Effects of Oxygen Inhalation on Skin Microcirculation in Patients With Peripheral Arterial Occlusive Disease

Olivier Bongard, MD; Henri Bounameaux, MD; and Bengt Fagrell, MD, PhD

Background. Oxygen administration is currently used in clinical medicine to improve peripheral oxygen delivery to tissues threatened by ischemia. However, conflicting results have been reported on the effects of oxygen in ischemic areas. This study was aimed at investigating the effects of 40% oxygen inhalation on the skin microcirculation in the feet of patients with peripheral arterial occlusive disease (PAOD).

Methods and Results. Transcutaneous oxygen tension (tc P02) was measured on the dorsal skin of the foot, and the nailfold microcirculation was investigated by a combination of laser Doppler flowmetry (LDF) and dynamic capillaroscopy (CBV) in the great toes of 17 legs of 11 patients, with 13 legs of eight normal subjects as a control group. Inhalation of oxygen induced a significant decrease of both the total (ΔLDF, -307%, p<0.02) and nutritional (ΔCBV, -17%, p<0.002) skin microcirculation in normal legs compared with baseline values. A similar response was observed in 10 legs of patients who showed a significant increase of the tc P02 (≥10 mm Hg) (ΔLDF, -14%, NS; ΔCBV, -13%, p<0.005). By contrast, both the total (+21%, p<0.03) and nutritional (+52%, p<0.05) circulation significantly increased in the seven legs without significant tc P02 increase. In addition, the flow motion, which was impaired in the patients, was significantly (p<0.05) improved by oxygen inhalation.

Conclusions. Inhalation of 40% oxygen induces a vasoconstriction in the skin microcirculation of toes of the normal subjects and patients with moderate PAOD but induces an increase of the skin microcirculation in patients with severe PAOD. (Circulation 1992;86:878–886)

KEY WORDS • vascular disease, peripheral • capillaroscopy, dynamic • flow motion • flowmetry, laser Doppler

Oxygen supplementation at atmospheric or high pressure is widely used in clinical medicine to improve oxygen delivery in tissues that are threatened by ischemia, e.g., in unstable angina, myocardial infarction, and stroke. This approach is largely accepted and is supported by several experimental and clinical studies.2,3 In patients with severe peripheral arterial occlusive disease (PAOD), however, a positive effect on the clinical outcome has not been convincingly shown.4

The systemic vasoconstrictory effects of oxygen inhalation have been well described for decades,5–7 and oxygen-induced decrease of regional blood flow has been clearly demonstrated in various vascular beds, e.g., the brain,8,9 the heart,1,2,10 and the limbs.11 This vasoconstriction represents an autoregulatory mechanism aimed at preventing an excessive and harmful increase in tissue oxygen tension. The results of several studies have shown that oxygen delivery to the tissues is not increased by oxygen inhalation in normal subjects because of this vasoconstriction.10–12

The exact mechanisms by which oxygen induces the vasoconstriction are not completely elucidated. Evidence is adduced that oxygen exhibits a direct constrictory effect on the vascular smooth muscle.5,9,13,14 Other mechanisms have also been proposed, such as the release of vasoactive substances from parenchymal cells triggered by changes in tissue oxygen tension13 and modulation by the endothelial cells via prostacyclin synthesis and release.9

The vascular effects of oxygen in ischemic regions are more conflicting. It has been shown by several authors, using different models and methods, that oxygen may improve perfusion in severely ischemic tissues. It has been postulated that the constriction of normal arteries increases the pressure gradient between normal and ischemic areas, diverting more blood to the threatened zone and consequently preventing or limiting the extent of tissue necrosis.1,10,11,15,16 On the other hand, oxygen administration might induce a further decrease of perfusion in ischemic tissues that may counteract the benefit of the increase of the blood oxygen content.13,14

Transcutaneous oxygen tension (tc P02) has been used for many years in clinical routine to evaluate the viability of the skin in severely ischemic extremities. More recently, the administration of oxygen at atmospheric pressure has been shown to markedly improve both the sensitivity and the specificity of the measurement. Thus, changes of the tc P02 with oxygen inhalation have been proposed for diagnostic purposes in

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TABLE 1. Characteristics of Patients and Normal Subjects

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=11) (17 legs)</th>
<th>Normal subjects (n=8) (13 legs)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range)</td>
<td>49 (28-79)</td>
<td>37 (25-72)</td>
<td></td>
</tr>
<tr>
<td>Men/women</td>
<td>8/3</td>
<td>7/1</td>
<td></td>
</tr>
<tr>
<td>Smoking (n)</td>
<td>9</td>
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<tr>
<td>Diabetes (n)</td>
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<td>0</td>
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<tr>
<td>Dyslipidemia (n)</td>
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<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypertension (n)</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Arterial systolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm</td>
<td>162±27</td>
<td>129±15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ankle</td>
<td>98±33</td>
<td>140±14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Great toe</td>
<td>35±17</td>
<td>106±18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Arm–ankle index</td>
<td>0.77±0.25</td>
<td>1.1±0.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arm–toe index</td>
<td>0.28±0.14</td>
<td>0.71±0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pedal (tc Po2) (mm Hg)</td>
<td>44±16</td>
<td>64.5±8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Arteriographic localization of significant stenoses (>50%) or occlusions:

One-level disease (legs, n) 9 (aortoiliac or thigh or calf segments)

Multilevel disease (legs, n) 8 (combination of two or more segments)

Values are mean±SD (mean and range for age).

*Mann-Whitney U test.

severe peripheral ischemia.16-19 These studies indicate that the responsiveness to oxygen inhalation reflects the reactivity of the vasculature in the ischemic area. In patients with PAOD, this responsiveness, as evaluated by the increase of the tc Po2, is a marker of the severity of the disease19 and has been shown to be an excellent predictor of the short-term prognosis of severely ischemic limbs17 and of the outcome of amputations18,20 and arterial reconstructions.19

The aims of the present study were to investigate the changes of the skin microcirculation in severely ischemic limbs induced by oxygen breathing at atmospheric pressure and to evaluate the relation between these changes and those of the pedal tc Po2. The combination of dynamic capillaroscopy and laser Doppler flowmetry was used to evaluate simultaneously the nutritional and the total skin microcirculation in toes of patients with PAOD, with normal subjects used as a control group.

Methods

Patients and Control Subjects

Seventeen legs of 11 patients with ischemia (severe claudication, n=4; rest pain, n=6; gangrene, n=1) and 13 legs of eight healthy subjects according to history and physical examination were investigated. All the patients had undergone arteriography. Patient characteristics are displayed in Table 1.

Transcutaneous Oxygen Tension

A polarographic Clark-type electrode that heated the skin at 44°C was used for measuring the tc Po2 (Roche-Kontron 630 Monitor).21 The probe was applied to the dorsal skin of the foot between the first and second metatarsi. A 20-minute equilibration period elapsed before the first tc Po2 values were recorded.

Dynamic Capillaroscopy

The method is shown in Figure 1 and has been described in detail elsewhere.22 The capillaries of the nailfold of the great toe were displayed on a video monitor by means of a Leitz epi-microscope connected to a video camera. The scenes (final magnification, ×500) were stored on videotape for further analysis. The sharpest capillaries with the best contrast were chosen for blood cell velocity measurements. The capillary blood cell velocity (CBV) was measured by a videophotometric technique with a computerized system (CapiFlow, CapiFlow AB, Kista, Sweden): two photometric windows are generated by the computer and placed along the arteriolar limb of the investigated capillary. The videodensitometric signals of the windows are cross-correlated, and the interwindow transit times for similar signals are determined. With a known interwindow distance, the CBV can be continuously calculated and displayed on the computer screen.

Laser Doppler Flowmetry

The laser Doppler flow (LDF) was measured close to the investigated nailfold area by means of a laser Doppler flowmeter (MBF3D, Moor, England). The LDF signal (time constant, 0.5 seconds) was displayed on a chart recorder, and the LDF values were automatically averaged by the flowmeter. Mean LDF values are expressed in arbitrary units (AU). An arterial occlusion was performed by inflating a miniature cuff placed at the base of the investigated finger to determine the
residual LDF value (biological zero), which was subsequently subtracted from all the LDF values.

**Investigating Procedure**

The patients were resting comfortably in the supine position for 20 minutes before the measurements started. The legs were placed in a flexed position over a support for the great toe to be in a favorable horizontal position on the microscope stage (Figure 1). Great care was taken to avoid impairment of the blood supply to the leg. The skin temperature, CBV, and LDF (see Figure 1) were continuously measured during the whole investigation according to the following procedure: 1) for 3 minutes during room air breathing, 2) for 6 minutes during oxygen breathing with a Venturi mask that was adjusted to provide a fraction of inspired oxygen (FIO2) of 40%, and 3) for 3 minutes after the oxygen had been discontinued. The dose (10 l/min at atmospheric pressure) and route (Venturi mask at 40%) of oxygen administration have been chosen as in previous studies17,18,20 because they are widely available and used in clinical routine and provide the highest supplementation of oxygen without special equipment.

In the control subjects, an additional measurement was performed for 3 minutes while the subject breathed oxygen through a face mask equipped with a rebreathing reservoir aimed at increasing the FIO2 to close to 100%. Mean CBV and LDF values were obtained by averaging, each time, a 3-minute recording. The last 3 minutes of the 6-minute period were used to calculate changes induced by oxygen breathing.

**Response of tc Po2 to Oxygen Breathing**

As in previous studies,17,18 an increase of the tc Po2 of ≥10 mm Hg during oxygen breathing was considered significant, and the patients were classified as O2 responders (O+) when the tc Po2 increased ≥10 mm Hg and as O2 nonresponders (O−) when the increase was <10 mm Hg.

**Skin Temperature**

The skin temperature was continuously recorded in the investigated area with a thermistor. The room temperature was between 22.3 and 24.6°C and varied by less than 0.5°C during the investigation time.

**Flow Motion Activity**

Rhythmic oscillations, i.e., flow motion, of the CBV and LDF were divided according to Seifert et al23 into large and small waves. The frequency of the large waves was expressed in cycles per minute. The amplitude of the large waves was measured from the nadir to the top of the wave and expressed in percent of the mean CBV and LDF. Frequencies and amplitudes were averaged from at least a 2-minute period. Flow motion was considered absent if there was no easily distinguishable rhythmic activity (maximal wave amplitude, <10%; sporadic waves). For the small waves, only the prevalence and the frequency in the LDF tracings were considered.

**Statistical Analysis**

Values are expressed as median and range. The Mann-Whitney U test (two tailed), Wilcoxon signed rank test, and χ² test were used for statistical analysis when appropriate. A probability value of less than 0.05 was considered significant.

**Results**

**Resting Microcirculation**

Both the CBV (0.39 [range, 0.12–1.8] versus 0.13 [range, 0.06–0.75] mm/sec, p<0.01) and LDF (19.1 [range, 1.6–94] versus 7.4 [range, 1.2–81] AU; NS) were higher in normal subjects than in PAOD patients, but the difference was significant only for CBV. The skin temperature was similar in the two groups (26.6°C [range, 23.5–33.3°C] versus 27.5°C [range, 23.1–33°C]; NS). The CBV and LDF were positively correlated to the skin temperature, both in normal subjects (r=0.77, p<0.003 and r=0.86, p<0.0001, respectively) and in PAOD patients (r=0.48, p<0.05 and r=0.74, p<0.02, respectively).

**Oxygen-Induced Changes in Normal Subjects**

Oxygen breathing with a FIO2 of 40% induced a significant increase of the tc Po2 from 65 (range, 47–80) to 90 (range, 60–165) mm Hg (p<0.002) and a significant decrease in both CBV (−17% [range, −58% to +13%], p<0.02) and LDF (−30% [range, −47% to −9%], p<0.002) (Figure 2). The tc Po2 returned to the basal values after oxygen breathing discontinued. However, the CBV and LDF did not return to baseline. Oxygen breathing at 100% induced a further increase of the tc Po2 (140 [range, 87–255] mm Hg, p<0.002) and a decrease of both the CBV (−29% [range, −47% to +70%]; NS) and LDF (−31% [range, −75% to +44%], p<0.02) in most subjects compared with the values obtained at 40%. No significant changes were observed in the skin temperature.

**Oxygen-Induced Changes in Patients with PAOD**

Ten legs had an increase of the tc Po2 ≥10 mm Hg during oxygen inhalation (O+ group), whereas seven other legs did not have a significant increase (O− group). As shown in Figure 3, the magnitude of oxygen-induced tc Po2 response was correlated to the great toe systolic blood pressure (r=0.46, p=0.062), and there was a strong relation (χ² 7.13, p<0.008) between the lack of significant tc Po2 increase and the presence of multilevel arterial disease (two or more significant stenoses and/or occlusions) as assessed by arteriography. However, the resting tc Po2 (48 [range, 10–64] mm Hg versus 50 [range, 16–60] mm Hg; NS), CBV (0.11 [range, 0.06–0.57] mm/sec versus 0.14 [range, 0.06–0.75] mm/sec; NS), LDF (8.5 [range, 1.5–81] AU versus 6.5 [range, 1.2–34] AU; NS), and skin temperature (29.3°C [range, 23.6–33°C] versus 25.6°C [range, 23.1–29.6°C]; NS) were similar in the O+ and O− groups.

Oxygen inhalation induced changes of the cutaneous blood flow in all toes of the patients. However, the changes consisted in either a decrease (Figure 4A) or an increase (Figure 4B) of the flow. The skin flow, as evaluated by both the CBV (−12.5% [range, −5.3% to 83%], p<0.05) and the LDF (−15% [range, −41% to −11.4%]; NS), decreased in 10 toes, whereas those parameters clearly increased in the seven other toes (CBV, +50% [range, 23.1% to 116%], p<0.05 and LDF, 20.6% [range, 2% to +78%], p<0.05). Changes of the CBV and the LDF were concordant in all except...
three instances. There was a weak, negative correlation between changes in the tc PO₂ and both the CBV (r=0.41, p=0.06) and LDF (r=0.38, p=0.16). The legs that had a decrease in the skin flow corresponded almost exactly to the O+ group, whereas the O- group corresponded to limbs in which an increase in the skin flow was observed. Consequently, as shown in Figure 4, opposite and significant changes were observed between the two groups: The O+ group behaved similarly to the control group with a decrease in both the CBV (-13% [range, -83% to -5.2%], p<0.05) and the LDF (-14% [range, -41% to 26%]; NS), although the level of significance was not reached for the latter. The decrease of the LDF was significantly less than in normal subjects, whereas the decrease in CBV was the same. By contrast, both CBV (+52% [range, -33% to 116%], p<0.05) and LDF (+21% [range, 2% to 78%], p<0.05) increased in the O- group. (See Figure 5.)

**Flow Motion Pattern of CBV and LDF**

Characteristics of the flow motion are summarized in Table 2. All except two tracings could be clearly analyzed. A large-wave flow motion activity was observed in all toes of the normal subjects for both the CBV and LDF. In the PAOD patients, the prevalence of the large waves was significantly decreased only in the LDF curves (8 of 15, p<0.01) and was lower in the O- than in the O+ group (16% versus 77%; NS). In both the normal subjects and the patients, no significant correlation was observed between CBV and LDF flow motion patterns regarding frequency and synchrony. In some patients, the discrepancy between the rhythmical oscillations of the CBV and LDF was striking. This is illustrated in Figure 6, where marked rhythmic oscillations of the CBV can be seen with a completely flat LDF curve.

No small waves were observed in the control group, but the prevalence of these small waves was 58% in the patients. There was a significant correlation with the severity of the disease as evaluated both by the clinical stage (p<0.002) and the tc PO₂ (p<0.003). Oxygen breathing did not have any influence on the LDF flow motion characteristics in the normal subjects but induced flow motion in all patients. This effect was predominant in the O- group. The prevalence of CBV flow motion was already high at room air (85%), and oxygen did not influence the prevalence or frequency of these waves.

**Discussion**

Dynamic capillaroscopy and laser Doppler flowmetry have been shown to be of value to investigate simultaneously the nutritional and the total skin microcirculation in fingers and toes of normal and ischemic limbs. By the combination of these techniques, we have previously shown that the dynamics of the skin microcirculation is impaired in toes of patients with PAOD and the blood flow is maldistributed rather than reduced. As oxygen administration has been shown to
A decrease blood flow in the normal skin microcirculation and to increase the flow in ischemic skin of toes of patients with severe PAOD, we used these techniques to investigate the effects of oxygen breathing on the skin microcirculation in toes of patients with PAOD, a region most susceptible to ischemia.

**FIGURE 4.** Simultaneous tracings of the capillary blood cell velocity (CBV) and laser Doppler flow (LDF) recorded in two patients with peripheral arterial occlusive disease showing (panel A) a decrease of the skin blood flow during oxygen breathing that was associated with a significant increase of the tcPO2 and (panel B) an augmentation of the flow without a significant increase of the tcPO2. Note the marked stimulation of the laser Doppler flow motion. AU, arbitrary units.
In the present study, baseline CBV was found to be significantly lower in toes of patients with PAOD than in normal subjects. In addition, the total skin microcirculation, as evaluated by the laser Doppler technique, was somewhat but not significantly reduced in the patients, which is consistent with earlier results.24-26

There was a dose-dependent reduction of the blood flow in the normal skin during oxygen breathing, in agreement with the vasoconstrictor effects of oxygen reported in the literature.3,8,10,12,27,28 The magnitude of the reduction of flow (CBV, -29% and LDF, -41%) was larger than that reported in the forearm with pure oxygen (-11.2% and -20.1% at 1 and 2 atmospheres, respectively),11 but it was similar to the reduction observed in normal foot (43%)28 at 2 atmospheres. One explanation for these discrepancies may be that forearm and calf blood flow is mainly muscular, and this is much less influenced by oxygen breathing than skin blood flow, which constitutes most of the flow that is measured at the foot.28 This view is supported by the twofold difference reported by Schraibman and Ledingham28 between the reduction of the flow measured at the calf and at the forefoot (21% versus 43%).

Oxygen breathing induced changes of the skin blood flow in all the legs of the patients. In contrast to the control subjects, however, the changes consisted of a marked and significant augmentation of the skin flow in seven extremities and a moderate reduction of the flow in 10 others. Such a "paradoxical" increase of the flow in ischemic tissues during oxygen administration has been previously reported in brain9,29 and extremities11,28 and hypothesized in heart,1,3 Direct or indirect evidence that oxygen may produce such a "paradoxical" increase of the blood flow in severely ischemic areas has been provided in various vascular beds by means of different methods. Schraibman and Ledingham28 measured the blood flow at the forefoot and reported an increase of flow in two of six patients with rest pain and/or gangrene. The flow also decreased in the four others, but markedly less than in the control subjects (13% versus 43%). Similar findings were reported by Fredenucci,15 who measured an increase of the pulse amplitude of the great toes in 42 of 104 patients with PAOD during hyperbaric oxygen administration. A vasoconstriction was seen in only 22 patients. In the present study, direct evidence of a "paradoxical" increase of the skin blood flow was found in seven of the toes in patients with PAOD. A reduction of flow was still observed in the 10 other limbs, but the magnitude of the change was much less for both the CBV and LDF compared with the normal legs, in agreement with the results of Schraibman and Ledingham28 and Fredenucci.15 One important finding was the augmentation of the blood flow, which was larger in the nutritional capillaries than in the nonnutritional skin vessels (52% versus 21%; NS), as evaluated by the CBV and LDF, respectively. These results suggest that oxygen inhalation may induce a significant augmentation of the blood flow in the skin of severely ischemic toes. This increase of the skin flow is likely to result from an increased pressure gradient.
between ischemic and normal tissues resulting from the oxygen-induced vasoconstriction in the latter. In the legs with moderate ischemia, where the reactivity of the microvasculature is impaired but not abolished, vasoconstriction is still observed. Schraiman and Ledingham28 postulated that the ischemic lesions had to be relatively extensive before the vasoconstriction response to oxygen was abolished. This is supported by the negative relation found between changes of skin blood flow and tc Po₂ in the present study. As shown in Figure 5, the absence (O− group) or the presence (O+ group) of a significant increase of the pedal tc Po₂ (change ≥10 mm Hg) appeared to be an excellent discriminant between legs with and without oxygen-induced skin flow augmentation. Several previous studies17-19 have shown that the response of tc Po₂ to oxygen breathing reflects the severity of PAOD. This is fully supported by the relation that was found in the present study between tc Po₂ changes and both great toe systolic blood pressure and severity of arteriographic lesions (Figure 3). Consequently, it may be concluded that oxygen induced an increase of the blood flow only in toes of legs with the most severe ischemia.

There are, however, two possible limitations to this conclusion. One refers to the variability of the techniques used. Indeed, CBV depends on several factors, e.g., skin temperature and vasomotion, and may vary considerably from one capillary to another in the same area. Similarly, the laser Doppler signal is also dependent on skin temperature and may vary considerably if the laser Doppler probe is moved. Consequently, there is a large variability of both CBV30,31 and LDF32,33 for interindividual or day-to-day measurements. In the present study, however, the same capillary was monitored during the whole investigation, the laser Doppler probe was not moved, and skin temperature was stable during the investigation period. Mean CBV and LDF were averaged from 3-minute periods, and oxygen-induced changes were calculated using baseline values within the same recording. Consequently, as both techniques have been shown to be accurate,24-37 it is very likely that the changes observed in the tracings result from the acute provocative test, i.e., oxygen inhalation. The second limitation of our study could be the poor matching of the control group for age and risk factors. Our aim, however, was to evaluate the physiological effects of oxygen inhalation in healthy subjects with normal arteries, i.e., without atherosclerosis. It would have been very difficult or impossible to recruit such a group among older healthy subjects with cardiovascular risk factors. Since the O− and O+ groups were comparable in regard to these parameters, we do not feel that our conclusions may be invalidated. Furthermore, the fact that the O+ group behaves similarly to the control group suggests that cardiovascular risk factors only weakly influenced the oxygen-induced response.

The flow motion activity was impaired in the patients with PAOD, and the modifications of the patterns are in full agreement with previous studies.25,24 Small waves were observed with a high prevalence (58%) in the patients, and their presence correlated with the severity of the disease. The prevalence of the large flow motion wave, as evaluated by LDF, was significantly decreased in the patients. The prevalence of the large wave was higher on the tracings of the CBV than LDF, and there was a complete lack of concordance regarding both

TABLE 2. Characteristics of Flow Motion Activity in Patients With Peripheral Arterial Occlusive Disease and Control Subjects

<table>
<thead>
<tr>
<th>Characteristics of large waves</th>
<th>CBV</th>
<th>LDF</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Room air</td>
<td>40% Oxygen</td>
</tr>
<tr>
<td>Control group</td>
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<tr>
<td>Prevalence (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Frequency (cpm)</td>
<td>4 (5-11)</td>
<td>6 (1.5-9)</td>
</tr>
<tr>
<td>Amplitude (%)</td>
<td>50 (20-70)</td>
<td>50 (10-100)</td>
</tr>
<tr>
<td>PAOD group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>85</td>
<td>90</td>
</tr>
<tr>
<td>Frequency (cpm)</td>
<td>5 (1.5-7)</td>
<td>3 (0.5-5)</td>
</tr>
<tr>
<td>Amplitude (%)</td>
<td>20 (10-100)</td>
<td>40 (20-100)</td>
</tr>
<tr>
<td>Prevalence of small waves, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>0/15 (0)*</td>
<td>0/15 (0)</td>
</tr>
<tr>
<td>PAOD group</td>
<td>10/17 (58)</td>
<td>10/17 (58)</td>
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<tr>
<td>Claudication</td>
<td>3/8 (37)</td>
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<tr>
<td>Rest pain</td>
<td>6/8 (75)</td>
<td></td>
</tr>
<tr>
<td>Gangrene</td>
<td>1/1 (100)</td>
<td></td>
</tr>
<tr>
<td>Frequency (cpm)</td>
<td>18 (14-22)</td>
<td></td>
</tr>
</tbody>
</table>

CBV, capillary blood cell velocity; LDF, laser Doppler flow; PAOD, peripheral arterial occlusive disease; cpm, cycles per minute.
Values are median and range.
*Significant difference between control subjects and patients.
frequency and synchrony between the respective flow motion activities (Figure 6). All these findings indicate that the flow motion activity is preserved longer in the nutritional than in the nonnutritional skin vessels and provide further evidence that the flow motion activities evaluated by CBV and LDF originate from different vascular structures. Oxygen breathing stimulated the flow motion activity of the LDF as indicated by the drastic increase in large-wave prevalence from 53% to 100% (Figure 4B). By contrast, the small waves were not significantly influenced by oxygen. The reason for this discrepancy is not clear. The tone of the vascular smooth muscle is dependent on the local arterial oxygen pressure, and vasomotion is directly dependent on the vascular tone in addition to the pacemaker-like activity present in the smooth muscles of the arterioles. Consequently, one explanation could be that a slight increase of the oxygen content in the blood may be sufficient to improve the tonus of the vascular smooth muscle and thus the large flow motion wave activity but that the hemodynamic changes in the nutritional vascular bed may not have been large enough to influence the prevalence of the small waves, which would be a compensatory mechanism to improve the nutritional blood flow in ischemic areas.

In normal subjects and in the O+ group, oxygen inhalation induced a vasoconstriction and an increase of the pedal tc PO2, whereas an augmentation of the skin blood flow was observed in the O− group. The tc PO2 depends on several factors that are temperature dependent, such as oxygen diffusion and metabolic consumption in the skin. After equilibration, however, the value of the tc PO2 is dependent only on tissue oxygen delivery, which is the product of the local blood flow and the arterial oxygen partial pressure. The augmentation of the FiO2 from 21% to 40% or 100% does not lead to a substantial increase of the oxygen content of the blood, which is about 10% for an FiO2 of 100%. The respective influence of increased FiO2 and blood flow on tc PO2 has been studied by Moosa et al, who used an experimental model in dogs in which the regional blood flow was gradually diminished at increased FiO2 (21% to 100%). It was shown that tc PO2 was dependent primarily on oxygen arterial tension at relatively preserved flow rates (>50% of baseline). At low flow rates (≤25%), however, tc PO2 was dependent solely on the flow and could not be augmented by an increase of the FiO2. Consequently, and as others have indicated as well, we doubt that the small augmentation of the arterial oxygen content alone explains the increase of the tc PO2 that was observed in some of the patients. In fact, this increase could result from an augmentation of the local blood flow. This view is supported by the results of the present study, which showed that significant oxygen-induced increases of the pedal tc PO2 were associated with decreases in the acral skin flow. As the regulation of the blood flow is locally abolished under the tc PO2 electrode because of the incorporated heating system, it may be hypothesized that the flow is diverted from the surrounded vasoconstricted area toward the vasodilated tissue under the tc PO2 electrode. Conversely, the tc PO2 did not change in the feet, showing an increase of the skin blood flow, which suggests that the blood was diverted toward the
ischemic toes instead of under the tc PO2 electrode. Thus, a lack of augmentation of the tc PO2 during oxygen breathing may paradoxically indicate that the skin microcirculation is open to improvement.

We conclude that the inhalation of 40% oxygen induces a decrease of the blood flow in the normal skin microcirculation and an increase of the blood flow in ischemic skin of toes of patients with severe PAOD. Consequently, oxygen delivery to tissues threatened by ischemia may be augmented by oxygen supplementation, which may be of paramount importance in patients with ischemic acral lesions. However, this benefit seems to be restricted to patients who show no significant increase (<10 mm Hg) of their pedal tc PO2 upon oxygen inhalation.

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