Review

The microcirculation in venous hypertension

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Abstract

Objective: To review the factors that result in skin ulceration of patients with chronic venous insufficiency. Data sources: Index Medicus was searched using an on-line computer system for years 1966–1995 to identify articles relating to venous ulceration and the microcirculation. Data extraction: Articles and sections of articles relating to the mechanisms which cause venous ulceration and the efficacy of the treatment of venous ulceration have been included. Data synthesis: It seems unlikely that venous ulceration is attributable to failure of diffusion of oxygen and other small nutritional molecules to the tissues of the skin. It is much more likely that neutrophils attach themselves to the cutaneous microcirculation, become activated and produce endothelial injury. Repeated over many months or years, this leads to the chronic inflammatory process of lipodermatosclerosis. The microvascular changes in the skin are characterised by activated endothelium and perivascular inflammatory cells. Conclusion: There is evidence of leucocyte involvement in the pathogenesis of venous ulceration. The exact mechanisms remain to be resolved. Improved treatment for patients may be devised with a better understanding of the basic causes of this condition.

Keywords. Ulceration, Varicose, vein, Hypertension, venous, Microcirculation, Neutrophils

1. Introduction

Venous diseases cost the healthcare systems of western countries large sums every year. These become more prevalent with advancing age and as the average age of populations increases more patients will require treatment. The most expensive problem is venous ulceration, a chronic relapsing condition estimated to have a prevalence of 0.2% in western countries [1]. This may be an underestimate since many patients treat their own ulcers. In the UK venous ulcers are treated in the community by General Practitioners and Community Nurses. Between 10 and 30% of nursing time may be occupied with dressing leg ulcers [2]. The cost of this is massive, amounting to £2000–£4000 per year for each of the 150,000–200,000 patients with leg ulcers. In the UK it is estimated that £600–£800 millions (US$ 1 billion) is spent on this condition per annum, about 2% of the healthcare budget.

2. Large vessel physiology

Ambulatory venous hypertension is a constant pathological feature in venous disease. This arises due to damage of the venous valves in the lower limb either from a previous deep vein thrombosis or by primary valve failure [3], a poorly understood process in which venous valves fail to maintain their competence without previous venous thrombosis. In either instance, blood is permitted to flow in the reverse direction, and the pumping efficiency if the musculo-venous pumps of the lower limb is impaired. Pressure in the superficial veins of the leg does not fall during exercise and this is the source of damage to the skin microcirculation.

The clinical syndrome that is produced by long-standing ambulatory venous hypertension includes haemosiderin deposition in the skin resulting in brown pigmentation near the ankle. Palpable induration and scarring of the skin—usually referred to as ‘lipodermatosclerosis’—may also...
develop and is probably a more severe stage of tissue injury, affecting both the skin and subcutaneous tissues. This often progresses to venous ulceration with skin loss in the region proximal to the medial or lateral malleolus. Nicolaides et al. have shown that the higher the venous pressure during walking, the higher the incidence of ulceration [4]. Patients with haemosiderosis, lipodermatosclerosis or ulceration of the leg due to venous disease are said to have ‘chronic venous insufficiency’ (CVI).

3. The microcirculation

Browse and Burnand proposed a theory suggesting that pericapillary fibrin cuffs act as a barrier to diffusion of oxygen and other small molecules. They demonstrated the presence of fibrin cuffs histologically surrounding skin capillaries in the cutaneous lesions produced by ambulatory venous hypertension. This hypothesis saw the explanation as a simple gas transfer problem, although few data were available at that time to support this proposal [5].

A number of authors have subsequently assessed transcutaneous oxygen tension, as an indicator of oxygen delivery to skin [6–8]. In this test a polarographic electrode covered with a gas-permeable membrane (a Clark electrode) is applied to the skin and heated to 43°C. This causes vasodilatation in the skin and increases the amount of oxygen reaching the skin surface. These measurements show reduced transcutaneous oxygen tension in the skin of patients with venous disease who have liposclerotic skin change. However, the vasodilatory response of skin damaged by venous disease is reduced compared with normal skin and the reduced oxygen tension measurements at the skin surface may merely represent an attenuated hyperaemic response to heating [9].

Objective assessments of gas transfer using either xenon clearance [10] or oxygen return time following a period of ischaemia [11] show no evidence of a gas transfer problem. Calculations based on a theoretical model of gas diffusion undertaken by Michel suggest that the composition of the fibrin cuff (99% water) would be unlikely to impair the diffusion of small molecules [12]. He also deduced that oedema of the tissues, often seen in patients with venous disease, would not influence tissue oxygenation, a conclusion that has received experimental support [13]. Subsequently direct needle electrode measurements have been made in liposclerotic skin, and these show a moderate reduction in tissue oxygenation, but insufficient to result in skin necrosis [14].

4. Active model of venous ulceration

In 1987 Moyses [15] noted that leucocyte sequestration occurred in the lower limb of normal subjects when experimental venous hypertension was produced over a 40-minute period. His volunteers sat without moving on a bicycle saddle and blood samples were taken from the long saphenous vein at the ankle. This raises the venous pressure in the superficial veins of the lower limb to 80–100 mmHg. Thomas et al. [16] repeated this experiment, comparing patients CVI to control subjects with normal lower limb veins. In this study the patients sat on a hospital bed with the legs dependent, resulting in venous pressures of about 60 mmHg. He observed a difference in white cell trapping between the two groups. Patients trapped 30% of white cells after 60 minutes of sitting, whilst control subjects trapped only 7% (Fig. 1). After return to the lying position efflux of white cells from the limb was also observed.

Subsequently Vanscheidt investigated the extent of leucocyte sequestration in patients with venous disease when the upper limb was subjected to venous hypertension produced by an arm cuff inflated to a pressure between diastolic and systolic blood pressure [17]. He showed more white cell trapping in the upper limb by patients with venous disease compared to controls (venous disease 18%, control 13%).

At the same time I had conducted some capillary microscopy studies which suggested that venous hypertension reduced the number of visible capillaries in the skin of patients with venous disease. These synthesis of these data was a hypothesis that suggested that the ‘trapped’ white cells were responsible for endothelial injury, which cumulated to produce microcirculatory damage in patients with long-standing ambulatory venous hypertension [18]. This suggestion included the mechanisms known to be responsible for critical ischaemia. I suggested that venous hypertension and the fall in blood flow which occurs in the lower limb on standing favours adhesion of leucocytes to the microcirculatory endothelium.

Capillary microscopy of lower limb skin capillaries during venous hypertension shows that they dilate and that there is a considerable reduction in flow velocity. These factors reduce the shear rate in the microcirculation. A reduction in shear rate favours neutrophil adhesion [19] which probably occurs in the post-capillary venule. The leucocyte adhesion detected by Moyses in control subjects is probably a physiological phenomenon that does not
normally persist for any length of time. Venous pressure in the lower limb falls rapidly on walking, so that venous hypertension is not normally present in the leg. In patients with CVI who have ambulatory venous hypertension, leucocyte trapping may be more persistent. It was proposed that the trapped leucocytes become activated, releasing free radicals and proteolytic enzymes, resulting in endothelial injury (Fig. 2). Over a long period this might lead to cumulative damage in the microcirculation.

I have subsequently studied the effect of venous hypertension using a series of markers of leucocyte activation. Control subjects exposed to lower limb venous hypertension produced by standing were studied by taking blood samples from the hand and the leg veins. Degranulation of neutrophils was studied by measuring plasma levels of neutrophil elastase (a primary neutrophil granule enzyme) and lactoferrin (a secondary neutrophil granule enzyme). After a 30-minute period of experimental venous hypertension, a rise in plasma lactoferrin concentration was observed in both the blood taken from the foot and from the arm [20]. When venous hypertension was produced by inflation of a cuff around one lower limb, a rise in lactoferrin was observed only in that limb. Subsequently neutrophil CD11b expression has been investigated as a marker of neutrophil activation. The experiment was repeated as before on control subjects. Blood was taken from a dorsal foot vein. CD11b expression was assessed by fluorescent-labelled monoclonal antibody used to label neutrophils in whole blood which were counted using flow cytometry. During the period of ambulatory venous hypertension in control subjects no rise in CD11b expression was seen in the lower limb blood [21]. Following return to the supine position, when neutrophils might be expected to leave the lower limb, according to the studies of Thomas [16], increased levels of CD11b were observed (Fig. 3). This indicates that neutrophils were upregulated by their period of adhesion to normal endothelium. An increased white cell/red cell ratio was also observed during this phase, confirming white cell egress from the lower limb.

Measurements have also been made in patients with venous disease. Both plasma lactoferrin and elastase have been assessed in groups of patients with active venous disease. Blood was taken from the arm veins of patients (not the lower limb veins) of patients with varicose veins, liposclerotic skin change and active venous ulceration [22,23]. In all samples, the levels of lactoferrin and elastase were higher in the patients than the age- and sex-matched control groups (Fig. 4). However, it was found that the highest levels of plasma lactoferrin were present in patients with active varicose veins. Subsequently blood was taken from the arms of patients for measurement of neutrophil CD11b expression. This was elevated in patients with varicose veins, but depressed in patients with lipodermatosclerosis [24]. The explanation may be that the more active leucocytes are attracted to the region of the inflammatory process and do not circulate in the peripheral blood. Alternatively, such patients may have high circulating levels of neutrophil inhibitors.

The microcirculation of the skin has been investigated by histology [25] and by capillary microscopy [26]. Both methods demonstrate capillary proliferation in patients with CVI—vastly more capillaries are visible by both techniques. However, capillary microscopy shows that these probably arise from a single capillary loop and appear like a glomerulus, rather than an increase in the numbers of

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**Fig. 2.** White cell trapping hypothesis, indicating the mechanisms that were originally proposed.

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**Fig. 3.** Neutrophil CD11b expression measured by flow cytometry in volunteers before and 10 minutes after a period of ambulatory venous hypertension produced by standing. Increased CD11b expression is noted on return to the supine position during the period of neutrophil efflux. Error bars show the median and inter-quartile range of data. Statistical significance was tested by the Mann-Whitney U-test.
capillaries. Recent immunohistochemical investigations have shown that the pericapillary cuff contains far more than fibrin. The capillary endothelium is perturbed, expressing increased amounts of factor-VIII-related antigen [27,28] and adhesion molecules, especially ICAM-1. ELAM-1 may be slightly upregulated, but VCAM appears to be normal in patients without venous ulceration. Perturbed endothelium is more likely to attract the adhesion of leucocytes. The presence of the pericapillary fibrin cuff has been confirmed, but it also contains collagen IV, laminin, fibronectin and tenascin [29]. A strong leucocyte infiltration has been measured in patients with venous disease [30]. These cells are macrophages and T-lymphocytes [27]. The cytokines involved include IL-1α and IL-1β. TNFα has not been detected in these histological sections. The presence of the perivascular ‘fibrin cuff’ (with other components) is a reflection of the inflammatory process and is seen in other chronic inflammatory conditions. In patients with venous disease, increased plasma D-dimer levels have been observed, suggesting enhanced deposition of fibrin [31]. The perturbed state of the endothelium allows the passage of large molecules through the endothelium, permitting their perivascular accumulation, and explains the presence of the ‘fibrin cuff’.

Many aspects of venous disease are incompletely understood. The progress from the chronic inflammatory state to ulceration is difficult to investigate and there is no animal model. A possible answer is that an initiating stimulus causes massive activation of the peri-vascular macrophages, resulting in extensive tissue and blood vessel destruction. This may be a spontaneous event such as thrombosis of one of the capillary loops, which has been observed using capillary microscopy [32]. Alternatively, minor trauma to the region may set in motion the series of events which leads to ulcer formation.

5. Treatment of venous disease

Hippocrates favoured the use of bandages some 2500 years ago [33]. Richard Wiseman, a 17th century physician, designed a leather garment to apply compression to the leg in patients with leg ulcers [34]. Compression remains the single most effective modality in the manage-

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Fig. 4. (a,b) Results of plasma neutrophil elastase measurements in patients and control subjects. (c,d) Results of plasma neutrophil lactoferrin measurements in patients and control subjects. Error bars show the median and inter-quartile range of data. Statistical significance was tested by the Mann-Whitney U-test.
ment of venous disease of the lower limb [35,36]. Interestingly, its mechanism of action is poorly understood. There is controversy in the literature as to whether it improves the physiology of large vein function or not. Some have found improvements and some have not [37–40]. Recently Abu-Own et al. have studied the effect of compression on the skin using laser Doppler fluxmetry [41]. With patients lying supine, low levels of compression (up to 20 mmHg) accelerate the flow velocity in superficial vessels. When the patient stands, compression of up to 60 mmHg causes accelerated flow. Above these levels perfusion of the skin declines, as capillaries become occluded. Presumably the effect of compression is to reduce the vessel lumen diameter. This results in the blood moving more quickly through the microcirculation. Laser Doppler fluxmetry does not provide data that would allow calculation of the shear rate in the post-capillary venules, but this is probably greatly increased by compression and would tend to favour white cell detachment from the endothelium and prevent adhesion. Compression probably exerts an important component of its effect directly on the cutaneous microcirculation.

6. Pharmacological treatment

Many pharmacological treatments are used in the management of patients with chronic venous disease. Anticoagulant drugs are ineffective in the management of chronic venous problems, except those associated with recurrent episodes of thrombosis, and will not be considered further.

6.1. ‘Oedema-protective’ drugs

A number of drugs based on plant extracts including aescin (horse chestnut extract), hydroxy-rutoside, diosmin, and hesperadine are widely used to reduce oedema. Synthetic ‘oedema-protective’ drugs include calcium dobesilate and tribenoside. All of these appear to reduce oedema associated with venous disease as well as the patients’ symptoms. There is a number of double-blind placebo-controlled clinical trials which demonstrate symptomatic improvement. Until recently no efficacy in venous ulcer healing or ulcer recurrence prevention had been shown. Only one of this group of drugs, hydroxyrutosides, is registered for use in the UK.

6.2. Hydroxyrutosides

Hydroxyrutosides are a class of flavanoid drug derived from plant glycosides. They initially gained favour 20 years ago when experimental studies indicated that they reduced capillary permeability following burns in dogs. A number of clinical studies evaluating their effect on symptoms associated with CVI followed [42,43]. In general these indicated that hydroxyrutosides appeared to be marginally more effective than placebo in reducing aching, tiredness, muscle cramps and other symptoms which are difficult to evaluate objectively. Hydroxyrutosides are more effective than placebo in reducing oedema [44], although the clinical relevance of this is uncertain. The use of hydroxyrutosides in venous disease appears to have significant symptomatic value [45–47]. A study on the effect of rutosides on symptoms in 112 patients with venous insufficiency included four with ulceration. All four took rutosides for 8 weeks; only one showed any evidence of improvement [48]. Other studies have shown no evidence that hydroxyrutosides improve venous ulcer healing or prevent its recurrence [49].

6.3. Diosmin

Diosmin is commercially available as a mixture with hesperidin (Daflon, Servier, France). It is active orally and several studies indicate its efficacy on oedema and the symptoms of venous disease, in a similar way to hydroxyrutosides. The mode of efficacy of this drug is incompletely understood. A recent paper has shown that it modifies the interaction of leucocytes with endothelium in a hamster skinfold model used to investigate the effect of Daflon on the microcirculation following ischaemia-reperfusion. The group of animals pre-treated with Daflon exhibited less neutrophil adhesion in the post-capillary venules at 30 minutes, 2 hours and 24 hours after reperfusion, compared to the control group [50]. The mechanism by which this is achieved has not been defined. The effect of Daflon in a venous ulcer healing study has been recently reported [51]. In 91 patients with an ulcer diameter of 10 cm or less, 14 of 44 patients receiving Daflon compared to 6 of 47 receiving placebo healed their ulcers ($P = 0.028$, chi square) after 8 weeks treatment. This is the only member of the ‘oedema-protective’ drug group which has been shown to modify ulcer healing. However, the study was small and studied patients over a short period (8 weeks), so the results should be interpreted with caution.

6.4. Fibrinolytic therapy

The concept of an oxygen diffusion barrier causing skin hypoxia proposed by Browse and Burnand [5] has influenced attempts at treatment of chronic venous insufficiency by pharmaceutical means. They demonstrated that fibrinolytic activity was reduced in patients with venous disease [52–54]. These observations led to attempts to reverse the damaging cutaneous effects of ambulatory venous hypertension by enhancing fibrinolysis. The effect of stanozolol, an anabolic steroid with pro-fibrinolytic properties, has been evaluated in a small number of studies. No effect on venous ulcer healing has been demonstrated [55]. Its effect on lipodermatosclerosis has been investigated in a study of moderate size. In a placebo-con-
trolled double-blind study 60 patients with lipodermatosclerosis were randomised to receive compression hosiery and stanozolol or placebo for 6 months [56]. Stanozolol combined with stockings caused a reduction of liposclerotic skin area of 28% over 6 months. However, when the separate contributions of compression and stockings were calculated using multivariate analysis, the effect attributable to stanozolol alone was not statistically significant. Adverse effects of this anabolic steroid were encountered during this study.

In summary, fibrinolytic enhancement may be of minor benefit in the symptomatic treatment of CVI, but it does not appear to improve ulcer healing.

6.5. Drugs directed towards leucocyte metabolism

The effect of an analogue of PGF \(_2\alpha\) has been investigated in a study in 44 patients with venous ulcers. Patients were randomised to receive either the active compound or placebo by daily intravenous infusion over a period for 6 weeks [57]. Improved venous ulcer scores were observed in patients treated with the active compound at the end of the study period. The duration of the investigation was too short to be able to assess the influence of PGF \(_2\alpha\) on the rate of ulcer healing. Unfortunately, this method of treatment requires the use of an intravenous infusion, and is rather impractical in its present form.

Two other studies have investigated the use of pentoxifylline (Trental, Hoechst, Germany) in the management of patients with venous ulceration [58,59]. Both have shown a beneficial effect on the rate of ulcer healing, but in the second where much more effective compression was applied, the influence of Trental did not reach statistical significance. Clearly this is a treatment with a definite efficacy, but of small magnitude. Its exact role in the management of patients with venous ulceration remains unclear.

7. Conclusions

Many of the pathophysiology of venous disease remain to be clarified, particularly the initial phases of microcirculatory injury which ultimately result in leg ulceration. Leucocyte activation occurs after short periods of venous hypertension, even in control subjects, and may be one of the factors that cause endothelial damage to cutaneous capillaries if it continues over many months or years. This might eventually be the target of pharmacological treatment. A number of drugs are currently used to treat CVI, but few have been shown to improve venous ulcer healing and none has been shown to prevent its recurrence. Compression stockings and bandages continue to be invaluable in the management of venous disease.

References


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