The effect of higher ATP cost of contraction on the metabolic response to graded exercise in patients with chronic obstructive pulmonary disease

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Layec G, Haseler LJ, Richardson RS. The effect of higher ATP cost of contraction on the metabolic response to graded exercise in patients with chronic obstructive pulmonary disease. J Appl Physiol 112: 1041–1048, 2012. First published December 15, 2011; doi:10.1152/japplphysiol.00986.2011.—To better understand the metabolic implications of a higher ATP cost of contraction in chronic obstructive pulmonary disease (COPD), we used 31P-magnetic resonance spectroscopy (31P-MRS) to examine muscle energetics and pH in response to graded exercise. Specifically, in six patients and six well-matched healthy controls, we determined the intracellular threshold for pH (TPH) and inorganic phosphate-to-phosphocreatine ratio (TPi/PCr) during progressive dynamic plantar flexion exercise with work rate expressed as both absolute and relative intensity. Patients with COPD displayed a lower peak power output (WRmax) compared with controls (controls 25 ± 4 W, COPD 15 ± 5 W, P = 0.01) while end-exercise pH (controls 6.79 ± 0.15, COPD 6.76 ± 0.21, P = 0.87) and PCr consumption (controls 82 ± 10%, COPD 70 ± 18%, P = 0.26) were similar between groups. Both TPH and TPi/PCr occurred at a significantly lower absolute work rate in patients with COPD compared with controls (controls: 14.7 ± 2.4 W for TPH and 15.3 ± 2.4 W for TPi/PCr; COPD: 9.7 ± 4.5 W for TPH and 10.0 ± 4.6 W for TPi/PCr, P < 0.05), but these thresholds occurred at the same percentage of WRmax (controls: 63 ± 11% WRmax for TPH and 67 ± 18% WRmax for TPi/PCr; COPD: 59 ± 9% WRmax for TPH and 61 ± 12% WRmax for TPi/PCr, P > 0.05). Indices of mitochondrial function, the PCR recovery time constant (controls 42 ± 7 s, COPD 45 ± 11 s, P = 0.66) and the PCR resynthesis rate (controls 105 ± 21%/min, COPD 91 ± 31%/min, P = 0.43) were similar between groups. In combination, these results reveal that when energy demand is normalized to WRmax, as a consequence of higher ATP cost of contraction, patients with COPD display the same metabolic pattern as healthy subjects, suggesting that skeletal muscle energy production is well preserved in these patients.

phosphorus-31 magnetic resonance spectroscopy; chronic obstructive pulmonary disease; muscle dysfunction; muscle energetics; skeletal muscle

IT HAS BEEN PREVIOUSLY DOCUMENTED that patients with chronic obstructive pulmonary disease (COPD) exhibit a decreased mechanical efficiency, defined as the chemical conversion of energy to mechanical work (1, 28). Furthermore, our group recently determined, in a small subset of patients with COPD, that their energy cost of muscle contraction (ATP consumed per work output) was more than twofold higher compared with age and activity-matched healthy controls (18). Given the key role of mechanical efficiency in exercise performance (14), these findings revealed that abnormal ATP consumption in the exercising skeletal muscle of these patients likely contributes significantly to their poor exercise tolerance. Indeed, the interplay between the different metabolic pathways is likely to be affected by the higher metabolic demand for a given absolute work load in patients with COPD compared with healthy controls. In this scenario, the greater metabolic demand for a given work rate might be associated with a higher anaerobic contribution to ATP production, to match the energy need, without necessarily implying an impaired energy production capacity. Thus the potentially large disparity in energy cost of muscle contraction in this population needs to be taken into account when investigating their metabolic response to exercise; however, such an approach has not yet been employed.

Previously, a greater reliance on glycolysis has been inferred from the excessive accumulation of lactate and reduction in venous pH at any given absolute work rate in patients with COPD during cycling exercise (19). In addition, several 31P-magnetic resonance spectroscopy (31P-MRS) studies previously revealed a greater decline in phosphocreatine (PCr) concentration, intracellular pH, and Pi/PCr ratio during exercise at the same absolute work rate in patients with COPD compared with controls (17, 24, 39), which was interpreted as evidence of metabolic deficiencies in the energy production pathways. However, such findings may not actually reflect an abnormal metabolic response to exercise but rather a greater metabolic challenge as a consequence of a greater energy cost of muscle contraction in these patients. To resolve this issue and determine whether the mechanisms of energy production are impaired with COPD, it would be more appropriate to examine the metabolic response at similar relative intensities between patients with COPD and healthy controls.

Therefore, the purpose of the present study was to utilize 31P-MRS to examine skeletal muscle energetics and pH in relation to the work rate expressed as absolute and relative intensity in patients with COPD during progressive plantar flexion exercise to fatigue compared with well-matched healthy control subjects. We hypothesized that if ATP cost of contraction is enhanced, but the mechanisms of energy production are well preserved in patients with COPD, then 1) intracellular pH (TPH) and Pi/PCr (TPi/PCr) thresholds, which are considered markers of muscle oxidative potential (4, 6) and the capacity of muscle to maintain pH (31), will occur at lower absolute work rates but similar relative intensity compared with controls; and 2) the mitochondrial function in patients with COPD will be similar to controls.
METHODS

Subjects. Six male hypoxemic, noncachexic patients with severe COPD (GOLD stage III) and six healthy sex-, 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 (UCSD). The control subjects were recruited based on a lack of regular or occasional physical activity above that required for daily activities (self report and interview), while all the patients with COPD had completed the UCSD Pulmonary Rehabilitation Program (within 8–24 mo). Patients were not currently taking any steroid medications and if inhaled medications were used they were timed such that their use occurred >4 h before all protocols. All the subjects included in the control group were nonsmokers and were free of diabetes and overt cardiovascular, peripheral vascular, neuromuscular or pulmonary disease. Additionally, these subjects were not taking any medications recognized to affect skeletal muscle function or blood flow. These are the same subjects that partook in a previously published study of muscle energetics in COPD (18).

Exercise protocol. On the first laboratory visit, all subjects performed a graded exercise test on a cycle ergometer to determine maximum work rate (WRmax) and maximal oxygen uptake (VO₂max), and provide an index of the oxygen cost of work during whole body exercise. Subjects were then familiarized with supine plantar flexion exercise using the same system as the one used in the whole body MRI system (GE 1.5T Medical Systems, Milwaukee, WI). Individual maximum work rate (WRmax) was determined by performing an incremental dynamic plantar flexion exercise until exhaustion (2-W increments per min, frequency of 1 Hz) in the scanner with 31P data collection while lying supine in a superconducting magnet.

Lower leg muscle mass. Muscle mass of the lower leg was calculated based on lower leg circumference (3 sites: distal, middle, and proximal), lower leg length, and skinfold measurements (13), which has been validated in both healthy individuals (16) and patients with COPD (38).

31P MRS. MRS was performed using a clinical 1.5T General Electric Signa system (LX 8.3 version) operating at 25.86 MHz for 31P. 31P MRS data were acquired with a dual-frequency flexible array phosphorus coil (Medical Advances, Milwaukee, WI) positioned around the calf at its maximum diameter. The phosphorus coil was an 11.5-cm square, centered between two 14-proximal), lower leg length, and skinfold measurements (13), which has been validated in both healthy individuals (16) and patients with COPD (38).

During a ramp exercise, the increase in Pi/PCr initially has a shallow slope and as exercise progresses, the slope of work vs. Pi/PCr becomes markedly steeper, with a similar response for intracellular pH. The breakpoint, i.e., the point of change in the slope of pH or Pi/PCr, provides an index of oxidative capacity as it is correlated with citrate synthase activity (4) and occurs at a higher percentage of WRmax following endurance training (21). Specifically, the breakpoint in pH corresponds to the work rate at which increased glycolytic energy production overwhelms [H+] consumption (PCr consumption, buffering capacity, and [H+] efflux) (22). The logarithms of Pi/PCr [log(Pi/PCr)] and pH were each plotted against power output, and a piecewise linear regression analysis was applied to individual data plots (37). A previous study reported high test-retest correlations for identifying TPi/PCr and TpH, respectively, demonstrating the reliability and reproducibility of these threshold measurements (22).

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 following equation: [PCr(t) = [PCr]end + [PCr]cons·[1 − e(−t/τPCr)], where [PCr]end is the concentration of [PCr] measured at end-of-exercise and [PCr]cons refers to the amount of PCr consumed at the end of the exercise session. The initial rate of PCr resynthesis (ViPCr) was calculated as follows: ViPCr = k·[PCr]cons, in

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. of subjects, M/F</td>
<td>6 (6/0)</td>
<td>6 (6/0)</td>
<td>0.42</td>
</tr>
<tr>
<td>Age, yr</td>
<td>69 ± 3</td>
<td>65 ± 5</td>
<td>0.04</td>
</tr>
<tr>
<td>Height, cm</td>
<td>180 ± 3</td>
<td>172 ± 3</td>
<td>0.2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>83 ± 4</td>
<td>76 ± 5</td>
<td>0.87</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26 ± 2</td>
<td>26 ± 4</td>
<td>0.15</td>
</tr>
<tr>
<td>Muscle mass, kg</td>
<td>2.5 ± 0.4</td>
<td>2.1 ± 0.4</td>
<td>0.01</td>
</tr>
<tr>
<td>FEV₁, liters (% predicted)</td>
<td>3.12 ± 0.35 (87 ± 7)</td>
<td>0.92 ± 0.05 (29 ± 1)</td>
<td>0.01</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>0.01</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>76 ± 5</td>
<td>37 ± 2</td>
<td>0.01</td>
</tr>
<tr>
<td>Resting arterial P O₂, mmHg</td>
<td>102 ± 8</td>
<td>75 ± 4</td>
<td>0.04</td>
</tr>
<tr>
<td>Resting arterial P CO₂, mmHg</td>
<td>38 ± 1</td>
<td>47 ± 3</td>
<td>0.01</td>
</tr>
<tr>
<td>Resting arterial pH</td>
<td>7.41 ± 0.01</td>
<td>7.34 ± 0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>HCO₃⁻, meq/L</td>
<td>24 ± 1</td>
<td>35 ± 3</td>
<td>0.01</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>42 ± 1</td>
<td>41 ± 2</td>
<td>0.81</td>
</tr>
<tr>
<td>VO₂max, l/min</td>
<td>1.8 ± 0.2</td>
<td>1.3 ± 0.2</td>
<td>0.01</td>
</tr>
</tbody>
</table>

All values are expressed as means ± SD. BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; VO₂max, maximal oxygen uptake; COPD, chronic obstructive pulmonary disease. Some of these data were previously published in Ref. 18.

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which \([\text{PCr}]_{\text{cons}}\) indicates the amount of PCr consumed at end of exercise and the rate constant \(k = 1/\tau\).

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 by visual inspection of the profile of the residual plot as well as the Chi square values and the coefficient of determination \((r^2)\) between the fitted function and the observed values.

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

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 \(\dot{V}O_{2\text{max}}\), which, although expected to be attenuated in the patients with COPD, was, by experimental design, also relatively low in the controls who were selected to be sedentary (Table 1). The oxygen cost of work during cycle exercise was significantly elevated in patients with COPD (21 ± 2 ml·min\(^{-1}\)·kg\(^{-1}\)) compared with controls (15 ± 1 ml·min\(^{-1}\)·kg\(^{-1}\), \(P = 0.01\)). Although most of these data have been previously published (18), for completeness, detailed subject characteristics are presented in Table 1.

Plantar flexion exercise testing and muscle volume. At the end of the graded plantar flexion exercise test all subjects reported a >9/10 rate of perceived exertion on the modified Borg scale and WRmax was significantly lower in the patients with COPD compared with the control group (Table 1, \(P = 0.010\)). Muscle volume was not significantly different in the patients with COPD compared with the control group (Table 1, \(P = 0.15\)).

Metabolic variables and intracellular threshold during progressive exercise. Typical examples of Pi/PCr and pH response with corresponding \(T_{\text{Pi/PCr}}\) and \(T_{\text{pH}}\) in patients with COPD and controls are presented in Fig. 1. Although the absolute work rates at which \(T_{\text{Pi/PCr}}\) and \(T_{\text{pH}}\) occurred were significantly lower in patients with COPD compared with controls (Fig. 2, Table 2), these parameters were no longer significantly different between groups when expressed relative to WRmax (Fig. 2, Table 2, \(P = 0.045\) for both). At the end of exercise, PCr consumption, Pi accumulation, and pH values were not significantly different between COPD and control (Table 2, \(P = 0.26, P = 0.63\) and \(P = 0.87\), respectively).

pH recovery and PCr offset kinetics. During the post plantar flexion exercise recovery period, the PCr time constant (Fig. 3, Table 2, \(P = 0.66\)) and \(V_{\text{Pi/PCr}}\) \((P = 0.43)\) were not significantly different between the controls and patients with COPD. Similarly, the minimum pH values reached during the recovery period were not significantly different between groups (Table 2, \(P = 0.87\)). PCr recovery time constant was significantly correlated to WRmax in the controls \((r^2 = 0.66, P < 0.05)\) but not in the COPD \((r^2 = 0.003, P > 0.05)\). Across both subject groups, lower leg muscle mass was not correlated to WRmax \((r^2 = 0.18, P > 0.05, n = 12)\).

DISCUSSION

Here we examined skeletal muscle energetic changes and pH in relation to the work rate expressed as absolute and relative intensity in patients with COPD during progressive plantar flexion exercise to volitional fatigue compared with well-
matched healthy control subjects. Despite evidence of preserved oxidative capacity and pH homeostasis, we observed a ~40% lower peak power output during plantar flexion exercise test in patients with COPD compared with controls. According to our primary hypothesis, intracellular thresholds for Pi/PCr and pH occurred at a lower absolute work rate, but at the same relative work rate (~60% of WRmax) in patients with COPD compared with controls. In addition, mitochondrial function was preserved as illustrated by the similar PCr recovery time constant and PCr resynthesis rate between COPD and controls. Such findings indicate that the mechanisms of energy production are well preserved in patients with COPD.

Evidence of preserved energy metabolism in patients with COPD. A major goal of this study was to determine whether any metabolic abnormalities in skeletal muscle of patients with COPD would be evident when the metabolic variables were normalized by the attenuated peak power output, such that the higher ATP cost of contraction in patients with COPD was taken into account. According to our hypothesis, T_{Pi/PCr} and T_{pH} did, in fact, occur at the same relative work rate (~60% WRmax) in patients with COPD and controls (Fig. 2, right panel). Interestingly, on average, these values for both groups are similar to those previously reported during forearm (22) and plantar flexion (33) exercise in young active adults (~60–65% WRmax), suggesting a preserved capacity to supply ATP aerobically in both patients with COPD and older healthy controls.

These results are also consistent with the similar postexercise PCr recovery kinetics in both patients with COPD and healthy controls, which are now largely acknowledged to reflect in vivo mitochondrial oxidative capacity (15), independent of muscle mass (35) and when O2 delivery is not limited (7, 9). Specifically, the preserved postexercise PCr recovery time constant in the patients illustrates unaltered mitochondrial function in these age-matched subjects (Fig. 3). It is noteworthy that the PCr recovery time constant is highly dependent on end-exercise pH (12, 30), which can affect the interpretation of this parameter, especially as pH was substantially reduced at the end of the progressive exercise (~6.80). However, exercise-induced acidosis was remarkably similar between controls and the patients with COPD, supporting the validity of comparing the time constant between groups in the current conditions without correction. In agreement with these findings, it has been previously revealed, both in vivo (23) and in permeabilized muscle fibers (25), that muscle oxidative capacity was preserved in patients with COPD. In addition, Richardson et al. (28) reported an almost identical muscle VO_{2max} achieved during single-leg knee-extensor exercise in patients with COPD and controls, although it must be noted that mechanical efficiency appeared to be much lower in the patients.

Considering the dependence of PCr resynthesis on O2 delivery (7, 9) and the low resting arterial PO2 in patients with COPD (Table 1), it is interesting that PCr recovery rate in patients with COPD was still akin to controls. Interestingly, using different fractions of inspired O2, Haseler et al. (8) have previously demonstrated that O2 availability was apparently in excess in sedentary individuals during the recovery from a plantar flexion exercise in ambient air. Specifically, PCr resynthesis was not affected by reduced O2 availability until arterial PO2 dropped below ~70 mmHg. In the present study, resting arterial PO2 was still ~75 mmHg in the patients with COPD and it is very unlikely that plantar flexion exercise, which involves a small muscle mass, decreased arterial PO2 below this critical value such that O2 availability did not match mitochondrial respiration rate in these patients.

With regard to intracellular threshold (Fig. 2) and PCr recovery kinetics (Fig. 3), the present findings do not support the hypothesis that there is a metabolic dysfunction associated with COPD. However, using progressive (19) or constant-load (32) cycling exercise to exhaustion, some studies have reported a greater glycogen utilization and lactate accumulation in patients with COPD. The reason for this discrepancy is unclear,
important aspect of the present study considering the potentially confounding effects of muscle disuse on metabolic function. Some studies also reported a longer PCr recovery time constant (more than double) in patients with COPD compared with controls (24, 39) suggestive of impaired mitochondrial function. However, in these studies differences in end-exercise pH between groups undoubtedly affected the interpretation of the PCr recovery time constant. Overall, the majority of the existing evidence in favor of metabolic dysfunction with COPD suffers from some methodological issues that may have confounded the interpretation of the results and may explain the discrepancy with the present findings. It is acknowledged that $T_{\text{Pi/PCr}}$ and $T_{\text{pH}}$ in the present study occurred at a lower absolute work rate in patients with COPD compared with controls, which may indicate an abnormal metabolic response to exercise. However, we would suggest that this does not imply an impaired energy production but rather a greater metabolic challenge experienced by these patients in relation to their higher ATP cost of muscle contraction.

**Evidence of preserved acid-base balance in patients with COPD.** An interesting finding of the present study was that pH homeostasis appeared to be preserved in skeletal muscle of patients with COPD as illustrated by the comparable relative work rate corresponding to $T_{\text{ph}}$ in COPD and controls (Fig. 2, right panel). Indeed, $T_{\text{pH}}$ reflects the work load at which the mechanisms responsible for $[\text{H}^+]$ generation (anaerobic glycolysis and oxidative phosphorylation) exceed $[\text{H}^+]$ consumption (PCr consumption, buffering capacity, and $[\text{H}^+]$ efflux) (31). Although unfortunately in the present study it is not possible to quantify the relative contribution of each component of $\text{H}^+$ handling, the similarity in the relative work rate for $T_{\text{pH}}$ in COPD and controls does suggest that global $[\text{H}^+]$ balance was not altered in the patients with COPD.

In agreement with this result, the minimum pH achieved during postexercise recovery period in patients with COPD was akin to the controls (Table 2). This observation is particularly insightful with regard to $[\text{H}^+]$ handling as glycolysis ceased during this period (5) and $[\text{H}^+]$ generated by PCr resynthesis and oxidative phosphorylation were similar between controls and COPD as inferred by the similar PCr recovery kinetics. Therefore, in this context, the similarity between controls and patients with COPD in terms of the minimum pH reached during recovery suggests that $[\text{H}^+]$ efflux and buffering capacity were likely unaltered in patients with COPD. This finding is also supported by the similar proton efflux rates previously reported in the calf muscle of hypoxemic patients with COPD and controls (36), which

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**Table 2. Intracellular metabolic responses and thresholds to progressive plantar flexion exercise to fatigue in patients with COPD and controls**

<table>
<thead>
<tr>
<th>COPD</th>
<th>Control</th>
<th>$P$ Value</th>
<th>$d$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rest</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pi/PCr rest</td>
<td>0.15 ± 0.05</td>
<td>0.18 ± 0.07</td>
<td>0.34</td>
</tr>
<tr>
<td>pH rest</td>
<td>7.02 ± 0.04</td>
<td>7.12 ± 0.15</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal power</td>
<td>15 ± 5</td>
<td>24 ± 4</td>
<td>0.03</td>
</tr>
<tr>
<td>PCr consumption, %</td>
<td>70 ± 18</td>
<td>82 ± 10</td>
<td>0.42</td>
</tr>
<tr>
<td>Pi accumulation, %</td>
<td>547 ± 168</td>
<td>498 ± 338</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>Recovery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH min</td>
<td>6.76 ± 0.21</td>
<td>6.79 ± 0.15</td>
<td>0.87</td>
</tr>
<tr>
<td>Slope 1 Pi/PCr</td>
<td>0.0047 ± 0.0035</td>
<td>0.0022 ± 0.0014</td>
<td>0.15</td>
</tr>
<tr>
<td>Slope 2 Pi/PCr</td>
<td>0.0032 ± 0.0017</td>
<td>0.0017 ± 0.0007</td>
<td>0.11</td>
</tr>
<tr>
<td>$T_{\text{Pi/PCr}}$, W</td>
<td>10 ± 5</td>
<td>15 ± 2</td>
<td>0.04</td>
</tr>
<tr>
<td>$T_{\text{Pi/PCr}}$, %WRmax</td>
<td>61 ± 12</td>
<td>67 ± 18</td>
<td>0.52</td>
</tr>
<tr>
<td>$T_{\text{pH}, W}$</td>
<td>0.26 ± 0.19</td>
<td>0.34 ± 0.29</td>
<td></td>
</tr>
<tr>
<td>$T_{\text{pH},}$</td>
<td>0.97 ± 0.01</td>
<td>0.94 ± 0.08</td>
<td></td>
</tr>
<tr>
<td>Slope 1 pH</td>
<td>-0.0003 ± 0.0008</td>
<td>-0.0005 ± 0.0004</td>
<td>0.15</td>
</tr>
<tr>
<td>Slope 2 pH</td>
<td>-0.0018 ± 0.0016</td>
<td>-0.0010 ± 0.0004</td>
<td>0.63</td>
</tr>
<tr>
<td>$T_{\text{IC50}, W}$</td>
<td>10 ± 4</td>
<td>15 ± 2</td>
<td>0.04</td>
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<tr>
<td>$T_{\text{IC50},}$</td>
<td>8.4 ± 0.24</td>
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<tr>
<td>$T_{\text{IC50},}$</td>
<td>0.95 ± 0.05</td>
<td>0.91 ± 0.07</td>
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</table>

All values are expressed as means ± SD. Vi, initial PCr resynthesis rate; WRmax, peak power output; slope 1, slope preceding the threshold; slope 2, slope following the threshold; $T_{\text{Pi/PCr}}$, intracellular threshold for inorganic phosphate to phosphocreatine ratio; $T_{\text{pH}}$, intracellular threshold for pH; IC50, 95% confidence interval, RSS, sum of squared residuals.

but could partly be explained by methodological differences. First, the difference in muscle metabolism between patients with COPD and controls reported in the study of Maltais et al. (19) could be largely attributed to the contrasting fitness level between patients and controls, as evidenced by a $\sim 2$-fold difference in $V_{\text{O2max}}$ (19). It is noteworthy, and highly germane to the findings of the present study, that when lactate release was plotted according to the relative work load the metabolic response was similar between controls and COPD (26). In contrast, our subjects were matched for physical activity as indicated by the minor difference in $V_{\text{O2max}}$ ($\sim 3$ ml·min$^{-1}$·kg$^{-1}$, Table 1) during cycling exercise, which is likely partly related to pulmonary limitation in patients with COPD during whole body exercise. Second, as mentioned in the introduction, exercise involving a large muscle mass, such as cycling, imposes a greater challenge on the ventilatory capacity of patients with COPD and thus in this scenario they likely experience $O_2$ supply limitation, which subsequently may affect lactate production (10). However, we acknowledge that alterations in energy production have also been reported during isolated muscle mass exercise (20, 29).

Additionally, a higher Pi/PCr ratio has been previously recorded in COPD during exercise involving calf (24, 39) and forearm muscles (17, 34), with the higher ratio indicating a lower mitochondrial respiration rate. However, in these studies subjects were not matched for physical activity, which is an
suggest that the mechanisms responsible for [H+] consumption were likely unaltered in COPD. Therefore, overall these findings contradict the hypothesis that there is abnormal acidification in the muscle during exercise in patients with COPD (19, 32).

Potential role of abnormal ATP consumption in exercise intolerance with COPD. Although our results suggest a preserved metabolic capacity to supply ATP appropriately through aerobic and anaerobic pathways in patients with COPD, there is no doubt that these patients were characterized by a reduced cycle exercise tolerance. As illustrated in Fig. 4 (top panels), the patients with COPD achieved a ∼50% lower power output during whole body exercise, while VO2max was reduced by 17% when taking into account body mass. Interestingly, when patients only exercised the calf muscle, which diminishes the potential role of cardiorespiratory limitation, muscle oxidative capacity, as inferred from PCr recovery kinetics, was akin to that of the controls (Fig. 4, bottom left panel). However, despite this similarity in oxidative capacity, peak power output during a progressive plantar flexion exercise test was still ∼40% lower than the controls (Fig. 4, bottom right panel), revealing that although pulmonary function may have played a role in whole body exercise intolerance, muscle dysfunction was likely the major contributor to exercise limitation in these patients during plantar flexion exercise.

Indeed, the lower exercise capacity during small muscle mass exercise in patients with COPD in the present study could be related to an abnormal ATP consumption (associated with myosin ATPase and/or ion transport ATPase) (18) as maximal capacity for oxidative ATP production was well preserved (Fig. 4, lower left panel). Such a decreased mechanical efficiency has previously been reported in patients with COPD (1, 28), and our group has recently revealed that a considerably higher ATP cost of muscle contraction (2.2-fold higher in COPD) was likely primarily responsible for this lower mechanical efficiency previously observed in patients with COPD (18). Additionally, it is noteworthy that in the present study at a comparable PCr resynthesis rate, which reflects end-exercise oxidative ATP production (3, 30), peak plantar flexion power output was ∼40% lower in patients with COPD compared with controls, which is again in agreement with a higher energy cost of muscle contraction. Interestingly, during the cycle exercise test the O2 cost of work calculated from pulmonary oxygen uptake measurements and power output was not only 43% higher in patients with COPD, but was significantly correlated with the ATP cost of muscle contraction assessed by NMR during plantar flexion exercise (r² = 0.44, P = 0.04) (Fig. 5). Although such a comparison between ATP cost from 31P-MRS (18) and the O2 cost of work calculated in this manner presents several pitfalls (e.g., different muscles recruited, substrate oxidation, exercise intensity, and energy contributions from anaerobic sources), it is quite remarkable that there was a reasonably strong and significant relationship between these independently derived indexes of the cost of work. This is not only an interesting finding, but further validates the documented increased cost of contraction in patients with COPD assessed by the 31P-MRS approach.

A potential abnormality in skeletal muscle ATP consumption can also explain the differences in the present study.

Fig. 4. Top: maximal oxygen uptake (VO2max; left) and peak work rate (right) during incremental cycling exercise in patients with COPD and controls. Bottom: PCr offset time constant (left) and peak power output during incremental plantar flexion (right) in patients with COPD and controls. All values are expressed as means ± SE. *P < 0.05, **P < 0.01: significantly different from the control group.

Fig. 5. Relationship between O2 cost of work calculated from pulmonary oxygen uptake measurements and power output during cycling and ATP cost of contraction calculated from 31P-MRS during plantar flexion exercise (○, COPD; ●, controls).
between patients with COPD and controls with regard to $T_{	ext{Pi/PCr}}$ and $T_{\text{pH}}$ when expressed as absolute or relative work rate. Specifically, in the face of a higher ATP cost of contraction, a given absolute work load required a greater energy supply in patients with COPD to match ATP demand. Accordingly, we observed that $T_{	ext{Pi/PCr}}$ and $T_{\text{pH}}$ occurred at a lower absolute work rate in patients with COPD compared with controls. A similar standardization of $T_{	ext{Pi/PCr}}$ and $T_{\text{pH}}$ to WRmax has previously been employed to compare metabolic responses between children and adults during ramp exercise, as these populations differ in muscle body mass and WRmax (40). By normalizing these parameters to the WRmax, $T_{	ext{Pi/PCr}}$ and $T_{\text{pH}}$ were actually normalized for the metabolic demand experienced by the subject. In this context, our finding that $T_{	ext{Pi/PCr}}$ and $T_{\text{pH}}$ occurred at the same relative intensity in both groups therefore supports the hypothesis that the mechanisms responsible for energy production were unaltered in these patients.

Methodological considerations. One could suggest that the results of this study might have been influenced by differences in muscle mass between patients with COPD and controls rather than higher ATP cost of contraction. However, three lines of evidence oppose this concern. First, muscle mass of the lower limb was not significantly different between the patients and controls. Second, the uncoupling between oxidative ATP production and power output in patients with COPD, implied by the lower WRmax but comparable PCR resynthesis rate compared with controls, cannot be explained by differences in muscle mass as there was no significant relationship between WRmax and leg muscle mass ($r^2 = 0.18$, $P > 0.05$, $n = 12$). Finally, although muscle mass may play a role in determining WRmax during incremental plantar flexion, this type of aerobic exercise is predominantly determined by other common factors related to aerobic performance such as aerobic capacity, intracellular threshold ($T_{	ext{Pi/PCr}}$ and $T_{\text{pH}}$), and exercise economy (2, 11, 14, 27, 28). Accordingly, we observed a significant correlation between WRmax and PCR recovery time constant in the controls ($r^2 = 0.66$, $P < 0.05$) but not in the COPD ($r^2 = 0.003$, $P > 0.05$), which confirms the validity of this protocol to evaluate maximal aerobic power in healthy subjects and constitutes additional evidence of uncoupling between aerobic energy production and power output in patients with COPD.

Additionally, we acknowledge that given the small sample size in the present study, 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 mechanisms of energy production are well preserved in patients with COPD while abnormal ATP consumption in exercising skeletal muscle limits their exercise capacity.

Conclusion. In summary, this study has revealed that patients with COPD exhibited a reduced exercise capacity that is likely related to an abnormal ATP consumption in the exercising skeletal muscle of these patients. However, our results illustrate that mechanisms of energy production from aerobic and anaerobic pathways and pH homeostasis are well preserved in these patients when normalized to the actual metabolic challenge encountered by each individual.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS


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