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Tissue oxygen partial pressure in the tibialis anterior muscle in patients with claudication before, during and after a two-stage treadmill stress test

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Abstract

The role of microcirculation in the pathophysiology and symptoms of peripheral arterial obliterative disease (PAOD) has been progressively emphasized during the past decades. Under resting conditions, already, the tissue oxygen partial pressure in the m. tibialis anterior is reduced to about 50% compared to healthy subjects.

In the framework of this study the oxygen partial pressure of patients with PAOD stage II according to Fontaine (n=16) in the m. tibialis anterior was measured under resting conditions and during walking on a treadmill in comparison to healthy subjects (n=10).

Under resting conditions the skeletal muscle oxygen partial pressure $pO2_{im}$ only marginally differed between PAOD patients and healthy subjects. But during exercise the $pO2_{im}$ dropped significantly more severely in PAOD patients and a return to baseline values could only be reached when the treadmill was stopped and the patients stood still. The $pO2_{im}$ minima correlated clearly with the clinical symptom of calf pain. The strongest $pO2_{im}$ decreases during walking occurred in PAOD patients not exercising regularly. Regular walk training seemed to improve the $pO2_{im}$ as well as the compensation of short-lasting ischemic events.

Key words: tissue oxygen partial pressure, peripheral arterial occlusive disease, treadmill test

Introduction

Arteriosclerosis is considered to be a disease of multifactorial etiology. Based on the early concept of Virchow in 1847 [38], Ross and Glomset [34] introduced the 'response to injury' hypothesis of atherogenesis, postulating that initial endothelial cell injuries lead to endothelial cell dysfunction or detachment. Ross [35] discussed later that atherosclerosis associated changes in the microcirculation can be caused by damages inflicted upon the vessel wall, by protective defence mechanisms intrinsic to the vessel wall and/or by components of the blood. Peripheral arterial occlusive disease (PAOD) is not just a problem of arterial transport vessels, but it induces - dependent on type, location and severity of stenosis - a disorder of the microcirculation in the post-stenotic terminal vessels of the supplied tissue.

Clinically relevant microcirculatory disorders can occur due to an endothelial dysfunction in precapillary arterioles or distal of stenoses due to a reduced perfusion pressure in the supplying arteries and last but not least due to a reduced draining in case of a dysfunction of the post-capillary venous system [10, 32]. In patients with claudication such disorders can lead to the onset of pain in the lower extremities during walking exercise due to an insufficient oxygen supply [3, 18, 30, 31, 37]. Under resting conditions, already, the tissue oxygen partial pressure in the m. tibialis anterior is reduced to about 50% compared to healthy subjects [8, 12, 14, 17, 27].

In the framework of this study the oxygen partial pressure of patients with PAOD stage II in the m. tibialis anterior was measured under resting conditions and during walking on a treadmill in comparison to healthy subjects.

Study design

The examination was performed as explorative diagnostic study in patients with PAOD stage II according to Fontaine and according to the ethical guidelines of *Clinical Hemorheology and Microcirculation* (*Clin Hemorheol Microcirc* **44** (2010),1-2.). Target parameter of the study was the intramuscular oxygen partial pressure in the m. tibialis anterior ($pO2_{im}$ in [mmHg]) prior, during, and after a walking test on a treadmill.

Sixteen patients with PAOD stage II were included in the study. Since the tissue oxygen partial pressure strongly depends on different influencing factors the following conditions were stringently met by the patients [21]:

1.) No smoking at least 2 hours prior to the examination,
2.) No coffee one hour prior to the examination,
3.) No alcohol on the day of the examination as well as on the day before,
4.) No physical activity at least 2 hours prior to the examination,
5.) No fat ingestion up to 5 hours prior to the examination,
6.) No drug intake (if no washout-phase was possible, the medication was registered).

Prior to the pO_{2im}-measurements the patients stayed for one hour in the department in a thermostated waiting room (22 °C) so that the microcirculation could adapt to physiologic conditions (especially in winter time cold-induced vasoconstriction might occur). Skin temperature was controlled before pO_2 measurement to be normalized [21]. Before starting the measurements the skin surface temperature was controlled and the study started after reaching a skin temperature of $32^{\circ}C$.

The pO_2 microcatheter (CC1.2, Integra NeuroSciences, Great Britain) was placed in the anterior tibial muscle and fixed in position prior to the start of the experiments (for details of the method see [22, 25]). The patients then stepped up on the treadmill. The first exercise level **A** (3 km/h at an inclination of 5 degree) was started where the patient started walking after one minute pause and the initiation of the pO_2 registration. The first exercise period was finished as soon as calf muscle pain appeared and the treadmill was stopped. Thereafter the patients waited standing on the treadmill till pO_2 values returned to the baseline values.

Then the second exercise period **B** was started (velocity 5 km/h at an inclination of 10 degree). Again, the treadmill was stopped as soon as muscle pain occurred. The skeletal oxygen partial pressure was recorded until the baseline value was reached.

For all samples mean values and standard deviations are given. To analyze the influence of the walking intensity on the tissue oxygen partial pressure a variance analysis for repeated measures was performed. For the comparison between PAOD patients and apparently healthy subjects a variance analysis was performed using a model "one within one between". Differences were considered significant if $\alpha < 0.05$.

Results

Patients

Fifteen patients in stage IIa, and one patient in stage IIb according to Fontaine were included. Six of the patients participated regularly in a walking training group. The mean age of the patients was 60.6±5.2 years, the mean height was 175±5 cm, and the mean body weight 86±18 kg. The mean systolic blood pressure was 165±8 mmHg, the diastolic one 86±8 mmHg. Thirteen patients suffered from hypertension, 4 patients from diabetes mellitus (3 Type II, 1 Type I), 8 patients from a lipid metabolism disorder, 4 from a hyperuricemia and 10 of the 16 patients were smokers.

The mean pain-free walking distance was 178±42 m (measured at treadmill velocity 3.2 km/h at an inclination of 12.0 %).

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Tissue oxygen partial pressure (pO2$_{im}$ in mmHg) in the M. tibialis anterior before, during and after a two-stage treadmill stress test

Figure 1 shows mean pO2$_{im}$ values in the m. tibialis anterior before, during and after a two-stage treadmill stress test in 16 PAOD patients. During exercise the pO2$_{im}$ values changed significantly ($p=0.0001$). At baseline (**A1**) the pO2$_{im}$ was 16.7 ± 6.6 mmHg. Immediately after starting to walk at exercise level **A** (3 km/h and 5 degree inclination) the pO2$_{im}$ increased - despite walking – to a maximum value (**A2**) of 23.3 ± 10.9 mmHg ($p<0.05$). Continuous walking at this exercise level **A** led to a pO2$_{im}$ decrease to a minimum value (**A3**) of 10.4 ± 4.4 mmHg ($p<0.05$). At this pO2$_{im}$ calf pain occurred. The treadmill was stopped and the patients stood still. Now, the pO2$_{im}$ started to increase up to (**A4**) 17.2 ± 6.5 mmHg ($p<0.05$) just above the baseline values.
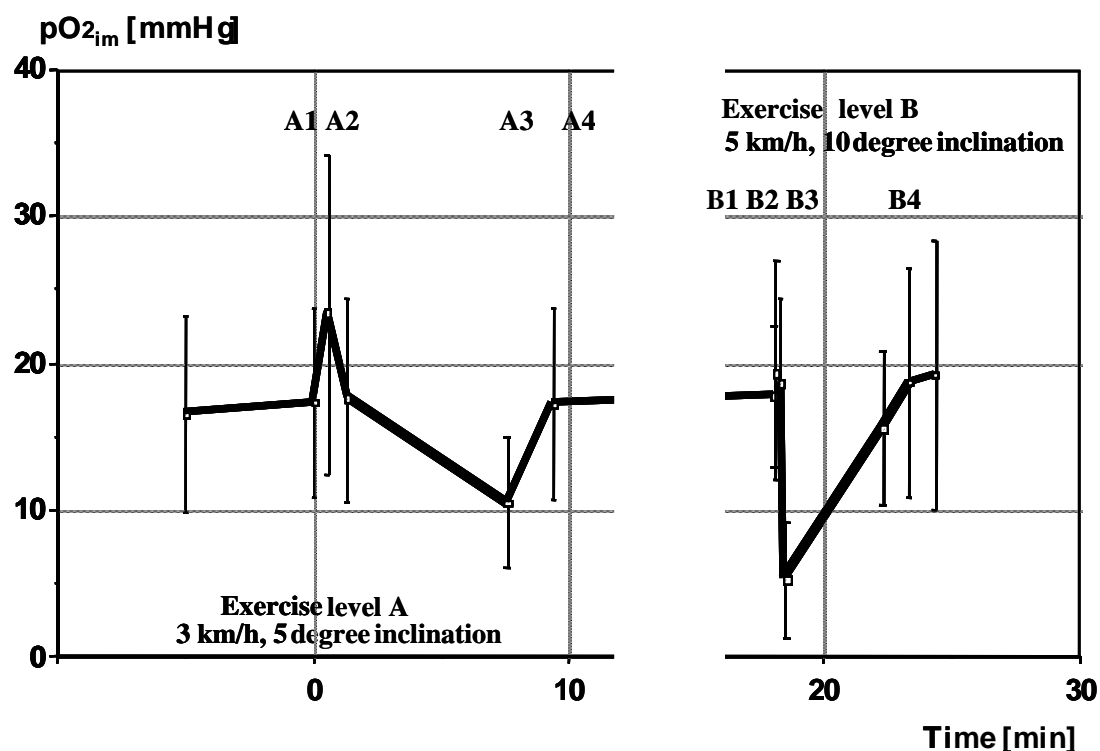

Figure 1:   Skeletal muscle oxygen partial pressure in the m. tibialis anterior (pO2$_{im}$ in [mmHg]) before, during and after a two-stage treadmill stress test in n=16 claudicants
(mean values ± standard deviation)

After a short break of 2 minutes (the patients continued to stay on the treadmill), the exercise level **B** (5 km/h at an inclination of 10 degree) was applied. At the beginning of period **B** (**B1**) the pO2$_{im}$ mean value was 17.7 ± 4.8 mmHg. During

walking the pO2$_{im}$ rapidly decreased to a minimum value (**B3**) of 5.2±3.9 mmHg, accompanied by calf pain (p<0.05). Then, the treadmill was stopped and the patient stood still. The pO2$_{im}$ increased again to 15.5±5.2 mmHg and 1 Minute later (**B4**) up to 18.7±7.8 mmHg (p<0.05), a value slightly above the baseline.

Table 1: Significance table of a variance analysis for repeated measures

Exercise period I:
pA1 - pA2: p<0.05   pA2 - pA3: p<0.05   pA3 - pA4: p<0.05
PA1 - PA3: p<0.05   pA2 - pA4: p<0.05

Exercise period II:
pB1 – pB3: p<0.05   pB3 - pB4: p<0.05

Skeletal muscle oxygen partial pressure pO2$_{im}$ in PAOD patients (n=16) in comparison to apparently healthy subjects (n=10) during and after a two-stage treadmill stress test

Figure 2 shows pO2$_{im}$ values of n=16 PAOD patients (black lines) in comparison to the pO2$_{im}$ values of n=10 apparently healthy subjects (grey lines) during a two-stage treadmill test. The healthy subjects were examined in a former study under identical test conditions [22].
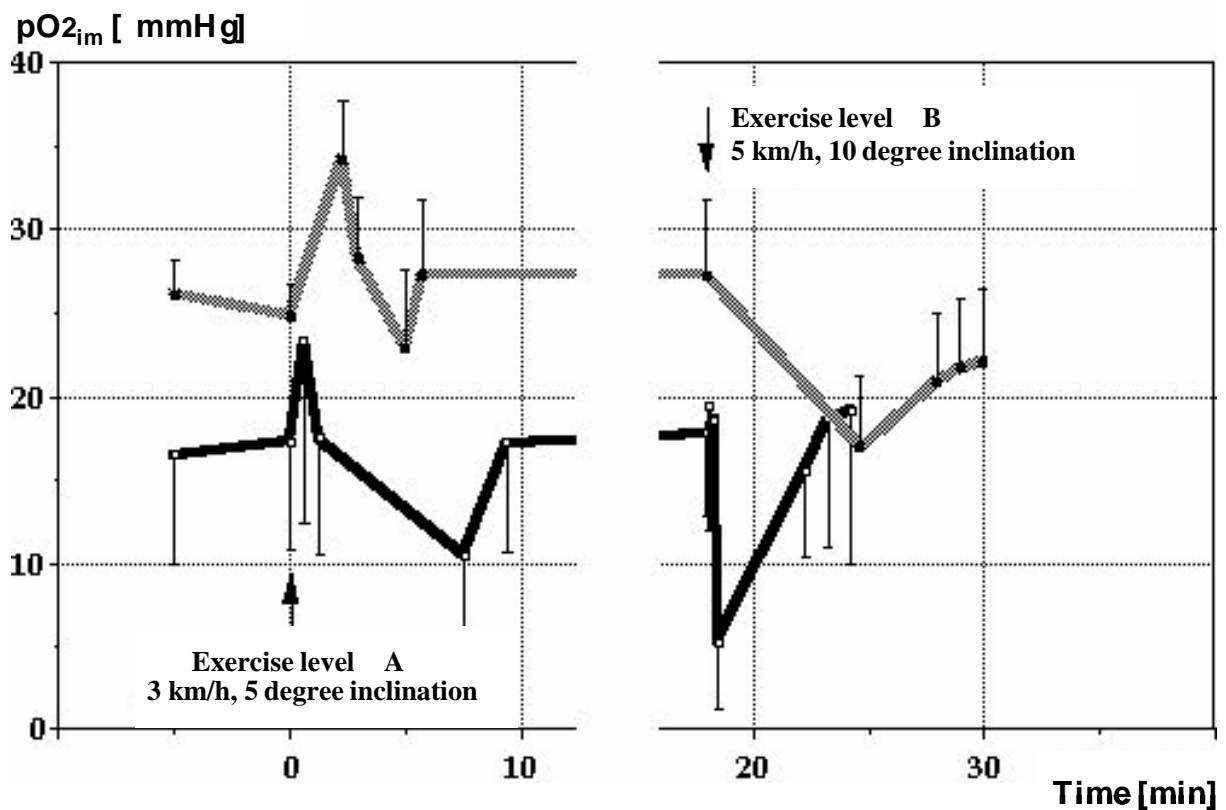
Figure 2: Skeletal muscle oxygen partial pressure in the m. tibialis anterior (pO2$_{im}$ in [mmHg]) in claudicants (n=16, black lines) in comparison to healthy subjects (n=10, grey lines) before, during and after a two-stage treadmill stress test
(mean values ± standard deviation)

A PAOD stage II disease significantly influenced the pO2$_{im}$ in comparison to apparently healthy subjects (factor „PAOD": p=0.0014). Walking on a treadmill led to a significant drop of the pO2$_{im}$ (factor time point: p<0.0001). A PAOD stage II significantly influenced the pO2$_{im}$ during walking (PAOD * time point: p<0.0001). Under resting conditions, already, but particularly after walking on the treadmill, the pO2$_{im}$ significantly differed at all time points (p<0.05 each).

Discussion
The intramuscular oxygen partial pressure pO2$_{im}$ was 16.7±6.6 mmHg in PAOD patients and significantly lower than in healthy subjects with 27.3±12.1 mmHg [22] which was similar to a former study of Ehrly et al. [13]. But Ehrly reported even lower resting pO2$_{im}$ values with an average of 13.3 mm Hg. This could be attributed to the fact that of those 10 patients, seven were in stage IIb with painfree walking distances <100 m, 1 patient was in stage III - IV, and 1 patient in stage IV, whereas in the present study none of the patients had a walking distance less than 100 m and all patients, except one in stage IIb, were in stage IIa according to Fontaine. A compromised microcirculation was demonstrated in PAOD patients using different methods [1, 30, 31, 36]. Rossi et al. described a reduced microcirculation in the cutaneous vasculature [36] following ischemia. The post-ischemic hyperemia was impaired in the cutaneous vasculature and the skin capillary nutritional blood flow dropped in the diseased leg of stage II PAOD patients.

Immediately after onset of walking the pO2$_{im}$ values significantly increased stronger and the increase lasted longer in apparently healthy subjects than in PAOD patients. The exercise-induced significant decline of pO2$_{im}$ in PAOD patients fell far below the baseline values (around 10 mmHg), when the calf pain appeared the treadmill had to be stopped. In the group of the apparently healthy subjects the pO2$_{im}$ values fell only slightly below the baseline values – despite continuous walking.
At exercise level **B** (5 km/h and an inclination of 10 degree) the walking-dependent drop of pO2$_{im}$ values in PAOD patients happened earlier and more rapidly reaching very low pO2$_{im}$ values (around 5 mmHg) with severe calf pain (which was never observed in healthy subjects). Here, again, the healthy subjects reached normal pO2$_{im}$ values during walking, while the patients had to stand still to recover.

Various causes are thought to contribute to the observed differing effects. The main factor seems to be that the maximum blood flow during muscular work - the key element of the supply of the muscle tissue with oxygen - is markedly lower in PAOD patients than in healthy subjects [9, 19, 24]. Under resting conditions the blood flow might be only slightly lower in patients with mild claudication [11]. The muscular oxygen partial pressure measurements revealed that the microcirculation is disturbed already with no obvious alterations in the macrocirculation. Obviously, a sufficient capillary blood flow with an appropriate oxygen supply did not exist during exercise leading to symptoms associated with peripheral arterial insufficiency like claudication. Such symptoms are suggestive of a lack of blood flow in the nutritional capillaries of the microcirculation not meeting the metabolic demand of the surrounding tissues [20]. Ehrly hypothesized that in a relatively large part of the capillaries the blood flow is higher than necessary (called luxury perfusion) while other capillaries are underperfused not meeting the metabolic demand [14]. Such an inhomogeneous state of perfusion with an attenuation of the effective and nutritive capillary density was later stated "microcirculatory maldistribution" [12, 5]. The sources of such maldistributions are on the one hand disturbed regulatory mechanisms of the endothelium and the smooth muscle cells and, on the other hand, an imbalance between oxygen demand and oxygen supply.

Under physiological conditions the energy demand during muscular activity is initially met by an-aerobical metabolism, which later on switches over to aerobical energy production utilizing fatty acids and glycerol. In the follow-up the energy production is more or less exclusively an-anaerobical leading to the production of lactic acid then inducing the symptom of muscle fatigue. This accumulation of acid metabolites occurs earlier and more severely in PAOD patients (compared to healthy subjects with normal perfusion and drainage of the tissues) and can start – depending on the severity of the stenoses – at very low muscular load [4]. The acidosis leads to a vasodilation in the post-stenotic region causing a disturbation of the local regulatory mechanisms. A vicious circle develops: a microcirculatory maldistribution leads to a decreased oxygen supply, which can induce an acidosis, particularly under exercise conditions. The tissue acidosis was shown to intensify the local vasodilation inducing a further amplification of the maldistribution and the ischemic pain [13].
Another factor discussed to aggravate the microcirculatory disorder in PAOD patients [Ricci] is the deteriorated blood fluidity [33]. Compared to healthy subjects the plasma viscosity, particularly, and also the erythrocyte aggregation are elevated while the deformability of the red cells is significantly decreased [2, 6, 15, 16, 28, 29, 33]. It could be shown, recently, that the elevated plasma viscosity especially leads to a significant decrease of the blood flow velocity in human capillaries [23]. In addition, Connes et al. suggested a potential role for RBC deformability and the interaction between viscosity and hematocrit as a

factor to affect aerobic performance via oxygen delivery to tissues [7, 39]. The reduced shear forces in the microcirculation of PAOD patients thus could have an additional effect since the deformability of erythrocytes deteriorates when shear forces decrease [26].

Conclusion
While under resting conditions the skeletal muscle oxygen partial pressure $pO2_{im}$ only marginally differed between PAOD patients and healthy subjects, the $pO2_{im}$ dropped during exercise significantly more severe in PAOD patients and a return to baseline values could only be reached when the treadmill was stopped and the patients stood still. The $pO2_{im}$ minima correlated clearly with the clinical symptom of calf pain. The strongest $pO2_{im}$ decreases during walking occurred in PAOD patients not exercising regularly. Regular walk training seemed to improve the $pO2_{im}$ as well as the compensation of short-lasting ischemic events.

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