

Leg Blood Flow in Patients with Venous Ulcers: Relationship to Site and Ulcer Area

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Abstract: The purpose of this study was to determine blood flow in the ulcer bearing leg of venous ulcer patients and its relationship to ulcer area and to flow in non-ulcerated legs.

Blood flow at five below-knee sites was measured in 10 patients with unilateral venous ulcers and in the paired non-ulcerated legs. Flows from the ulcer limb sites were compared prior to treatment on a site-by-site basis with the paired limb and with a group of normal legs (n=74). Flow in both legs of five of the patients were re-measured and compared after treatment and ulcer closure. The relationship between initial ulcer area and blood flow was determined using regression analysis.

Leg blood flow of the ulcer leg near the ulcer site was found to exceed that measured in the paired non-ulcer leg, whereas total below-knee flows were similar. The ulcer leg hyperperfusion correlated with the area of the ulcer. Treatment was associated with a reduction in the ulcer limb hyperperfusion to levels comparable to the non-ulcer limb. Finally, both limbs of the venous ulcer patients had higher blood flow than in subjects with normal legs.

The results of the study suggest that the hemodynamic response to venous ulcer presence helps supply the enhanced metabolic needs of the ulcer. This process may be mediated by arteriolar vasodilation beginning at about mid-calf, but it is unknown whether the hyperperfusion is necessary for timely ulcer healing. The need for increased perfusion may be a factor to consider in patients with compromised vascular reserve and delayed healing.

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Introduction

The sequence of events which causes chronic venous insufficiency (CVI) of the legs to lead to ulceration is not fully understood. Chronic venous hypertension due to deep venous and/or ankle perforator incompetence^{1,2} together with an increased reflux index³ is thought to set the stage for subsequent ulcer development. Associated changes in skin microvessel metrics and morphology,⁴⁻⁶ rheology,⁷ hemodynamics,⁸⁻¹¹ leukocyte dynamics and activation,¹²⁻¹⁵ and interstitium changes^{16,17} have been observed and documented. One or more of these may provide the final link in the pathway that leads to chronic venous ulceration, a condition that has an estimated prevalence of from 0.06 to 1.3% with about

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57 to 80% of patients with leg ulcers having demonstrable venous disease.¹⁸ Various elements of the observed microangiopathies have been incorporated into several theories to account for the ulceration and these are presently being debated. Bearing on this issue are functional measurements of skin near venous ulcers or on non-ulcerated skin in patients with CVI at probable pre-ulcer skin regions. These have demonstrated a decreased transcutaneous oxygen tension ($TcPO_2$),^{9,11,19} an elevated transcutaneous carbon dioxide tension ($TcPCO_2$),^{20,21} yet an increased skin blood perfusion as measured with laser Doppler methods.⁹⁻¹¹ The significance of the elevated microperfusion and its possible relationship to overall leg circulation, is unknown and the basic mechanisms controlling it are unclear. The purpose of the present study was to evaluate, in patients with unilateral venous ulcers ($n=10$), the macrovascular blood flow at multiple below-knee sites, some of which encompassed the region of the ulcer and some of which did not; to compare, on a site-by-site basis, the blood flow in the ulcer bearing limb with its non-ulcer pair and with a group of normal legs ($n=74$); to determine if ulcer leg blood flow correlates with ulcer area; and to determine the effect of ulcer treatment on pre-treatment flow ($n=5$).

Methods

Patients. The primary patient group consisted of 10 consecutive patients with unilateral venous ulcers having ankle brachial pressure indices >0.8 . Initial blood flow evaluations were done prior to initiation of any treatment or compression. The presence of venous pathology was demonstrated using duplex color flow imaging. All 10 patients had deep venous pathology on the ulcer bearing limb (femoral, tibial, or popliteal) with five patients having single vessel involvement and five having two vessel involvement. All patients included in the present report had demonstrable venous reflux in the ulcer bearing leg but no detectable clinically significant venous pathology of the contralateral limb as judged by duplex imaging. The ulcer in all patients was located in the medial gaiter region. Ulcer areas as measured by tracing and subsequent electronic planimetry ranged from 1.0 to 29.4 cm^2 and had been present for durations ranging from 2 to 72 months. The average patient age was 61.1 years

(range 43–83) and 70% were male. The protocol was approved by the IRB and informed consent was obtained from all patients.

The secondary patient group consisted of five of the original 10 patients who completed up to 12 weeks of treatment and returned for a follow-up leg blood flow assessment. These follow-ups were done one week after the wound had healed. During this week the patients continued with compression therapy as used during the healing phase; blood flow measurements were done approximately one hour after bandage removal. During the initial treatment interval, seven of the wounds were dressed with a hydrocellular polyurethane foam dressing (Allevyn®, Smith & Nephew United) and three with a hydrocolloid dressing (DuoDerm®, ConvaTec). All ulcer bearing legs were wrapped with a compression bandage (Tensopress® Wrap, Smith & Nephew United) and covered by a stockinette (Tensoshape®, Smith & Nephew United). Dressings were changed weekly.

Measurements. Approximately one hour after bandage removal and with the patient resting supine, pulsatile leg blood flow was measured bilaterally with magnetic resonance flowmetry^{22,23} (Qmrf, ml/min Metriflow AFM100, Milwaukee) at five sites on each leg corresponding to 10, 25, 50, 75, and 90% of the malleolar-knee length as measured from the medial malleolus. Leg circumference measurements at each site were used together with an algorithm incorporated in the AFM100 system to calculate the site blood perfusion (Pmrf) expressed as ml/min/100cc of distal tissue volume.

Analysis. Flow and perfusion values obtained at each site were compared with respect to the values obtained on the ulcer bearing leg and the paired non-ulcer leg. Statistical analysis of paired differences was based on the non-parametric Wilcoxon test with a p -value of <0.05 taken as statistically significant. In addition, comparisons were made between both legs of the present ulcer patients and corresponding values previously measured in 74 legs (one leg from each of 74 persons) free of arterial or venous disease as judged by history and bilateral non-invasive testing. These subjects, whose age range paralleled the venous ulcer patients, serve as a reference group. Statistical analysis was done using the non-parametric Mann-Whitney test for independent samples.

For leg sites which showed a statistical difference in blood flow between ulcer and non-ulcer legs, regression analyses were used to determine the relationship between ulcer leg blood flow and ulcer area.

Results

Figure 1 graphically summarizes the relationship of Qmrf and Pmrf to leg site for all legs evaluated. Leg blood flow declined as expected from knee to ankle for all legs. For the ulcer patients, Qmrf of the ulcer bearing leg is significantly greater than the contralateral other leg beginning at the 50% site and extending to the 10% site. The ulcer sites lie between the 10% and 25% regions. Except for the 90% site, all normal leg Qmrf values are significantly less than corresponding values measured on both of the ulcer patient's legs.

The leg blood perfusion, shown in the bottom part of Figure 1, demonstrates a different pattern for the ulcer leg as compared with the other non-ulcer leg and more strikingly as compared with the perfusion-site relationship of the normal legs. Whereas both the normal legs and the non-ulcer leg show a slight decline in perfusion from the 50% to the 25% sites, the ulcer bearing leg shows a sharp increase in perfusion which continues to the 10% site. The elevated perfusion at the 10 and 25% sites of the ulcer leg are statistically greater than corresponding values obtained for the non-ulcer leg. The perfusion of the normal legs at the 50 through 10% sites are statistically less than either leg of the venous ulcer patient.

Figure 2 shows the blood flow ratios obtained at each site for the ulcer patients and for the normal subjects. For the ulcer patients, the ratio is plotted as the ulcer flow/non-ulcer flow. For the 74 bilateral studies of the normal legs, the ratio is arbitrarily taken as left leg flow/right leg flow. For the ulcer patients, the flow ratio is seen to increase almost linearly from knee to ankle; with the normals, the ratio is near flat below the 75% site. Statistical significance in these ratios between patients and normals is found at and below the 50% site.

Figure 3 compares the flow-site relationship of the five patients evaluated pre and post treatment. The overall flow-site patterns are similar but the significant elevation in ulcer leg flow at the 10 and 25% sites prior to treatment is no longer present after treatment.

Figure 4 shows the relationship between the

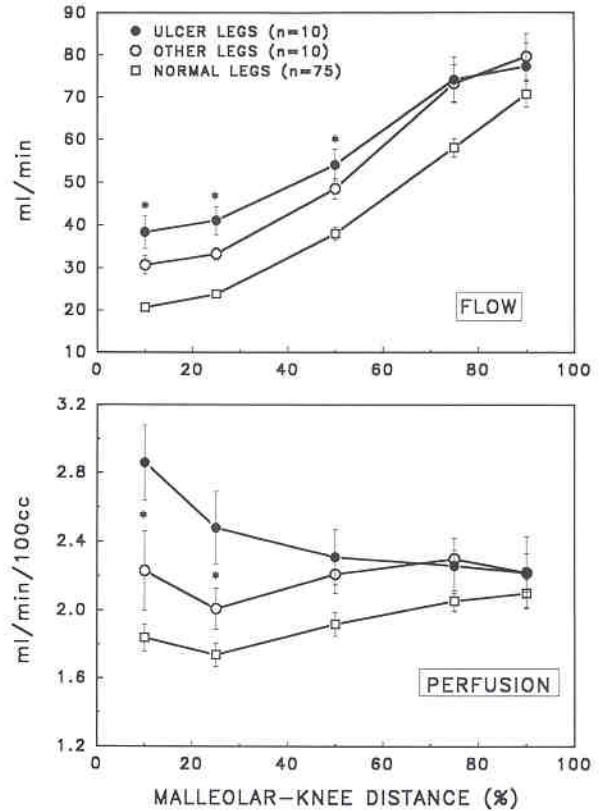


Figure 1. Leg blood flow and perfusion in patients with venous ulcers and a control group of normal legs. * = $p < 0.05$ between ulcer leg and paired non-ulcer leg. For FLOW, normal legs differed significantly from both legs of patients at all sites, for PERFUSION, only site 90% was not significantly different.

ulcer area and the ulcer leg blood flow at the 50, 25, and 10% sites. The leg blood flow at each site is seen to increase linearly with ulcer area. The associated linear regression parameters are shown in the figure. The most significant regression is that between ulcer area and flow at the 10% site.

Discussion

The main findings of the present study may be summarized as follows: leg blood flow of the ulcer bearing leg in the vicinity of the ulcer site exceeds that measured in the paired non-ulcer leg; the amount of ulcer leg hyperperfusion correlates with the area of the ulcer as measured prior to treatment; treatment is associated with a reduction in the ulcer limb hyperperfusion to levels comparable to the non-ulcer limb; and both limbs of the venous ulcer patients demonstrate

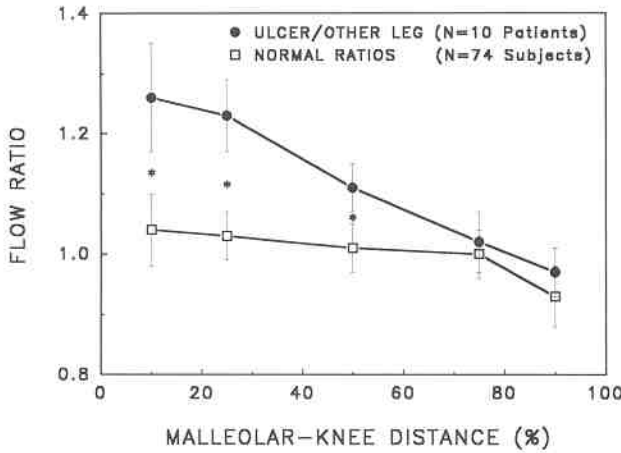


Figure 2. Ratio of leg blood flow in ulcer bearing leg to non-ulcerated other leg (closed circles) and left leg to right leg in normal group (open circles). * $p < .05$.

higher blood flow than those of subjects with normal legs and no history of venous disease.

An increase in leg blood flow in patients with venous ulcers has been previously demonstrated⁸ using positron emission tomography. The present work confirms this and by examining the flow pattern at multiple leg sites shows that it is not total (below-knee) leg blood flow that is elevated, rather the elevated flow is confined to regions in the vicinity of the ulcer. This suggests a redistribution of the flow toward the ulcer bearing region possibly mediated by arteriolar vasodilation starting at sites in the vicinity of the mid-calf. Measurements of skin microvascular perfusion in the peri-ulcer region have also been shown to be elevated as compared with the non-ulcerated limb.^{9,11} The present findings suggest that this increase in microvascular perfusion is in part related to the increase in net blood flow to the region. It is possible that the increase in leg flow is secondary to vasodilatory stimuli at the microvascular level.

Based on the present observations, one is inclined to ascribe the macrovascular hemodynamic response to the presence of venous ulceration as one which, at least in part, functions to supply the enhanced metabolic needs associated with the ulcer. Though it is unknown whether this hyperperfusion is necessary for timely ulcer healing to occur, it raises that possibility. The fact that the flow returned to levels comparable to that measured on the non-ulcerated leg following treatment and wound closure may be evidence in support of this concept. In the present study, no patient had significant arterial disease and all

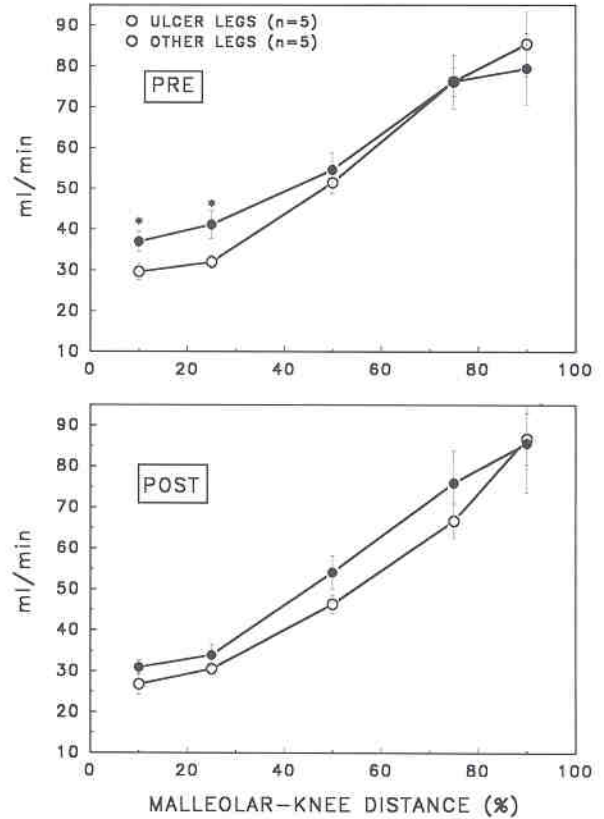


Figure 3. Leg blood flow in venous ulcer patients prior to treatment (PRE) and after treatment and ulcer closure (POST). * $p < .05$. Closed circles are the ulcer bearing leg and open circles are the contralateral leg.

limbs were capable of a vasodilatory response adequate to demonstrate the observed elevated blood flow in the ulcer region. As compared with normal limbs, this elevation was large, being almost 2:1 in flow and about 1.5:1 in perfusion at the 10% site. The clinical question that immediately presents itself relates to the implications of these findings to patients in whom such vasodilatory capacity is not available. Such limitations would be expected to occur under a variety of conditions including superimposed lower extremity arterial disease and diminished microvascular reserve as is present in some patients with diabetes. Since the mainstay of standard treatment of venous ulcers is elastic compression, the possibility that such compression might limit the level of required hyperperfusion in susceptible patients needs to be considered. This would be an especially important consideration when standard treatment fails to produce timely improvement in ulcer status. In the pre-

sent study, all measurements were made with the compression wrapping removed, thus we can not yet comment on the direct effects of compression as a flow modulator.

The present findings also show that in spite of the absence of an ulcer on the control limb, its blood flow was elevated as compared with that measured in normal limbs. The elevation in flow was not restricted to one particular leg site but was greater overall. In patients with unilateral venous ulcers, there is evidence that the contralateral non-ulcerated leg may also have abnormalities. In a group of 16 unilateral venous ulcer patients, the $TcPO_2$ of the non-ulcerated paired leg was decreased and skin temperature was elevated as compared with normal legs, although both parameters were significantly more abnormal on the ulcer bearing limb.¹¹ Other aspects of abnormal hemodynamics for the asymptomatic other limb have been reported.²⁴ The present results also show flow differences of the non-ulcerated limb as compared with normal legs, though the non-ulcer limbs are closer to normal than the ulcer limbs. Although significant venous pathology was not detected via imaging, sub-clinical abnormalities of the paired non-ulcer leg may have been present with potential implications as discussed below. However, its use as a comparison has many advantages. By the nature of the present study design in using the ulcer bearing limb and the contralateral limb as comparison, the possibility that the blood flow differences are due to differences in hematocrit, systemic blood pressure, or other systemic variables is unlikely.

The reason for the elevated flow in the non-ulcerated limb is unknown but it is possible to offer some theories. Since chronic venous insufficiency (CVI) and ambulatory venous hypertension precede venous ulcer development, it may be that the paired non-ulcer leg had undetected venous pathology, albeit less pronounced than on the ulcerated limb. If true, then one may speculate on possible links between chronic venous distension effects and arteriolar vasodilation which might account for the greater flow on the ulcerated limb vs the contralateral limb and the elevated flow of both limbs of the patients with respect to normal limbs. One such possible link could be related to demonstrated elevations in $TcPO_2$ in patients with CVI.^{20,21} Increases in local CO_2 concentration as well as the pH changes

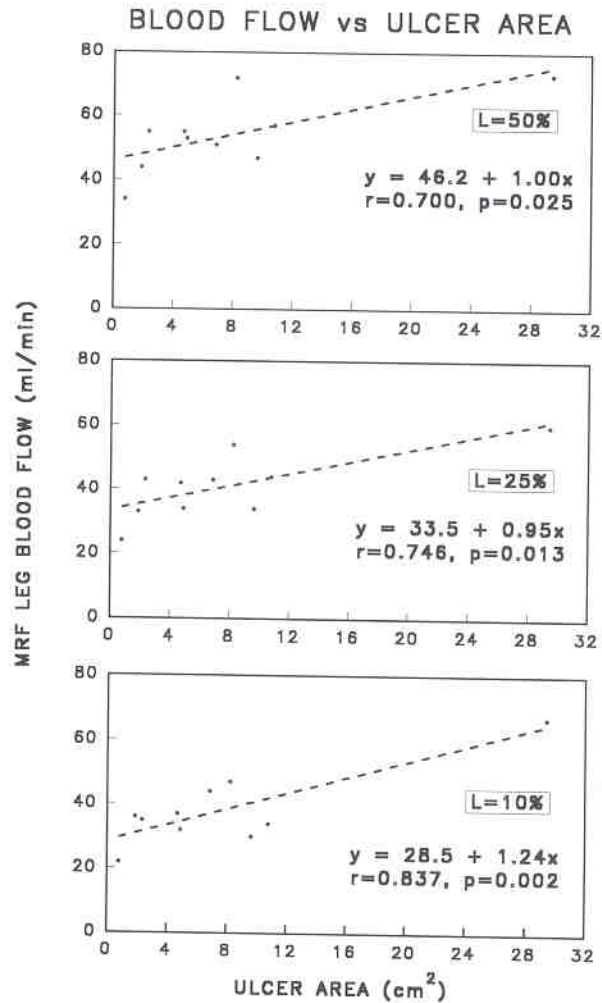


Figure 4. Leg blood flow vs initial ulcer area. L=leg measurement site expressed as % of malleolar-knee length. Dashed line is linear regression.

that accompany them have long been recognized as having vasodilating properties. An additional and possibly coexisting effect may be related to the low $TcPO_2$ levels present on the lower limbs of patients with CVI.¹⁹ It has also been shown that in patients with unilateral venous ulcers, $TcPO_2$ is reduced in both limbs although the reduction in the ulcer bearing limb is significantly more pronounced.¹¹ These O_2 and CO_2 deficits, which are thought to arise as a consequence of microvascular impairments, may thus prove to be the controlling elements responsible for a portion of the leg blood flow elevation herein observed. Venular endothelial cell changes which modulate arteriolar vasodilation^{25,26} may also play a role. Further work and additional data will be necessary to sort out these issues.

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