronic venous hypertension. Nevertheless, healing is improved with compression, and more so with intermittent compression. Further explanation of how compression contributes to the healing of ulcers and other skin pathology must await further study.[9,10]

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Address reprint requests to: A.N. Nicolaides - Irvine Laboratory for Cardiovascular Investigation and Research, Academic Surgical Unit, St. Mary's Hospital Medical School, South Wharf Road, London W2 1NY, UK.

ADDENDUM

THESIS:

G.V. BELCARO

VENOUS HYPERTENSIVE MICROANGIOPATHY:
EVALUATION WITH LASER DOPPLER FLOWMETRY

ADDENDUM

1. SKIN BIOPSY. Technical details and reproducibility:
No reproducibility studies are available for perimalleolar skin needle biopsy. Repeating the biopsy just for reproducibility seemed unethical at the time the thesis was planned. It is definitely possible that the decision of the surgeon-researcher in locating the sampling size may influence the biopsy results. However considering simple rules such as taking the biopsy specimen:

a. at least 2 cm from the edge or border of an ulcerated area or scarring tissue;

b. on an ideal median line between the anterior and posterior lines of the limb;

c. always proximally to the medial malleolus;

the results of the biopsy may show consistent results both in normal limbs and in limb with perimalleolar venous hypertension.
The techniques of skin biopsy are indicated in the thesis at 2.17 (pg 114) and in 6.2 (pg 148). Punch biopsy was only used in the preliminary pre-thesis experiment published by *Laurora G, Pizzicannella G, Cesarone MR, Fisher C, Belcaro G, Nicolaides AN (Skin flux and histology in venous hypertension. Angiology 1993;27:110-114)* and in a following paper by *Belcaro G, Laurora G, Cesarone MR, De Sanctis MT, Incandela L. (Microcirculation in High perfusion microangiopathy. J Cardiovasc Surg 1995;36:393-8)*.
The following comparable and consistent histology findings are obtained with punch or blade biopsy in venous hypertension:
a: elongation and glomerular-like aspect of capillaries (in 100% of the specimens); **b:** venular dilatation and elongation (in 100% of the specimens); **c:** thickening of the capillary walls (in 100% of the specimens).
The punch biopsy (using a Terumo kidney biopsy needle) is possibly simpler and less traumatic but the blade technique used in the thesis is definitely more informative as the edge-shaped slice is more prone to larger histology sections and less sensitive to the pressure artifacts observed in a skin cylinder.
All thesis specimens were taken with two small, curved, 3-mm edge-shaped skin incisions (depth 4 mm, distance between the two skin incision = 2 mm)) to obtain a skin edge which was immediately fixed in formalin and sent to pathology for histology. A new, disposable Swann-Morton stich cutter blade (cutting edge lenght = 2 mm) was used for each biopsy.

2. REPRODUCIBILITY OF LASER DOPPLER MEASUREMENTS
The reproducibility of all laser Doppler (LDF) techniques (particularly of resting flux and standing or dependency flux), described in 1.5 pg 68, and 1.414 pg 82 has been previously tested and published and therefore it was not extensively indicated in the methods section of the present thesis. Reproducibility was reported in *Belcaro G, Laurora G, Cesarone MR, De Sanctis MT, Incandela L. Microcirculation in high perfusion microangiopathy. J Cardiovasc Surg 1995;36:393-8)* and in *Laurora G, Pizzicannella G, Cesarone MR, Fisher C, Belcaro G, Nicolaides AN. Skin flux and histology in venous hypertension. Angiology 1993;27:110-114*. Results of reproducibility tests in

these papers were as follows:

Resting skin flux	14%	In normal limbs
Standing or dependency flux	12.5%	In normal limbs
Resting skin flux	12%	In postphlebitic limbs
Standing or dependency flux	16%	In postphlebitic limbs

The average coefficient of variation (COF) in VAR (venoarteriolar reflex) was 13.2% in normal limbs and 14% in postphlebitic limbs. In a study concerning diabetic microangiopathy *(Belcaro G, Laurora G, Cesarone MR, Pomante P. Elastic stockings in diabetic microangiopathy. Long term clinical and mircrocirculatory evaluation. Vasa 1992;21:193-97)* the reproducibility of the measurement of resting flux and dependency flux were respectively 13% and 8% (tested in 20 patients, 10 times in each limb, in comparable conditions) with the resulting VAR variating on average of 11.5%. In another study *(Belcaro G, Cesarone MR, Incandela L, Belcaro G. Skin flux and the venoarteriolar response in the perimalleolar area in patients with venous hypertension. Panminerva Med 1992;34:115-9)* LDF measurements were repeated 10 times in 25 normal limbs. The COF for resting flux and standing flux was found to be respectively 13% and 14% (the corresponding VAR had an average COF of 13.5%). Other studies indicate that a lower COF in resting flux and in standing or dependency flux may be obtained placing the probe on the pulp of the toe and on the dorsum of the foot *(Henriksen 1977; Rayman, Hassan and Tooke, 1986 and Rayman, Williams SA, Spencer PD, Smaje LH, Tooke JE, 1986)*.
However in a more recent study *(Gniadecka M, Gniadecki R, Serup J, Söndergaard J. Impairment of the postural venoarteriolar reflex in aged individuals. Acta Dermat Venereol 1994;74:194-96)* measurements of VAR were taken at perimalleolar region malleolus. The COF in this stuy was in the range of 10-12% for resting, dependency flux and VAR.

3. REPRODUCIBILITY OF WEAL DISAPPEARANCE TIME

Using the vacuum suction chamber device (1.54, pg 90) to evaluate capillary filtration the reproducibility study concerning the weal disappearance time has been previously reported *(Belcaro G, Rulo A, Renton s. Capillary filtration in venous hypertension). Comparison between the vaccum suction chanber (VSC) device and straingauge plethysmography. Panminerva Med 1992;34:151-4* In this study the following COFs were observed:

Superficial venous incompetence	(50 patients)	COF 10.2%
Deep venous incompetence	(50 patients)	COF 12%
Normal individuals	(50 subjects)	COF 8%

The percent variation in time (in minutes) relative to the weal disappearance time were based on serial photographs taken with a 45% light angle incidence. The use of sequential photographs as planned in the thesis may show a better accuracy than subjective visualisation. Hovever this experimental method aimed to assess **local** capillary filtration needs to be made simpler and more reproducible to become more objective and more validation studies are still needed.