Near Infrared Spectroscopy for Noninvasive Assessment of Claudication

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The purpose of this study was to explore the application of near-infrared spectroscopy (NIRS) to the assessment of peripheral arterial occlusive disease (PAOD). Muscle blood flow, oxygen consumption, arterial inflow capacity, O2 resaturation, and recovery times were determined at rest, under ischemic and hyperemic conditions, and continuously during and after walking exercise in 11 claudicants and 15 nonclaudicants. Blood flow and oxygen consumption (VO2) at rest and blood flow following walking exercise did not differ significantly between claudicants and nonclaudicants. In contrast, VO2 after walking exercise was increased by a factor of 4.1 in claudicants compared to a factor of 1.7 in nonclaudicants. The oxygen resaturation rate after arterial occlusion and the oxygen resaturation rate after walking exercise were significantly lower in claudicants. Claudicants showed a higher degree of hemoglobin deoxygenation during walking exercise than nonclaudicants. A high postexercise VO2 is correlated with a low ankle-brachial index (ABI). The resaturation rates and recovery times following walking exercise and arterial occlusion correlated significantly with ABI parameters. A significant negative correlation was found between hemoglobin deoxygenation during exercise and the ABI parameters. A high correlation was observed between the oxygenated hemoglobin (O2Hb) recovery time and the ABI recovery time after walking exercise. NIRS appears to be an effective noninvasive method for assessing the imbalance between oxygen demand and oxygen delivery in the leg muscles of PAOD patients at rest and during exercise.

INTRODUCTION

Several methods are used to assess the severity of peripheral arterial occlusive disease (PAOD). Measurement of ankle-brachial systolic blood pressure index (ABI) is the most common technique [1]. It gives an indication of a hemodynamically significant obstruction, but does not measure blood flow directly. Doppler ultrasound can be used to measure arterial blood flow [2]. Lewis et al. [3], however, concluded that determination of blood flow in the femoral artery is not an accurate hemodynamic indication of muscle ischemia. Venous occlusion plethysmography indirectly quantifies and detects vascular abnormalities based on volume changes in the leg, which are related to blood flow [2, 4]. Magnetic resonance spectroscopy has been applied to determine the rate of recovery of high-energy phosphates following exercise [5]. Zatina et al. [5] showed that magnetic resonance spectroscopy is a valid method for assessing PAOD. However, its clinical use is limited due to high costs and poor availability. Two other noninvasive techniques designed to measure blood flow and oxygen levels in the lower extremities are laser Doppler fluxmetry [6] and transcutaneous oxygen tension measurement [7, 8]. Saumet et al. [9] compared these two techniques and concluded that the results of laser Doppler fluxmetry and transcutaneous oxygen tension monitoring need to be interpreted with caution. These methods are considered to measure skin blood flow rather than muscle blood flow.

The clinical presentation of intermittent claudication is an effect of oxygen transport limitation by an arterial obstruction resulting in insufficient oxygen delivery. However, the alternative collateral pathway compensates muscle blood flow and oxygen delivery. Therefore, to assess the mismatch between oxygen delivery and oxygen demand in the affected limb in PAOD patients, an objective assessment of muscle blood flow and oxygenation level is essential.

Near-infrared spectroscopy (NIRS), a noninvasive method, has been shown to be capable of measuring muscle blood flow and oxygen consumption in muscles continuously [10–13]. Recently the NIRS technique has been used to assess muscle oxygen consumption (VO2) in patients with PAOD [14]. VO2 at rest was reported to be lower and recovery times after arterial occlusion were longer in PAOD patients compared to nonclaudicants. Arterial inflow capacity was not quantified. Furthermore, measurements in this study were taken at rest while muscle ischemia (i.e., mismatch) occurs during exercise. To assess the mismatch in the affected limb, VO2 should be determined during and
after a walking test. Another method for assessing PAOD using NIRS following walking exercise is to determine oxygen resaturation, as an indication of oxygen debt and arterial inflow capacity [15, 16]. McCully et al. [15] and Komiyama et al. [16] have correlated the oxygen resaturation with the ankle-brachial index at rest and reported a significant correlation. However, to find a correlation between oxygen resaturation and recovery of arterial blood flow, the ABI should be determined after a walking test. Hickman et al. [17] determined recovery of ABI after a walking test; however, their light-guide reflectance measurements were not taken continuously.

The purpose of this study was therefore to explore the application of NIRS to the assessment of PAOD in greater detail: muscle blood flow, oxygen consumption, arterial inflow capacity, O₂ resaturation, and recovery times were determined at rest, under ischemic and hyperemic conditions, and continuously during and after walking exercise in claudicants complaining of intermittent claudication and in matched nonclaudicants.

METHODS

Subjects

Eleven claudicants (7 men and 4 women, mean age 61.9, range 48–74 years) with PAOD clinically classified at Fontaine stage IIa–IIb (or SVS/SCS stage I–II) [18]) and 15 healthy nonclaudicants (10 men and 5 women, mean age 62.1, range 58–67 years) matched for age and gender took part in the study, after giving informed consent.

All subjects refrained from caffeine and alcohol for at least 3 hr before the test and were asked not to perform any extensive physical activity on the day of the test. All the experiments were carried out at an ambient temperature of 21°C.

NIRS

NIRS is based on the relative transparency of muscle tissue to infrared light and on the existence of five chromophores in the biological tissues whose light-absorbing properties vary with oxygenation. These chromophores are oxy- and deoxyhemoglobin (O₂Hb and HHb), oxy- and deoxymyoglobin (O₂Mb and HMb), and cytochrome oxidase. By means of NIRS, changes in concentrations of the chromophores (O₂Hb and HHb), in the banana-shaped volume of several cubic centimeters underneath the optodes, can be used to determine blood flow [12] and oxygen consumption [13] in muscle tissue. The NIRS instrument (Radiometer Medical A/S, Denmark) used in this experiment employs four wavelengths ranging from 775 to 904 nm. Measurements were taken every second and were stored on disk.

Setup

Hemoglobin content (mmole·L⁻¹) was measured from a fingertip blood sample using a spectrophotometer (Hemocue, Elektrolux Mectronik, Helsingborg, Sweden). The optodes of the NIRS instrument were attached to a holder, which was fixed to the skin with two double-sided adhesive disks (No. 2181, 3M, U.S.A.) and positioned on the lateral surface of the gastrocnemius muscle. The distance between the optodes was 3.5 cm. For the normal healthy subjects the left leg was studied. For those with visible varicose veins the less affected leg was chosen. In claudicants the more affected leg was studied.

With the subject in supine position, systolic and diastolic blood pressure in both arms was measured (Erkameter, Germany). The systolic pressure in both ankles was obtained using Doppler (Pie Data Medical, Huntleigh Technology, Luton, UK) pressure measurements. The highest systolic pressure measured at the arm was taken to calculate the ABI. The ABI was calculated for both legs as the ratio of the ankle to arm measurements of systolic pressure.

Timetable Protocol

The timetable protocol was divided into three parts (Fig. 1).

Part 1. A cuff (CC17, Hokanson, Bellevue, WA) was placed around the thigh and was connected to a pressurized nitrogen bottle. The cuff was inflated pneumatically to a pressure similar to diastolic blood pressure. This venous occlusion was maintained for 1 min to determine blood flow using NIRS. The total hemoglobin signal (tHb = O₂Hb + HHb) during venous occlusion is a measure of the arterial inflow. The blood flow can be calculated from the initial rate of tHb increase during venous occlusion [12] (Fig. 2a). The increment of tHb was converted into milliliters of blood, taking into account the Hb concentration of each subject (see Appendix). The venous occlusion was followed by a 1-min recovery. The whole procedure was repeated to test for reproducibility.

Each subject performed a standard walking test of 4 min on a treadmill, at a speed of 3.2 km/hr and a gradient of 6°. Subjects who reported claudication pain were asked to continue the test, unless claudication pain forced them to stop. During this walking test hemodynamic changes were measured continuously using NIRS. After the walking test the subject was brought back into the supine position. After 1 min the cuff around the thigh was inflated pneumatically to a pressure similar to diastolic blood pressure to measure arterial inflow after performing the walking test. The venous occlusion was maintained for 1 min and was then released and followed by a 1-min recovery. After recovery the pressure cuff was inflated at least 50 mm Hg above systolic pressure (minimum of 200 mm Hg). This results in a complete arterial occlusion, which was maintained for 1 min. Oxygen consumption (VO₂) after the walking test was determined using NIRS by calculating the slope of the linear decrement of the oxyhemoglobin signal (O₂Hb) during the arterial occlusion (Fig. 2b, Appendix).

FIG. 1. Timetable protocol. The characters represent the time periods. The numbers represent the duration per period. a, venous occlusion; b, venous occlusion; c, walking exercise; d, venous occlusion after walking exercise; e, arterial occlusion after walking exercise; f, arterial occlusion; and g, walking exercise.
Part 1 and Part 2 were separated by a break (minimum of 30 min). The subject recovered in supine position until the NIRS signals were back to baseline values and the ABI to the resting value.

Part 2. During the second part of the test, the cuff around the thigh was pneumatically inflated to a pressure of 50 mm Hg above systolic blood pressure with a minimum of 200 mm Hg to achieve muscle ischemia. The arterial occlusion was sustained for 5 min. The oxygen consumption at rest was measured, considering the linear decrement of the \( O_2 \text{Hb} \) signal during arterial occlusion. After release of the occlusion NIRS continued to record the hyperemic reaction, providing information about arterial inflow capacity and recovery time. Simultaneously, the systolic blood pressure at the ankle and the arm was measured to determine the recovery time after arterial occlusion. The first measurement was taken after 15 sec, and the second after 30 sec. After that, measurements were taken at time intervals of 30 sec until ankle pressure was back to the resting value and the NIRS signals were back to baseline values.

Part 3. The walking test was repeated to measure recovery times of ABI and the NIRS signal (\( O_2 \text{Hb} \)) simultaneously after the walking exercise. The same walking protocol was used as in Part 1. During and after exercise the hemodynamic changes were recorded by NIRS. Immediately after the walking test the subject was brought into the supine position. Pressure cuffs were still positioned on the ankle and the arm. One minute after exercise the systolic pressure at the ankle and the arm were measured. These measurements were repeated after 30 sec and 1 min. Thereafter the measurements were taken every minute until the NIRS signals were back to baseline and the ABI was back to resting value.

**Statistical Analysis**

Student's \( t \) test was used to compare ABI parameters, normally distributed, between the PAOD and the control group. Parameters measured with NIRS, nonnormally distributed, were compared using the Mann–Whitney \( U \) test. Regression analysis and the Spearman correlation coefficient were used to compare the NIRS parameters and the ABI parameters in all the subjects. The statistically significant level was taken at \( P < 0.05 \).

**RESULTS**

**Differences between Groups**

The physical characteristics of the patient group were weight, 72.3 (SD 10.7) kg; height, 168.7 (SD 6.4) cm; and body fat percentage, 30.2% (SD 8.8). The physical characteristics of the control group were weight, 76.5 kg (SD 11.9); height, 173.8 cm (SD 10.2); and body fat percentage, 31.7% (SD 7.0).

**Blood flow and oxygen consumption.** No differences in blood flow between the patient and control groups were found at rest or following walking exercise (Table 1). \( \dot{V}O_2 \) at rest was not significantly different between the patient and the control groups. One minute after

| TABLE 1 |

<table>
<thead>
<tr>
<th>BF (ml·100 ml(^{-1})·min(^{-1}))</th>
<th>VO(_2) ((\mu\text{mole}O_2)·100 ml(^{-1})·min(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>After exercise</td>
</tr>
<tr>
<td>PAOD</td>
<td>0.58, (n = 9)</td>
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<tr>
<td></td>
<td>(0.50–0.82)</td>
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<tr>
<td>NC</td>
<td>0.68, (n = 15)</td>
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<tr>
<td></td>
<td>(0.54–0.97)</td>
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<tr>
<td>(P) values</td>
<td>0.27</td>
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*Note. Results of the Mann–Whitney \( U \) test are presented as \( P \) values. BF, blood flow; \( \dot{V}O_2 \), oxygen consumption; PAOD, claudicants; NC, nonclaudicants. * \( P < 0.05 \), statistically significant.
walking exercise $\dot{V}O_2$ in claudicants was significantly increased by a factor 4.1 in comparison to a factor 1.7 in nonclaudicants.

Resaturation rates and recovery times. Resaturation rates and recovery times after arterial occlusion and walking exercise and deoxygenation during walking exercise are presented in Table 2. Resaturation rate following occlusion (RR(O)) as well as following walking exercise (RR(W)) were significantly lower in claudicants than in nonclaudicants. The recovery times (RP(O), RT(O), RT(W)) were significantly higher in claudicants. The claudicants had significantly higher Hb deoxygenation during walking exercise.

ABI parameters. Results for ABI parameters are presented in Table 3. All claudicants had an ABI at rest lower than 0.90. The ABI after occlusion and following exercise was significantly more decreased in claudicants than in nonclaudicants (rel. diff. (AO), rel. diff. (AW)). The recovery times of ABI after arterial occlusion and following walking exercise (ABI-RT(AO) and ABI-RT(AW), respectively, were significantly longer in the patient group.

Correlations between ABI Parameters and NIRS Parameters

ABI at rest compared to $\dot{V}O_2$ and blood flow. Using regression analysis no significant relationship was found between blood flow at rest and ABI at rest ($r^2 = 0.15, P = 0.07$). Blood flow after exercise and $\dot{V}O_2$ at rest were also not significantly correlated with ABI at rest (Spearman correlation coefficient, $r = 0.18, P = 0.42; r = -0.16, P = 0.45$, respectively). A significant negative correlation was observed between ABI at rest and $\dot{V}O_2$ after exercise ($r^2 = 0.37, P < 0.005$) (Fig. 3).

ABI parameters compared to oxygen resaturation rate following arterial occlusion. ABI at rest, ABI after arterial occlusion, and the recovery time of ABI after arterial occlusion all correlated significantly with oxygen resaturation rate (Spearman correlation coefficient, $r = 0.77, P = 0.0001; r = 0.79, P = 0.0001$ and $P = 0.003$, respectively). A higher oxygen resaturation rate was correlated with lower recovery times of ABI after arterial occlusion.

ABI parameters compared to oxygen resaturation rate and deoxygenation after and during walking exercise.

<table>
<thead>
<tr>
<th>TABLE 2</th>
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<tr>
<td>Median Values (25th–75th Percentile) of Resaturation Rates and Recovery Times after Arterial Occlusion and Walking Exercise and Deoxygenation during Exercise</td>
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<td></td>
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<tr>
<td>PAOD (n = 11)</td>
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<tr>
<td>NC (n = 15)</td>
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<td>P Values</td>
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Note. Results of the Mann-Whitney U test are presented as P values. RR(O), resaturation rate of O₂Hb after arterial occlusion; RP(O) time to reach O₂Hb peak during hyperaemia; RT(O), total recovery time after arterial occlusion. RR(W), resaturation rate of O₂Hb after walking exercise; RT(W), total recovery time after walking exercise; Deoxy, deoxygenation of O₂Hb during walking exercise. PAOD, claudicants; NC, nonclaudicants.

* P < 0.05, statistically significant.

<table>
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<th>TABLE 3</th>
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<tr>
<td>Mean Values (SD) of ABI at Rest and ABI after Walking Exercise and Arterial Occlusion and Recovery Times of ABI after Arterial Occlusion and After Walking Exercise</td>
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<td>PAOD (n = 11)</td>
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<td>NC (n = 15)</td>
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<td>P values</td>
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Note. Results of Student’s t test are presented as P values. ABI(R), ABI at rest; ABI(AO), ABI after arterial occlusion; Rel. diff. (AO), relative difference between ABI at rest and ABI after occlusion; ABI-RT (AO), recovery time of ABI after arterial occlusion. ABI(AW), ABI after arterial occlusion; Rel. diff. (AW), relative difference between ABI at rest and ABI after walking exercise. ABI-RT (AW), recovery time of ABI after arterial occlusion. PAOD, claudicants; NC, nonclaudicants.

* P < 0.05, statistically significant.
shorter. This, however, does not affect the outcome of this study. In the first place, in human limbs the Mb contribution to the signal will be smaller than 25% [19]. Second, the deoxygenation of Hb and Mb will occur sequentially, in other words: $O_2$Mb deoxygenation occurs after almost complete deoxygenation of $O_2$Hb [20]. One difficulty using NIRS is the application of the optodes to ensure that movement artifacts are minimal. In this study movement artifacts occurred only at the beginning and at the end of the walking exercise. The movement artifacts disappeared as soon as the subjects were in supine position or were walking with a constant speed, making the same movement constantly. Some subjects showed an increase of $t$Hb during arterial occlusion. A possible explanation for this observation is a redistribution of blood in the calf muscle during arterial occlusion. Increase of $t$Hb during arterial occlusion was also found in other studies [13, 14].

There was no significant difference found in blood flow at rest between claudicants and nonclaudicants, which corresponds with the results of Lewis et al. [4]. The lack of a significant difference in blood flow following exercise is not in agreement with the expectation that blood flow is impaired during walking exercise in PAOD patients [2]. However, Lubbers et al. [21] found that in some patients with intermittent claudication, blood flow to the calf muscle after exercise was in the same range as that in normals. They formulated the hypothesis that this finding in claudicants is a result of nonuniform perfusion of the calf muscles. Another explanation for the present results may be related to the fact that blood flow was measured 1 min after walking exercise. The production of metabolites during walking exercise in patients with intermittent claudication will result in vasodilation to compensate and to maintain an increased blood flow after walking exercise. However, in healthy nonclaudicants, blood flow will drop after cessation of exercise. In this study we found lower muscle blood flow values than De Blasi et al. [12] found using NIRS. There are two reasons that may explain this phenomenon. First, the interoptode distance in our study (3.5 cm) may have been too small, so that the penetration of infrared light was not deep enough. This may have resulted in the measurement

![FIG. 3. There is a negative relationship between ABI at rest and VO2 after walking exercise in all subjects ($r^2 = 0.37, P < 0.005$). Solid circles represent controls. Open circles represent patients. (There are two missing values in the control group).](image)

**DISCUSSION**

Various NIRS variables were measured in this study in patients with intermittent claudication and compared with those of healthy control subjects. Since it has been shown that NIRS can be used to measure tissue oxygenation accurately, this noninvasive method was used to assess the severity of PAOD, by determining the mismatch between oxygen demand and oxygen delivery in lower limb muscle. The NIRS technique measures the combined effect of changes in concentrations of Hb and Mb. It is not possible to distinguish between the changes in concentrations between hemoglobin and myoglobin. This, however, does not affect the outcome of this study. In the first place, in human limbs the Mb contribution to the signal will be smaller than 25% [19].

![FIG. 4. The relationship between recovery time of ABI (ABI-RT) and NIRS recovery time (RT) following walking exercise. Solid circles represent controls. Open circles represent patients. (There are three missing values in the control and one in the patient group).](image)
of a portion of subcutaneous blood flow, which is lower than muscle blood flow, instead of muscle blood flow only. Second, we examined the lateral segment of the gastrocnemius muscle, which is considered to have a higher content of fast glycolytic fibers. A study in rats showed that muscles consisting of fast glycolytic fibers had a lower capillary density and a lower blood flow capacity than muscles with high oxidative capacity [22].

\[ \text{VO}_2 \text{ at rest} \text{ was not significantly different between the patient and the control groups. In contrast, Cheatle et al. [14] found a reduced VO}_2 \text{ at rest in claudicants.} \]

\[ \text{A possible explanation for this difference is that the claudicants in the present study had not totally recovered from the walking exercise when arterial occlusion started, which may have overestimated VO}_2 \text{ at rest.} \]

\[ \text{VO}_2 \text{ after walking exercise is more increased in claudicants than in nonclaudicants. This continued oxygen consumption after exercise may be related to the resynthesis of high-energy phosphates [23]. NMR studies have shown a slower resynthesis of phosphocreatine in claudicants than in nonclaudicants [24]. This phenomenon can also explain the longer O}_2\text{Hb recovery times and the slower resaturation rates in PAOD patients, which supports the hypothesis that O}_2\text{Hb recovery times and the resaturation rates are a function of PCr resynthesis. During walking exercise PAOD patients showed a higher degree of deoxygenation than nonclaudicants. This may be an indicator of an imbalance between oxygen delivery and oxygen demand in the muscle tissue during walking exercise resulting in leg ischemia in PAOD subjects. Not only claudicants but also healthy control subjects showed O}_2\text{Hb deoxygenation at the onset of the walking exercise, which was also found by Chance et al. [25] using NIRS. They concluded that the deoxygenation at the onset of exercise is caused by a greater oxygen consumption than oxygen delivery [26].} \]

In agreement with others, no significant correlation between ABI at rest and the resting blood flow was found [27]. No significant correlation between ABI at rest and blood flow after exercise was observed. A high VO\textsubscript{2} after walking exercise correlated with peripheral arterial disease. Claudicants, who show a low ABI at rest, consume more oxygen after walking exercise due to the oxygen deficit during walking exercise. This is caused by an insufficient blood flow during exercise and thus an insufficient oxygen delivery to contracting muscles. Because the increase in blood flow is not sufficient after walking exercise there is an imbalance between oxygen supply and oxygen demand, causing an oxygen debt and a longer recovery time in claudicants. The oxygen resaturation rate following arterial occlusion correlated strongly with all ABI parameters, suggesting that it is a good measure of the severity of PAOD. The oxygen resaturation rate after walking exercise also showed a relationship with all ABI parameters, although the correlations were weaker than those following occlusion. An advantage of performing arterial occlusion over walking exercise is that this can also be done in claudicants who are unable to walk. Furthermore, it is easy to perform and it gives the same load in each patient.

In this study we found the recovery time of O\textsubscript{2}Hb to be a reproducible parameter that showed significant correlation with the ABI at rest. This result is supported by previous studies [15, 16]. The recovery times measured with NIRS corresponded with the ABI recovery times, which was also found by Hickman et al. [17]. The ABI recovers faster, because it depends only on recovery of arterial blood flow, while NIRS recovery depends not only on recovery of arterial blood flow but also on several other metabolic mechanisms in the muscle. Thus, the advantage of NIRS measurements over ABI measurements is that NIRS measures muscle recovery directly.

From the results of this study it can be concluded that NIRS appears to be a suitable noninvasive method for assessing the imbalance between oxygen delivery and oxygen demand in leg muscles of PAOD patients at rest and during exercise. The hyperemic reaction following arterial occlusion especially yields valuable information about the severity of PAOD. Furthermore, NIRS is a more direct method than blood pressure measurements, providing information on the adaptation of the collateral circulation and on the metabolic state of the muscle. This could be useful in monitoring the effectiveness of therapy. Additional research is needed to investigate the relationship between clinical parameters of PAOD, such as pain-free walking distance, and NIRS variables.

**APPENDIX**

**Calculation of Oxygen Consumption of a Muscle**

The oxygen consumption in muscle tissue can be determined by applying an arterial occlusion to a limb by inflating a pneumatic cuff. There will be no inflow, but also no outflow of blood. This will result in a decrease of the O\textsubscript{2}Hb signal and a simultaneous increase of deoxyhemoglobin. This will reflect the oxygen consumption of the investigated muscle. The oxygen consumption of the muscle was calculated by determining the slope of the linear decrement of the O\textsubscript{2}Hb signal, expressed in micromoles of O\textsubscript{2}Hb per liter of (muscle) tissue per minute. Taking into account that 1 mole of oxyhemoglobin binds 4 mole of oxygen (O\textsubscript{2}) and that 1 mole of oxygen equals 22.4 liters of O\textsubscript{2}, the oxygen consumption can be converted into milliliters of O\textsubscript{2} per liter per minute.

**Calculation of the Blood Flow**

When a venous occlusion is applied to a limb, there will still be arterial inflow of blood, but no more venous outflow. This will result in an increase in blood volume in the limb. The increase in blood volume is monitored with NIRS. The slope of the linear increase of the sum of the oxy- and deoxyhemoglobin (tHb) signal during the first seconds after the venous occlusion is represen-
tative for the blood flow into the limb. The hemoglobin flow is expressed as micromoles of O$_2$Hb per liter of tissue per minute. To convert the hemoglobin flow measured with NIRS into a blood flow, expressed in milliliters per liter per minute, the hemoglobin concentration (expressed in tetramer form) of whole blood of the subject has to be taken into account. Division by 10 gives the blood flow in milliliters per 100 ml (of tissue) per minute.

REFERENCES


