Venous ulcer

An editorial in this Journal 4 years ago considered the problem of venous ulceration. More than 2000 articles on the subject of varicose veins and venous ulcers have been cited in the pages of Index Medicus since then. A number of important advances have been made in the investigation of the venous system and understanding of the pathological processes that result in ulceration but, as yet, only modest progress has been made in the treatment of this condition.

Venous ulceration is a common problem in patients with chronic venous disease. The prevalence of venous disease severe enough to lead to ulceration in Western countries is 1-2 per cent and approximately one-fifth of those affected suffer an ulcer of the leg at any one time. The cost to health services is considerable. A venous ulcer costs £2000-4000 per year to manage, much of this spent in the community on nursing services; an estimated 150,000 patients in the UK with active leg ulceration result in an annual bill of £300-600 million. In comparison, 20,000 patients per year receive treatment for critical ischaemia of the lower limb in the vascular surgical units of the UK.

Between 10 and 50 per cent of patients with venous ulcer have ulceration attributable to superficial venous incompetence alone. Such patients cannot easily be identified clinically and hand-held Doppler ultrasonography is of limited accuracy, especially in the popliteal fossa. While venography has been widely used, colour duplex ultrasonographic imaging has seen vast technological improvements in the past 4 years and is more effective at assessing the competence of venous valves, particularly in the popliteal vein. All patients presenting with venous ulceration who are fit enough to undergo treatment of superficial venous disease should be evaluated by this technique. The cost of ultrasonographic imaging is half that of venography; the results provide anatomical and functional information and the test is non-invasive. At present, few radiologists and vascular surgeons in the UK are familiar with the methods required to perform ultrasonographic scanning for venous valvular incompetence. However, there is growing interest in this field and the provision of suitable equipment in many district general hospitals will soon permit vascular surgeons access to this invaluable investigation.

The events in the microcirculation that lead to skin ulceration have not been fully resolved. Browse and Burnand suggested that perivascular fibrin cuffing might prevent oxygen reaching the tissues but theoretical considerations indicate that it is unlikely such cuffs present a barrier to the diffusion of oxygen or other small molecules. Direct needle electrode measurements of skin oxygen tension in patients with venous disease have shown only modest reductions of skin oxygenation compared with normal values. The finding of fibrin cuffs in other pathological processes and the failure of fibrinolytic treatments to heal venous ulcers have led some authors to conclude that these are not the main mechanism behind tissue injury.

In a small number of studies the changes in liposclerotic skin and ulcers of the leg have been investigated by electron microscopy and modern immunohistochemical techniques. These have shown that the perivascular cuff of skin capillaries is much more complex than previously suspected, containing collagen type IV, laminin, fibronectin, tenasin, macrophages and some T lymphocytes, as well as fibrin. The endothelium of these capillaries is very prolific and is 'perturbed', expressing intercellular and endothelium–leucocyte adhesion molecules, which participate in the mechanism of neutrophil adhesion. In addition, expression of factor VIII-related antigen is upregulated. The presence of the cytokine interleukin 1 has been reported in two studies, and tumour necrosis factor α in one. These observations confirm that lipodermatosclerosis is a chronic inflammatory condition but do not indicate the causal factors. Systemic neutrophil activation has been observed in a number of studies in patients with chronic venous disease, ranging from uncomplicated varicose veins to active ulceration, compared with that in age-matched control subjects. This may simply reflect a response to the presence of venous disease. To understand the events leading to these end-stage findings it is necessary to study the earliest events after the onset of venous hypertension.
In 1988 I suggested that white cell sequestration ('trapping') in the legs of patients with venous disease might be the main cause of tissue damage. Trapping occurs within 30 min of raising the venous pressure in control subjects and is greater in extent in patients with venous disease. It has since been reported that venous hypertension lasting 30 min produced by standing leads to increased neutrophil degranulation and adhesion molecule expression in the legs of control subjects. Laser Doppler fluxmetry measurement of postischaemic reactive hyperaemia after a period of venous hypertension shows a reduced response compared with that before venous hypertension in control subjects. This suggests that microcirculatory injury occurs in association with neutrophil degranulation. In individuals with calf muscle pump failure venous hypertension will occur whenever the patient stands, presumably leading to neutrophil activation. Repeated endothelial injury may result in the changes seen in liposclerotic skin. Variability between individuals in susceptibility to venous disease may be the result of alterations in any of the complex mechanisms involved in neutrophil adhesion, activation or endothelial repair.

The mechanism of white cell–endothelial cell interaction and the metabolism of neutrophils are the subject of intense study as these are crucial in the development of tissue ischaemia. Adhesion of white cells to endothelium, activation of neutrophils and release of free radicals all cause tissue damage during ischaemia. Drugs that influence these events are under development and might be used to prevent or heal venous ulcers. A preliminary study of one such drug, oxpentifylline, has reported encouraging results.

Venous ulceration remains a common, expensive, though unspectacular clinical problem in Western countries. The investigation of patients with leg ulcer by duplex ultrasonographic imaging will ensure that all those in whom superficial venous incompetence is the cause will receive the correct surgical treatment. In the future, adjunctive pharmacological methods may be employed to assist and maintain the healing of venous ulcers. The selection of the best drugs will depend on a better understanding of the processes causing venous ulceration.

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