Evidence that a higher ATP cost of muscular contraction contributes to the lower mechanical efficiency associated with COPD: preliminary findings

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Layec G, Haseler LJ, Hoff J, Richardson RS. Evidence that a higher ATP cost of muscular contraction contributes to the lower mechanical efficiency associated with COPD: preliminary findings. Am J Physiol Regul Integr Comp Physiol 300: R1142–R1147, 2011. First published February 9, 2011; doi:10.1152/ajpregu.00835.2010.— Impaired metabolism in peripheral skeletal muscles potentially contributes to exercise intolerance in chronic obstructive pulmonary disease (COPD). We used 31P-magnetic resonance spectroscopy (31P-MRS) to examine the energy cost and skeletal muscle energetics in six patients with COPD compared with six well-matched healthy control subjects. Patients with COPD displayed a higher energy cost of muscle contraction compared with the controls (control: 6.1 ± 3.1% of rest·min⁻¹·W⁻¹, COPD: 13.6 ± 8.3% of rest·min⁻¹·W⁻¹, P = 0.01). Although, the initial phosphocreatine resynthesis rate was also significantly attenuated in patients with COPD compared with controls (control: 74 ± 17% of rest/min, COPD: 52 ± 13% of rest/min, P = 0.04), when scaled to power output, oxidative ATP synthesis was similar between groups (6.5 ± 2.3% of rest·min⁻¹·W⁻¹ in control and 7.8 ± 3.9% of rest·min⁻¹·W⁻¹ in COPD, P = 0.52). Therefore, our results reveal, for the first time that in a small subset of patients with COPD a higher ATP cost of muscle contraction may substantially contribute to the lower mechanical efficiency previously reported in this population. In addition, it appears that some patients with COPD have preserved mitochondrial function and normal energy supply in lower limb skeletal muscle.

31P-MRS; muscle metabolism; exercise; mitochondrial function

LIMITED EXERCISE CAPACITY not only plays a central role in the life of patients with chronic obstructive pulmonary disease (COPD), but also acts both as a marker of well-being and a prognostic tool. Given that COPD is a disease of the lung, it has long been proposed that the inability to sustain a high level of ventilation was the main factor that limited exercise performance in these patients (3). However, as leg discomfort was a frequent exercise-limiting symptom invoked by patients with COPD during cycling exercise (15), peripheral muscle dysfunction has also been implicated (19). To date, the mechanistic basis for this exercise intolerance is still unresolved (6, 22), although a decrease in muscle strength and endurance along with reduced capillarization, percentage of oxidative fibers, and a reduced activity of different oxidative enzymes measured in vitro may play a role.

These biochemical and histochemical changes observed in the peripheral skeletal muscle of patients with COPD (32) likely alter muscle energy production during exercise and recovery, which may, in turn, affect exercise capacity. Previously, a decreased mechanical efficiency (the chemical conversion of energy to mechanical work) has been reported in a small subset of patients with COPD (1, 25). In these studies, such a decrease in mechanical efficiency could represent an increased energy cost of breathing during exercise, an altered efficiency in ATP production (ATP produced per O₂ consumed), or a higher ATP cost of contraction (ATP consumed per work output). However, it is currently unclear which of these potential mechanisms underpins the reduced mechanical efficiency in patients with COPD.

A shift from type I to type II fibers is also commonly reported in patients with COPD (25). Given the reduced oxidative capacity of these fibers (17) and the reduction in maximal activity of some enzymes involved in Krebs cycle in patients with COPD (13, 18), it has been suggested that the relative contribution of oxidative and anaerobic metabolism during exercise may be altered in patients with COPD (30). However, an issue that has probably magnified the difference between patients and controls is the starkly contrasting activity levels between such groups (31).

Previously, the activity of cytochrome-c oxidase, which is the terminal complex of the mitochondrial electron transport chain, has been documented to be increased in the quadriceps femoris of patients with COPD (27). This implies a potential uncoupling between Krebs cycle and the electron transport chain in some patients with COPD to preserve mitochondrial function. Therefore, the evaluation of pH and the rate of oxidative ATP synthesis with 31P-MRS in patients with COPD and healthy controls matched for physical activity level, may provide useful insight into potential alterations in oxidative capacity and muscle energy production in COPD.

Therefore, the purpose of the present study was to utilize 31P-magnetic resonance spectroscopy (31P-MRS) to explore skeletal muscle energetics in patients with COPD during plantar flexion exercise compared with well-matched healthy control subjects. We hypothesized that in this small subset of patients with COPD: 1) the muscle energy cost of contraction will be increased due to mechanical inefficiency associated with COPD; 2) the rate of oxidative ATP synthesis at the end of exercise, inferred from phosphocreatine (PCr) resynthesis rate and scaled to power output and muscle volume, will be similar in patients with COPD and control subjects; and 3) this will be the result of preserved oxidative capacity in the patients.
MATERIALS AND METHODS

Subjects. Six male patients with severe COPD (stage III according to the ATS guidelines) and six healthy age-, weight-, and activity-matched subjects volunteered to participate in this study and gave written informed consent (Table 1). The study was approved by the Human Research Protection Program of the University of California, San Diego, CA. The control subjects were recruited based upon no regular or occasional physical activity above that required for daily activities (self report and interview), while all the patients with COPD had recently completed the University of California, San Diego Pulmonary Rehabilitation Program.

Exercise protocol. On the first laboratory visit, all subjects performed a graded exercise test on a cycle ergometer to determine maximal oxygen uptake $V_{O2\text{max}}$. Subjects were then familiarized with supine plantar flexion exercise in the confines of a whole body MRI system (model GE 1.5T; Medical Systems, Milwaukee, WI). At this time, the maximum work rate ($WR_{\text{max}}$) for each subject was determined by performing a graded test to maximum in the scanner with supine supine plantar flexion at a frequency of 1 Hz, while lying supine in a superconducting magnet on a different day. Specifically, after 5 min of rest, subjects exercised for 4 min followed by 5 min of recovery.

$^{31}$P-MRS. MRS was performed using a clinical 1.5T General Electric Signa System (version LX 8.3) operating at 25.86 MHz for $^{31}$P. $^{31}$P-MRS was acquired with a dual-frequency flexible array spectroscopy coil (Medical Advances, Milwaukee, Wisconsin) positioned around the calf at its maximum diameter. The phosphorus coil was an 11.5-cm square, centered between two 14 × 15.5-cm Helmholtz-type proton coils. The centering of the coil around the leg was confirmed by T1-weighted, 1H-localizing images obtained in the axial plane, and the coil was repositioned if the majority of the gastrocnemius muscle was not encompassed. For all subjects, a similar ratio between the volume of gastrocnemius/soleus muscles was maintained within the coil. Magnetic field homogeneity was optimized by shimming on the proton signal from tissue water, and the $^{31}$P-MRS signal was optimized by prescan transmitter gain adjustment. The MR data were then acquired throughout the graded and constant-load exercise protocol with the following parameters (radiofrequency hard-pulse filling and Fourier transformation). All spectra were manually phased and were then acquired throughout the graded and constant-load exercise protocol. The MR data were then acquired throughout the graded and constant-load exercise protocol with the following parameters (radiofrequency hard-pulse filling and Fourier transformation). All spectra were manually phased.

DATA ANALYSIS

Data analysis. Data were processed using SAGE/IDL software on a Silicon Graphics INDIGO workstation. Each free induction decay was processed with 5 Hz exponential line broadening prior to zero filling and Fourier transformation. All spectra were manually phased and zero and first-order phase corrections. The levels of PCr determined from the intensity of that peak were normalized to 100% 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 P, peak relative to the PCr peak using the following equation: $pH = 6.75 + \log([P]/[Pc] - 6.75)$. Signal-to-noise ratios (~30:1) were sufficient to allow PCr levels to be determined with a temporal resolution of 4 s during rest, exercise, and recovery.

CONSIDERATION OF MARKER AS THE MAJOR ENERGY SOURCE AT THE ONSET OF EXERCISE, THE INITIAL RATE OF PCr CONSUMPTION ($V_{\text{IPCR}}$) CAN BE USED TO INFER THE ENERGY COST (EC) OF MUSCLE CONTRACTION WHEN POWER OUTPUT IS TAKEN INTO ACCOUNT: $EC = V_{\text{IPCR}}/W$.

As the metabolic changes are strongly related to the power output normalized to muscle volume and normalization of power-to-muscle volume results in a similar metabolic stress between individuals of different sizes (8), EC was normalized for muscle volume.

The PCr recovery kinetics were determined by fitting the PCr time-dependent changes during the recovery period to a single exponential curve described by the equation: $[\text{PCr}]_t = \left[\text{PCr}\right]_{\text{end}} + [\text{PCr}]_{\text{cons}} \cdot [1 - e^{(-k \cdot t)}]$, where $[\text{PCr}]_{\text{end}}$ is the concentration of [PCr] measured at end of exercise and $[\text{PCr}]_{\text{cons}}$ refers to the amount of PCr consumed at the end of the exercise session. The initial rate of PCr resynthesis ($V_{\text{IPCR}}$) was calculated as follows: $V_{\text{IPCR}} = k[\text{PCr}]_{\text{cons}}$ in which $[\text{PCr}]_{\text{cons}}$ indicates the amount of PCr consumed at end of exercise and the rate constant, $k = 1/t$.

Model variables were determined with an iterative process by minimizing the sum of the squared errors between the fitted function and the observed values. Goodness of the fit was assessed via visual inspection of the profile of residual plot as well as the $x^2$ values and the coefficient of correlation between the fitted function and the observed values.

Statistical analysis. Group differences were analyzed using Mann-Whitney U-test for nonparametric variables (Statsoft, version 5.5; Statistica, Tulsa, OK). In addition, effect size ($d$) statistics were calculated using a pooled standard deviation of COPD and control groups. Potential relationships between variables were analyzed using the nonparametric Spearman rank-order correlation. Statistical significance was accepted at $P < 0.05$. Results are presented as means ± SD in tables and means ± SE in figures for the sake of clarity.

RESULTS

Subject characteristics. The self report and interview assessment of current physical activity revealed that the patients with COPD and the controls did not differ from one another, with all subjects being defined as sedentary. This subjective assessment of activity was then confirmed by the measurement of $V_{O2\text{max}}$.

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>COPD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Subjects</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>70 ± 3</td>
<td>70 ± 3</td>
<td>0.421</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80 ± 3</td>
<td>80 ± 3</td>
<td>0.200</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25 ± 2</td>
<td>25 ± 2</td>
<td>0.672</td>
</tr>
<tr>
<td>FEV₁, liters (%predicted)</td>
<td>3.12 ± 0.05 (87 ± 7)</td>
<td>0.92 ± 0.05 (29 ± 1)</td>
<td>0.011</td>
</tr>
<tr>
<td>FVC, liters (%predicted)</td>
<td>4.12 ± 0.34 (88 ± 6)</td>
<td>2.54 ± 0.24 (61 ± 3)</td>
<td>0.011</td>
</tr>
<tr>
<td>Resting arterial PO₂, mmHg</td>
<td>88 ± 4</td>
<td>88 ± 4</td>
<td>0.037</td>
</tr>
<tr>
<td>$V_{O2\text{max}}$, ml/min</td>
<td>1.8 ± 0.2</td>
<td>1.3 ± 0.2</td>
<td>0.044</td>
</tr>
<tr>
<td>$V_{O2\text{max}}$, ml·min⁻¹·kg⁻¹</td>
<td>2.02 ± 0.7</td>
<td>1.67 ± 1.0</td>
<td>0.004</td>
</tr>
<tr>
<td>Peak plantar flexion work rate, W</td>
<td>25 ± 4</td>
<td>15 ± 5</td>
<td>0.010</td>
</tr>
<tr>
<td>Muscle volume, kg</td>
<td>2.5 ± 4</td>
<td>2.1 ± 0.4</td>
<td>0.15</td>
</tr>
</tbody>
</table>

All values are expressed as means ± SD. FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.
which, although expected to be attenuated in the patients with COPD, was also relatively low in the controls (Table 1). Additional, subject characteristics are presented in Table 1.

**Plantar flexion exercise testing and muscle volume.** Plantar flexion $WR_{max}$ was significantly lower in COPD patients compared with the control group (Table 1, $P = 0.010$), such that the corresponding power output during constant load exercise was 12 ± 1 W and 8 ± 1 W in control and COPD subjects, respectively ($P = 0.010$). Muscle volume was not significantly different in the patients with COPD compared with the control group (Table 1, $P = 0.15$).

**PCR onset and energy cost of muscle contraction at the onset of exercise.** Although, on average, the PCR consumption rate was faster in patients with COPD compared with controls ($72 \pm 32\% / \text{min in control and } 95 \pm 36\% / \text{min in patients with COPD}$), this observation was not statistically significant ($P = 0.37; d = 0.68$). Compared with the control group, the energy cost of muscle contraction was significantly higher in patients with COPD (Fig. 1, $P = 0.006, d = 1.06$).

**End exercise PCR and intracellular pH.** End exercise pH during constant load exercise was not significantly different between COPD and control ($7.06 \pm 0.10$ in control and $6.95 \pm 0.22$ in COPD, $P = 0.262, d = -0.61$). Similarly, end exercise PCR was not significantly different between these groups (control: $59 \pm 13\%$; COPD: $68 \pm 15\%$, $P = 0.337, d = 0.69$).

**PCR offset kinetics.** The group mean PCR recovery response in both patients with COPD and controls is illustrated in Fig. 2. During the postexercise recovery period, the PCR time constant (Table 2, $P = 0.749, d = 0.35$) and the corresponding amplitude ($P = 0.200, d = -0.61$) were not significantly different between the controls and patients with COPD. Although, the initial PCR resynthesis rate was significantly attenuated in patients with COPD compared with controls ($P = 0.041, d = -1.4$), when normalized for muscle volume and power output, oxidative ATP synthesis was similar between the controls and patients with COPD ($P = 0.34$, Fig. 3).

**DISCUSSION**

In the present study, we examined exercise-induced skeletal muscle energetics in vivo in patients with COPD compared with well-matched healthy control subjects. The main finding of the present study was that patients with COPD displayed a higher energy cost of muscular contraction compared with the controls. In contrast, and according to our hypothesis, following exercise, mitochondrial function was well preserved in patients with COPD as illustrated by the similar PCR recovery time constant between controls and patients with COPD. This preserved mitochondrial function resulted in a comparable rate of oxidative ATP synthesis between patients and controls at the end of exercise when normalized to the power output. Overall, our findings suggest that, while energy supply from oxidative pathways in skeletal muscle appears to be well preserved in our small subset of patients with COPD, the greater energy cost of muscle contraction reveals an abnormal ATP consumption in these patients.

**Energy cost of muscle contraction and COPD.** A decreased mechanical efficiency has previously been reported in patients with COPD (1, 25). In these prior studies, such a decrease in mechanical efficiency could represent an increased energy cost of breathing during exercise, an altered efficiency in ATP production (ATP produced per $O_2$ consumed), or a higher ATP cost of contraction (ATP consumed per work output). As illustrated in Fig. 1, the results of the present study suggest that the higher ATP cost of muscle contraction (2.2-fold higher in COPD) is likely primarily responsible for the lower mechanical efficiency previously observed in patients with COPD. In support of this, we have previously documented a greater muscle $O_2$ cost in patients with COPD during knee extension exercise (25).

The ATP cost of contraction in skeletal muscle is essentially determined by ATP consumption from myosin-ATPase and other pathways in skeletal muscle appears to be well preserved in our findings suggest that the lower mechanical efficiency in patients with COPD (1, 25). In these prior studies, such a decrease in mechanical efficiency could represent an increased energy cost of breathing during exercise, an altered efficiency in ATP production (ATP produced per $O_2$ consumed), or a higher ATP cost of contraction (ATP consumed per work output). As illustrated in Fig. 1, the results of the present study suggest that the higher ATP cost of muscle contraction (2.2-fold higher in COPD) is likely primarily responsible for the lower mechanical efficiency previously observed in patients with COPD. In support of this, we have previously documented a greater muscle $O_2$ cost in patients with COPD during knee extension exercise (25).
noncontractile processes related to ion transport associated with the contraction-relaxation cycle (mainly calcium ATPase and to a lesser extent Na⁺-K⁺-ATPase). Thus, any increase of one of these processes would explain the increase in energy cost of contraction. COPD is generally associated with increased proportion of type II fibers (25, 32) with an energy cost of contraction which is approximately three- to fourfold higher than type I fibers (4, 11), due to differences in both the myosin ATPase (11) and the cost of calcium handling (28). Therefore, the shift in fiber-type composition could be responsible for the increased ATP cost in muscle of patients with COPD. Additionally, the previously reported trend for the force-stimulation relationship to be shifted to the right in muscle of patients with COPD (5) may result in greater stimulation frequencies to maintain a given relative force and increase in the energy required for ion transport (Ca²⁺ uptake and Na⁺ pumping) as more action potentials and [Ca⁺⁺] are necessary to sustain the work. In addition, the slower relaxation rate documented in this population (7) probably caused by the disturbance in calcium cycling observed in vitro (9), likely also contributes to this greater ATP cost. Therefore, in agreement with the current results (Fig. 1), fiber-type change could synergistically alter excitation-contraction coupling to increase the ATP cost of muscle contraction in patients with COPD.

Muscle metabolism and COPD. A major goal of this study was to better examine the metabolic changes within the skeletal muscle of patients with COPD in response to exercise. According to our hypothesis, the oxidative flux in skeletal muscle was remarkably similar between controls and patients with COPD when normalized to power output. Specifically, the initial PCr resynthesis rate, which reflects the rate of oxidative ATP production at end of exercise (2) was comparable in controls and patients with COPD when scaled to power output (Fig. 3). In addition, the postexercise PCr recovery time constant was unaltered in patients with COPD (Fig. 2), illustrating a preserved mitochondrial function. It is noteworthy that the PCr recovery time constant is strongly dependent upon end exercise pH (12, 26). Given the tendency for a greater acidosis in patients with COPD (7.06 ± 0.10 in control and 6.95 ± 0.22 in COPD), lower end exercise pH may have slowed the PCr recovery time constant, confounding our interpretation of this parameter. However, despite this difference in pH in this group, the PCr recovery time constant was not significantly different between controls and COPD, which further illustrates that muscle oxidative capacity was preserved in patients with COPD as previously suggested in vivo (20) and in permeabilized muscle fibers (24).

The present findings contrast with other studies of skeletal muscle oxidative pathways and COPD. A higher Pj/PCr ratio has been previously recorded in COPD during exercise involving calf (23, 33) and forearm muscles (29), with the higher ratio indicating a lower mitochondrial respiration rate. In this line, in vitro studies revealed a reduced maximal activity of citrate synthase and/or 3-hydroxacyl-coA dehydrogenase, two enzymes involved in Krebs cycle and β-oxidation in patients with COPD (13, 18). In contrast, we have reported similar activity in some of these enzymes between patients with COPD and well-matched healthy controls (25), again in general agreement with our current results. In addition, the activity of cytochrome-c oxidase, which is the terminal complex of the mitochondrial electron transport chain, has been documented to be increased in the quadriceps femoris of patients with COPD (27), suggesting a potential uncoupling between Krebs cycle and the electron transport chain in some patients with COPD to preserve mitochondrial function. These disparate findings illustrate that further studies are clearly needed to continue to clarify the potential interaction between physical activity, disease development, and energetic changes in patients with COPD.

Methodological considerations. Difference in muscle activation, use of synergistic muscles, or difference in exercise intensity may be confounding factors when investigating muscle metabolism. However, these potential flaws seem very unlikely to have affected the current conclusion, because exercise intensity was normalized to the maximum work rate reached during an incremental plantar flexion exercise test, such that each subject performed plantar flexion at the same relative intensity. In addition, care was taken that each subject exercised in the same moderate intensity domain during constant-load exercise. This is confirmed by the relatively similar level of PCr consumption (~43% in control and ~35% in patients with COPD, P > 0.05) and the minor change in pH observed in both groups (~7.06 in control and ~6.95 in patients with COPD, P > 0.05), with a large overlap between controls and patients with COPD, which further confirms that exercise intensity was adequately normalized.

With regard to muscle activation or use of synergistic muscles, one should keep in mind that the MR signal was detected with a surface coil over a muscle volume proportional to the surface coil radius, making this signal the weighting average of the muscle fibers within the sampling volume. Based on previous measurements performed in our laboratory and previously published studies (16, 34), care was taken to sample exercising muscles using a relatively small surface coil (11 cm). Indeed, the sensitivity of the reception probe is greater in the region close to the coil, such that gastrocnemius (lateral and medial) and soleus, the muscles predominantly recruited during plantar flexion exercise (34), contribute the most to the MR signal. Therefore, it is unlikely that the findings of the present study were affected by a difference in muscle activation or the use of synergistic muscles.

We decided to report the PCr data as a percentage of rest based upon previous studies, suggesting that ATP concentration at rest may be reduced in patients with moderate-to-severe COPD (10, 21), such that PCr concentration may be overestimated, assuming a constant ATP of 8.2 mM.

Study limitation. We acknowledge that given the small sample size in the present study, the existence of many severe
comorbidities with COPD, and the heterogeneous pathophysiology of this disease, care should be taken in terms of extrapolating the current findings to the mechanisms of exercise intolerance in the general population of patients with COPD. Further clinical studies in a larger patient population with a range of disease severity are therefore warranted to confirm that the greater ATP cost of muscle contraction is a common feature in patients with COPD.

**Perspectives and Significance**

For patients with COPD, the ability to perform repeated muscle contractions is critical to activities of daily living and requires that muscle generates ATP proportionally to energy demand with both aerobic and anaerobic processes. The understanding of how muscle energetics are altered in patients with COPD is of utmost importance to determine the mechanisms responsible for exercise intolerance and muscle dysfunction in COPD and to optimally design rehabilitation strategies. To address existing gaps in our knowledge, we compared muscle energetics in patients with COPD to well-matched healthy control subjects. The results suggest preserved metabolic control of skeletal muscle energy supply, while the greater energy cost of muscle contraction reveals abnormal ATP consumption (likely associated with myosin ATPase and/or ion transport ATPase) in the exercising skeletal muscle of these patients, which may greatly affect exercise tolerance.

In summary, our results illustrate, for the first time, that in a small subset of patients with COPD a higher ATP cost of muscle contraction may contribute substantially to the lower mechanical efficiency previously reported. In addition, it appears that some patients with COPD have preserved mitochondrial function and normal energy supply in lower limb skeletal muscle.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

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