

## Simultaneous Changes in Leg Arterial Pulsatile Blood Flow and Toe Laser-Doppler Perfusion Accompanying Graded Thigh Compression

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### ABSTRACT

Previous findings showed that regional ankle cuff compression and below-knee compression bandaging cause significant decreases in skin blood perfusion distal to the compressed regions. Contrastingly, with compression bandaging, as is commonly used in the treatment of venous ulcers and other conditions, an increase in leg pulsatile blood flow in compressed regions has been reported without corresponding decreases in sub-bandage skin blood perfusion. The explanation for these differential effects is unclear in part because of the fact that foot-to-knee compression bandaging has both direct sub-bandage tissue effects and effects on distal and sub-bandage venous hemodynamics. To help clarify this issue, the present study was done to determine the role of compression-induced changes in venous pressure per se on both skin microvascular and calf pulsatile blood flow. This was done using graded thigh cuff compression up to 50 mm Hg to modify lower extremity venous pressure. During these compressions mid-calf pulsatile blood flow via magnetic resonance flowmetry and toe-skin laser-Doppler blood perfusion

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(Abstract continued)

were simultaneously measured. Results showed that increased venous pressure secondary to thigh compression does not contribute to a pulsatile blood flow augmentation and in fact produces graded decreases in pulsatile flow and distal microcirculation with increasing cuff-compression levels. This finding implies that neither venous distention, nor distal intravenous pressure increases, are significantly involved in the pulsatile flow increase phenomena. Further, a significant ( $r^2 = 0.49$ ) linear relationship between flow and perfusion decrements demonstrates an important linkage between lower extremity laser-Doppler perfusion measurements and leg pulsatile blood flow.

### Introduction

Compression bandaging of the lower extremities is the mainstay of treatment of venous ulcers<sup>1</sup> and as therapy and prophylaxis for other conditions.<sup>2</sup> Sub-bandage pressures range between 20 to 50 mm Hg<sup>3</sup> depending on bandage type and method, with vascular effects thought to be due to changes in venous hemodynamics.<sup>4</sup> Recently, however, forefoot-to-knee compression with a 4-layer bandaging system<sup>5</sup> and standard Unna boot<sup>6</sup> at sub-bandage pressures within this range showed significant increases in below-knee arterial pulsatile blood flow. The compression-related flow augmentation was associated with increases in flow-pulse amplitude and width. But other findings indicate decreases in distal, non-compressed skin microvascular perfusion at high-end<sup>7-8</sup> and medium level<sup>9</sup> sub-bandage pressures. Interpreting these flow changes based solely on these previous findings is complex, because compression bandaging produces multiple vascular and tissue changes, some acting at the site of flow measurement and some acting proximal and distal. In bandaged regions, venous and surrounding tissue compression, distortion and pressure changes are present and changes in arterial transmural pressure and effective compliance occur. Contrastingly, distal and proximal effects are mainly due to compression-induced changes in venous pressure and distention. Thus the aim of the present study was to determine the effect of compression-induced venous pressure changes alone with respect to its impact on both lower extremity arterial pulsatile blood flow and simultaneously measured skin microvascular blood perfusion. This was accomplished using graded thigh cuff compression up to 50 mm Hg

to modify lower extremity venous pressure while pulsatile blood flow via magnetic resonance flowmetry and skin laser-Doppler blood perfusion responses to this compression were simultaneously determined.

### Methods

#### Subjects

Ten volunteer subjects ( $37.1 \pm 2.9$  years, six women) participated in this study after reading and signing an Institutional Review-Board approved informed consent. No subject had diabetes, history of venous or arterial disease, or was taking any vasoactive medication. Two subjects were current cigarette smokers. Absence of significant lower extremity arterial disease was confirmed in each participant based on prior screening with bilateral nuclear magnetic resonance flowmetry<sup>10,11</sup> and ankle-brachial systolic pressure indices (ABI) obtained using standard Doppler ultrasound at the posterior tibia and dorsal pedis arteries. Blood pressures measured with standard pressure cuffs also verified that no subject was hypertensive.

#### Toe Microvascular Measurements

Subjects, dressed in shorts or hospital gown, took a supine position on a motorized table that is part of the nuclear magnetic resonance flowmetry (NMRF) system subsequently described. The testing laboratory is temperature controlled to between 22 and 23°C. Laser-Doppler probes (Moor Instruments) were placed on the plantar surface of the right and left great toes and both feet were



covered with light foot coverings to minimize effects of environmental variables (room temperature, drafts if any, etc.) on skin temperature and possibly blood flow. The fiberoptic bundle from each probe was connected to a dual-channel laser-Doppler system (MOOR, MBF3D). The laser-Doppler data from the distal toe sites, which represent signals obtained from a depth of about one mm, were acquired by computer and analyzed at the end of the procedure. There are three components of the detected signal<sup>12</sup>; one corresponds to red blood cell (RCB) flux and is referred to as blood perfusion, one corresponds to the volume concentration of moving RCBs within the measuring volume, referred to as the volume signal, and one corresponds to the mean RCB speed, referred to as velocity. Separate channels on the instrument provide each of these components separately. Each of the three laser-Doppler components is herein reported in arbitrary units (AU), as is standard practice for laser-Doppler measurements. All laser-Doppler data were obtained using a time constant of one sec and cut-off frequencies of 14.9 KHz. Other technical aspects, operating principles, and features of the laser-Doppler blood perfusion measurements are described in several recent monographs.<sup>13-15</sup>

#### Leg Pulsatile Blood Flow

Pulsatile blood flow (mL/min) was measured under resting supine conditions by nuclear magnetic resonance flowmetry (NMRF). The subject is on a moveable table that is advanced by an operator to position any chosen leg site within the center of a tubular measurement section of the NMRF system (Metriflow AFM100, Milwaukee, WI). Within the measurement section, a fixed magnet (0.1 Tesla) causes hydrogen nuclei of the fluids within the leg to precess and an NMR sensor detects the amount of precession. The main NMR signal detected and processed is due to precession of hydrogen nuclei associated with intravascular water. The magnitude of the detected signal is proportional to the number of precessing hydrogen nuclei and is thus proportional to the amount of vascular water flowing into and out of the measurement section. Flow is measured by integrating each pulse waveform over a cardiac cycle and then ensemble averaging for 15 to 20 beats. The leg measurement site was standardized for all subjects by measuring the distance (L) between the lateral malleolus and the

tibial tubercle and measuring flow midway between. Pulsatile flow measured at this site includes the sum of all pulsatile arterial flow passing peripherally through the leg cross section within an axial segment five cm in length and represents the approximate pulsatile flow perfusing the lower limb distally. Nonpulsatile flow (e.g., tissue water, venous flow) produces small contributions, which in any case are filtered out by the system. Calibration to obtain absolute pulsatile blood flow is done with a pulsatile flow pump that drives water doped with a paramagnetic solute to simulate the NMR characteristics of blood through a phantom limb. The phantom is composed of simulated vessels that are positioned within the NMRF measurement region. The pump pulsatile flow is registered using an electromagnetic sensor and a range of calibration flows are used (0 to 120 mL/min) to obtain a calibration curve. Calibration is done each day prior to use and a calibration factor relating actual pulsatile flow to NMR magnitude is automatically determined by the system software. Further NMRF technical details, theoretical aspects, and applications are found in the literature.<sup>16-20</sup>

#### Protocol Sequence and Thigh Compression

A large thigh cuff (20 cm width  $\times$  100 cm in length) was placed around the thigh of one leg. After 15 min of supine rest, baseline precompression blood flow was measured at midcalf three times during a 10-min baseline data acquisition interval. Thereafter, the cuff was inflated to 10, 20, 30, 40 and 50 mm Hg with five min of zero pressure between successive five-min duration compressions. Laser-Doppler data were acquired continuously throughout the procedure and leg blood flow was measured once during the last minute of each compression interval.

#### Analyses

Laser-Doppler data were analyzed by first computing the average skin blood perfusion (Q), volume (V), and velocity (U) during baseline (10 min) and during each of the five, five-min compression intervals. Baseline values of these parameters were compared between paired legs using raw laser-Doppler values in arbitrary units (AU), as is standard for laser-Doppler methods. Effects of compression on toe microcirculation were determined by comparing each compressed limb's

values with the noncompressed contralateral control limb during each compression interval. This was done by expressing the perfusion in each compression interval relative to its baseline (zero pressure) average and then forming the paired-toe ratio (compressed limb/control limb). This method of analysis was adopted to minimize potential confounding effects of systemic changes over the course of the procedure. The relationship between compression-induced microcirculatory (perfusion) and macrocirculatory (pulsatile flow) changes in the compressed limb alone was evaluated by comparing the laser-Doppler averages and the NMRF blood flow values in each compression interval normalized to each subject's baseline average. To determine the presence of significant cuff pressure effects, laser-Doppler perfusion and NMRF blood flow in the five compression intervals were tested for overall differences by analysis of variance, with 0.05 being accepted as statistically significant. Linear regression analysis was used to test for a correlation between laser-Doppler perfusion and blood flow using the normalized variables.

## Results

### Baseline Hemodynamics

Prior to compression, paired-limb laser-Doppler parameters and pulsatile flows and pressures were very similar with no significant difference in any parameter as summarized in Table I.

### Paired-toe Microcirculatory Changes

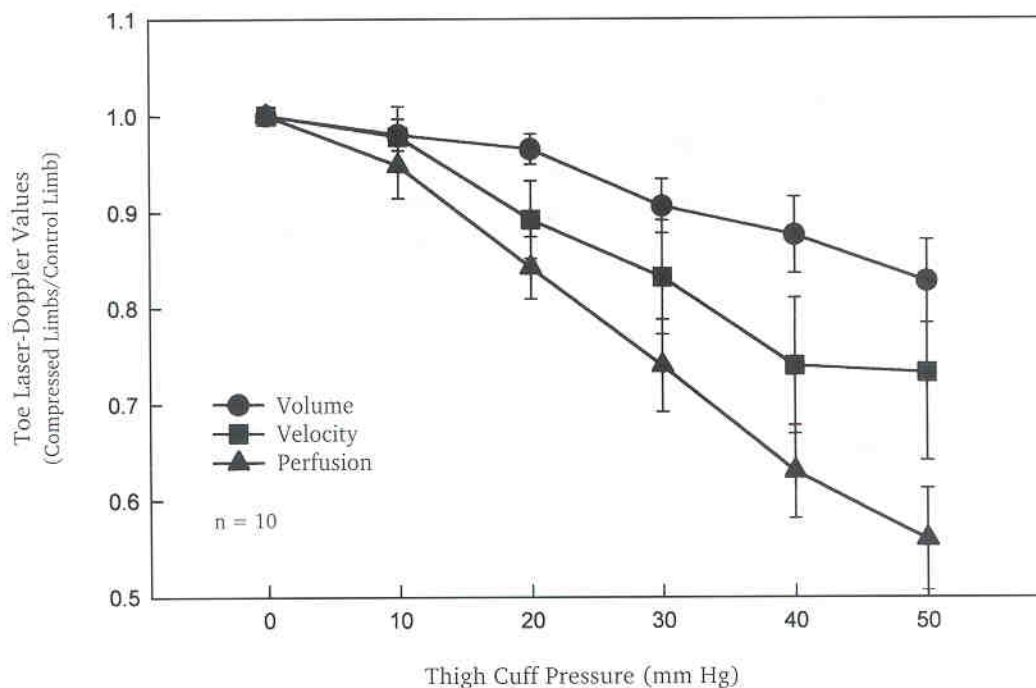
All paired-toe laser-Doppler ratios (compressed limb/control limb) decreased with increasing thigh compression pressure as shown in Figure 1. Overall, the mean laser-Doppler perfusion ratio (QQr) at the highest compression pressure was  $0.56 \pm 0.05$  (mean  $\pm$  SEM) with associated volume and velocity ratios of  $0.83 \pm 0.04$  and  $0.73 \pm 0.09$ , respectively. The decline in perfusion over the 10 to 50 mm Hg range was near linear and expressible by an overall regression ( $n = 50$ ) of  $QQr = -0.009 P + 1.02$ ,  $P < 0.001$ ,  $r^2 = 0.43$ .

**Table I**  
*Baseline Hemodynamic Values*

Parameter	Compressed Limb	Contralateral Limb
Laser-Doppler (AU)		
Perfusion	$121.9 \pm 40.1$	$120.1 \pm 35.38$
Volume	$197.5 \pm 12.2$	$191.5 \pm 13.5$
Velocity	$27.1 \pm 8.4$	$28.2 \pm 7.6$
Leg blood flow (mL/min)	$44.4 \pm 2.2$	$43.8 \pm 2.1$
Ankle systolic pressure (mm Hg)	$118.2 \pm 3.5$	$118.5 \pm 3.3$
Ankle-brachial pressure index	$1.07 \pm 0.04$	$1.06 \pm 0.04$

No paired-limb parameter differed significantly at baseline (zero thigh cuff pressure). Laser-Doppler values expressed in arbitrary units (AU).





**Figure 1.** Compression induced decreases in laser-Doppler parameters. Data points are ratios of simultaneously measured values on the great toe of compressed limbs to contralateral control limbs. The decline in blood perfusion with increasing thigh cuff pressure over the 10 to 50 mm Hg range was near linear. Bars are  $\pm$  SEM.

#### Compressed-limb Blood Perfusion and Flow

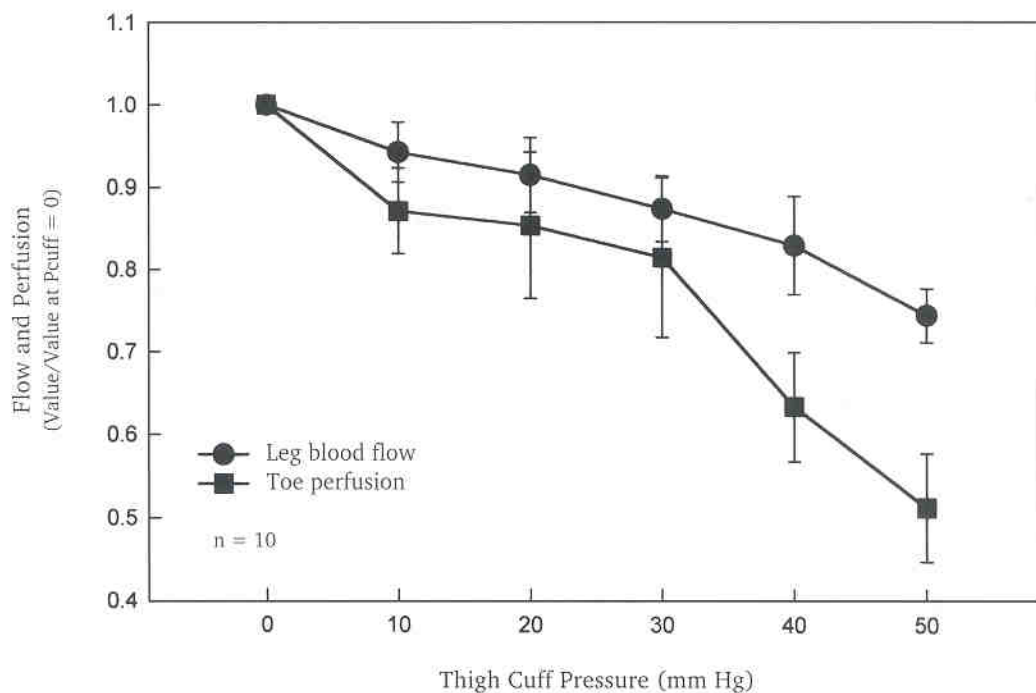
Toe perfusion and midcalf pulsatile blood flow decreased with increasing thigh cuff pressure is shown in Figure 2. However, whereas the pulsatile flow decreased in a near linear manner over the 10 to 50 mm Hg range, toe laser-Doppler perfusion displayed an accelerated decline beyond 30 mm Hg. At 50 mm Hg compression, toe perfusion and flow were reduced to  $51 \pm 6\%$  and to  $75 \pm 3\%$  of baseline, respectively. The fractional decline in pulsatile blood flow ( $Fr$  = compressed flow/baseline flow) with increasing compression pressures over the 0 to 50 mm Hg range is expressible by an overall regression as  $Fr = -0.0047 P + 1.00$ ,  $P < 0.001$ ,  $r^2 = 0.33$ ,  $n = 60$ . The corresponding decline in laser-Doppler fractional toe perfusion ( $Qr$ ) is expressible as  $Qr = -0.009 P + 1.00$ ,  $P < 0.001$ ,  $r^2 = 0.40$ . There was a significant direct correlation between the toe perfusion and mid-calf flow decrements as illustrated in

Figure 3. The relationship was expressible by the overall linear regression  $Qr = 1.25 Fr - 0.34$ ,  $P < 0.001$ ,  $r^2 = 0.49$ ,  $n = 60$ .

#### Discussion

##### Compression Effects on Pulsatile Flow

The present results demonstrate that increased venous pressure secondary to thigh compression does not contribute to a pulsatile blood flow augmentation and is thus ruled out as a possible mechanism to account for the previously observed pulsatile blood flow augmentation associated with forefoot-to-knee compression bandaging<sup>5,6</sup>. Indeed, midcalf pulsatile blood flow decreased in a near linear fashion with increasing levels of cuff compression pressure. This finding implies that neither venous distention nor distal intravenous pressure increases that accompany



**Figure 2.** Compressed limb midcalf pulsatile blood flow and toe perfusion decreases. Data points are simultaneously measured flows and perfusions normalized to baseline noncompressed values. Both measures decrease with increasing thigh cuff pressure with the toe perfusion showing an accelerated decline after 30 mm Hg.

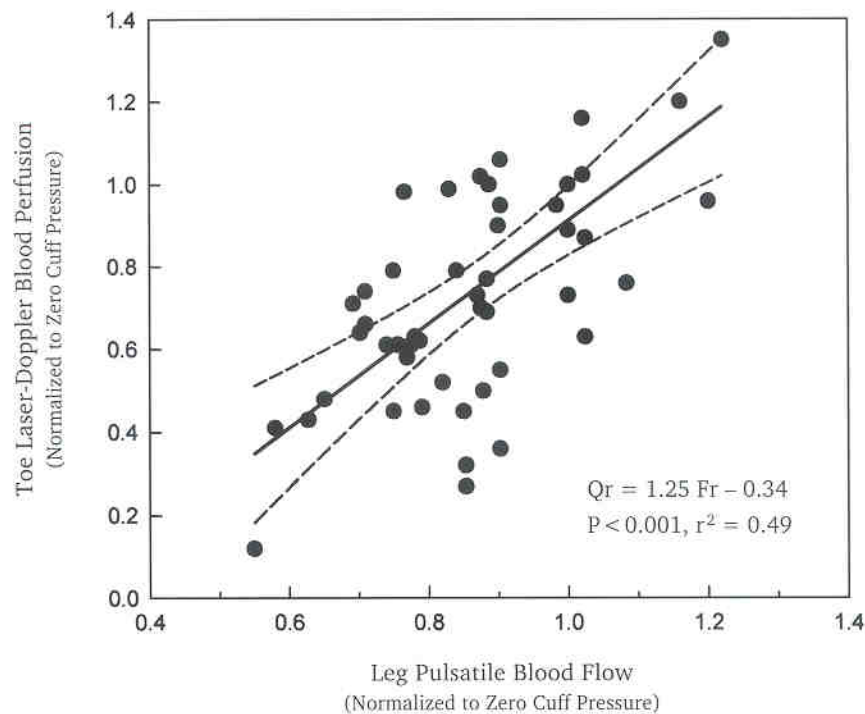
compression bandaging are significantly involved in the pulsatile flow increase phenomena. The present results are in accord with previous plethysmographic estimates of mean calf blood flow reductions due to proximal leg compression.<sup>21-23</sup> However, the present report appears to be among the first to describe the pulsatile arterial flow response. On the compressed limb this response was observed as a detectable reduction in midcalf blood flow, which began at the same thigh compression levels (10 to 20 mm Hg) as with the onset of distal microcirculatory reductions and paralleled these over the range of 10 to 30 mm Hg. But, above 30 mm Hg compression, blood flow continued to show a near linear decline, whereas relative decreases in distal skin perfusion were accentuated. This finding suggests the possible presence of a mechanistic alteration that occurs somewhere between 30 and 40 mm Hg. At least two possibilities to account for this observation may be put forward. At lower com-

pression pressures, venous distention (increased vascular conductance) may partially compensate for the reduced perfusion pressure.<sup>24,25</sup> But, at a certain threshold pressure (between 30 and 40 mm Hg), reserve distention may become exhausted and skin perfusion decrement becomes dominated by subsequent perfusion pressure reductions.<sup>26</sup> Alternatively (or coexistingly), a critical threshold between 30 and 40 mm Hg may need to be exceeded to reflexly trigger arteriolar vasoconstriction,<sup>27</sup> thereby accounting for the accelerated perfusion decrease.

#### Compression Effects on Distal Microcirculation

The present results also provide new information and insight about the impact of subarterial pressure compression on lower extremity distal (toe) skin microcirculation and its relationship to comeasured changes in lower extremity arterial





**Figure 3.** Pulsatile blood flow—Toe perfusion relationship. Data points ( $n = 60$ ) are all flow-perfusion pairs expressed as a fraction of baseline noncompressed values for 10 subjects. Solid line is linear regression with equation and statistics shown in the figure. Dashed lines are 95% confidence bands.

pulsatile blood flow. Reduction of distal microcirculation due to thigh compression began at a level of 10 to 20 mm Hg and progressed in a near linear fashion with 35% and 45% reductions in laser-Doppler perfusion noted at 40 and 50 mm Hg, respectively. These findings are consistent with other measurement methods. Ankle-to-knee compression produced by inflating the limb portion of an anti-gravity suit showed that midcalf local relative subcutaneous blood flow when compressed to 40 mm Hg was reduced by about 40% in the presence of vascular distention.<sup>25</sup> Interestingly, similar microcirculatory reductions (32% to 38%) on the foot dorsum have been reported for sustained ankle cuff-compression of 40 mm Hg<sup>28</sup> and for toe (36.8%) as a consequence of ankle-to-knee compression bandaging to an ankle pressure of 40 mm Hg.<sup>7</sup> It thus appears that these significant reductions in distal skin microcirculation as measured with laser-Doppler are relatively insensitive to the site of

application of the proximal compression. A common feature is the compression-related reduction in perfusion pressure to the distal site. If systolic ankle pressures are used as indices of noncompressed perfusion pressure (about 118 mm Hg for the present group), then compression to 40 mm Hg would be associated with a 33.9% reduction, a value that corresponds closely to the measured perfusion reduction. Thus, a plausible explanation of the main observed reduction in distal microcirculation is that it is primarily a consequence of compression-induced reductions in perfusion pressure. However, it is unlikely that this is a full account. Proximal compression also causes increased distal venous and venular distention that could contribute to the observed decrease in the laser-Doppler perfusion. Distention per se could reduce linear velocity in the venules sampled by the laser-Doppler and distention may also trigger reflex arteriolar constriction,<sup>29-31</sup> thereby reducing either or both the laser-Doppler

volume and velocity components. The relative amounts that these mechanisms may have contributed to the observed distal perfusion changes is at present unknown.

#### Microcirculatory— Macrocirculatory Relationships

In spite of a burgeoning literature on the assessment of lower extremity skin microcirculation using laser-Doppler methods, the way such measurements are related to or are impacted by arterial and venous hemodynamics still is unresolved. Although studies have shown certain group differences in distal skin blood perfusion between normal limbs and those with various levels of arterial<sup>32-37</sup> and venous disease,<sup>38-40</sup> the impact and relationship of changes in leg arterial blood flow on skin perfusion in the same leg at the same time essentially is unknown. Because of complex interactive vascular controls and interrelationships between arterial, microvascular, and venous circulations, it is not intuitively obvious how changes in one compartment will affect the others. Knowledge of such relationships is of fundamental and clinical importance but is accessible only by simultaneous micro- and macrocirculatory measurements. The present finding of a near-linear relationship between fractional decreases in distal laser-Doppler perfusion and simultaneously measured decreases in proximal pulsatile leg blood flow is the first direct demonstration of this linkage in human limbs. The analyses show that about 50% of the variation in distal skin perfusion is explainable on the basis of associated midcalf flow changes produced by graded thigh compression. One aspect of importance of this finding goes to the issue of confidence level of laser-Doppler perfusion as an index of microcirculatory versus macrocirculatory dysfunction. Much work has been directed to the use laser-Doppler measurements in both research and clinical settings to diagnosis, stratify, or grade lower extremity arterial and venous disease. Because changes in leg pulsatile blood flow accompany both arterial<sup>10</sup> and venous disease,<sup>20</sup> laser-Doppler measurements will reflect these changes but are also sensitive to local microvascular-based changes that may also be present. In patients with chronic venous disease or venous ulceration, laser-Doppler skin perfusion is reported to be elevated<sup>38-39</sup> and has been interpreted to be a local manifestation or feature of the underlying venous

disease. However, because leg pulsatile blood flow is also elevated,<sup>20</sup> interpretation of local skin perfusion data with respect to proximal and local contributions and affects should be viewed as more complex in view of the present findings. In limbs with peripheral arterial disease, with or without superimposed diabetic microvascular complications,<sup>34,37</sup> the problem may be more complex, because the impact of proximal arterial disease on leg pulsatile blood flow is variable and rarely is measured in a clinical setting. The demonstrated linkage between distal microvascular skin perfusion and calf pulsatile blood flow suggests that the utility of laser-Doppler diagnostic tests, findings, and ultimately their interpretation might be enhanced if due consideration were given the micro-macrovascular interactions.

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