Altered metabolic and transporter characteristics of vastus lateralis in chronic obstructive pulmonary disease

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Green HJ, Burnett ME, D’Arsigny CL, O’Donnell DE, Ouyang J, Webb KA. Altered metabolic and transporter characteristics of vastus lateralis in chronic obstructive pulmonary disease. J Appl Physiol 105: 879–886, 2008. First published July 17, 2008; doi:10.1152/japplphysiol.90458.2008.—To investigate energy metabolic and transporter characteristics in resting muscle of patients with moderate to severe chronic obstructive pulmonary disease (COPD; forced expiratory volume in 1 s (FEV1) = 42 ± 6.0% (mean ± SE)), tissue was extracted from resting vastus lateralis (VL) of 9 COPD patients and compared with that of 12 healthy control subjects (FEV1 = 114 ± 3.4%). Compared with controls, lower (P < 0.05) concentrations (mmol/kg dry wt) of ATP (19.6 ± 0.65 vs. 17.8 ± 0.69) and phosphocreatine (81.3 ± 2.3 vs. 69.1 ± 4.2) were observed in COPD, which occurred in the absence of differences in the total adenosine nucleotide and total creatine pools. Higher concentrations were observed in COPD for several glycolytic metabolites (glucose-1-phosphate, glucose-6-phosphate, fructose-6-phosphate, pyruvate) but not lactate. Glycogen storage was not affected by the disease (289 ± 20 vs. 269 ± 20 mmol glucosyl units/kg dry wt). Although no difference between groups was observed for the glucose transporter GLUT1, GLUT4 was reduced by 28% in COPD. For the monocarboxylate transporters, MCT4 was 35% lower in COPD, with no differences observed for MCT1. These results indicate that in resting VL, moderate to severe COPD results in a reduction in phosphorylation potential, an apparent elevation of glycolytic flux rate, and a potential defect in glucose and lactate transport as a result of reduced levels of the principal isoforms. In healthy muscle at rest, the relatively low ATP requirements are met primarily via oxidative phosphorylation while maintaining a high phosphorylation potential (content of high-energy phosphate bonds), a low accumulation of metabolic by-products such as lactate and hydrogen ions, and a large reserve of the endogenous substrate glycogen.

Although this is the expected response in the healthy muscle cell, it is unclear what occurs in a disease state such as chronic obstructive pulmonary disease (COPD) where hypoxemia is present, potentially reducing the supply of O2 to the mitochondria unless compensatory adjustments are made. The situation may be compounded by the lower capillarization of the muscle cell (32) or changes in the muscle cell itself such as reductions in oxidative potential (16, 36), both of which have been reported to occur in COPD. In studies completed to date investigating the differences between COPD patients and healthy controls, the energetic status of resting muscle remains in dispute. In one study, using moderate to severe COPD patients, no differences were reported in the tibialis anterior (TA) muscle between groups for ATP, ADP, AMP, or in total adenine nucleotide concentration (TAN) (40). Similarly, no differences were reported for phosphocreatine (PCr), creatine (Cr), and total creatine (TCr) or in the substrates glucose and glycogen, or the glycolytic metabolite lactate (40). Such was not the case in the vastus lateralis (VL) of patients with severe hypoxemia where decreases in ATP and TAN were accompanied by decreases in PCr and increases in Cr, inosine monophosphate (IMP), and lactate (12). A lower ATP and PCr but not TAN and TCr has also been reported in patients with moderate COPD (39). In patients with moderate COPD and without emphysema, a higher pyruvate has been found in VL that was unaccompanied by differences in lactate compared with COPD patients with emphysema (11). As with an earlier study (40), the substrates glucose and glycogen appear unaltered by the disease (11). Evidence that disease severity is important has been provided by Jakobsson et al. (31), who reported that in COPD patients those with respiratory failure had lower PCr and glycogen concentrations in VL than COPD patients not in respiratory failure. In summary, it is unclear based on current evidence whether the effects of COPD on resting muscle are specific to the muscle or to the severity of the disease.

Preservation of cellular energy homeostasis relies on a ready supply of substrates and, in particular, carbohydrates (CHO). Blood glucose serves as the source of CHO both directly in muscle metabolism and as precursor for muscle glycogen (46). Blood glucose entry into the cell is regulated by a family of glucose transporters (GLUT), of which GLUT1 and GLUT4 appear to be the principal ones in skeletal muscle (29). The use of glucose by the muscle cell also depends on the phosphorylation of glucose to glucose-6-phosphate by hexokinase (Hex) (46). Given the apparent increased dependence on CHO in COPD (16), it is surprising that maximal Hex activity has not been reported to be higher in COPD (1, 37). Increases might be expected, however, if the energy status of the cell is compromised. The 5′-AMP-activated protein kinase (AMPK), which is regulated by disturbances in energy status, is also believed to be a potent regulator of GLUT4 expression (33).

Cellular homeostasis also depends on management of metabolic by-product accumulation. In the case of lactate and hydrogen, diffusion across the cell membrane is facilitated by a family of lactate transporters (MCT), of which MCT4 and MCT1 are the major and minor forms in muscle, respectively. The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
Accordingly, a more pronounced increase in glycolysis thought to occur both at rest and during exercise in COPD may promote an upregulation. It should be emphasized that both the muscle GLUT and MCT proteins are highly adaptable, responding rapidly to conditions such as increased contractile activity where the demands for glucose availability and H⁺ and lactate disposal are greatly increased (29, 34). Surprisingly, no studies appear to have been published investigating the effect of COPD on these transporters in locomotor muscles.

The objective of this study was to assess the resting metabolic and transporter protein status in VL of patients with stable moderate to severe COPD and age-matched healthy controls. We have hypothesized that the phosphorylation potential, as indicated by the concentrations of ATP and PCR, would be lower and the related metabolites, free ADP (ADPf), free AMP (AMPf), IMP, Cr, and Pᵢ, would be higher in COPD compared with control subjects. We have also hypothesized that these differences would be accompanied by a higher level of glycolytic by-products including lactate in COPD. Finally, we postulate that these differences would also extend to the transporters, resulting in higher levels of GLUT4 and MCT4 in COPD compared with control subjects.

METHODS

Participants. The COPD patients consisted of seven women and two men with moderate to severe disease while the control subjects consisted of eight women and four men, free of disease and matched in age to the COPD group. These patients were volunteers who had completed previous research studies at Queen’s University (Respiratory Investigation Unit) or recruits from outpatient respiratory clinics. All COPD volunteers had chronic airflow limitation, as measured by forced expiratory volume in 1 s (FEV₁) and FEV₁/forced vital capacity (FVC) of less than 60% and 70% of age-matched predicted values. The COPD volunteers had chronic airflow limitation, as measured by forced expiratory volume in 1 s (FEV₁) and FEV₁/forced vital capacity (FVC) of less than 60% and 70% of age-matched predicted values. Inclusion criteria for controls included an FEV₁ and FEV₁/FVC equal to or greater than 80% and 70%, respectively. These patients were recruited from the local community using newspaper advertisements and notices posted on community facilities. Exclusion criteria for the COPD patients included clinical instability with exacerbations or changes in respiratory medications in the 4 wk before the beginning of the study or the presence of cardiovascular, metabolic, or other diseases that could impair exercise performance. Control recruits were excluded if there was the presence of a disease that might contribute to breathlessness and/or limit exercise performance. At the time of the study, the medications for the COPD patients included long-acting β₂-agonists (6), short-acting bronchodilators (5), long-acting anticholinergics (4), and inhaled corticosteroids (all). In addition, supplemental oxygen was used (6). For the control subjects, only short-acting β₂-agonists (2) and inhaled corticosteroids (2) were prescribed. In this group, the inhaled corticosteroids were taken because of a past history of bronchitis. Written informed consent was obtained from all COPD and control volunteers before the beginning of the study and following approval of the study by the Hospital Health Sciences Human Research Committee at Queen’s University.

Experimental procedures. This was part of a much larger study involving extensive pulmonary function, blood gas, anthropometric, and muscle mechanical assessment. The participants involved in this study represented a subgroup of patients who volunteered for the tissue sampling. The information presented here emphasizes primarily the pulmonary and blood gas measurements necessary to understand the severity of COPD disease for the subject pool specific to this study. Also included is the measurement of peak aerobic power (V̇O₂peak), obtained during a progressive cycle test to fatigue following recommended guidelines (3). The V̇O₂peak was measured using progressive (power output incremented by 10 W each minute) cycle (Ergometrics 8005; Sensor Medics) exercise and a Cardiopulmonary Exercise Testing System (Sensor Medics). Exercise tests were terminated at the point of symptom limitation (2), and the highest V̇O₂ was recorded as V̇O₂peak.

Analytical procedures. To obtain tissue from the vastus lateralis, the muscle biopsy technique was employed (4). The biopsies, which were performed by trained personnel with extensive experience in the procedure, involved making a small incision in the lateral part of the thigh, following local freezing of the area with lidocaine, and inserting the biopsy needle deep into the tissue (40–60 mm). Two to three tissue samples were extracted from the prepared site. To obtain the first sample, the needle was rapidly inserted into the muscle, the tissue sample was captured, and the needle was quickly withdrawn and immediately plunged into liquid N₂. The tissue was used for measurement of the high-energy phosphagens and related metabolites as well as glycogen and the glycolytic intermediates. Tissue obtained from the second biopsy, which was performed without hesitation following the first sampling, was extracted from the needle before freezing in liquid N₂. This tissue was used for measurement of the GLUTs and MCT isoforms. All tissue was stored at −80°C pending measurement.

For the metabolic measurements, fluorometric and ion-pair reversed-phase high-performance liquid chromatography (HPLC) techniques were employed. For these measurements, the tissue was freeze dried, and the metabolites were extracted according to procedures previously published (23, 27). The adenine nucleotides (ATP, ADP, AMP) and IMP concentrations were determined using HPLC procedures as originally developed by Ingebretson et al. (30) and subsequently modified by our group (22). The concentrations of ADPf and AMPf were estimated on the basis of the near-equilibrium constants for creatine kinase (Kobs = 1.66 × 10⁻⁹ M) and the adenylyl kinase (Kₐ₅₄ = 1.05) (10). The muscle pH (and H⁺) concentrations were estimated from the concentrations of pyruvate and lactate according to the regression equation established by Sahlin et al. (41). The concentration of free Mg²⁺ was assumed to be 1.0 mM (10). The standardized protocols used to measure the concentrations of PCR, Cr, and Pi, as well as glycogen and the glycolytic intermediates have been described in detail in earlier publications (22, 27).

Each property was measured in duplicate and analyzed during a single analytical session with samples from both the control and COPD groups.

The transporters, both GLUT1 and GLUT4 and MCT1 and MCT4, were assessed using electrophoresis and Western blotting techniques in homogenate prepared from frozen tissue (20–30 mg). Since complete details have been described in a recent publication (19), only a brief description is provided here. The homogenizing buffer (tissue diluted 1:20) consisted of 10 mM HEPES, pH 7.4, 250 mM sucrose, 2 mM EGTA, and a protease inhibitor cocktail (Roche Diagnostics, Mannheim, Germany). A homogenate obtained from a pellet, isolated by centrifugation (230,000 g for 75 min at 4°C) and homogenized in 1–2 ml buffer (10 mM Tris base, 1 mM EDTA, pH 7.4) was applied to a 10% polyacrylamide gel, separated with standard SDS-PAGE protocols (35) and transferred to polyvinylidene difluoride (PVDF) membranes. After blocking (5% skim milk suspension for 1 h at 22°C), the membranes were incubated with antisera. For GLUT 1 and GLUT4, the anti-GLUT polyclonal antisera (CBL242 and CB243, respectively) were obtained from Chemicon International with dilution 1:20. For MCT1 and MCT4, the antisera (AB3538P and AB3316P, respectively) were also obtained from Chemicon International and diluted 1:400.

After washing (Tris·HCl, pH 7.5, 150 mM NaCl, 0.1% Tween), the membranes were treated with horseradish peroxidase-conjugated antirabbit secondary antibody (Santa Cruz Biotechnology) for 1 h and then washed in the Tween solution. Isobaric detection was performed with an enhanced chemiluminescence procedure (Amersham, Little Chalfont, UK), and the blots were analyzed with a Chemi Genius 2 model bioimaging system (Syngene, Frederick, MD) with Syngene
software version 1.0. All samples were run in duplicate on separate gels with control and COPD samples matched. Each gel was also run with a standard amount of α-actin to verify protein loading. As with earlier studies, we have examined the linearity of measurement over the full range of concentrations for each of the transporters. Protein was measured by the Bio-Rad assay, in which detergent was present. To determine the relative difference between groups, the value for the control group was set at 100%, and the value of the COPD was calculated accordingly.

Statistical procedures. To examine for differences between groups for the total sample (control vs. COPD), Studentized t-tests were employed for independent groups. Significance was set at $P < 0.05$. Where differences are indicated in the present study, significance is implied.

RESULTS

Participant characteristics. No differences were found between the control and COPD groups in age, body weight, and height (Table 1). Clear differences were observed in the pulmonary and arterial properties affected by the disease, such as $FEV_1$ (% predicted), $FEV_1/FVC$ (%), diffusing capacity of the lung for carbon monoxide ($D_lCO_2$, %), arterial $P_O_2$ ($PaO_2$, mmHg), and arterial $O_2$ saturation ($SaO_2$, %), where the values were lower in COPD compared with controls. In contrast, the COPD patients displayed a higher arterial $PCO_2$ ($PaCO_2$, mmHg). Measurements of $V_\text{O}_2\text{peak}$, obtained during a progressive cycle test to fatigue, indicated a severely compromised ability for oxidative phosphorylation in COPD. Body mass index was not different between the groups.

Resting energy metabolism. Our measurements indicate an ~7.1% lower ATP concentration in COPD compared with the control group (Fig. 1). The lower ATP concentration was not accompanied by differences in any of the other nucleotides, namely $ADP$, and $AMP$ or in total TAN. The level of IMP, formed by the degradation of AMP by the AMP deaminase reaction, was also not different between groups (0.090 ± 0.03 vs. 0.11 ± 0.03 mmol/kg dry wt). In contrast, higher calculated concentrations (μmol/kg dry wt) were found in COPD for both $ADP_f$ (102 ± 11 vs. 79 ± 4.0) and $AMP_f$ (0.63 ± 0.2 vs. 0.32 ± 0.03). The high-energy phosphagen $PCr$ was 7.2% lower in COPD (Fig. 2). The lower $PCr$ was accompanied by near stoichiometric higher concentrations of both $Cr$ and $Pi$. The total creatine pool was not different between groups.

Glycogen and glycolytic metabolites. With the exception of lactate, which was not different between control and COPD (2.19 ± 0.31 vs. 2.33 ± 0.20 mmol/kg), all other metabolites, namely glucose-1-phosphate, glucose-6-phosphate, fructose-6-phosphate, and pyruvate, were elevated in COPD (Fig. 3). The lactate-to-pyruvate ratio, a measure of the cytosolic redox potential, was 33.4 ± 5.6 and 22.8 ± 2.8 for the control and

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**Table 1. Selected anthropometric and pulmonary function characteristics in patients with COPD and healthy controls**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control</th>
<th>COPD</th>
</tr>
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<tbody>
<tr>
<td>Age, yr</td>
<td>67.6±1.8</td>
<td>67.6±3.1</td>
</tr>
<tr>
<td>Ht, cm</td>
<td>165±3.0</td>
<td>159±2.8</td>
</tr>
<tr>
<td>Wt, kg</td>
<td>71.4±4.1</td>
<td>67.4±4.7</td>
</tr>
<tr>
<td>$FEV_1$, % predicted</td>
<td>114±2.4</td>
<td>42±6.0*</td>
</tr>
<tr>
<td>$FEV_1/FVC$, %</td>
<td>109±2.7</td>
<td>61.7±4.1*</td>
</tr>
<tr>
<td>$DlCO_2$, %</td>
<td>113±8.0</td>
<td>48.7±3.8*</td>
</tr>
<tr>
<td>$PaCO_2$, mmHg</td>
<td>84.2±2.0</td>
<td>58.5±2.8*</td>
</tr>
<tr>
<td>$PaCO_2$, mmHg</td>
<td>38.7±1.2</td>
<td>43.7±1.9*</td>
</tr>
<tr>
<td>$SaO_2$, %</td>
<td>96.2±0.24</td>
<td>89.8±1.4*</td>
</tr>
<tr>
<td>$V_\text{O}_2\text{peak}$, ml·kg$^{-1}$·min$^{-1}$</td>
<td>24.3±2.0</td>
<td>8.6±1.0*</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.1±1.2</td>
<td>26.9±2.2</td>
</tr>
</tbody>
</table>

Values are means ± SE; for controls, n = 12, and for chronic obstructive pulmonary disease (COPD), n = 9. Ht, height; Wt, weight; $FEV_1$ (% predicted), forced expiratory volume in 1 s as percent of normal predicted volume; $FEV_1/FVC$, ratio of forced expiratory volume in 1 s to forced vital capacity; $DlCO_2$, diffusing capacity of the lung for carbon monoxide; $PaCO_2$, arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension; $V_\text{O}_2\text{peak}$, peak oxygen consumption; $SaO_2$, arterial oxygen saturation. *Significantly different from control ($P < 0.05$).
COPD groups, respectively. This difference was not significant. Endogenous levels of glycogen were unaffected by the disease state (Fig. 4), nor was any difference observed between groups in glucose concentration.

Transporters. Disease resulted in a pronounced reduction in both GLUT4 and MCT4, where the relative concentration was 72.5 ± 4.6% and 65.2 ± 10%, respectively of control (Figs. 5 and 6). These differences appeared to be specific to these major transporters since no effects were observed for the minor transporters, namely GLUT1 and MCT1.

**DISCUSSION**

It is clear that differences in the metabolic status of the resting VL muscle exists between patients with moderate to severe COPD and age-matched healthy controls. Patients with COPD exhibit a lower phosphorylation potential as a consequence of lower concentrations of ATP and PCr. The lower concentrations of these high-energy phosphagens is also accompanied by elevations in AMP, and ADP, but not in TAN or TCr. These findings are essentially what has been reported previously in the VL of patients with moderate COPD (39).

**Fig. 2.** Concentrations of creatine phosphate (PCr; A), creatine (Cr; B), total creatine (TCr; C), and Pi (D) in resting vastus lateralis muscle of patients with COPD and healthy controls. Values are means ± SE. For COPD, n = 9; for control, n = 12. *Significantly different from control (P < 0.05).

**Fig. 3.** Concentrations of selected glycolytic metabolites in resting vastus lateralis muscle of patients with COPD and healthy controls. Values are means ± SE. For COPD, n = 9; for control, n = 12. A: glucose-1-phosphate (G-1-P). B: glucose-6-phosphate (G-6-P). C: fructose-6-phosphate (F-6-P). D: pyruvate. *Significantly different from control (P < 0.05).
The failure to find differences between groups in TAN and TCr is important since it demonstrates that no net degradation in the pool size occurs for the high-energy compounds. The lack of a difference between groups in the pool size for both TAN and TCr suggests that the lower ATP and PCr observed in COPD is due simply to a change in one or more of the substrates or by-products, given the near-equilibrium nature of the enzymes involved in the high-energy phosphate transfer reactions (8). A plausible scenario is that as a result of reductions in ATP, a net increase in PCr breakdown occurred, resulting in increases in Cr and Pi, both of which were found.

The reduction in phosphorylation potential, resulting in increases in ADP, and other potential adenine nucleotide regulators, could act to increase the drive for oxidative phosphorylation, serving to protect ATP synthesis, given the arterial hypoxemia that occurs in COPD and probable reduction in cellular PO2 (8). The reduction in phosphorylation state could also serve to increase glycogenolytic and glycolytic flux rates via increases in phosphorylase and phosphofructokinase activities, a possibility consistent with the elevation in the pathway intermediates observed (8, 38). The higher resting concentrations of the glycolytic intermediates is a novel finding not reported previously in VL of COPD patients. An increase in muscle lactate, which would be expected in COPD with an increase in glycolytic flux rate, was not observed. Normal resting muscle lactate has also been reported in other studies (39, 40), even in COPD patients with severe

![Fig. 4. Concentrations of glucose (A) and glycogen (B) in resting vastus lateralis muscle of patients with COPD and healthy controls. Values are means ± SE. For COPD, n = 9; for control, n = 12.](image1)

![Fig. 5. Representative Western blots (A) and relative changes in the concentration of the glucose transporters GLUT1 and GLUT4 (B) in vastus lateralis muscle of patients with COPD and healthy controls. Values are means ± SD. For COPD, n = 8; for control, n = 10. Changes in both GLUT isoforms were first calculated against a standard and then calculated as a relative change (COPD) from 100% (control). *Significantly different from control (P < 0.05).](image2)

![Fig. 6. Representative Western blots (A) and relative changes in the concentration of the monocarboxylate transporters MCT1 and MCT4 (B) in vastus lateralis muscle of patients with COPD and healthy controls. Values are means ± SE. For COPD, n = 8; for control, n = 10. Changes in both MCT isoforms were first calculated against a standard and then calculated as a relative change (COPD) from 100% (control). *Significantly different from control (P < 0.05).](image3)
hypercapnia and hypoxemia (12) and between COPD patients with and without respiratory failure (31). However, there are conflicting reports since others have reported elevated resting lactate concentrations (11). In most of these studies involving VL there is a clear trend for higher resting lactates in COPD; however, the large interindividual variability in concentration obscures statistical inference.

The failure to observe increases in muscle lactate concentration, as would be expected, could occur secondarily to increased removal from the cell or via activation of pyruvate dehydrogenase (PDH), leading to increased utilization of pyruvate as a substrate for mitochondrial respiration (43). The higher ADP\textsubscript{f} and lower phosphorylation potential observed in COPD are consistent with increased PDH activation. However, if increased removal of lactate resulted, it would have to occur in the face of a lower MCT4. In the absence of direct measurements of lactate flux using labeled isotopes, the actual mechanisms involved remain speculative.

The effects of aging may also be involved in the metabolic changes occurring in COPD. It has long been known that aging results in a reduction in mitochondrial density, compromising the maximal activity of the oxidative enzymes and the potential for oxidative phosphorylation (7). This change in itself could reduce mitochondrial sensitivity, increasing the need to elevate the mitochondrial respiratory control signals (14). Recently aging has also been reported to decrease the metabolic efficiency, resulting in a decrease in ATP synthesis per unit oxygen consumed (P/O ratio) (7). The reduction in the P/O ratio is believed to be due to an H\textsuperscript{+} leak through the inner mitochondrial membrane as a result of oxidative damage mediated by increases in reactive oxygen species (ROS) (26). Aging muscle is also characterized by a lower phosphorylation potential (7). Increases in muscle ROS and oxidative damage have also been postulated to occur in COPD (9). If such is the case, phosphorylation potential would also be reduced in COPD, similar to what we have found in this study. Alternatively, an elevation in V\textsubscript{O\textsubscript{2}} would be needed to protect ATP homeostasis, given the inefficiency that occurs.

The pronounced reduction in the principal transporters, GLUT4 and MCT4, a novel finding not previously reported in COPD, could occur as a result of an increased degradation and/or decreased synthesis. It is known that in the case of GLUT4, expression is regulated by cellular energy status via activation of AMPK (33). In the absence of changes in degradation rates, it would appear that the depressed phosphorylation potential observed in COPD in this study did not reach the threshold necessary to stimulate increased synthesis. This isoform is extremely sensitive to the level of contractile activity, with pronounced increases observed soon after onset (29). GLUT1, the minor isoform in skeletal muscle, has been functionally associated with facilitating the transport of glucose during recovery when endogenous glycogen stores are restored (29). Given that there is little evidence that this isoform can be altered, regardless of the stressor (29), it is not surprising that no differences were observed between the COPD and control groups.

As with GLUT4, the pronounced reduction in MCT4, the principal isoform in skeletal muscle, could be due to altered expression and/or degradation. Increased expression is thought to be related to elevations in lactate and H\textsuperscript{+} in muscle, which can increase dramatically with exercise (34). Increases in cellular lactate is also thought to upregulate MCT1, the minor isoform (25). As with GLUT4, MCT4 is very sensitive to the level of contractile activity (34). From a functional standpoint, MCT4 is believed to facilitate the transport of lactate out of the muscle while MCT1 is more adapted to facilitating transport into the muscle (34).

COPD is known to be accompanied by an increase in the percentage of the fast, type II fibers and a decrease in the percentage of the slow, type I fibers (16, 36). In this study, we have found that the percentage of type I was also lower in COPD (30.6 ± 5.2 vs. 57.9 ± 4.6%) (unpublished). It has been assumed that the shift in fiber type percentage, which is based on a shift in the myosin heavy chain isoform type (6), represents a simple transformation accompanied by the multiple other properties characteristic of the transformed type (16). If such were the case, it would be expected that in the absence of any other effects of the disease per se, the concentration of the transporters would change toward that characteristic of type II fibers. It is known that in type II fibers, the concentration of MCT4 is highest while the concentration of MCT1 is highest in type I fibers (5). Since MCT4 was depressed and MCT1 was unchanged in COPD, factors other than fiber type transformation would appear to be involved. For GLUT 4 and GLUT1, GLUT4 is higher in type I while GLUT1 is higher in type II fibers (29). Accordingly, a simple transformation toward type II fiber types may explain the lower GLUT4 transporter distribution but not the normal GLUT1 that we have found in this study in the COPD patients. A simple transformation of fiber types toward type II would also not explain the lower phosphorylation potential observed in COPD since in human VL, type II fibers in contrast to type I tend to have higher concentrations of ATP and PCr (24).

As with any study employing cross-sectional designs, it is difficult to isolate the differences observed between the healthy controls and the COPD patients to either the disease itself or to secondary factors such as differences in contractile activity, diet, or the medications employed to treat COPD. In this study, neither group was engaged in regular physical activity either during the study or for at least 2 mo prior (20). Moreover, daily total caloric intake as well as the percentage of protein, fat, and carbohydrate were not different (20). However, as expected, the COPD patients were on several medications, the effects of each in altering muscle phenotype unknown. Numerous other factors associated with COPD, such as arterial hypoxemia, systemic inflammation, and hormonal disturbances, which have been suggested to explain cachexia in COPD (45), may also be involved. Interestingly, many of the muscular defects observed in COPD have also been reported for chronic heart failure (16, 44), raising the possibility that common factors are involved.

Given the role of regular contractile activity in modifying muscle phenotype, the possibility remains that at least some of the changes observed in COPD could result from a reduction in daily weight-supported tasks that typically occur with moderate to severe COPD. An extended period of bed rest, as an example, results in a shift from type I to type IIA fibers (13), and this could explain some of the change observed in COPD. Decreased activity levels also result in a significant reduction in oxidative potential and fiber cross-sectional area, both of which have been observed in COPD (15, 36, 47). Inactivity is also known to reduce the content of GLUT4 (29) and MCT4.
Collectively, these effects suggest that increased regular activity in COPD patients may, at least partly, reverse some of the phenotype changes.

Perspectives and Significance

The most dramatic and potentially important finding in this study was the substantially lower concentration of the principal glucose and lactate transporters, namely GLUT4 and MCT4, in the VL of COPD patients. Although, the defects in these transporters do not appear to affect endogenous glycogen and lactate homeostasis at rest, they would be expected to have an important role during and after exercise when the demands for glucose and lactate transport are greatly exaggerated. The greater accumulation of lactate, which has been commonly observed in muscle during exercise and which has been attributed to increased glycolysis, may well result, at least in part, from impaired removal from the muscle. As with the transporters, further studies are required to determine the cause of the lower phosphorylation potential in resting muscle and whether it is due simply to the need to increase the drive for mitochondrial respiration as a result of hypoxemia or defects in mitochondrial metabolism.

GRANTS

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GLUCOSE AND LACTATE TRANSPORTERS IN COPD


