Patterns of Skin Flowmotion in the Lower Limbs of Patients with Chronic Critical Limb Ischaemia (CLI) and Oedema

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Objective: To study flowmotion (FM) in lower limbs with critical limb ischaemia (CLI) and oedema and to elucidate FM patterns when skin viability is threatened.

Material and methods: Fourteen patients with unilateral CLI and oedema and two control groups were included – one consisting of 10 healthy participants and the other nine patients with unilateral CLI without oedema. Laser Doppler was used to evaluate the foot skin microcirculation simultaneously at four different areas, with the limbs in supine and dependent position. FM was expressed using fast Fourier transformation (FFT) as low frequency (LF) and high frequency (HF) waves and their respective FFT-powers.

Results: All patients with CLI, both with and without oedema, showed HF waves in both diseased and contralateral limbs. These were absent in healthy controls. There were no regional differences in frequency in the critically ischaemic feet (with and without oedema) and between ischaemic and their contralateral feet. Changing the position of ischaemic limbs from supine to dependency had no significant effect on the frequency, while a significant increase of the median FFT-powers of LF and HF waves at the pulp of the first toe was observed. This manoeuvre resulted in decrease of the median FFT-powers of LF in healthy controls.

Conclusions: HF waves are associated with CLI. Ischaemia also appears to influence the FFT-power of each frequency domain. Ischaemic oedema does not seem to affect the pattern of FM in the foot of patients with CLI.

Key Words: Chronic critical limb ischaemia; Ischaemic oedema; Flowmotion; Laser-Doppler fluxmetry.

Introduction

Oedema is commonly observed in limbs with critical limb ischaemia (CLI) and may be related to the severity of ischaemia.1,6

Electron microscopic studies of skin in patients with CLI and oedema showed that the arterioles were dilated. The same study demonstrated an uneven distribution of erythrocytes in dilated capillaries.2 The vasodilatation of arterioles may occur as a consequence of ischaemia per se and a disturbance in the veno-arteriolar reflex (VAR) in the foot of these patients.7,10 The cause of an uneven distribution of erythrocytes in these dilated capillaries is not understood. It might be related to other regulatory mechanisms which try to compensate for the “low flow state” in critically ischaemic tissue, e.g. “flowmotion”.

Flowmotion (FM) is a rhythmical, cyclic variation of blood perfusion in a tissue. Three frequency components of FM can be distinguished: (1) low frequency waves (LF: 1–10 cycles per min), (2) high frequency waves (HF: 10–25 cycles per min), (3) pulsations related to cardiac rhythms.11 Its underlying mechanism is called vasomotion, and is due to the changes in smooth muscle cell tone in the wall of small arteries and arterioles.12–15 The precise physiology of vasomotion is not completely understood, but neurogenic, myogenic, humoral, and metabolic factors may all play a role.16

Since oedema probably adds to the severity of CLI, and FM supposedly promotes homeostasis of the microcirculation,17,18 the purpose of the present study was to elucidate the possible consequences of local oedema formation on FM in critically ischaemic skin.

Patients

Fourteen patients with unilateral CLI and oedema were included.19 There were nine women and five men with a mean age of 77 ± 9.8 years. The control group
Table 1. Summary of patients’ characteristics and vasoactive medication.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CLI with oedema (n=14)</th>
<th>CLI without oedema (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest pain</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Ischaemic skin ulcer</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Gangrene</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Signs of infection</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Smoking</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Antiplatelet drugs</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Warfarin</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>*ACE-inhibitors</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>β-Blocking agents</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

* Angiotensin Converting Enzyme.

was six women and three men with a mean age of 75 ± 11 with unilateral CLI but without oedema (Table 1).

Patients who previously had undergone vascular surgery, those with an amputated contralateral limb, bilateral CLI, clinical signs of congestive heart failure, diabetes mellitus, manifest venous insufficiency or lymph oedema were excluded. Smokers had abstained from smoking since admission to the hospital.

Another age-matched control group, 10 healthy voluntary subjects, seven women and three men, without clinical signs of peripheral atherosclerosis and a normal ankle brachial blood pressure index (ABI) were included.

The study was accepted by the Regional Ethical Committee of Southern Norway. All patients gave their written consent.

Methods

Ankle and brachial pressures index (ABI) was measured with ultrasound Doppler technique.²⁰²¹ In the limbs where Doppler signals were not detected, ankle pressure was defined at 15 mmHg.

Laser Doppler fluxmetry

Two laser Doppler (LD) fluxometers (Periflux PF 4001 and 4002, Perimed AB Järfalla, Sweden),²² with two channels each was used to simultaneously evaluate the microcirculation at four different areas of the skin. The depth of measurement by using PF 4001 and 4002 is approximately 0.5–1 mm, but varies depending on blood content of the tissue, degree of oxygenation and skin pigmentation.²² The laser Doppler flux (LDF) values, expressed as perfusion units, (PU) were saved by means of a Perisoft acquisition and analysis software program (Perimed AB) in a computer for offline analysis.

Recording of foot position

To record alteration in foot position, a water-filled, open-ended manometer line connected to a pressure monitor (Pressure Monitor, Stranden) was attached to the skin at the dorsum of the foot. This device recorded vertical movements of the foot during the measurements. Changes in pressure indicated variations in the height of the foot.

Procedure

The laser probes were applied at four different areas by using a probe holder and double adhesive tape (Fig. 1): the pulp of the first toe (Site 1), at the level of the second metatarsal body (Site 2) and at the anterolateral part of ankle (Site 3). A fourth probe was attached to the first toe of the contralateral limb as a reference. “M” is a water filled, open ended manometer line connected to a pressure monitor for recording of variations in foot position.
for 3 min, and the mean value of the last 2.5 min during that period represented the LDF value for the supine position. Subsequently, the CLI limb was passively lowered by flexion in the knee joint with the three laser probes still being attached (Fig. 1). The LDF values were recorded for 3 min and the final 2.5 min represented the LDF values for the dependent limb. The limb was lifted up again to the horizontal position to repeat the same measurements. This procedure was repeated three times for each patient with a total sampling time of more than 18 min for each participant.

Data analysis

The laser Doppler (LD) signal was transformed to a frequency domain by fast Fourier transformation (FFT, Perisoft for Windows ver. 1.19, Perimed AB, Järfälla, Sweden). The software allowed changes in time scale (x-axis) and signal amplification (y-axis) to facilitate the analyses.

Various physiological activities which occur in time (“attractors”), such as cardiac activity, respiration, and variations in the microcirculation caused by neuronal or myogenic activity, may be represented in different frequency regions following the FFT. The results of FFT are expressed as frequency (cycles per second) of the attractors and FFT-power (“intensity”, arbitrary units, Fig. 2) of each of the frequency regions. There is a positive correlation between the derived FFT-power in both LF and HF regions and skin perfusion (LD) at the different measuring sites. A high power indicates that a specific frequency occurs regularly with a LD signal well above the noise level, and acts as a “quality-parameter”.

Leg and foot volume measurements

The distal leg and foot volumes were measured by using water displacement volumetry (WDV) as previously described in detail. The differences in distal leg and foot volume between the two limbs were calculated.

Statistics

Wilcoxon matched-pairs signed-ranks test was used for comparing changes in ABL, ASP, median frequency waves and FFT-power for both LF and HF waves between horizontal and dependent position in each site, and between CLI limbs and the contralateral limbs, and between the limbs in the control group. Mann–Whitney and ANOVA tests were used to compare differences in median frequency waves and FFT-power for both LF waves between limbs with CLI, with and without oedema, and healthy control group, both in horizontal and dependent position. The results were presented as medians with ranges in parentheses, and mean ± standard deviation (s.d.), with \( p < 0.05 \) as the level of statistical significance. GraphPad Prism 3.0 was used for analysis and presentation of data (GraphPad Software, Inc., San Diego, CA, U.S.A., www.graphpad.com).

Results

There was no statistically significantly difference in mean ankle brachial index (ABI) and ankle systolic pressure (ASP) between the critically ischaemic limbs with (0.19 ± 0.13 with a mean ASP of 28 ± 18 mmHg) and without oedema (0.27 ± 0.14, and 35 ± 20, both \( p > 0.05 \)). In the healthy control group, mean ABI was 0.94 ± 0.28 with a mean ASP of 121 ± 49 mmHg. In seven of 14 limbs with CLI and oedema and three of nine limbs with CLI and without oedema ultrasound Doppler signals could not be detected, and blood pressure at the ankle was defined at 15 mmHg.

In patients with CLI with and without oedema, three distinct frequency domains were detected and are denoted respectively as low frequency (LF) waves, high frequency (HF) waves, and cardiac activity related, i.e. heart rate (HR) waves, while high frequency (HF) waves were absent in the healthy control group in all measured sites.

Low frequency (LF) waves

With the limbs in horizontal position, there were no significant differences in median frequency of LF waves between the patients with CLI or between patients, and the healthy control group. There were no significant differences in median frequency of LF waves between the limbs within each of these groups either (Fig. 3).

Altering the position of the ischaemic limbs from horizontal to dependency did not significantly change the median frequency of LF waves in any of the three groups (Fig. 3).

The changes in position resulted, however, in a significant increase of the median FFT-power of LF
Patterns of Skin Flowmotion in the Lower Limbs

Fig. 2. (A) A sample of recorded laser Doppler flux (LDF) with the limb in horizontal and dependent position in a healthy control participant. In the panel at the top a portion of the curve is expanded to better distinguish fluctuations caused by cardiac activity from flowmotion. (B) A 3D plot of spectrum analysis by fast Fourier transformation (FFT) in the same temporal selection of the curve is shown in the respective time and frequency domains. Pr: manometer line pressure, PU: perfusion units.
[0.12 (0.015–3.3) vs. 0.82 (0.06–5.1), p<0.005] at the pulp of the first toe (Site 1) in the ischaemic limbs while unchanged in the other two sites (Fig. 3). In healthy controls this manoeuvre resulted in a decrease of the median FFT-power of LF in all three sites; site 1 [5.9 (0.8–11.1) vs. 3.7 (0.48–9.0), p<0.03], site 2 [1.8 (1.1–4.4) vs. 0.8 (0.25–3.5), p<0.002], site 3 [1.4 (0.8–2.9) vs. 0.6 (0.24–3.1), p<0.006].

The median FFT-power of LF of ischaemic limbs in site 1, 0.12 (0.015–3.3, Fig. 3), with the limbs in horizontal position was significantly lower than both the contralateral limbs 3.8 (0.34–8.15), p<0.001 and healthy control limbs, 5.9 (0.8–11.1), (p<0.0001) (Fig. 4).

All patients with CLI, (with and without oedema) showed HF waves in both diseased and contralateral limbs, while HF waves were absent in the healthy control group.

With the limbs in horizontal position, there were no significant differences in median HF waves between the ischaemic limbs and the contralateral side. Altering the position of the CLI limbs from horizontal to dependency did not significantly change the median frequency of HF waves in the CLI feet (Fig. 5).

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Fig. 3. Laser Doppler measurements of low frequency (LF) frequency waves with the limb in the horizontal and dependent position in healthy controls, CLI without oedema and CLI with oedema. There were three measuring sites: the pulp of the first toe (Site 1), at the level of the second metatarsal body (Site 2) and the anterolateral part of the ankle (Site 3). Frequencies are expressed in cycles/min, including FFT-power of each of the frequency regions. Both values are given as medians and range.
By lowering the ischaemic limbs the median FFT-power of HF increased only at the pulp of the first toe in both patients groups 0.08 (0.02–0.38) vs. 0.39 (0.09–1.45), (p<0.001) (Fig. 5).

The median FFT-power of HF in the ischaemic limbs were significantly lower than the contralateral limbs [0.06 (0.01–0.12) vs. 0.2 (0.06–1.6), (p<0.01)].

Heart rate (HR) waves

The median rate of heart waves in patients with CLI and oedema was 72 (58–81), and without oedema 74 (58–84). In the supine position, HR waves were present in all contralateral sites i.e. site 4, in 50% of site 3 but not detected in the analysis of sites 1 and 2 in all CLI limbs both with and without oedema. Lowering the ischaemic foot resulted in appearance of HR waves in all sites. All subjects in the control group showed heart pulsatile flux with the limbs both in supine and dependent position at all measured sites with a median frequency of 68 (48–75) (Fig. 2).

Leg volume

There was a mean leg–foot volume difference of 11 ±7% between limbs with CLI and oedema and contralateral sides measured by WDV. On the other hand, we did not find any significant differences between the limbs with CLI and without oedema and contralateral sides measured by WDV.

Discussion

The LF waves were as frequently observed in ischaemic as in healthy feet. However, HF waves were exclusively seen in the patients with CLI. This finding is in accordance with a previous study and indicates that the prevalence of HF waves is associated with a certain degree of ischaemia.25 This interpretation is supported by the observation that the number of HF waves decreases after successful angioplasty for severe ischaemia.26 Several investigators have reported that LF waves are associated with diameter changes in larger arterioles, and HF waves with diameter changes of terminal arterioles.16,27 Morphological studies by transmission electron microscopy have recently demonstrated dilated terminal skin arterioles in the feet of patients with CLI and oedema.2 However, it is a matter of speculation whether these findings are related to the occurrence of HF waves. Besides, it is not known how HF waves may contribute in compensating for the drastically decreased blood flow in CLI limbs.

There were no significant differences in occurrence of LF or HF waves between ischaemic limbs with and without oedema and between the contralateral feet. Thus, it seems that ischaemic oedema formation does
not affect the manifestation of LF and HF waves. The ranges for both LF and HF waves in the present study are comparable with findings of previous studies.\textsuperscript{11,26}

The cause and effect of LF and HF waves are still unknown. Both central and local nervous regulation may play a role.\textsuperscript{18} The central sympathetic nervous activity promotes homeostasis of blood pressure by constricting the arterioles, a local regulating system maintains blood perfusion of tissues by dilatating the arterioles. However, we found in this study that the distribution of the frequency waves is almost constant in different ischaemic areas of the foot. Furthermore, there was no difference in the frequency of LF and HF waves in the ischaemic limbs and the contralateral sides. These findings may indicate the superimposition of a local metabolic vasodilatory effect of hypoxia on centrally controlled vasoconstriction.

There was a positive correlation between the FFT-power and perfusion as measured by LDF, in all frequency domains. The power of LF waves was three times greater in the contralateral and five times greater in the healthy control limbs, compared to the ischaemic limbs. Therefore, it seems that the intensity of flow-motion curves, as indicated by the FFT-power, is related to the severity of ischaemia. A decrease of FFT-power probably varies in parallel with a reduced perfusion of the microcirculation in a certain area. Again, exactly how this effect could contribute to maintain homeostasis in ischaemic tissue is still unclear.

Although there were no regional differences in LF or HF waves in the ischaemic feet, either with or without oedema, there were regional differences in the FFT-power for both LF and HF waves in the
ischaemic foot for both horizontal and dependent position. The power was lowest for both frequency waves at site 1 with the ischaemic feet in horizontal position, while the power in ischaemic feet in dependency increased more than 5-fold for both frequency domains at the pulp of the first toe (site 1). In contrast, the power of LF waves in healthy subjects was greatest at site 1 and lowest at the ankle, and lowering the limbs reduced power in all sites (Fig. 2). The effect of dependency and the regional difference in FFT-power of both LF and HF waves could be ascribed the different density of arteriovenous anastomoses (AVA) in the pulp of the toe as compared to site 2 and 3. The pulp of the toe contains the highest number of AVA per skin area, and hence possesses the greatest potential for varying skin perfusion. This is illustrated by the finding of a more pronounced increase in perfusion and FFT-power in site 1 compared with site 2 and 3, respectively (Figs 3 and 5).

Several investigators have previously demonstrated that lowering an ischaemic leg below heart level improves the blood supply of poorly perfused skin regions, while lowering a healthy limb reduces the skin perfusion. There might be several possible physiological mechanisms that are involved in this phenomenon:

1. It has been postulated that paralysed arterioles and collapsed capillaries might be passively distended or even reopened by elevated transmural pressure when the leg is lowered.
2. A disturbed VAR may improve the blood perfusion due to lowering the critically ischaemic limb, while it reduces blood perfusion in normal limb in dependency.
3. Subdermal thermoregulatory blood flow might be directed to nutritional capillaries during dependency in limbs with CLI. Furthermore, blood supply from the proximal leg may be distributed to acral skin regions during dependency. Thus, there are indications that redistribution of the microcirculation plays a compensatory role in maintaining optimal perfusion in severely ischaemic tissues.

In conclusion, HF waves are typically associated with a state of extreme skin ischaemia. Ischaemia also appears to influence the FFT-power of each frequency domains. It seems that ischaemic oedema per se does not affect the pattern of FM in the foot of patients with CLI. Furthermore, the study showed that alteration in the microcirculation when lowering an ischaemic limb occurs as enhancement of the FM-waves (both occurrence and amplitude), while the frequency domains remain unchanged.

References
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