Capillary Recruitment and Pain Relief on Leg Dependency in Patients With Severe Lower Limb Ischemia

Dirk Th. Ubbink, MD; Michael J.H.M. Jacobs, MD, PhD; Dick W. Slaaf, PhD; Geert Jan W.J.M. Tangelder, MD, PhD; and Robert S. Reneman, MD, PhD

Background. Patients suffering from severe lower limb ischemia may experience pain relief on leg dependency despite the fact that dependency normally results in arteriolar vasoconstriction. To clarify this possible paradox, skin microcirculation of the limb was investigated in 75 patients with different stages of lower limb ischemia and in 12 asymptomatic subjects.

Methods and Results. Using nailfold capillary video microscopy, red blood cell–perfused capillary density and diameter and red blood cell velocity were assessed in supine and sitting positions. Capillary density increased by changing from the supine to the sitting position, especially in patients with limb-threatening ischemia (showing a 4.5-fold increase versus a 1.5-fold increase in asymptomatic subjects). In subjects without or with mild ischemia, capillary perfusion was two to four times lower in the sitting than in the supine position. In patients with limb-threatening ischemia, perfusion was strongly reduced, being slightly higher in the sitting position. Patients with relief of pain while sitting did not always have a higher capillary perfusion but did have a higher capillary density in the sitting position.

Conclusions. The arteriolar postural vasoconstrictive mechanism at the nutritive level is still intact in subjects without or with mild ischemia but not in patients with severe ischemia. Capillary recruitment rather than disturbed arteriolar vasoconstriction could explain why patients with severe leg ischemia prefer leg dependency. (Circulation 1992;85:223–229)

Patients with severe lower limb ischemia may experience relief of nocturnal or rest pain on leg dependency. As yet, this phenomenon has not been explained satisfactorily. Under physiological conditions, arteriolar vasoconstrictive mechanisms lead to reduced lower limb perfusion when changing from the supine to the sitting position. The mechanism involved can be of central sympathetic and/or local origin. In the latter case, myogenic response and venoarteriolar axon reflex have been considered. There are indications that these mechanisms are disturbed in patients experiencing relief of pain on leg dependency, resulting in enhanced rather than decreased perfusion on dependency. In these studies, skin perfusion was measured with the use of the $^{133}$Xe washout method, transcutaneous oximetry, or laser Doppler fluxmetry. Techniques measuring total skin microcirculatory blood flow do not allow the distinction between capillary and thermoregulatory flow. Moreover, the measured increases in flow were often limited.

It was the aim of the present study to investigate the microcirculatory changes induced by leg dependency in patients with different stages of lower limb ischemia. To this end, in these patients skin nutritive flow was determined in both the supine and the sitting positions by using intravital video microscopy of the toe nailfold. Besides dynamic parameters, morphological parameters were also assessed because improvement on dependency might not only result from enhanced flow but also by an increase in erythrocyte-perfused capillary density leading to an enlarged surface area for exchange.

Methods

Patients

Twelve asymptomatic subjects and 75 patients suffering from arterial obstructive disease in at least one leg participated in the study. The age of the 62 men and 25 women ranged from 43 to 95 years (mean, 71

From the Department of Surgery (D.Th.U., M.J.H.M.J.), Academic Hospital Maastricht, Departments of Biophysics (D.W.S.) and Physiology (G.W.J.M.T., R.S.R.), Cardiovascular Research Institute, Maastricht, The Netherlands.

Address for correspondence: M.J.H.M. Jacobs, MD, Department of Surgery, Academic Hospital, PO Box 5800, 6202 AZ Maastricht, The Netherlands.

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years). Their symptoms were intermittent claudication, rest pain, and/or ulceration. The patients were divided into five groups (Table 1) according to their ankle-to-brachial pressure index (ABI). This ABI varied from 0% to 125%, being lowest in group 1 and highest in group 5. Fifteen of the 25 patients with rest pain experienced relief of pain on leg dependency. They all had an ABI of 50% or less and clinically belonged to Fontaine stage 3 or 4. Smoking habits and drug treatment, especially those interfering with vasoconstriction, are shown in Table 2.

Of the 12 subjects in group 5, two received medication for cardiac angina, one for hypertension, one for a recent myocardial infarction, and one for atherosclerotic symptoms of the leg not investigated here. These 12 subjects had a normal arterial system in the investigated leg not only because the ABI in this leg was higher than 95% but also because analysis of the Doppler signals of the major leg arteries showed no pathology, as opposed to the arterial Doppler signals of the patients in groups 1–4. The criteria to consider Doppler tracings to be pathological were 1) no backflow, 2) decrease of systolic signal and increased diastolic level caused by reduced peripheral vascular resistance (i.e., diminished pulsatility), and 3) prolonged rise time to peak velocity. Reduced backflow or a slightly reduced signal amplitude was not considered pathological.

Subjects with insulin-dependent diabetes mellitus were excluded from the study because this disease per se influences microcirculatory autoregulation mechanisms. However, 18 non-insulin-dependent diabetics did participate in this study. Their findings were interpreted separately to assess possible differences in microvascular reactivity between diabetic and nondiabetic patients. All were well-regulated diabetics. Peripheral neuropathy was ruled out when patients stated no experience of paresis or loss of sensibility and skin tactile sensibility showed no abnormalities during clinical examination. Patients refrained from smoking and did not take caffeine or alcohol for at least 1 hour before examination.

**Experimental Protocol**

Measurements were performed after 20 minutes of acclimatization in sitting position in a room between 23° and 24°C. Patients were subjected to capillary microscopy of the nailfold of the great toe (see “Equipment”) first in the sitting position and then in the supine position. Measurements in the sitting position were followed by a 10-minute interval in which the setup was readjusted and the patient could adapt to the supine position before repeating the measurements. In this position, capillary microscopy was performed after tilting the microscope and stage about 45°. The patient was positioned on a bench with the knee slightly (approximately 30°) flexed so that the foot could be placed on the stage of the microscope.

In both positions, capillary density was investigated first. Capillary diameter and red blood cell velocity (RBCV) were then measured in usually four but at least three capillaries. In patients in group 1, sometimes only three capillaries could sufficiently be investigated. The same capillaries could be identified and measured easily in either position because every capillary has a unique morphology. RBCV was assessed both at rest and during reactive hyperemia after a 1-minute arterial occlusion induced by inflating a cuff around the ankle. This hyperemia procedure was performed in each of the at least three capillaries investigated in both positions. To ensure that the previous hyperemic response had subsided, the measurements in the different capillaries were performed with an interval of at least 3 minutes, which is longer than the duration of reactive hyperemia. In the supine position, the leg was not completely straight but had 30° flexion in the knee. In this position, inflation of the ankle cuff cannot cause movement artifacts of the foot under the microscope. The aver-

<table>
<thead>
<tr>
<th>Group</th>
<th>ABI</th>
<th>n</th>
<th>Age (years, range)</th>
<th>Ankle blood pressure (mm Hg)</th>
<th>Fontaine clinical stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0–19%</td>
<td>12</td>
<td>81 (77–89)</td>
<td>16</td>
<td>0 0 0 5 7</td>
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<tr>
<td>2</td>
<td>20–39%</td>
<td>24</td>
<td>72 (53–81)</td>
<td>52</td>
<td>0 0 15 5 4</td>
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<tr>
<td>3</td>
<td>40–59%</td>
<td>23</td>
<td>70 (43–95)</td>
<td>75</td>
<td>0 0 19 1 3</td>
</tr>
<tr>
<td>4</td>
<td>60–95%</td>
<td>16</td>
<td>65 (45–76)</td>
<td>97</td>
<td>0 2 14 0 0</td>
</tr>
<tr>
<td>5</td>
<td>96–123%</td>
<td>12</td>
<td>67 (51–82)</td>
<td>150</td>
<td>12 0 0 0 0</td>
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ABI, ankle-to-brachial systolic blood pressure index; Fontaine '0', no arterial disease.

Table 1. Patient Groups

Table 2. Patient Characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Relief</th>
<th>Diabetes</th>
<th>Smokers</th>
<th>Vasoactive drugs</th>
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<td>3</td>
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Table shows number of patients who experienced relief of pain on dependency, nondiabetic-dependent diabetics, smokers, and number of patients using vasoactive drugs. Column A includes arterial and venous dilators (one patient in group 2 and one in group 4 used an angiotensin converting enzyme inhibitor); B, β-blocking agents; C, calcium antagonists.
average values of the capillary diameters and velocities, as measured at rest and during reactive hyperemia, were taken as the readings in both positions.

Systolic ankle and brachial blood pressure were measured in the supine position by means of a cuff and an 8-MHz Doppler probe to assess ABI. Brachial blood pressure was also measured with the Riva Rocci method to calculate mean arterial pressure (2/3 diastolic pressure + 1/3 systolic pressure). Finally, systolic ankle blood pressure was measured in the sitting position to calculate the orthostatic pressure increase after the change in posture.

**Equipment**

Capillary microscopy of the nailfold of the great toe is an established technique to assess nutritional skin circulation in patients with arterial occlusive disease.

The methods and equipment used have been described in detail elsewhere. In short, the nailfold to be investigated was covered with a drop of paraffin oil to improve skin transparency. Capillaries were visualized using a modified Leitz Orthoplan microscope and a Leitz 4× objective (numerical aperture, 0.14) to measure capillary density. A Leitz 10× objective (numerical aperture, 0.30) was used for velocity measurements. Magnification at the front plane of the television camera (Philips Newvic XQ 1275, 2/3-in. tube), positioned at the intermediate image plane, was 5× and 12.5×, respectively. The camera was rotated to orientate the capillaries parallel to the video lines. An image was produced on a monitor screen (Philips LDH 2122, 12 in.) with a final magnification of 165× and 410×. The images were stored on tape for off-line analysis using a videocassette recorder (Sony Betamax SL-C9 ES). A schematic drawing of the system used is presented in Figure 1.

Incident illumination was achieved using a Leitz Ploemopak 2.1 system equipped with a Leitz polarizer (POL) cube. The light from a 100-W mercury arc was projected directly through the POL cube and the objective lens onto the nailfold. The POL cube consists of a 50% transmission/50% reflection mirror in a 45° position with respect to the optical axis of the microscope. The POL cube contains a polarizer in the illumination pathway and a crossed analyzer in the image-forming pathway to cancel the light reflected from lenses and skin surface. Neutral density filters were used to adjust the light intensity at the camera, and a heat absorption/reflection filter was used to protect the skin against local temperature increases caused by the incident light.

**Off-line Analysis**

From the stored video images, the following parameters were assessed: 1) the number of erythrocyte-perfused capillaries per square millimeter of nailfold skin (density) as counted (at rest) in a video screen (effective surface area 1.86 mm²), that is, about 1.6 mm proximal of the terminal row of capillaries; 2) RBC (red blood cell) column width (representing the diameter) in the arteriolar limbs of the capillary loops in micrometers, measured halfway between the visible base and the crest of the loop: The distance between the measuring site and the capillary crest varied from about 50 to 250 μm. Within this distance, the diameter did not vary substantially; 3) RBCV (in micrometers/sec) assessed at rest (Restv) and at peak reactive hyperemia (Peakv): The velocity was measured with a flying spot device. This instrument generates dots that move over the monitor screen at a known, adjustable speed. RBCV is assessed by synchronizing the moving dots with the blood cells and plasma gaps in the arteriolar branch of the capillary.

This technique was used because very low velocities, as can be expected in the patients studied, can be assessed in a reproducible and more accurate manner than with other techniques currently in use. Peak RBCV was measured as follows: from the release of the cuff on, the reactive hyperemia response is observed and the velocity of the moving dots is synchronized continuously with the moving blood cells until the speed no longer increases. At this moment, RBCV is read from the display and is recorded as the peak velocity; 4) Capillary volume flow (Volflow) at rest per square micrometer of nailfold skin, that is, average Restv×π×(average capillary radius)²×capillary density per square micrometer; and 5) supine to sitting velocity ratios, obtained by dividing the RBCV in both positions in each patient: This ratio was used to obtain better insight into the individual changes in perfusion caused by changes in posture because it is an index for the effectiveness of the postural vasoconstrictive mechanisms (vasoconstriction index). This approach was taken because median ratios for a group may be different from the ratios calculated from the group median values. When RBCV was zero in both the supine and the sitting positions, the ratio was also regarded as zero.
Statistics

Because in each ABI group the results of all parameters obtained were not symmetrically distributed, medians are presented to characterize group values. The nonparametric Kruskal-Wallis test was used to evaluate differences between the five groups for statistical significance. The paired Wilcoxon signed ranks test was used for statistical analysis of differences between the two positions.

Results

Mean arterial blood pressures did not differ significantly between patient groups. Systolic ankle pressure was on the average 48 mm Hg higher in the sitting than in the supine position because of the increase in orthostatic pressure. This was a consistent finding independent of ankle blood pressure in the supine position. In each group, capillary microscopic parameters in diabetics did not differ significantly from those in nondiabetics in both positions and, therefore, the diabetic and nondiabetic data were pooled.

The individual data on RBC-perfused capillary density are presented in Figure 2. In the supine position, densities were similar in groups 2–5. In group 1, however, the median density was only 8/mm², which was significantly lower than the median density of 27/mm² in group 2 ($p<0.005$). RBC-perfused capillary density was lower in the supine than in the sitting position in all groups ($p<0.05$, NS in group 4). This was especially noticeable in group 1 (supine, 8/mm²; sitting, 34/mm²). In the sitting position, densities did not differ significantly between all groups and ranged from 34/mm² in group 1 to 62/mm² in group 2.

In Figure 3, individual data on capillary diameter are shown. In all groups, the diameter was significantly smaller in the supine than in the sitting position ($p<0.05$). Capillary diameters did not change significantly between the groups but tended to increase with a decrease in ABI.

The individual data on capillary Restv are presented in Figure 4. Induction of reactive hyperemia did not lead to an increase of the Restv in the
capillary examined subsequently, indicating sufficiently long time intervals. In the supine position, Restv was fairly similar in groups 2–5. In group 1, however, the median velocity (17 μm/sec) was significantly (p<0.001) lower than the median values in group 2 (168 μm/sec) through group 5. Restv in the sitting position was not significantly different between the five groups.

As can be seen in Figure 4, individual capillary Restv was about four to six times higher in the supine than in the sitting position in groups 2–5 (p<0.005), illustrating effective arteriolar vasoconstriction in the sitting position. In contrast, Restv in group 1 increased on dependency, leading to ratios below unity. However, this increase did not reach the level of significance.

In both positions, the trends in Peakv were similar to those in Restv (Figure 5). In the supine position, median Peakv was very low in group 1 (55 μm/sec compared with 175 μm/sec in group 2). In groups 1 and 2, Peakv appeared to be only slightly higher than the Restv, indicating the absence of reactive hyperemia. In the sitting position, Peakv decreased slightly from a median of 120 μm/sec in group 5 to a median of 59 μm/sec in group 1 and was two to four times higher in the supine than in the sitting position in groups 2–5.

In groups 3–5, volume flow (Figure 6) was persistently lower in the sitting than in the supine position. In group 1, however, in the supine position, volume flow was markedly reduced (p<0.005) compared with the other groups and increased significantly in the sitting position (p<0.05), most probably due to capillary recruitment.

All patients with relief on dependency had an ABI ≤50%. In this ABI range, the median ABI between patients with and without relief did not differ significantly (data are shown in Table 3). Patients with relief had considerably worse nutritive perfusion and showed a significantly (p<0.05) larger capillary diameter and a lower RBCV and Peak RBCV in the supine position and a lower vasoconstriction index (1.21 and 3.48, respectively) than patients without relief. However, capillary density in patients with pain relief increased (p<0.002) when changing from the supine to the sitting position and tended to be more than the increase (p<0.005) in patients without pain relief (2.7 versus twofold increase). Similar changes were found for volume flow. The patients with pain relief showed a fourfold increase, whereas those without pain relief showed a decrease.

Discussion

The findings in the present study show that in limb-threatening ischemia associated with ankle-to-brachial pressure indexes below 20%, skin capillary perfusion is significantly impaired and cannot cope with increasing demands, and the number of RBC-perfused capillaries is significantly reduced. A change in posture from the supine to the sitting position leads to reduced skin perfusion in asymptomatic subjects and patients with mild disease. However, in severely diseased patients, skin perfusion tends to increase with this change in posture.
These findings indicate that in subjects with normal or limited compromised circulation, the dependency-induced arteriolar vasoconstriction is still intact, but that this mechanism is disturbed in patients with severe ischemia. This disturbance is likely to be local in origin, but it is unknown whether it is caused by diminished contractile properties of the smooth muscle cells in the arteriolar wall or by disturbances in local reflex mechanisms.

It is an interesting observation that in both the asymptomatic subjects and the patients with mild or severe peripheral vascular disease, RBC-perfused capillary density increased significantly on dependency, thereby enlarging the surface area for exchange. This increase in density can possibly be explained by a rise in transmural pressure because the effective perfusion pressure does not change on dependency. In asymptomatic subjects and in patients with mild disease, the increase in density is associated with arteriolar constriction; therefore, the rise in capillary transmural pressure, if any, probably results from the increase in venous pressure. The transmural pressure increase on dependency is also indicated by the tendency of the capillary diameter to increase under these circumstances.

The observation that in not all patients with rest pain, dependency leads to pain relief (despite the fact that capillary density and blood flow increase when changing to the sitting position) may be explained by the progressed state of the disease in several of these patients. In some of them, rest pain was present in both the supine and sitting positions; although they reported having experienced pain relief on dependency in the past. This is of important clinical diagnostic value because it indicates a terminal stage of the disease in which the nutritional circulation will be insufficient in either position, inevitably resulting in tissue necrosis. The same can be said concerning severely diseased patients showing absence of reactive hyperemic response (i.e., loss of flow reserve). Further reduction of arterial perfusion pressure with progression of the disease will not lead to compensatory microvascular dilatation and will thus induce tissue loss.

In this study, postural microvascular reactivity in patients with noninsulin-dependent diabetes mellitus could not be discerned from nondiabetics. It is also possible that in both types of patients, atherosclerosis is the dominating disease.

It is concluded that in the clinic, posturally induced arteriolar vasoconstriction leading to diminished leg perfusion on dependency can be assessed with the use of capillary video microscopy. The findings in this study show that patients with limb-threatening ischemia (ABI <20%) show disturbed arteriolar vasoconstriction resulting in enhanced capillary recruitment and increased nutritive RBCV. The relief of pain on dependency may be explained by an increase in RBC-perfused capillary density, which enlarges the surface area for exchange rather than an increase in capillary perfusion.

References


**KEY WORDS** • ischemia • capillary microscopy • posture • vasoconstriction
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