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Skeletal muscle phosphocreatine recovery in exercise-trained humans is dependent on O₂ availability

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Haseler, Luke J., Michael C. Hogan, and Russell S. Richardson. Skeletal muscle phosphocreatine recovery in exercise-trained humans is dependent on O₂ availability. J. Appl. Physiol. 86(6): 2013–2018, 1999.—In skeletal muscle, phosphocreatine (PCr) recovery from submaximal exercise has become a reliable and accepted measure of muscle oxidative capacity. During exercise, O₂ availability plays a role in determining maximal oxidative metabolism, but the relationship between O₂ availability and oxidative metabolism measured by 31P-magnetic resonance spectroscopy (MRS) during recovery from exercise has never been studied. We used 31P-MRS to study exercising human gastrocnemius muscle under conditions of varied fractions of inspired O₂ (FIO₂) to test the hypothesis that varied O₂ availability modulates PCr recovery from submaximal exercise. Six male subjects performed three bouts of 5-min steady-state submaximal plantar flexion exercise followed by 5 min of recovery in a 1.5-T magnet while breathing three different FIO₂ concentrations (0.10, 0.21, and 1.00). Under each FIO₂ treatment, the PCr recovery time constants were significantly different, being longer in hypoxia (33.5 ± 4.1 s (SE)) and shorter in hyperoxia (20.0 ± 1.8 s) than in normoxia (25.0 ± 2.7 s) (P ≤ 0.05). End-exercise pH was not significantly different among the three treatments (7.08 ± 0.01 for 0.10, 7.04 ± 0.01 for 0.21, and 7.04 ± 0.02 for 1.00). These results demonstrate that PCr recovery is significantly altered by FIO₂, and suggest that, after submaximal exercise, PCr recovery, under normoxic conditions, is limited by O₂ availability.

oxidative capacity; mitochondria; intracellular oxygenation; 31-phosphorus-magnetic resonance spectroscopy; fraction of inspired oxygen

After submaximal exercise conditions in which the intracellular pH fall is not severe, resynthesis of phosphocreatine (PCr) occurs primarily by oxidative processes (3, 5, 17, 19). Under such conditions, the recovery of PCr is described by a monoexponential time course (23, 28, 40), and the time constant for PCr recovery (τ) has been shown to be independent of stimulation frequency, exercise intensity, and end-exercise levels of PCr (26, 40). Thus PCr recovery data are generally considered to be an important and robust measure of mitochondrial respiration that provide an index of skeletal muscle oxidative capacity (3, 17, 19).

Consequently, the measurement of PCr recovery has proven useful in identifying a range of skeletal muscle oxidative capacities. PCr recovery was slowed in clinically proven cases of mitochondrial myopathy (2, 8, 30) and in chronic disease conditions such as cardiac failure that are known to result in reduced mitochondrial content and oxidative capacity (38–40). In contrast, PCr recovery was enhanced with endurance training in athletes (22, 26, 42), consistent with the increased mitochondrial content and activities of the enzymes associated with oxidative metabolism allowing a greater capacity for oxidative generation of ATP (6, 14, 24). Additionally, McCully et al. (27) have demonstrated a linear relationship between PCr recovery and citrate synthase activity in human skeletal muscle. More recently, Paganini et al. (29) demonstrated in rats that the rate constant for PCr recovery in skeletal muscle is linearly dependent on oxidative capacity as indicated by the mitochondrial marker enzyme citrate synthase. These authors concluded that PCr recovery measurements can be used as an index of relative oxidative capacity or mitochondrial content in muscle.

During exercise, O₂ availability has been well documented as both a modulator of muscle bioenergetics (10, 11) and a determinant of maximal oxidative capacity (32, 35). However, the role of O₂ availability, manipulated by the fraction of inspired O₂ (FIO₂), in the determination of skeletal muscle oxidative metabolism assessed in recovery by 31P-magnetic resonance spectroscopy (MRS) has never been examined. Consequently, we studied the effect of FIO₂ on PCr recovery in humans after submaximal plantar flexion exercise to test the hypothesis that increased O₂ availability would enhance PCr recovery whereas decreased O₂ availability would slow PCr recovery, which would illustrate that, under normoxic conditions, trained skeletal muscle mitochondrial respiration during recovery from submaximal exercise is limited by O₂ availability.

METHODS

Subjects. Six healthy men aged 21–42 yr volunteered to participate in this study and gave written informed consent. The study was approved by the Human Subjects Committee of the University of California, San Diego. Subjects were all healthy and active, ranging from moderately to well-trained athletes. The subjects refrained from strenuous exercise for 24 h before data collection.

Exercise protocol. Subjects were familiarized with plantar flexion exercise in the confines of a whole body magnetic resonance imaging system. At this time, –60% of maximum work rate was determined for each subject. Subjects performed constant-load submaximal plantar flexion at this intensity (range 7–8 W) at a frequency of 1 contraction/s (keeping time with an electronic metronome) while lying supine in a superconducting 1.5-T magnet. Throughout each exercise bout, subjects breathed through a low-resistance two-way breathing valve (model 2700, Hans-Rudolph, Kansas City, MO), and end-tidal O₂ and CO₂ were sampled.
continuously, allowing the calculation of arterial O₂ saturation (assuming no alveolar to arterial PO₂ gradient and no significant metabolic acidosis). Heart rate was monitored continuously throughout the experiment with a finger probe (Omni-Trak, In Vivo Research). In each FIO₂ (0.1, 0.21, and 1.00), subjects performed a 5-min warm-up period followed by 5 min of rest, and then they performed 5 min of exercise followed by 5 min of recovery. Subjects were allowed 40 min of rest between each complete exercise bout. The order of the three treatments was varied to allow all six possible orders to be performed once and to minimize any ordering effects. Throughout the study subjects were unaware of the treatment order.

3¹P-MRS. MRS was performed by using a clinical 1.5-T General Electric Signa system (version 4.8) operating at 25.86 MHz for 3¹P. 3¹P-MRS data were acquired with a transmit/receive surface coil (diameters 20 and 10 cm, respectively) placed under the calf at its maximum diameter. The centering of the leg over the coil was confirmed by T₁-weighted ¹H localizing images obtained in the axial plane. Magnetic field homogeneity was optimized by shimming on the proton signal from tissue water. For 3¹P-MRS the pulse power was adjusted so that ~72% of the signal acquired was from tissue within 5 cm of the surface coil. The spectral width was 2,500 Hz, and a single free induction decay (FID) was acquired every 4 s for the 5 min of exercise and 5 min of recovery. As a result, the data are expressed with a time resolution of 4 s.

Data analysis. Data were processed by using SAGE/IDL software on a Silicon Graphics Indigo workstation. Each FID consisted of 1,024 complex points and was processed with 5-Hz exponential line broadening before zero filling and Fourier transformation. All spectra were manually phased by using zero- and first-order phase corrections. There were no phase variations among rest, exercise, and recovery during the experiment. The levels of PCr determined from the intensity of that peak were normalized to 100% by using the average value obtained from the last 40 s of rest acquired for each subject as a reference. Muscle intracellular pH was calculated from the chemical shift difference (δ) of the P₃ peak relative to the PCr peak by using the following equation:

$$\text{pH} = 6.75 + \log(\delta - 3.27)/(5.69 - \delta)$$

(37). Signal-to-noise ratios (~20:1) were sufficient to allow PCr levels to be determined with a temporal resolution of 4 s during exercise and recovery. Changes in PCr during recovery were fit to a monoexponential function

$$\text{PCr}(t) = \text{PCr}_0 + \text{PCr}_1 [1 - e^{-(t-\text{TD})/\text{t}}]$$

where PCr₀ is the baseline value, PCr₁ is the difference between the baseline and the recovery value, t is time, TD is the time delay, and t is the time constant.

Statistical analysis. Data were tested with repeatedmeasures ANOVA (Tukey post hoc) by using a commercially available software package (Instat, San Diego, CA). Data were considered significantly different when P < 0.05. The results are presented as means ± SE.

**RESULTS**

A stack plot showing typical signal-to-noise ratios (~20:1 for the PCr resonance) during exercise and the recovery transition is shown in Fig. 1. Each spectrum represents a single acquisition with a temporal resolu-
Fig. 2. Recovery curves for an individual subject showing raw data and monoexponential fit. ○, Hypoxia; ●, hypoxia. For clarity, normoxic data are not shown. Time constants calculated from the monoexponential fit for this subject were 19.5 and 26.6 s for hyperoxia and hypoxia, respectively (normoxia = 21.8 s, not shown). PCr, phosphocreatine.

tion of 4 s. Figure 2 illustrates recovery curves for an individual subject. For clarity, only the hypoxic and hyperoxic treatments are shown with the $\tau$ values calculated from the monoexponential fit 26.6 and 19.5 s, respectively (normoxia = 21.8 s, not shown) for this individual. For the complete subject pool, $\tau$ values were significantly different in each of the three $F_{IO2}$ treatments and are shown in Table 1.

The mean work done by the subjects in each exercise bout was 7.2 ± 0.6 W. At rest, $F_{IO2}$ had no effect on PCr levels. The end-exercise levels of PCr, expressed as a percentage of resting levels, were not significantly different among $F_{IO2}$ treatments: 64.0 ± 3.5% for 0.10, 68.6 ± 3.6% for 0.21, and 70.2 ± 5.5% for 1.00 (averaged over last 40 s of exercise). End-exercise pH values showed no significant differences in each of the gases: 7.08 ± 0.01 for 0.10, 7.04 ± 0.01 for 0.21, and 7.04 ± 0.02 for 1.00 and were not significantly different from the initial resting pH values (7.04 ± 0.01 for 0.10, 7.04 ± 0.01 for 0.21, and 7.03 ± 0.01 for 1.00).

The calculated arterial $O_2$ saturations for the three $F_{IO2}$ treatments were 77.0 ± 0.5, 97.4 ± 0.5, and 100% for 0.10, 0.21, and 1.00, respectively. These arterial $O_2$ saturations for the different $F_{IO2}$ correspond to arterial $PO_2$ values of ~45, 100, and 600 Torr, respectively.

DISCUSSION

Previously, Idstrom et al. (16) have demonstrated that PCr recovery is slowed in perfused rat hindlimb muscles when $O_2$ delivery is reduced. The results of the present study build on these observations and, in fact, demonstrate that PCr recovery from submaximal exercise in exercise-trained humans is altered by increases and decreases in $F_{IO2}$. The increase in $\tau$ with hypoxia and decrease in $\tau$ with hypoxia suggest that $O_2$ availability plays a role in mitochondrial function. These results suggest limited metabolic capacity due to $O_2$ availability during recovery from exercise, similar to that previously documented during maximal exercise (31, 35).

$F_{IO2}$ and cellular oxygenation. During exercise, the $O_2$ required for oxidative phosphorylation in skeletal muscle moves from the blood to mitochondria down a $PO_2$ pressure gradient between the capillary and the cell (32). The flux of $O_2$ is dependent on this diffusion-induced pressure difference between the capillary and the cytoplasm and is determined by the rate of mitochondrial respiration. Previously, it has been demonstrated that breathing hyperoxic and hypoxic gases during exercise results in a rise and fall in the calculated mean capillary $PO_2$ (32, 33). In the cell this results in increased or decreased intracellular $PO_2$ (32, 33). These studies also revealed that intracellular $PO_2$ remained constant, in a given $F_{IO2}$, over a range of submaximal to maximal exercise intensities. Because the present work intensity was similar (50–60% of maximum), it seems reasonable to assume a similar level of intramuscular oxygenation. Additionally, on the basis of this prior work, it can be assumed that changes in $F_{IO2}$ and the subsequent changes in arterial and capillary $PO_2$ altered the intracellular $PO_2$ of the exercising muscle. Therefore, it is likely that the results of the present study were due to changes in intracellular $PO_2$ caused by breathing the different $F_{IO2}$.

Altered PCr recovery: oxidative capacity vs. mitochondrial function. The measurement of PCr recovery data has proven useful in determining the oxidative capacity of skeletal muscle to synthesize ATP in a variety of conditions (22, 26, 29, 30, 39, 42). In mass, these studies illustrate the sensitivity of PCr recovery to changes in oxidative capacity. Thus the present results could be interpreted as a change in the oxidative capacity of the muscle, similar to the increase seen in response to training (22, 26, 42) or the decrease as a result of disuse or myopathy (29, 40), although smaller in magnitude. Because this was an acute repeated-measures design, it is clear that such structural changes (e.g., altered mitochondrial content) cannot explain the altered PCr $\tau$ and apparent change in oxidative capacity with varied $F_{IO2}$.

As discussed above, it is unlikely that the present data represent a change in mitochondrial capacity but rather a change in mitochondrial function. Maximal mitochondrial respiratory rate is dependent on substrate availability; including not only $O_2$ but also ADP, $P_i$, and NAD+/NADH. It is speculated that this altered mitochondrial function may be specifically due to changes in $O_2$ availability, the result of varied $F_{IO2}$, and take the form of either altered mitochondrial recruitment as previously hypothesized (11) or another ex-

<table>
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<tr>
<th>$F_{IO2}$</th>
<th>$\tau$, s</th>
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<tr>
<td>0.10</td>
<td>33.5 ± 4.1*</td>
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<td>0.21</td>
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<tr>
<td>1.00</td>
<td>20.0 ± 1.8*</td>
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Values are means ± SE in hypoxia (0.10 fraction of inspired $O_2$ ($F_{IO2}$)), normoxia (0.21 $F_{IO2}$), and hyperoxia (1.00 $F_{IO2}$). PCr, phosphocreatine; $\tau$, time constant. *Significantly different from normoxia, $P < 0.05$. 

The calculated arterial $O_2$ saturations for the three $F_{IO2}$ treatments were 77.0 ± 0.5, 97.4 ± 0.5, and 100% for 0.10, 0.21, and 1.00, respectively. These arterial $O_2$ saturations for the different $F_{IO2}$ correspond to arterial $PO_2$ values of ~45, 100, and 600 Torr, respectively.

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ample of limited mitochondrial function due to O$_2$ supply (32, 35). It is noteworthy that both of these theories are complementary and may be somewhat interrelated. The latter theory is supported by previous studies that have observed slowed PCR recovery due to a reduction in the arterial Po$_2$ (1) and in cases of reduced muscle blood flow (9) (discussed in detail in Evidence of mitochondrial O$_2$ supply-dependent ATP synthesis). However, the former theory is supported by the observation that altered tissue oxygenation during steady-state submaximal exercise results in altered PCR levels, suggesting that tissue or intracellular oxygenation plays a role in modulating regulators of cellular respiration (10, 11). Thus cellular levels of O$_2$ may influence metabolic control even during submaximal exercise. It is also known that exercise training increases the mitochondrial content of the cell (12, 13), and this alters the mitochondrial sensitivity to the regulators of respiration (7). Thus mitochondrial content itself has been shown to play a role in controlling oxidative phosphorylation (6, 7). Under conditions of identical submaximal stimulation, PCR decreased less and ADP and P$_i$ increased less in muscle from trained rats compared with untrained rats (6, 7). Greater mitochondrial density results in less energy production per mitochondria; thus less stimulus for respiration is required. Additionally, the effect of exercise training in humans has been demonstrated by $^{31}$P-MRS to show that trained muscle has an increased potential for oxidative metabolism (20). Because intracellular Po$_2$ during submaximal exercise varies with different F IO$_2$ (32, 33), it has previously been postulated that O$_2$ availability affects mitochondrial sensitivity through mitochondrial recruitment (11). Under hyperoxic conditions and a higher mean intracellular Po$_2$, there would be a greater number of mitochondria with adequate oxygenation resulting in enhanced PCR recovery from exercise, analogous to a trained state. Conversely, under hypoxic conditions, there may be fewer mitochondria that have adequate O$_2$. Subsequently, PCR recovery would be slowed, eliciting a similar response to that of reduced mitochondrial content. This suggests that greater intracellular oxygenation results in a more tightly controlled system, allowing faster rates of recovery. The converse is true in hypoxia, resulting in slower rates of recovery.

Evidence of mitochondrial O$_2$ supply-dependent ATP synthesis. At the end of exercise, PCR $\tau$ represents mitochondrial ATP synthesis (i.e., function) (3, 4). Provided that end exercise pH has not reached a low value, recovery can be thought of as an aerobic challenge in which the rate constant for PCR recovery ($1/\tau$) is a function of the maximum rate of oxidative ATP synthesis ($Q_{max}$), which can be estimated as $Q_{max} = (1/\tau)[PCr_{rest}]$, with the apparent $Q_{max}$ a function of the density and capacity of working mitochondria and the supply of substrate and O$_2$, independent of muscle mass, and where [PCr$_{rest}$] is PCR concentration in resting muscle (18). Recently, it has been shown that the rate constant for PCR recovery can be directly interpreted as a measure of oxidative capacity with a linear dependence of $1/\tau$ on oxidative capacity (27, 29). Because [PCr$_{rest}$] is constant for a given subject, the rate constant for PCR recovery, $Q_{max}$, and maximal O$_2$ consumption (VO$_{2max}$) are all indicative of the maximal rate of oxidative ATP synthesis. Thus it is not surprising that there is a strong similarity between O$_2$ consumption and PCR on- and off-exercise kinetics (25) or that both $Q_{max}$ and VO$_{2max}$ are linearly dependent on muscle oxidative capacity (15, 29). Consequently, PCR exercise-recovery data are clearly indicative of both muscle VO$_{2max}$ and muscle oxidative capacity: a greater oxidative capacity leads to a greater capacity to consume O$_2$ and a shorter PCR $\tau$ and vice versa. The present data provide the first MRS evidence of a dissociation between the first two variables (muscle VO$_{2max}$ and oxidative capacity) due to altered F IO$_2$. This is evident by the fact that the rate constant for PCR recovery (similar in many respects to VO$_{2max}$) is altered by varying O$_2$ availability while oxidative capacity remained unchanged due to the acute nature of the study. This dependence of PCR recovery on F IO$_2$ may be due to the altered intracellular oxygenation. Because of hardware constraints of the present magnetic resonance system, intracellular Po$_2$ measurements were not obtained. However, with the assumption that the intracellular Po$_2$ of exercising human gastrocnemius muscle has a similar intracellular Po$_2$ response to changes in F IO$_2$ as observed in the human quadriceps (32, 33), it can be illustrated that the rate constant for PCR recovery measured here has a dependence on intracellular oxygenation (Fig. 3). The dependence of

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PHOSPHOCREATINE RECOVERY WITH VARIED FIO2

the PCr rate constant on oxygenation seen in Fig. 3 suggests that PCr recovery from submaximal exercise is limited by O2 availability. The observation here that PCr recovery is enhanced with increased intracellular oxygenation provides evidence that under normoxic conditions Qmax is determined by O2 availability and not mitochondrial metabolic limits. Figure 3 provides further evidence of an in vivo correlate of the effect of O2 tension on cellular respiration rate (32), as originally demonstrated in vitro by Wilson et al. (41). These data suggest that the dependence of the rate constant for PCr recovery, Qmax, and PmO2 on O2 availability may be approaching a plateau whereby further increments in intracellular PmO2 will have a diminishing effect. These findings are consistent with the concept that VO2max is dependent on the availability of O2 (31, 35).

There is prior evidence in untrained subjects performing small-muscle-mass exercise that suggests the effect of varying FIO2 on O2 delivery is dampened by an alteration in muscle blood flow (36). In that case, convective O2 delivery would remain constant, whereas the diffusive component of O2 transport would be altered (35). Such a scenario has been reported previously, where the convective delivery of O2 and the O2 diffusing capacity (DO2) were unchanged between hypoxia and normoxia, but the significantly reduced VO2 gradient from capillary (PCO2) to tissue (PmO2) decreased both VO2max and PmO2 [VO2max = DO2(PCO2 - PmO2)] (34). In a study of cyanotic patients with congenital heart disease, slowed PCr recovery times have been reported, again consistent with the reduced PO2 gradient available to drive O2 into the myocyte (1). In the present study, the similar increase in the PCr recovery rate constant in hypoxia (20%) and decrease in hypoxia (23%) are also suggestive of this scenario because the most significant effect of hypoxia is to raise blood PO2 because Hb saturation is already close to its ceiling in normoxia. Hence, it is suggested that in hypoxia the gradient from blood to muscle was enhanced, resulting in an elevated intracellular PO2, facilitating increased oxidative metabolism, and ultimately a shorter PCr recovery rate (Fig. 2). The converse occurs in hypoxia. These data indicate that under normoxic conditions, the rate constant for PCr recovery, Qmax, and therefore VO2max are limited by O2 availability. It should be recognized that mitochondrial capacity is unaltered in these conditions. Therefore, the conclusions are identical, but the scientific approach is very different from many studies that have previously illustrated a strong dependency between O2 supply and skeletal muscle oxidative capacity during maximal exercise (21, 31).

Summary. This study demonstrated that PCr recovery after submaximal exercise is slowed with breathing of a hypoxic gas mixture and enhanced with breathing of a hyperoxic gas compared with normoxia. This suggests that tissue oxygenation plays a role in mitochondrial function, resulting in changes similar to those observed in situations of altered oxidative capacity. The increase in PCr recovery rate constant observed by increasing the PO2 driving gradient for O2 into the cell suggests that under normal conditions the recovery of PCr is limited by O2 supply. This can be interpreted as further evidence that diffusion of O2 from erythrocyte to mitochondria, and ultimately intracellular PmO2, plays an important role in determining skeletal muscle VO2max. Finally, the practical implication of these data is that PCr recovery measurements should be interpreted with caution because differences in Qmax between subjects may not be due to metabolic limitations but rather to variations in O2 availability. Hence a lengthened PCr recovery exhibited in a diseased state may be due to O2 supply limitations and not to a metabolic abnormality.

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