Review Article

Leg ulceration in venous disease

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Summary: We have given a brief summary of the scale of the problem caused by venous ulceration in the UK, and have then reviewed the various theories of causation, including a historical survey, and presented the evidence for and against the two main current theories of fibrin cuffs and white cell trapping. We also outline previous hypotheses of the aetiology of venous ulceration, including arteriovenous microanastomoses, stasis and oedema. The contribution of superficial venous incompetence in the pathogenesis of ulceration is also examined.

Introduction

Ulceration of the leg is a major cause of morbidity, venous causes accounting for the majority. Other causes include arterial disease, diabetes, and vasculitis resulting from connective tissue diseases such as rheumatoid disease or scleroderma. Less common causes include hypertension (Martorell's ulcer), trauma, lymphoedema, tropical ulcers, ulceration associated with steroid treatment, and blood diseases such as sickle cell anaemia, thalassaemia, haemolytic anaemia and hereditary spherocytosis.

The prevalence of venous ulceration in western countries is estimated at 0.1–0.3%.^{1–4} It has also been estimated that for every patient with an ulcer there are 20–30 patients with the characteristic skin changes of lipodermatosclerosis (LDS) which precede ulceration.⁵ This suggests that 100,000 patients have active ulceration at a given time in the United Kingdom, which causes an enormous drain on the Health Service in both in-patient and outpatient treatment. The cost to the National Health Service for the treatment of leg ulceration has been estimated at being at least £100,000,000 per annum⁶ and to cost £1,200 for each unhealed ulcer per year.⁷

The cause of skin ulceration in venous disease is not known and a number of hypotheses regarding its pathogenesis have been suggested. This paper provides a critical review of these hypotheses.

History

Although varicose veins were probably recognized in prehistory, the first written reference appears to be the Ebers papyrus, dated 1550 BC. However, Hippocrates was the first to note the association between varicose veins and ulceration.⁸ During Roman times, a number of physicians, including Galen, Celsus, Aetius of Amida and Paulus Aegineta advised avulsion and cauterization for the treatment of varicose veins, and the use of bandages for the treatment of leg ulcers.⁹ Following this, from the 10th to the 18th century, various physicians, including Haly Abbas, Avicenna, Fallopio and Paré attributed ulceration of the legs to the accumulation of black bile, bad humours, menstrual blood and faeculant humours.¹⁰ They believed that ulceration in the legs served a useful purpose in getting rid of these vile substances. Thus, they did not encourage healing of ulcers, and some went as far as advocating re-opening ulcers that had healed spontaneously, as they believed that ill-health and madness would ensue if this was not done. Richard Wiseman¹¹ was aware that varicose veins were associated with leg ulcers in the 17th century but, during the 18th century, various authors including Bell, Baynton and Whately did not believe that leg ulceration was attributable to or associated with varicose veins. During this time, plaster and bandages were used in the treatment of ulcers.¹² In the 19th century, writers including Brodie, Astley Cooper, Home and Hodgson stressed the importance of varicose veins in the aetiology of leg ulceration, and the term 'varicose ulcer' was coined.⁹

In 1868, two important books on venous ulcers were written by Gay¹³ and Spender.¹⁴ These authors stressed the role of deep venous thrombosis and other lesions of the arterial and venous system (both deep and superficial) in the aetiology of leg ulceration, and advocated that the term 'varicose ulcer' be dropped. Gay also described ankle-perforating veins and suggested the use of the term 'venous ulceration'. Homans¹⁵ found that deep vein thrombosis was frequently the cause of such damage. In more recent years, Linton¹⁶ and Cockett¹⁷ have drawn attention to incompetence of the communicating veins of the calf as a potential cause of venous ulceration.

The role of superficial, deep and perforator incompetence

There has never been any doubt of the role of deep venous incompetence in the aetiology of venous ulceration. However, there has never been agreement on the ability of superficial venous incompetence alone to result in ulceration. Homans' finding¹⁵ that deep vein thrombosis was frequently the cause of venous ulceration seemed to have eclipsed the earlier observations of Hippocrates and Wiseman to such an extent that, even today, several authorities believe that ulceration is not possible in superficial vein incompetence alone. This view has recently been reflected in leading articles in two of our most eminent medical journals, ruling out the possibility that superficial venous incompetence alone may be responsible for skin ulceration.^{18,19} Sethia and Darke, however, reported an incidence of 28.3% superficial venous incompetence alone in a study on patients with venous ulcers in which venous function was assessed by venography and foot vein pressure measurement.²⁰ An earlier study using Doppler ultrasound, ambulatory foot vein pressure measurement and photoplethysmography had indicated an incidence of 25%,²¹ and another more recent Doppler-based study indicated that 43% of 117 ulcerated limbs had superficial venous incompetence; about one fifth had some deep venous reflux demonstrable as well.⁴

Therefore, it would appear that venous ulceration is possible in the presence of superficial incompetence alone, and there is uncontrolled data²² which show a lower rate of recurrent ulceration in those patients with venous ulcers associated with superficial venous disease only when treated surgically than in those with deep venous disease. Healing rates of 90% have been recorded (mean follow-up of 3.5 years) following sapheno-femoral junction ligation in patients with long saphenous incompetence alone.²³

The importance of communicating vein incom-

petence remains controversial. Since the work of Linton in the 1930s and 1940s,¹⁶ their role in the development of venous ulceration has been unclear, though many authors have ascribed a pivotal position to them in ulcer pathogenesis.²⁴ Others, by contrast, have found disappointing results following their ligation, with very high rates of ulcer recurrence where venography had clearly shown the perforating veins to be incompetent.²⁵ Part of the problem lies in uncertainty of the definition of incompetence in these veins. There is doubt about which direction of flow should be considered 'normal'; it may be bidirectional.²⁶ In a detailed study using ambulatory venous pressure measurement, Zukowski *et al.* have suggested that poor venous function associated with 'incompetent' calf perforators is likely to be due to undetected deep vein pathology.²⁷

Stasis

Homans was probably the first to advance the concept of venous stasis as an aetiological factor in venous ulceration. He suggested that stagnant blood in varicosities was responsible for ulceration as a result of impaired tissue nutrition.¹⁵ This concept was reinforced by the work of De Takats,²⁸ who showed decreased levels of oxygen in the veins of patients with leg ulceration. However, many studies, starting with Blalock,²⁹ have shown the opposite, and demonstrated that the oxygen content of venous blood in patients with chronic venous insufficiency and ulceration is, in fact, higher than normal.³⁰⁻³² Despite this evidence, anoxia and hyponutrition caused by stasis is still discussed in relatively modern works, and the terms 'stasis ulcers' and 'gravitational ulcer' are still used, especially in the American literature.³³⁻³⁵ Recent studies using laser Doppler fluxmetry have shown increased blood flow in the lipodermatosclerotic skin of patients with chronic venous insufficiency,³⁶⁻³⁹ as has positron emission tomography,³⁷ although this also showed marked heterogeneity in tissue perfusion. This evidence should be sufficient to dispel any notion that microcirculatory stasis exists in patients with chronic venous insufficiency.

Arteriovenous shunts

The increased blood flow in the skin of patients with venous insufficiency and the finding that venous blood in the legs of patients with varicose ulcers had a higher oxygen tension than venous blood in normal legs^{29,31,40} led to the hypothesis that venous ulceration was due to hypoxia of the skin as a result of blood being shunted away from the nutritional capillaries by arteriovenous com-

munications.^{30,41,42} Guis was able to identify such shunts in 13 patients undergoing varicose vein surgery.⁴³ This work has not been confirmed by others, although Ryan⁴⁴ has claimed that small arteriovenous communications at capillary level play a significant role in the development of skin changes with chronic venous insufficiency.

Other workers have been unable to show increased shunting in patients with chronic venous insufficiency using a variety of methods including venous occlusion plethysmography,⁴⁵ macroaggregates⁴⁶ and microspheres.⁴⁷ However, reports of increased partial pressure of oxygen in blood taken from leg veins of patients with varicose veins compared to normal controls continue to emerge.^{32,48} Rapid venous filling at arteriography has also been described in patients with varicose veins, though arteriovenous anastomoses were not visualized.⁴⁹ Overall, this hypothesis for the cause of venous ulcers has been disproved, even though it is difficult to deny that shunting occurs. These communications exist but are not of haemodynamic significance.

Role of oedema

Patients with chronic venous insufficiency and venous ulceration suffer from oedema of the lower limb, especially if compression therapy is not used.^{9,12,50} This may interfere with normal transfer of nutrients to the tissues,⁵¹ and cause tissue ischaemia by separation and collapse of the capillaries due to the high interstitial pressure.⁵² Further indirect evidence supporting the importance of oedema in leg ulceration is the observation that healing of ulceration occurs more rapidly if oedema of the leg is satisfactorily controlled.⁵³

Oedema in chronic venous insufficiency may result from several factors – increased capillary filtration as a result of high intracapillary pressure due to increased venous pressure, increased hydraulic conductivity due to endothelial damage, loss of the veno-arteriolar (anti-oedema) reflex, or failure to clear interstitial fluid due to lymphangiopathy. Partsch has shown an increased capillary permeability to proteins using labelled albumin.⁵⁴ Other workers, using a variety of techniques, have reported similar findings,^{55–57} although these have not been universally confirmed.^{58–60} Lymphatic obstruction in chronic venous insufficiency was described by Veal and Hussey in 1942,⁶¹ and more recently Bollinger⁶² has described microlymphangiopathy in patients with chronic venous insufficiency using fluorescein microlymphography. In this study, obliteration of parts of the superficial lymphatic network and increased permeability of the lymphatics was observed.

Abnormalities of capillary blood flow and morphology

Convuluted capillaries have been described in the edges of venous ulcers using capillary microscopy in 1956.⁶³ This has been confirmed in more recent work by Fagrell who has shown that there is often a reduction in the total numbers of capillaries in the gaiter area of patients with deep venous insufficiency, the remaining capillaries being widely dilated, coiled and tortuous.^{64,65} This is contrary to histological studies that indicate that there are increased capillaries in lipodermatosclerotic (LDS) skin,⁶⁶ though it may be that when histological sections are taken through a coiled capillary, it is not appreciated that there are several cuts through the same convoluted capillary, rather than cuts through different capillaries. Furthermore, histological sections of the skin often include dermal capillaries rather than just the papillary nutritional capillaries seen on capillary microscopy. The capillaries in venous disease are not only dilated, coiled, and reduced in number, but also more widely separated, which Fagrell believed was due to micro-oedema formation. This may result in an inability to supply enough oxygen to the tissue during periods of increased demand, for example, following injury. Another feature of the microcirculation in LDS is the increased skin blood flow as measured by laser Doppler fluxmetry. This has been shown to be 1.5–2 times greater than comparable skin in normal controls.^{67,38} although the cause of this is not known.

Fibrin cuff theory

In 1982, Browse and Burnand put forward their fibrin cuff hypothesis to explain the cause of venous ulceration.⁶⁸ This was based on the observations of Landis⁶⁹ who showed that elevated venous pressure resulted in elevated capillary pressure and permeability, and of Whimster,⁶⁶ who reported enlargement of the dermal capillaries in patients with venous disease. The 'fibrin cuff' hypothesis suggested that with increased venous pressure, pores between the endothelial cells lining the capillaries stretched, increasing the permeability of capillaries and allowing large molecules, in particular fibrinogen, to escape into the interstitial tissue. Fibrinogen then polymerizes into fibrin to form pericapillary fibrin cuffs. These pericapillary cuffs act as a diffusion barrier, preventing oxygen and 'other nutrients' from reaching the skin and resulting in cell death and ulceration. Patients with venous disease also have reduced fibrinolytic capacity to clear fibrin. This work was supported by animal experiments which showed increased fibrinogen in the lymph draining the hind leg of dogs following

femoral vein ligation.⁷⁰ Thus this hypothesis could explain the high venous oxygen and the low tissue oxygen concentrations seen in patients with lipodermatosclerosis and ulceration.

Much work has been done that supports the 'fibrin-cuff' hypothesis. There is no doubt of the existence of the fibrin cuffs themselves, as they have been observed in a number of histological studies.^{71,72} There is also little doubt that there is reduced fibrinolytic activity in patients with venous disease.^{73–76} However, although a commercially available fibrin membrane has been shown to delay the diffusion of oxygen across it,⁷² other calculations have shown that pericapillary fibrin cuffs are unlikely to cause a significant block to the diffusion of oxygen.⁷⁷ In addition, if this hypothesis were to be correct, it would be expected that the reduction of fibrin cuffs would result in ulcer healing. Studies have shown that fibrin cuffs and the area of LDS can be reduced using profibrinolytic therapy (stanazolol–Stromba, Sterling Research),⁷⁸ but that such therapy was no better than placebo at healing ulcers.⁷⁹ In another trial, the effects of stanozolol and compression therapy on LDS were studied in a double-blind placebo-controlled trial.⁸⁰ It was found that the treatment group had a 28% reduction in the area of LDS compared to 14% in the placebo group but, when multivariate analysis of the effects of each component in the treatment was analysed, the effect attributable to stanozolol alone was not statistically significant. Furthermore, no changes in the tissue pressure of oxygen (TcPO₂) in the skin of either group was seen despite the reduction in the area of LDS.

The fibrin cuff hypothesis is also supported by studies that have shown reduced levels of TcPO₂ using a Clark-type surface skin electrode over the LDS skin of patients with venous disease.^{81–85} However, the technique of TcPO₂ measurement depends on the ability to cause maximal vasodilatation by heating the skin to 43–44°C, and it has been shown recently that it may not be possible to cause maximal vasodilatation in the areas of LDS in patients with venous disease.³⁹ This may invalidate studies where the TcPO₂ reading was taken at 43–44°C; in fact, when the TcPO₂ has been measured at 37°C instead of 43°C, the oxygenation of the skin of patients with venous disease appears to be higher than that in normal controls.⁸⁶ As there have been no direct measurements of the tissue oxygen tension in patients with venous disease, the assumption that skin oxygenation is reduced in venous disease remains unproven.

Oxygen extraction in the skin, using positron emission tomography, has been found to be lower in the affected limb compared to the 'normal' limb in patients with venous disease.³⁷ However, this study can be criticized on the grounds that the apparently normal limb in patients with venous

disease was used as the control limb. This is unsatisfactory as it has been shown that the 'normal' limb in such patients often has unsuspected abnormalities such as a low skin TcPO₂ reading and increased venous refilling time following exercise.⁸⁷

The white cell trapping theory

In 1988, Coleridge Smith *et al.* proposed a new hypothesis for the cause of venous ulceration.⁸⁸ This was based on observations that a reduction in blood flow through capillaries and post-capillary venules results in adhesion of white cells to both activated and non-activated endothelium,⁸⁹ and that such margination of white cells in the post-capillary venules occurs due to their slow rate of flow compared to red cells.⁹⁰ Venous hypertension has been shown to cause white blood cells to become sequestered in the legs. This was demonstrated by Moyses *et al.*⁹¹ in a study where they measured the haematocrit, red and white blood cell counts before and after lower limb dependency for a period of 40 minutes. They found that the haematocrit and red cell count increased proportionally, due to increased capillary filtration as a consequence of the increased capillary pressure following venous hypertension, but that the white cell count in blood taken from the saphenous vein at the ankle remained unchanged. This suggested that white cells were 'lost' to the circulation and remained in the lower limb. In a similar study in patients with LDS and venous ulceration, 30% of white blood cells were 'lost' from the leg circulation in the patient group, compared to 7% in normal controls following 60 minutes of leg dependency.⁹² Activated white cells have been shown to be mediators of tissue damage in a number of organs including the heart,^{93,94} brain,⁹⁵ lung,⁹⁶ and kidney.^{97,98} Bollinger *et al.* showed increased diffusion of fluorescein out of capillaries in patients with venous disease using fluorescence video capillary microscopy,⁶⁰ indicating that capillaries in venous disease are much more permeable than normal to this molecule, suggesting abnormal endothelial function and, using simultaneous fluorescence and light capillary microscopy, Franzeck *et al.* described the appearance of capillary loops filled with red blood cells, which did not appear to be perfused, and suggested capillary thrombosis to be a feature of venous disease.⁹⁹ Using microscopy, capillaries have been shown to reduce in number following limb dependency in patients with venous disease.¹⁰⁰ This suggested that as well as 'capillary thrombosis', capillaries became 'invisible' to microscopy due to the inability of red cells to get past the white cells 'plugging' them.

The 'white cell hypothesis' postulates that an increase in venous pressure during standing or walking causes a reduction in capillary flow rate, resulting in trapping of white blood cells in the leg. The trapped white cells may cause 'plugging' of the capillaries and result in areas of ischaemia around these capillary loops, and become activated, releasing toxic oxygen metabolites (free radicals), proteolytic enzymes and chemotactic substances that attract more white cells. Monocytes, particularly, on activation, release the cytokines interleukin-1 (IL-1) and possibly also tumour necrosis factor alpha (alpha-TNF).¹⁰¹ These may also activate endothelial cells resulting in increased vascular permeability,¹⁰² which may be the mechanism by which fibrinogen passes into the pericapillary spaces and forms fibrin cuffs.

The first part of the 'white cell hypothesis' suggesting tissue hypoxia as a result of capillary plugging cannot be supported, as there is no proof that there is tissue hypoxia in LDS skin. However, there is evidence that white cell activation occurs. Skin biopsies taken from patients with venous disease showed that there was a low number of white cells in the skin of patients without LDS, while in patients with LDS without ulceration, the number of white cells in the skin was increased eight-fold, and in patients with ulceration, there was a 40-fold increase.¹⁰³ However, neither the type of white cells nor their relationship to capillaries was addressed, and this study may be interpreted as confirmatory evidence of the presence of inflammation in the skin of patients with LDS and ulceration. There is other indirect evidence confirming white cell activity. Pentoxifylline (Trental, Hoechst), which antagonizes the effects of alpha-TNF and IL-1, has been shown to promote ulcer healing when used in conjunction with compres-

sion therapy,¹⁰⁴ although it has many other rheological properties which may also be important. Prostaglandin E₁, which prevents the release of free radicals from neutrophils, has been shown to be beneficial in patients with venous ulceration,¹⁰⁵ as have free-radical scavengers applied topically to ulcers.¹⁰⁶ To date, there have been no studies showing activation of white cells and the release of free radicals on increasing the venous pressure. This is because of difficulty in measuring this phenomenon, although we are currently attempting to address the problem by measuring chemiluminescence from activated white cells *in vivo*. As with the fibrin cuff hypothesis, the white cell hypothesis waits to be proven.

Conclusion

Of the many theories of venous ulceration outlined above, all postulate raised venous pressure as the initiating agent, and all agree that damage to the microcirculation is the initiator of cell damage. However, only two theories are currently in vogue – the fibrin cuff theory and white cell trapping theory. Of the former, although the presence of fibrin cuffs is not in doubt, their role as causative agent is unproven, as currently no adverse effects directly attributable to their presence has been shown. Plugging of capillaries by white blood cells as postulated by the white cell trapping theory has not been shown, although there is considerable evidence of their margination and migration from within the circulation during periods of venous hypertension, and some evidence that free radical and proteolytic enzyme release could be the causation of venous ulceration.

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