Deoxygenated Hemoglobin/Myoglobin Kinetics of Forearm Muscles from Rest to Exercise in Patients with Chronic Obstructive Pulmonary Disease

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Exercise capacity is frequently decreased in patients with chronic obstructive pulmonary disease (COPD), and muscle dysfunction is one factor in this reduction. Studies using 31P-phosphorus magnetic resonance spectroscopy (31P-MRS) have shown that phosphocreatine (PCr) and muscle pH (pHi) are significantly decreased in patients with COPD during mild exercise, suggesting the early activation of anaerobic glycolysis in their muscles. Thus, muscle oxygenation states during exercise might differ between patients with COPD and healthy individuals. We simultaneously measured oxygenation state and pHi in the muscles of patients with COPD during the transition from rest to exercise (on-transition) using near infrared spectroscopy (NIRS) and 31P-MRS. Sixteen patients with COPD (aged 68.6 ± 7.5 years) and 7 healthy males (controls; aged 63.3 ± 7.5 years) performed dynamic handgrip exercise (lifting a weight by gripping at a rate of 20 grips per min for 3 min). Patients were classified based on pHi data at the completion of exercise as having a normal (≥6.9; n = 8) or a low (<6.9; n = 8) pHi. The deoxygenated hemoglobin/myoglobin (deoxy-Hb/Mb) in NIRS recordings remained constant or slightly decreased initially (time delay), then increased to reach a plateau. We calculated the time delay and the time constant of deoxy-Hb/Mb kinetics during the on-transition. The time delay was shorter in the group with a low pHi than in the controls. These findings might reflect a slower increase in O2 delivery in patients with a low pHi, which might partly account for altered muscle energy metabolism. —— near-infrared spectroscopy; on-transition; oxygenation state; muscle pHi; chronic obstructive pulmonary disease.


The exercise capacity of patients with chronic obstructive pulmonary disease (COPD) is frequently decreased due to ventilatory limitations, hypoxemia, and pulmonary hypertension. In addition, recent studies have revealed that muscle wasting and muscle dysfunction might significantly contribute to exercise limitations in patients with COPD. Metabolic and morphological changes in the skeletal muscles of patients with COPD have been demonstrated, such as decreased oxidative enzyme activity (Jakobsson et al. 1995; Maltais et al. 1996) and an increased proportion of type II fibers in the lower limbs (Jobin et al. 1998). We also found changes in the skeletal muscle metabolism of patients with chronic respiratory impairment using 31-phosphorus nuclear magnetic resonance spectroscopy (31P-MRS) (Kutsuzawa et al. 1992, 1995). Skeletal muscle intracellular pH (pHi) and high-energy phosphate compounds can be dynamically measured using noninvasive 31P-MRS (Taylor et al. 1983). A decrease in pHi during exercise suggests lactic acid accumulation in exercising muscle (Taylor et al. 1983). Patients with chronic respiratory impairment have significant decreases in phosphocreatine (PCr) and pHi during mild exercise, suggesting reduced oxidative capacity and the early accumulation of lactate in their muscles (Kutsuzawa et al. 1992). Thus, muscle oxygenation states during exercise might differ between patients with COPD and healthy individuals.

Near-infrared spectroscopy (NIRS) has recently been used to evaluate muscle oxygenation during exercise in healthy individuals (Belardinelli et al. 1995; Mancini et al. 1994) as well as in patients with peripheral vascular disease (McCully et al. 1994) and with heart failure (Mancini 1997). This technique uses the absorption of near-infrared (NIR) light at a specific wavelength and allows the qualitative and noninvasive assessment of changes in oxygenated (oxy-) and deoxygenated (deoxy-) hemoglobin and myoglobin (Hb/Mb) at the level of small arterioles and venules, capillaries, and intracellular sites in vivo (Mancini 1997). The skeletal muscles of patients with lung disease have been studied using NIRS (Okamoto et al. 2003; Puente-Maestu et al. 2003). These studies investigated the rate of re-oxygenation during recovery in vastus lateralis muscles, and demonstrated that the rate of re-oxygenation is slower in patients...
with COPD than in healthy controls. However, the oxygenation kinetics of exercising muscles in patients with COPD during the transition from rest to exercise (on-transition) has not been investigated.

Muscle deoxy-Hb/Mb kinetics during the on-transition showed a dynamic balance between oxygen delivery and utilization. Two studies have shown that deoxy-Hb/Mb remains relatively unchanged or slightly decreased in healthy individuals during the initial 15 s of the transition from rest to exercise and mono-exponentially increases thereafter (DeLorey et al. 2003; Grassi et al. 2003). Behnke et al. (2002) and Diederich et al. (2002) proposed a model of microvascular O$_2$ pressure kinetics, measured by phosphorescence quenching, after the onset of exercise that included potential differences in the initial time delay and the primary component between healthy and 7-week post-myocardial infarction rats.

The present study simultaneously measured oxygenation state and muscle energy metabolism in the muscles of patients with COPD during the on-transition, using near infrared spectroscopy (NIRS) and $^{31}$P-MRS, respectively. We postulated that deoxy-Hb/Mb kinetics during on-transition in patients with COPD, especially low pH$i$ at the completion of exercise, would significantly differ (shorter time delay and/or slower time constant) from that of healthy individuals.

**METHODS**

**Subjects**

We studied 16 ambulatory male outpatients with stable COPD (aged 68.6 ± 7.5 y) diagnosed according to spirometric findings from moderate to very severe airflow limitation (FEV$_1$/FVC < 70% and FEV$_1$/FEV$_{pred}$ < 80%, FEV$_{pred}$, forced expiratory volume in 1 s; FVC, forced vital capacity; FEV$_{pred}$, predicted value of FEV$_1$) (Global Initiative for Chronic Obstructive Pulmonary Disease 2006). None had received systemic corticosteroid therapy. The exclusion criteria were malignancy, cardiac failure, infection and severe endocrine, hepatic, gastrointestinal or renal disorders. Patients were classified based on $^{31}$P-MRS pH$i$ data at the completion of exercise as follows: group 1, normal pH$i$ (PtN; pH$i$ ≥ 6.9; n = 8); and group 2, low pH$i$ (PtA; pH$i$ < 6.9; n = 8).

We also examined a control group of 7 healthy males (aged 63.3 ± 7.5 y) who were recruited from advertisements posted at our institution and at an outpatient clinic. We determined their history of pulmonary disease, routine activities, and annual health check findings. None of them regularly participated in exercise. The ethics committee at our institution approved the study and all patients and healthy volunteers provided written informed consent to participate. Tables 1 and 2 show the physical characteristics of the participants.

**Study design**

The anthropometric parameters of height, weight, forearm circumference and skin fold thickness at the proximal third of the non-dominant forearm were measured. The MRS and NIRS probes were placed at the proximal third of the non-dominant forearm. The skin fold thickness of the forearms of all participants was <5 mm, which is optimal for NIR measurements because a thicker fat layer causes light scattering and a lower optical density (Homma et al. 1996) when the light source and detector are positioned at a specific distance apart. The maximal voluntary grip power of the non-dominant arm was measured using a dynamometer (DM-100N; Yagami, Nagoya, Japan) and arterial blood gases of the patients were analyzed while breathing room air. After an overnight fast, all participants performed constant work-load exercise with the non-dominant forearm from a supine position while breathing room air. Muscle metabolism and oxygenation were simultaneously measured using $^{31}$P-MRS and NIRS during 1.5 min of rest, 3 min of exercise, and 4 min of recovery.

**Exercise**

The exercise consisted of repetitively gripping a lever at a rate of 20 grips per min for 3 min. The lever was attached to a weight via a pulley system. Gripping the lever caused the weight to be lifted a distance of 5 cm. To normalize the exercise intensity, the weight was adjusted to 7% of the maximal grip strength. Our preliminary study using $^{31}$P-MRS showed that the intracellular pH in healthy individuals does not decrease at the end of exercise at this intensity (Kutsuzawa et al. 1995).

We investigated oxygenation kinetics of the non-dominant arm because the difference among individuals in terms of routine activity might be smaller than in the dominant arm. Minotti et al. (1989) reported that a cumulative effect of differences in routine activities might cause differences in skeletal muscle metabolism between the dominant and non-dominant forearms.

**Near infrared spectroscopy**

We obtained NIRS measurements using a computer-controlled spectrophotometer with 3 channels and 3 wavelengths (OM-100A, Shimadzu, Kyoto, Japan). The NIRS optode distance was 2 cm on the proximal third of the ulnar side of the non-dominant forearm. Thus, the NIRS signal was derived mainly from superficial flexor muscles. The examined forearm was lightly secured to a table using fabric tape. Relative changes in oxy-Hb/Mb, deoxy-Hb/Mb and total Hb/Mb were calculated using the least squares method from changes in absorbance at 780, 805, and 830 nm (Kutsuzawa et al. 2001).

**Magnetic resonance spectroscopy**

Unlocalized magnetic resonance (MR) spectra were obtained using a 2.0-Tesla, 31-cm-bore superconducting magnet (BEM 250/80; Otsuka Electronics Co., Osaka, Japan). The spectrometer was operated at 85 MHz for $^1$H and at 34.5 MHz for $^{31}$P. A surface coil (4 cm) was placed on the proximal third of the non-dominant forearm. The $^{31}$P-MR spectra were obtained using a single 90° pulse (50 μsec) (Kutsuzawa et al. 1992) with a repetition time of 3 s and accumulated for 15 s.

The signal intensity was determined as the area under the spectral line for inorganic phosphates (Pi) and PCr, which was determined by means of Gaussian curve fitting (Kutsuzawa et al. 1992) from each spectrum. Relative concentrations of PCr and Pi were evaluated using normalized units of the PCr index (PCr/[PCr + Pi]). The pH$i$ was calculated as a difference in chemical shift between the Pi and PCr peaks (Taylor et al. 1983). When the Pi peak was split, the pH was determined from the greater peak. When split Pi peaks were the same height, the pH was determined from the mean of both peaks.

**Data analysis**

We adopted deoxy-Hb/Mb as a measure of the muscle oxygen-
ation state as described (Grassi et al. 2003) because oxy-Hb/Mb signals might be elevated by blood volume increasing in the skin during exercise. Relative changes in deoxy-Hb/Mb were obtained every second. Deoxy-Hb/Mb remained constant or slightly decreased during the initial 10-20 s, and then increased to reach a plateau (Fig. 1). Previous studies have fitted the kinetics of deoxygenation as a mono- or two-exponential function (Grassi et al. 2003). We fitted the deoxy-Hb/Mb data from onset to 60 s to a mono-exponential model using KaleidaGraph software (Kaleidagraph 4.0), since the deoxy-Hb/Mb of the primary component reaches a steady state level within ~60 s during moderate exercise (Grassi et al. 2003):

\[ Y(t) = Y(TD) + A \left(1-e^{-t/\tau}\right) \] (1),

where \( \tau \) is the time constant of the response and \( A \) is the amplitude. The time delay (TD) was defined as the lag time from the onset of exercise to the start of an increase in deoxy-Hb/Mb by visual inspection. Mean response time (MRT) was calculated as TD + \( \tau \).

**Statistical analysis**

All data are presented as means ± s.d. The blood gas data between PtN and PtA were compared using an unpaired t test. The anthropometric data, as well as the MRS and NIRS variables among groups were compared using a one-factor analysis of variance and the Fisher PSLD post hoc test. A \( p \) value of < 0.05 was considered to represent a significant difference.

**Results**

**Physical characteristics**

Tables 1 and 2 show the physical characteristics of the participants. Age, BMI, forearm circumference and maximal grip power of the non-dominant arm did not significantly differ among the 3 groups. The PtA findings indicat-

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls ((n = 7))</th>
<th>Patients</th>
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<tbody>
<tr>
<td></td>
<td>Normal pH ((n = 8))</td>
<td>Low pH ((n = 8))</td>
</tr>
<tr>
<td>Age ((y))</td>
<td>63.3 ± 7.5</td>
<td>67.1 ± 7.4</td>
</tr>
<tr>
<td>Height ((cm))</td>
<td>164.7 ± 5.4</td>
<td>164.8 ± 2.7</td>
</tr>
<tr>
<td>Weight ((kg))</td>
<td>60.0 ± 6.0</td>
<td>62.0 ± 5.9</td>
</tr>
<tr>
<td>BMI ((kg/m^2))</td>
<td>22.1 ± 2.2</td>
<td>22.9 ± 2.5</td>
</tr>
<tr>
<td>Forearm circumference ((cm))</td>
<td>23.9 ± 1.6</td>
<td>24.5 ± 1.1</td>
</tr>
<tr>
<td>Grip strength ((kg))</td>
<td>33.3 ± 2.9</td>
<td>34.6 ± 6.6</td>
</tr>
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Values are means ± s.d.

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<tr>
<th></th>
<th>Healthy controls ((n = 7))</th>
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<tbody>
<tr>
<td></td>
<td>Normal pH ((n = 8))</td>
<td>Low pH ((n = 8))</td>
</tr>
<tr>
<td>VC ((L))</td>
<td>4.22 ± 1.06</td>
<td>2.96 ± 0.48*</td>
</tr>
<tr>
<td>%VC ((%))</td>
<td>110.8 ± 20.5</td>
<td>89.2 ± 15.2*</td>
</tr>
<tr>
<td>FEV₁ ((L))</td>
<td>3.47 ± 0.61</td>
<td>1.35 ± 0.26*</td>
</tr>
<tr>
<td>FEV₁/FVC ((%))</td>
<td>83.0 ± 11.7</td>
<td>49.5 ± 10.2*</td>
</tr>
<tr>
<td>FEV₁/FEV₁,pred ((%))</td>
<td>117.9 ± 7.8</td>
<td>47.7 ± 11.9*</td>
</tr>
<tr>
<td>pH</td>
<td>NA</td>
<td>7.409 ± 0.033</td>
</tr>
<tr>
<td>PaCO₂ ((Torr))</td>
<td>NA</td>
<td>40.4 ± 5.1</td>
</tr>
<tr>
<td>PaO₂ ((Torr))</td>
<td>NA</td>
<td>79.9 ± 3.4</td>
</tr>
<tr>
<td>SaO₂ ((%))</td>
<td>NA</td>
<td>95.9 ± 0.6</td>
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</table>

Values are means ± s.d. * \( p < 0.01 \) vs. healthy individuals; † \( p < 0.05 \) vs. healthy individuals; ‡ \( p < 0.05 \) vs. patients with normal pH; ** \( p < 0.01 \) vs. patients with normal pH.
ed severe airflow limitation compared with PtN (Table 2). Despite moderate to severe airflow limitations (Table 2), none of the patients developed severe hypoxemia.

$^{31}$P-MRS findings

Table 3 shows the mean values of pH and the PCr index at rest and at the completion of the exercise. Neither value significantly differed at rest among the 3 groups. At the completion of exercise, the mean values of pH and PCr index were significantly lower in PtA than in the healthy individuals and in PtN. Fig. 2A and B shows time course changes in pH and PCr index during exercise. In PtA, the mean value of the PCr index began to decrease during 15 s of exercise and was significantly lower at 60 s of exercise than in healthy individuals and in PtN. The pH from 45 s to 180 s was also significantly lower in PtA than in healthy individuals.

**NIRS findings**

Fig. 3 shows representative NIRS recordings from a healthy 57-year-old and an age-matched patient with COPD. Deoxy-Hb/Mb decreased within ~12 s of exercise (initial dip), then increased to reach a plateau ($\tau$: 19.1 s) in the healthy individual (Fig. 3A). The initial profile of deoxy-Hb/Mb (initial dip) was identical in 5 of the 7 healthy individuals. Deoxy-Hb/Mb remained constant in one patient with COPD whose pH at the completion of exercise (pHi-ex) was 6.62 for ~3 s and then increased to reach a plateau ($\tau$: 11.2 s) (Fig. 3B). Thereafter, deoxy-Hb/Mb gradually increased (slow component). Deoxy-Hb/Mb during the initial seconds of exercise remained constant in 9 of the 16 patients and dipped in the remainder.

Fig. 2C shows time course changes in deoxy-Hb/Mb among 3 groups. Changes in deoxy-Hb/Mb were calculated as follows:

$$\Delta$$deoxy-Hb/Mb

$$= \text{deoxy-Hb/Mb}(t)/ (\text{deoxy-Hb/Mb}(\text{max}) - \text{deoxy-Hb/Mb}(0))$$

where deoxy-Hb/Mb(max) is the maximal value of deoxy-

### Table 3. MRS data.

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<tr>
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<th>Healthy controls ($n = 7$)</th>
<th>Patients</th>
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<tbody>
<tr>
<td></td>
<td>Normal pH ($n = 8$)</td>
<td>Low pH ($n = 8$)</td>
</tr>
<tr>
<td>At rest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH ($^a$)</td>
<td>7.02 ± 0.04</td>
<td>7.04 ± 0.07</td>
</tr>
<tr>
<td>PCr/(PCr+Pi) ($^\dagger$)</td>
<td>0.861 ± 0.041</td>
<td>0.865 ± 0.037</td>
</tr>
<tr>
<td>At completion of exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH ($^a$)</td>
<td>7.05 ± 0.06</td>
<td>6.95 ± 0.05$^\dagger$</td>
</tr>
<tr>
<td>PCr/(PCr+Pi) ($^\dagger$)</td>
<td>0.654 ± 0.047</td>
<td>0.598 ± 0.076</td>
</tr>
</tbody>
</table>

Values are means ± s.d. $^a$, intracellular pH; $^\dagger$, phosphocreatine/(phosphocreatine + inorganic phosphate); $^\ddagger$, p < 0.05 vs. healthy individuals; $^{**}$, p < 0.01 vs. healthy individuals; $^\section{\dagger}$, p < 0.01 vs. patients with normal pH.
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Hb/Mb and deoxy-Hb/Mb(0) is the value at onset. Since the time resolution of the MRS variable was 15 s, \( \Delta \text{deoxy-Hb/Mb} \) was averaged every 15 s. The first 15 s of \( \Delta \text{deoxy-Hb/Mb} \) was significantly lower in healthy individuals than in PtN and PtA.

The mean value for TD was significantly shorter in PtA than in healthy individuals and in PtN (Table 4). Mean values of \( \tau \) did not significantly differ among the 3 groups. Mean values of MRT were lower in PtA than in healthy individuals, but the difference did not reach significance.

**DISCUSSION**

The present study examined muscle oxygenation kinetics using NIRS during constant-rate forearm exercise in patients with COPD. The results showed that the time delay (TD) in deoxy-Hb/Mb at the onset of exercise was shorter in patients with a low pH during exercise than in healthy individuals and patients with a normal pH during exercise.

The kinetics of deoxy-Hb/Mb in our study can be determined as the relationship between muscle oxygen utilization and local muscle oxygen delivery within the region of NIRS investigation. A faster increase in deoxy-Hb/Mb reflects a slower increase in O\(_2\) delivery, and this in turn leads to a faster decrease in intramuscular Po\(_2\), which might serve to slow Vo\(_2\) kinetics, increase the O\(_2\) deficit, and therefore produce a greater decrease in PCr (McDonough et al. 2005).

We found that deoxy-Hb/Mb remained constant or decreased during the initial phase of exercise. Other studies using NIRS have found similar oxygenation kinetics in the vastus lateralis muscle during constant-rate exercise in healthy individuals (DeLorey et al. 2003; Grassi et al. 2003). Our TD values from healthy individuals were similar to those of the lower limb muscles described in these reports. During the on-transition, an immediate and pronounced increase in muscle blood flow is induced by the muscle pump and vasodilation (Tschakovsky et al. 2004). The transient decrease (initial dip) in deoxy-Hb/Mb during the initial phase of exercise might result from excess oxygen delivery, that is, increased blood flow, compared with O\(_2\) utilization (i.e., O\(_2\) delivery/O\(_2\) utilization ratio) (Grassi et al. 1996; Behnke et al. 2001; DeLorey et al. 2003; Grassi et al. 2003). The constant deoxy-Hb/Mb during the initial phase suggested that balance is maintained between the immediate increase in muscle blood flow and O\(_2\) utilization (DeLorey et al. 2003; Grassi et al. 2003).

The TD in PtA was significantly shorter than that of healthy individuals, suggesting that the O\(_2\) delivery did not balance O\(_2\) utilization in patients with COPD and a low pH during exercise. This might be caused by a rapid increase in muscle oxygen utilization or a comparatively sluggish increase in O\(_2\) utilization (Behnke et al. 2002). Whether or not muscle oxygenation kinetics are related to exercise intensity remains controversial. One study has demonstrated that TD is shorter during exercise at higher, than at moderate intensity (Grassi et al. 2003). Another study (Shibuya et al. 2004) has shown that TD does not change in healthy individuals over a wide range of exercise intensity. Here, we adjusted the lifted weight to 7% of the maximal grip power, and the exercise intensity did not differ between

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**Table 4.** NIRS data.

<table>
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<tr>
<th></th>
<th>Healthy controls (n = 7)</th>
<th>Normal pH (n = 8)</th>
<th>Low pH (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD(^\dagger)</td>
<td>11.6 ± 3.3</td>
<td>9.1 ± 4.5</td>
<td>5.5 ± 3.2(^\dagger)</td>
</tr>
<tr>
<td>( \tau )(^\ddagger)</td>
<td>14.2 ± 10.6</td>
<td>12.9 ± 3.8</td>
<td>14.7 ± 4.2</td>
</tr>
<tr>
<td>MRT(^\S)</td>
<td>25.3 ± 8.1</td>
<td>22.1 ± 5.4</td>
<td>20.2 ± 5.4</td>
</tr>
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</table>

Values are means ± s.d. \(^\dagger\), Time delay; \(^\ddagger\), p < 0.01 between healthy individuals and patients with low pH; \(^\S\), mean response time.
patients and healthy individuals.

Since our previous study showed that arterial oxygen saturation was constant during this exercise protocol in patients with COPD (Kutsuzawa et al. 1992), a smaller increase in blood flow compared with that of $O_2$ utilization during the on-transition might cause the shorter TD in PtA. Vascular control during exercise might relate to a smaller increase in blood flow during the on-transition. This shorter time delay might also have been influenced by a decreased $O_2$ delivery/$O_2$ utilization ratio at rest which is normally characteristic of fast-twitch muscle fibers (type IIb) (Behnke et al. 2003; McDonough et al. 2005; Ferreira et al. 2006).

The $\tau$ value of the patients was not significantly shorter than that of healthy individuals. Since $\tau$ can be determined as the net combination of the relative rate of muscle oxygen utilization and oxygen delivery (DeLorey et al. 2003), it might become constant when reduced oxidative capacity is associated with impaired blood flow.

The nature of muscle fibers can affect TD and $\tau$ because oxidative enzyme activity and control of arteriolar vasodilation differ between type I and type II fibers. McDonough et al. (2005) found using phosphorescence quenching techniques that the kinetics of microvascular oxygen pressure at the onset of contraction during electrical stimulation in rat muscles were more rapid and steady-state values fell further for the gastrocnemius (types IIA and IIb) than for the soleus (type I). Thus, the $\tau$ value of patients with COPD might increase since type II fibers are predominant in patients with COPD (Jobin et al. 1998). Muscle biopsy data for our patients were not available, so we could not determine the influence of muscle fiber type on oxygenation kinetics in the presence of COPD.

A shorter TD in deoxy-Hb/Mb, which reflects a slower increase in $O_2$ delivery, might lead to a greater $O_2$ deficit. A decrease in pH during exercise suggests that lactic acid accumulates in exercising muscle cells due to anaerobic glycolysis (Taylor et al. 1983). Therefore, PtA decreased more in PCr and pH due to adenosine tri-phosphate (ATP) production from non-aerobic sources (such as PCr hydrolysis and glycolysis) (McDonough et al. 2005).

Expiratory gas has generally been analyzed to determine the kinetics of $O_2$ uptake ($V\dot{O}_2$) during exercise. Comparisons of pulmonary $V\dot{O}_2$ with kinetics of deoxy-Hb/Mb have revealed that muscle deoxygenation increases faster than pulmonary $V\dot{O}_2$ in healthy individuals (DeLorey et al. 2003). The time constant of pulmonary $V\dot{O}_2$ kinetics during on-transition is slower in patients with COPD than in healthy individuals (Nery et al. 1982; Palange et al. 1995). In contrast, the present study demonstrated that the TD of deoxy-Hb/Mb kinetics was shorter in patients with COPD than in healthy individuals, and that the $\tau$ value was not significantly shorter in the patients than in healthy individuals. Muscle deoxygenation kinetics during the on-transition might not estimate the pulmonary $V\dot{O}_2$ kinetics in patients with COPD, although the time constant of the decrease in deoxy-Hb/Mb during recovery correlates with that of the decrease in pulmonary $V\dot{O}_2$ in patients COPD (Okamoto et al. 2003).

We did not determine the absolute concentrations of oxy-Hb/Mb, deoxy-Hb/Mb and total Hb/Mb because the Hb calculations were based on an assumed constant optical path-length. One study (Poole et al. 2001) has demonstrated a lower microvascular $O_2$ pressure of the diaphragm in rats with COPD. We could not determine whether or not deoxy-Hb/Mb increased at rest. Changes in the absorption of hemoglobin (Hb) and myoglobin (Mb) cannot be differentiated by NIRS because their Mb absorption spectra are similar. However, signals from skeletal muscles are mostly attributable to Hb since the ratio of [Hb] to [Mb] is $\gg$ 5 in human skeletal muscle (Mancini et al. 1994). However, another study (Tran et al. 1999) found that the NIR signals actually monitor Mb desaturation. For our purpose, Hb and Mb signals showed heading in the same direction.

Near infrared spectroscopic measurements have usually been obtained from a single site on a muscle of interest. However, substantial heterogeneity exists in muscle blood flow (Laughlin et al. 1982; Mizuno et al. 2003), motor unit recruitment (Gollnick et al. 1974), and fiber type distribution. Simultaneous measurements of deoxy-Hb/Mb at 10 sites of the quadriceps muscle during exercise have revealed significant intersite variability of muscle deoxygenation kinetic parameters within individuals, but no intersubject variability (Koga et al. 2007). Multichannel NIRS is a powerful tool with which to investigate the spatial profiles of muscle deoxygenation between healthy individuals and patients.

In conclusion, the present study showed that the time delay of deoxygenation kinetics during the on-transition of forearm exercise was shorter in patients with COPD who developed a low muscle pH during exercise. Impaired muscle $O_2$ delivery, and, to a lesser degree, $O_2$ utilization during the on-transition, might be responsible for these effects and also account, at least in part, for the reduced muscle [PCr] that occurs during exercise in these patients.

Acknowledgments

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Conflict of interest statement
The authors have no conflict of interest regarding the manuscript.

References


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