Pathogenesis of Chronic Venous Insufficiency and Possible Effects of Compression and Pentoxifylline

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It has been recognized for over 2000 years that ulceration of the leg may be associated with visible varices of the lower limb. More recent physiological investigation has shown that the pressure in the veins of the lower limb remains raised in patients with venous ulceration during ambulation, whereas in normal subjects the pressure in superficial veins falls to a low level. This elevated pressure appears to cause damage to the superficial capillaries in the skin culminating in the production of venous ulceration. Events in the dermal capillaries which result in skin destruction have yet to be fully defined. Pericapillary fibrin cuffs have been demonstrated histologically and suggested as a cause of diminished nutrition to the skin. White blood cells have been shown to accumulate in the lower limb of patients with venous disease and these accumulations are particularly located around the dermal capillaries. Activated white blood cells releasing free radicals and destructive enzymes may precipitate skin destruction. An understanding of these mechanisms may help to explain the efficacy of compression hosiery and bandaging as well as some of the new pharmacological agents which have been shown to influence venous ulcer healing.

INTRODUCTION

It has been known for more than 2000 years that there is an association between ulcers of the lower limb and superficial varicosities. This association was observed by Hippocrates (450 BC) who recommended bandaging to aid healing. During the 20th Century a number of physiologists have investigated the venous circulation in the lower limb. Measurements of pressure in the superficial veins in the lower limb have been made in patients with chronic venous insufficiency compared with normal subjects. Under normal circumstances the foot vein pressure in both patients and subjects with normal lower limbs is the same, and depends upon the hydrostatic column of blood extending from the foot to the right atrium. However, on ambulation, subjects with normal lower limbs are able to reduce the pressure in superficial veins to low levels (less than 20mm Hg) whereas patients with chronic venous insufficiency show only modest falls in venous pressure [2,3]. It is widely accepted that “ambulatory venous hypertension” is the factor that results in venous ulceration.

Less well established are the reasons why this elevated pressure results in injury to the microcirculation of the skin and in turn how this then causes skin destruction. Theories have abounded throughout the ages, however, during recent years more likely explanations have emerged. One suggestion has been that a perivascular fibrin layer surrounding capillaries in the skin results in failure of oxygenation of the skin.
[4]. More recently it has been proposed that accumulation of white blood cells may result in capillary damage and that the collected white cells might release free radicals and inflammatory mediators which are actively responsible for tissue injury [5]. The aim of this article is to review the evidence supporting these hypotheses and hence consider how both compression modalities and pharmacotherapy might influence the lower limbs of patients with chronic venous insufficiency. A number of drugs have been identified which are beneficial in promoting healing. The mechanisms by which these work may indicate some of the factors involved in the pathogenesis of venous ulceration.

THE MICROCIRCULATION IN CHRONIC VENOUS INSUFFICIENCY

Mechanisms of Ulceration

Fibrin cuffs: In 1982 Browse and Burnand proposed that oxygen diffusion into the tissues of the skin was restricted by a pericapillary fibrin cuff that they had observed histologically [4]. They suggested that increased capillary pressure as a consequence of the raised venous pressure results in an increased loss of plasma proteins through the capillary wall. This includes fibrinogen which polymerizes to provide the "fibrin cuff" that may be seen around capillaries in the skin, using both histochemical and immunohistochemical methods. Measurements of protein loss from capillaries showed that fibrinogen was quantitatively the most important plasma protein leaking into the tissues in patients with venous disease. Subsequent measurements of fibrinolysis have shown that patients with venous disease have reduced fibrinolytic activity in the blood and veins which might explain why the fibrin cuff persists [6].

In this theory of ulceration, the role of the fibrin cuff in restricting the supply of oxygen to the tissues is central. There is no published evidence to prove that fibrin provides a barrier to oxygen diffusion. It seems probable from the composition of other human connective tissues that such a fibrin gel would contain much water with a small amount of fibrin. Diffusion of small molecules through such a cuff might be expected to be very similar to water and other human tissues. Michel has undertaken a theoretical study to assess the physiological effect of a fibrin layer enveloping the capillaries in the skin [7]. If the assumption is made that the fibrin layer contains 0.5 percent fibrin, similar to that of a fibrin blood clot, calculations reveal no impairment of oxygen delivery to the tissues. Even a cuff consisting of 100 times more fibrin that this would result in a reduction of oxygen delivery of only 50 percent. The results of these calculations have not been confirmed by measurement. Browse and Burnand employed a piece of commercial bovine fibrin from a suture manufacturer in order to assess the permeability of fibrin. They found that this material significantly impeded the passage of oxygen. However, it is unlikely that fibrin cuffs seen in man are of the same composition.

The disagreements between theory and practice might be resolved by direct measurement of tissue oxygenation in patients with venous disease. No such study has been reported in the literature, and this may reflect the technical difficulties involved. This sort of study would necessitate inserting a microelectrode into the skin, a potentially difficult exercise requiring skill and patience as well as accurate measuring equipment, but not outside the capabilities of current technology. There is a much larger literature in which transcutaneous oxygen measurements have been made [8,9]. In these studies a Clark-type electrode equipped with an integral heater
is applied to the skin. These devices were originally devised for neonatal monitoring, in which skin heating was used so that the resulting vasodilation would ensure that the measurement accurately reflected the arterial oxygen tension. In venous disease, different findings have been obtained depending on whether the transducer is heated to 43°C or 37°C. At the higher temperatures, used by most authors, it has been found that patients with venous disease tend to have lower tcPO₂ readings than normal subjects [8,9]. Measurements made with an electrode temperature of 37 C are even more paradoxical [10]. Under these circumstances, the oxygenation of the skin is greater in patients with venous disease than in normal subjects. This technique has a number of limitations and transcutaneous oxygen tensions may be influenced by many factors other than skin oxygenation.

Some authors have tried to assess gas exchange in the skin microcirculation by alternative methods. Hopkins used positron emission tomography techniques to assess blood flow and oxygen extraction in the skin and subcutaneous tissues of patients with venous disease [11]. He was able to show that there was a reduced oxygen extraction ratio in such tissues, but that skin flow was increased by a substantial amount, so it is unclear whether oxygen delivery was increased or decreased from these measurements. The diffusion of gases between the circulation and the tissues has been the subject of study in my own laboratory and the results of such experiments have been published previously [12,13]. The clearance of xenon from the skin has been measured to assess the efficiency of the microcirculation in handling a molecule of similar size to oxygen [12]. ¹³³Xenon gas which was used has a molecular weight four times that of oxygen, and would be expected to diffuse at half the speed of oxygen were there no other restriction to its progress, assuming similar water solubility for oxygen and xenon. The technique of Sjerson [14] was used in which the xenon gas is applied topically to the skin, avoiding the necessity for injections which might alter blood flow in the skin.

Measurements were made in liposclerotic skin of patients with venous disease, and compared to control subjects. No difference in xenon clearance was found between patients with venous disease and control subjects. Subsequently, the time taken for reoxygenation of the skin was measured after a period of ischemia produced by inflating a cuff on the leg above systolic arterial pressure. No difference was found between control and venous disease groups [13]. These results lead to the conclusion that it is unlikely there is an abnormality in the delivery of oxygen to the tissues in patients with chronic venous insufficiency.

A new theory: The search for additional or alternative mechanisms of skin damage in venous disease has resulted in investigation of the blood itself. Moyses studied the limbs of normal subjects in response to raised venous pressure and measured hematological parameters as an index of the effect of the venous hypertension [15]. His subjects sat on a bicycle saddle with the limbs dependent for a period of 40 min without moving. Blood samples were taken from the long saphenous vein at the ankle. He found that the hematocrit and red cell count increased in parallel as would be expected. He noticed that the white cell count remained unchanged, despite the increased hematocrit. White cells were being ‘lost’ from the circulation, which after 40 min accounted for a 25 percent change. Thomas performed a similar study in which he compared patients with normal lower limbs to those of patients with venous disease resulting in lipodermatosclerosis and ulceration [16]. His patients were permitted to sit with their legs dependent, a less stringent requirement than that of
Moyses. Blood sampling was again from the long saphenous vein at the ankle. After 60 min patients with venous disease were 'trapping' 30 percent of the white cells and normal subjects were trapping 7 percent. This lead me to examine the microcirculation using capillary microscopy. I found that venous hypertension appeared to reduce the number of visible capillary loops in patients with venous disease, but not in control subjects [17], suggesting that capillary damage may be occurring during venous hypertension.

Bollinger has investigated the events in venous disease using fluorescence video capillary microscopy [18]. He measured the rate of diffusion of fluorescein out of capillaries after an intravenous injection. He was able to show that capillaries in venous disease are much more permeable than normal to this molecule, contrary to the suggestions made in the fibrin cuff hypothesis. Using simultaneous fluorescence and light capillary microscopy Franzek has described the appearances of capillary loops which are filled with red blood cells, but do not appear to be perfused [19]. He suggests that this may be due to capillary 'thrombosis'.

White cell margination is a normal event in the arterioles, capillaries and venules. This phenomenon is thought to be important in the mechanism that results in tissue injury following ischemia. White blood cells are substantially larger than red cells and are responsible for many of the rheological properties of blood. White cells take 1000 times longer than red cells to deform on entering a capillary bed, and are responsible for about half the peripheral vascular resistance despite their small numbers in the circulation compared with red cells [20]. In myocardial infarction it has been shown that they cause capillary occlusion, which can be prevented in experimental animals by first rendering the animal leucopenic [21,22]. White blood cells have been implicated as the mediators of ischemia in many tissues including myocardium, brain, lung and kidneys [23,24,25,26]. Polymorphonuclear leucocytes, particularly those attached to capillary endothelium, may become activated in which cytoplasmic granules containing proteolytic enzymes are released [27]. In addition, a non-mitochondrial respiratory burst permits these cells to release free radicals, most notably, the superoxide radical, which have non-specific destructive effects on lipid membranes, proteins and many connective tissue compounds [28]. The chemotactic leukotrienes are also released, thereby attracting more polymorphonuclear cells.

We published a hypothesis suggesting that white cell trapping triggered such processes, causing degradation of tissues [5] (Fig. 1). Following the literature on critical ischemia in the myocardium, we proposed that white cells might cause occlusion of capillaries, a suggestion originally made by Moyses [15]. If some of the capillaries were occluded, heterogenous perfusion might occur and cause tissue hypoxia and ischemia. From the data presented above it can be seen that we have not been able to support the assertion that venous ulceration is due to tissue hypoxia.

The second part of the theory suggested that white cell activation was part of the process, resulting in release of proteolytic enzymes, superoxide radicals and chemotactic substances. All classes of white cells appear to become trapped so a wide range of phenomena is possible.

Monocytes might become activated releasing the cytokines interleukin 1 (IL-1) and tumour necrosis factor alpha (TNFα) [29]. These molecules may achieve many effects including endothelial cell activation in which these metabolically active cells permit the passage of much larger molecules than would normally be the case [30]. The decreased fibrinolysis in patients with venous disease may be a result of the
'White cell trapping' hypothesis

Reduced blood flow on standing

Reduced shear rate in microcirculation favours white cell margination

Capillary plugging and heterogeneity of perfusion result in hypoxia

White cell activation
Release of free radicals, proteolytic enzymes, cytokines and chemotactic substances

Tissue damage

FIG. 1. 'White cell trapping' hypothesis derived from reference 5. As may be seen from the text, capillary plugging phenomenon, if present, does not appear to result in the development of severe tissue hypoxia.

effects of IL-1. IL-1 acts on endothelial cells to stimulate production of the fibrinolytic inhibitor, plasminogen activator inhibitor–1 (PAI–1), and decreases the production of tissue plasminogen activator (tPA) producing a reduction in fibrinolysis that is observed in patients with chronic venous insufficiency [31]. Infiltration of the skin with inflammatory cells is described in dermatology textbooks where venous disease is discussed. Here they have been regarded as part of the inflammatory process rather than an instigator of damage. In order to investigate this hypothesis we took biopsies of the skin of the supra-malleolar region of patients undergoing varicose vein surgery, and performed quantitative histological examination of these samples; the results of this study have previously been published [32]. Three distinct groups of patients were studied. The first were patients with no evidence of skin changes as a consequence of their venous disease. The next group exhibited
lipodermatosclerosis, but there had never been ulceration of the limb. Finally, there
was a group of patients who had ulceration, but were left with lipodermatosclerosis
after healing of the ulcer. Patients with normal skin had a low number of white blood
cells visible (4 per mm²) in the upper 0.5 mm of the skin. There were eight times as
many white cells in patients with liposclerotic skin and 40 times as many white cells in
patients with healed venous ulcers. We have subsequently undertaken an immunohistol-
tological study to determine the types of white cell present in this infiltrate [33]. The
majority of cells are macrophages with a T-lymphocyte component, but no excess of
neutrophils compared with control sections taken from normal limbs. This infiltrate
is a reflection of a chronic inflammatory process, and suggests that an investigation of
the cell products of these leucocytes might indicate the mechanisms involved in
venous ulceration. We have also been able to identify IL-1 as an inflammatory
mediator in this process.

It has not yet been established whether or not the white blood cells we have
observed infiltrating the skin are the cause of subsequent ulceration. Tissue destruc-
tion may occur when an inflammatory response is produced in the skin, to be
followed later by an additional stimulus that activates the cells present in the tissues.
This produces rapid necrosis of the skin, and is known as the Schwarzmann reaction
[34]. In the skin of patients with venous disease conditions are set which might permit
such a reaction to progress. The inflammatory infiltrate is already present requiring
some minor trigger to precipitate tissue destruction. This situation might explain why
patients with lipodermatosclerosis are at high risk of ulceration in response to minor
trauma to the leg.

Compression Stockings and Bandages

The use of compression in the management of venous ulcers of the lower limb
dates back at least to the time of Hippocrates (450 BC) [1] who recommended
bandaging to aid healing. In the seventeenth century Richard Wiseman, Sergeant
Surgeon to Charles II, was sufficiently convinced of the efficacy of compression that
he designed a leather gaiter which could be laced tightly around the ankle [35]. More
modern data suggest that greater compression will achieve greater healing rates with
patients suffering venous ulceration [36]. It has also been shown that intermittent
compression may be helpful in aiding healing [37]. Despite the length of time for
which compression has been used it remains unclear why this is effective. Some
papers have confirmed that compression stockings improve venous function, but this
has not been found by everyone. In addition there remains the controversy about
which is the more effective—elastic or non-elastic compression. Until the question of
how compression achieves and maintains healing can be resolved, the best form of
compression cannot be designed.

A large number of investigations have attempted to determine whether compres-
sion stockings influence calf pump function or modify the competence of large veins.
These may be divided into those affecting parameters at rest (static tests) and those
used to assess the pumping efficiency of the calf muscle pump (dynamic tests).

Static Tests

Sigel has demonstrated that femoral vein velocity is increased with the application
of an appropriate pressure profile by assessing the femoral vein velocity using
Doppler ultrasound [38]. He demonstrated that a large increase in velocity would be
achieved by compressing the limb with a gradient compression profile. Other authors have investigated the speed of clearance of radioisotope markers and radiological contrast media from calf veins in recumbent patients [39,40,41]. It has been shown that compression stockings improve the rate of clearance of such markers and this may partially explain the efficacy of graduated compression stockings in preventing deep vein thrombosis in patients undergoing surgical procedures.

It is thought that damage to the skin occurs in limbs when patients with chronic venous insufficiency are standing. Assessments of foot vein pressure in standing patients show no difference from that of normal subjects, and the standing venous pressure is not influenced by the application of stockings [42,43,44].

Dynamic Assessments of Efficacy

There is now general agreement that venous ulceration results from a failure of exercise to lower the venous pressure in the veins of the lower limb. This failure may be due to disease of the deep veins, the superficial veins or the communicating veins [45]. Some controversy remains about the mechanisms of failure of the calf muscle pump, but the resulting pressure abnormalities are easy to observe and measure. During ambulation the dorsal foot vein pressure falls to low values in subjects with normal veins [2]. The resting level of 80–100 mm Hg, falls to 0–20 mm Hg. The pressure then returns to the resting level when the subject stands still. This recovery usually takes in excess of twenty seconds. Patients with venous insufficiency may fail to reduce the foot vein pressure to a low value, or may show a rapid return of venous pressure to resting levels at the end of exercise, or usually, a combination of both factors [3]. While foot vein pressures are not necessarily the same as those in the ankle region where ulcers commonly occur, it is generally accepted that they reflect pressure abnormalities in the supramalleolar region [46].

One of the more satisfactory predictors of ulceration in patients with chronic venous insufficiency is ambulatory foot vein pressure. This pressure is raised in patients with significant venous incompetence and it might be hoped that compression stockings would tend to restore this index to normal. Some authors have found that this is the case [42,47] while others have failed to find any effect [43,44]. The time required for the foot vein pressure to return to resting levels after the end of exercise is an indicator of the degree of reflux in a limb. This reflux may be assessed using foot vein pressure measurements or plethysmographic methods. Whether measured by air plethysmography, strain gauge plethysmography, foot volumetry or foot vein pressures, rather variable results have been obtained with some authors reporting an effect and others no effect [43,48,49]. Air plethysmography may permit a more detailed analysis of the calf muscle pump [47], but this method has not demonstrated reduced venous refilling times after the application of stockings.

Does external compression make the incompetent veins competent? In order to address this question we designed an external compression cuff which could be placed around the leg at the level of the knee and inflated with water (Fig. 2). The results of this study have been published previously, but are included here for completeness [50]. The experimental design permitted examination of the veins of the leg using duplex ultrasound imaging during limb compression. A series of patients was found in whom there was reflux in the long saphenous, short saphenous or popliteal veins at this level. The cuff was inflated with water until the veins became competent or the vessel was occluded by the compression. Calf vein competence was
FIG. 2. Means of applying external compression to the lower limbs while permitting duplex ultrasound imaging assessment of competence of the valves. A transducer attached directly to the cuff allows measurement of the actual cuff pressure.

tested by manual calf compression, with the direction of blood flow determined during relaxation. Reflux lasting more than 0.5 sec was judged to be significant. The results are shown in Table 1. In a small number of veins competence was restored by external compression, but a greater number were occluded before reflux was abolished. The pressures required to accomplish these effects were considerably above those likely to be achieved by even the strongest compression stockings. We conclude that the means by which stockings achieve their efficacy is not by restoring competence of the deep or superficial veins.
TABLE 1
Pressures Required to Achieve Competence or Occlude Veins by External Compression; the Majority of Veins were Occluded by External Compression before Competence was Restored

| Vein                  | Reflux Restored by External Compression Pressure mm Hg (IQR) | Vein Occluded before Competence Restored Pressure mm Hg (IQR) |
|-----------------------|-------------------------------------------------------------|-------------------------------------------------------------|
| Popliteal vein        | 62 (58–74)                                                  | 88 (72–110)                                                |
|                       | n = 4 (of 14)                                               | n = 10 (of 14)                                             |
| Long saphenous vein   | 32 (16–75)                                                  | 86 (68–106)                                               |
|                       | n = 8 (of 20)                                               | n = 12 (of 20)                                             |
| Short saphenous vein  | 56 (52–70)                                                  | 67 (60–94)                                                |
|                       | n = 3 (of 15)                                               | n = 12 (of 15)                                             |

IQR = inter quartile range.

Intermittent Pneumatic Compression

In an ulcer healing study we randomly allocated patients to standard therapy with or without intermittent pneumatic compression [37]. Standard therapy included regular wound cleaning and management combined with a non-adherent dressing and a stocking exerting 30 mm Hg at the ankle. Patients received regular instructions which included advice to elevate the limbs whenever possible. The patients randomized to receive intermittent pneumatic compression were treated using a Sequential Compression Device (SCD, Kendall Healthcare Products Company, Mansfield, MA, USA). This modality had not been investigated previously in an objective study of ulcer healing. Patients used this device at home for a period of four hours per day for a total of three months. The healing rate in the group treated in this way was ten times that of the control group.

The means of efficacy of this modality of treatment is also difficult to establish. There is no doubt that the SCD will reduce edema and enhance blood flow, however these may not be the effects that result in healing. Some data suggest that intermittent pneumatic compression will enhance fibrinolysis, and this effect may also play a role in improved healing [51,52]. We think that it probably is not the effects of intermittent pneumatic compression on the large veins that result in healing.

Since neither graduated compression nor intermittent pneumatic compression appear to rely exclusively on effects on large veins, perhaps it is appropriate to explore the microcirculation as the location of action of these modalities.

How does compression influence the microcirculation? This question has not been addressed in any detail but a few pieces of information have been published which indicate some of the mechanisms which may be at work. Liposclerotic skin in patients with chronic venous insufficiency shows a reduced hyperemic response to heating compared with healthy leg skin [53] and it has been reported that there is a reduced 'venoarterial' reflex in patients with venous disease. This is the postural vasoconstriction which normally protects the patient from venous hypertension on standing. As described above, there is also reduced transcutaneous oxygen tension in patients with venous disease. Do any of these characteristics alter with compression therapy? This has been investigated by Leu [54]. He treated patients with sclerotherapy and stockings for six months but could find no evidence of a change in any of these parameters. It is probable that they reflect long term venous hypertensive injury which is not rapidly reversed by appropriate treatment.
Thomas demonstrated white cell trapping in the lower limb, as described above, in response to raised venous pressure. He subsequently repeated his study using graduated compression stockings of a type suitable for management of chronic venous insufficiency. He assessed the red cell and white cell content of blood in the long saphenous vein at the ankle and found that the stockings were able to prevent the trapping phenomenon seen earlier (PRS Thomas, personal communication).

It has been observed in our laboratory as well as by others that the laser Doppler fluxmeter signal increases with compression of the skin under investigation (Fig. 3 and the author’s unpublished observations). This increase may be a consequence of the method of measurement or may point to an explanation of the efficacy of stockings. At low compression, up to 20–30 mm Hg with the patient lying and 50–60 mm Hg with the patient sitting, the laser Doppler flowmeter shows an increase in flux, however this declines at higher compression and eventually falls to a low level at pressures of over 100 mm Hg as the microcirculation becomes occluded. The increased flow velocity may in some way protect the microcirculation from the effects of raised venous pressure. The increased flow may result in greater shear forces within the capillaries and venules where white cells usually marginate and prevent adhesion to the endothelium. This series of events would provide possible explanation for the observations of Thomas, described above.

**Pharmacotherapy in Chronic Venous Ulceration**

Although bandaging has been used effectively for many years, modern pharmacological science may provide assistance in healing venous ulcers. The recent theories of pathogenesis of venous ulceration make such attempts more likely. Enhancing fibrinolysis has been attempted to promote removal of the fibrin cuff [55]. This particular treatment did not result in any improvement in ulcer healing. While the precise role of the white cell in chronic venous insufficiency remains unclear, their many complex interactions may be influenced by a wide variety of pharmacological agents. One drug that reduces white cell activation, pentoxifylline (Trental, Hoechst), has already been evaluated in this respect. Pentoxifylline down-regulates polymorpho-
nuclear neutrophils resulting in much lower likelihood of adhesion and activation [56]. In a multi-center study in which 82 patients were entered, pentoxifylline has been shown to result in much better healing rates of ulcers than placebo [57]. It has been recommended that this drug may be useful for the treatment of resistant ulcers [58].

A large number of other pharmacological manipulations is possible. Prostaglandin \( E_2 \) inhibits the respiratory burst of neutrophils, preventing the release of superoxide radicals. A preliminary study has suggested that this, too, is effective in healing venous ulcers [59]. Other treatments await evaluation and we think that adjuvant pharmacological treatments will become commonplace within the next decade for the management of this disease.

**CONCLUSIONS**

It is unlikely that we will understand how compression therapy works in chronic venous insufficiency until the mechanisms which result in venous ulceration are established. It seems doubtful that the influence on flow in major veins achieved by stockings and bandages is the sole explanation. It is more likely that compression influences the microcirculation in a way that prevents the inflammatory processes that are part of the mechanisms of skin destruction. Clearly some of these processes can be manipulated by pharmacological means, but it is certain that stockings and bandages will continue to be useful for many years to come.

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