Metabolic and hemodynamic responses of lower limb during exercise in patients with COPD

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Maltais, François, Jean Jobin, Martin J. Sullivan, Sarah Bernard, François Whittom, Kieran J. Killian, Marc Desmeules, Marthe Belanger, and Pierre Leblanc. Metabolic and hemodynamic responses of lower limb during exercise in patients with chronic obstructive pulmonary disease (COPD) may play a role in exercise intolerance. In this study, we evaluated whether the early exercise-induced lactic acidosis in these individuals can be explained by changes in peripheral O2 delivery (Do2). Measurements of leg blood flow by thermodilution and of arterial and femoral venous blood gases, pH, and lactate were obtained during a standard incremental exercise test to capacity in eight patients with severe COPD and in eight age-matched controls. No significant difference was found between the two groups in leg blood flow at rest or during exercise at the same power outputs. Blood lactate concentrations and lactate release from the lower limb were greater in COPD patients at all submaximal exercise levels (all P < 0.05). Leg Do2 at a given power output was not significantly different between the two groups, and no significant correlation was found between this parameter and blood lactate concentrations. COPD patients had lower arterial and venous pH at submaximal exercise, and there was a significant positive correlation between venous pH at 40 W and the peak O2 uptake (r = 0.91, P < 0.0001). The correlation between venous pH and peak O2 uptake suggests that early muscle acidosis may be involved in early exercise termination in COPD patients. The early lactate release from the lower limb during exercise could not be accounted for by changes in peripheral Do2. The present results point to skeletal muscle dysfunction as being responsible for the early onset of lactic acidosis in COPD.

chronic obstructive pulmonary disease; metabolism; skeletal muscle; leg blood flow

THE CAUSES OF EXERCISE intolerance in patients with chronic obstructive pulmonary disease (COPD) are traditionally focused on limitations in ventilation and gas exchange. Consequently, dyspnea, hypoxemia, and hypercapnia during exercise are the most common factors addressed. Recent studies have clearly shown that peripheral skeletal muscles are compromised in COPD (11, 22). Decreases in skeletal muscle mass, strength, and mitochondrial enzyme activities have been described in this disease and may play an important role in exercise limitation in COPD (11, 22).

It is still unclear whether there are changes in the metabolism and acid-base status during exercise of the contracting muscles in patients with COPD. In fact, it is commonly believed that, because of ventilatory limitation, the vast majority of COPD patients are unable to exercise sufficiently to produce significant amounts of lactic acid (2). On the contrary, recent studies have shown early lactic acidosis during exercise in COPD (5, 22). 31P-NMR studies have demonstrated a greater than normal decrease in muscle pH and in the ratio of phosphocreatine/PCr [(PCr/[PCr + P]),] in COPD patients during small muscle group contractions, consistent with an impaired energetic metabolism with a shift toward anaerobic glycolysis (18, 24). Because reduction in muscle pH is a contributory factor to muscle fatigue (13, 20), premature muscle acidosis may be another mechanism that contributes to exercise intolerance in COPD patients. In these patients, an impaired energy metabolism could be caused by several factors, including poor peripheral O2 delivery (Do2) or less-efficient oxidative metabolism. Although a decrease in activities of skeletal muscle oxidative enzymes has been reported (22), the possible influence of peripheral Do2 has not been evaluated in patients with COPD.

The specific objectives of this study were to address the following questions. 1) In COPD patients, is there any reduction in blood flow to peripheral contracting skeletal muscles during cycle exercise? 2) Is lactate release from the peripheral muscles excessive in patients with COPD compared with lactate release in age-matched normal subjects? 3) Do changes in peripheral Do2 have any influence on blood lactate concentration? 4) Do femoral venous gases and acid-base status, a reflection of intramuscular values, reach similar values at peak exercise in COPD patients compared with normal subjects? To address these issues, arterial and femoral venous blood was sampled and leg blood flow (Qleg) was measured during leg-cycle exercise in patients with COPD and in age-matched normal subjects.

METHODS

Patient Population

Eight patients with COPD volunteered to participate in this study. The diagnosis of COPD was based on previous (n = 6) or present (n = 2) smoking history and pulmonary function tests, including spirometry, lung volumes, and carbon monoxide-diffusion capacity (DLCO) showing moderate-to-severe irre-
versatile airflow obstruction [forced expiratory volume in 1 s (FEV1) <60% predicted value, and FEV1/forced vital capacity <60%] (1). Subjects were stable at the time of the study, and none suffered from cardiovascular, neurological, or any other condition that could alter their capacity to perform an exercise test. Eight healthy, nonsmoking men, aged 50–70 yr, who were recruited by means of newspaper advertisements, constituted the control group. The research protocol was approved by the institutional ethics committee, and a signed, informed consent document was obtained in each case.

Protocol

Catheter placements and Qleg measurements. Qleg of a single leg was measured with a thermodilution catheter (model 93A–105–5F; Edwards Laboratory, Santa Ana, CA) as previously described (32, 34). On this catheter, the injectate port and the thermistor are located 10 and 1.5 cm, respectively, from the tip. After the subject’s right groin was shaved, disinfected, and anesthetized with lidocaine, the catheter was inserted into the femoral vein 2 cm below the inguinal ligament, with the distal thermistor tip positioned 10–12 cm above the inguinal ligament in the external iliac vein. The catheter was interfaced with a model SP 1435 cardiac-output computer (Gould Statham, Oxnard, CA), and boluses of 1–5 ml iced or room temperature saline were injected to obtain two to four flow measurements at rest and during exercise. Thermodilution curves were displayed on the Gould recorder to ensure a monophasic curve with an exponential decay. The validity and the reproducibility of this technique have been confirmed in previous studies by Sullivan et al. (32, 34). To sample venous blood, we also inserted a 10-cm indwelling catheter in the right femoral vein, 1 cm below the thermodilution catheter, with its tip located in the external iliac vein. Finally, a cannula was placed in a radial artery.

Exercise test. Subjects were seated on an electrically braked ergocycle and connected to the exercise circuit through a mouthpiece. The exercise circuit consisted of a pneumotachograph, O2 and CO2 analyzers, and a mixing chamber (Quinton Qplex, A. H. Robins, Seattle, WA). After subjects rested for 5 min, a progressive, stepwise exercise test was performed up to the individual’s maximum capacity. Five-breath averages of minute ventilation (Ve), O2 uptake (VO2), and CO2 excretion (VCO2) were measured at rest and during exercise. Each exercise step lasted 3 min, and increments of 20 W were used. Qleg measurements were obtained during the second minute of each exercise step, whereas the arterial and femoral blood were sampled during the last minute. During the last minute of each exercise step, subjects were asked to rate their dyspnea and perception of leg fatigue on a modified Borg scale (3). Blood samples were placed on ice until the end of the exercise test; then they were rapidly processed. Arterial and venous PO2, PCO2, and pH were measured with a blood-gas machine (AVL 995; AVL Scientific, Roswell, GA), and oxygen saturation (SaO2) was measured with a CO-oximeter (OSM2 Hemoximeter; Radiometer, Copenhagen, Denmark). The standard HCO3- values were derived from the Siggard-Andersen nomogram. After blood was centrifuged at room temperature, lactate concentrations in plasma were determined with an enzymatic technique (lactate kit, Boehringer-Mannheim, Mannheim, Germany).

Statistical analysis. Results are expressed as means ± SE. The maximal voluntary ventilation was estimated by multiplying the FEV1 by 35 (6). The predicted values for spirometry, lung volume, and DLco are those of Knudson et al. (17), Goldman and Becklake (10), and Cotes and Hall (7), respectively. Blood O2 and CO2 content were calculated from standard formulas with appropriate modification for Hb concentration, SaO2, and pH (8). Single-leg VO2 and VCO2 (VO2leg and VCO2leg respectively) were derived by using the Fick principle. The lactate release from the lower limb was computed from the Qleg and venous-arterial (v-a) lactate difference product, and the single-leg O2 delivery (DO2leg) was computed from the Qleg and arterial O2 content product. The time-course changes of study parameters with exercise in both groups were compared with two approaches. 1) Changes of each parameter during exercise in normal subjects and in COPD patients were compared by using profile analysis, which allowed us to evaluate and to compare the time course of different variables between two groups (28). 2) The values at rest and at each exercise level were compared between both groups by using two-way ANOVA (group, exercise work rate) with repeated measures for the second factor (exercise work rate). A value of P < 0.05 was considered statistically significant.

RESULTS

The characteristics of the experimental and control groups are given in Table 1. Age, height, weight, body mass index, and Hb were comparable in the two groups. The experimental group had severe airflow obstruction, with an FEV1 of 37 ± 3% predicted normal values. All subjects completed the incremental exercise test to their maximal subjective capacity (Table 2). The peak power output achieved in the COPD group was 63 ± 5 W, with a peak VO2 (VO2peak) of 1.1 ± 0.1 l/min. The peak power output of the control group was significantly greater at 168 ± 15 W, with a VO2peak of 2.8 ± 0.2 l/min (P < 0.001). As expected, peak heart rate and VE were also lower in COPD (P < 0.001).

Peripheral Blood Flow to Peripheral Muscles During Exercise

Lower limb hemodynamic responses to incremental exercise are presented in Table 3. Resting Qleg was similar in both groups (0.43 ± 0.06 and 0.44 ± 0.04 l/min, in normal subjects and in COPD patients, respectively; P > 0.05). The increase in Qleg during exercise was similar for the two groups, although it tended to be greater in COPD.

Table 1. Subjects’ characteristics

<table>
<thead>
<tr>
<th></th>
<th>Normal Subjects</th>
<th>COPD Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Age, yr</td>
<td>61 ± 3</td>
<td>66 ± 2</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.75 ± 0.03</td>
<td>1.66 ± 0.03</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>84 ± 7</td>
<td>73 ± 5</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td>27.4 ± 1.8</td>
<td>26.2 ± 1.2</td>
</tr>
<tr>
<td>Hb, g/l</td>
<td>149 ± 4</td>
<td>152 ± 3</td>
</tr>
<tr>
<td>FEV1, liters</td>
<td>3.72 ± 0.20</td>
<td>1.00 ± 0.09T</td>
</tr>
<tr>
<td>FEV1, %pred</td>
<td>116 ± 5</td>
<td>37 ± 3T</td>
</tr>
<tr>
<td>FVC, liters</td>
<td>4.65 ± 0.24</td>
<td>2.87 ± 0.18T</td>
</tr>
<tr>
<td>FVC, %pred</td>
<td>100 ± 4</td>
<td>70 ± 5</td>
</tr>
<tr>
<td>TLC, %pred</td>
<td>106 ± 3</td>
<td>111 ± 6</td>
</tr>
<tr>
<td>DLco, %pred*</td>
<td>110 ± 8</td>
<td>79 ± 14</td>
</tr>
</tbody>
</table>

Values are means ± SE. COPD, chronic obstructive pulmonary disease; n, no. of subjects; BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; DLco, CO diffusion capacity; %pred, % predicted. *Single-breath DLco was obtained in 5 of 8 COPD patients. †P < 0.0001; ‡P < 0.05.
lower in COPD patients (at 60 W: 3.08 ± 0.19 vs. 2.72 ± 0.23 l/min in normal subjects and COPD patients, respectively).

Lactate Release in Lower Limb During Exercise

Resting values for arterial and venous lactate were similar for both groups (Fig. 1). The increase in these parameters was steeper in COPD patients, as indicated by the higher values obtained in these patients for each submaximal exercise work rate (P < 0.005). The change in v-a lactate difference and lactate release during exercise paralleled that of the arterial and venous concentrations. In addition, v-a lactate and lactate release, for each submaximal-exercise level, were greater in COPD patients compared with normal subjects (for P values see Fig. 1, C and D). Because of the greater peak work rate achieved in normal subjects, values of arterial and venous lactate concentrations at peak exercise capacity were greater in these individuals than in individuals with COPD (P < 0.001 and P < 0.01, respectively). At peak exercise, the v-a lactate was greater in COPD patients than in normal subjects (P < 0.01), whereas lactate release was similar for both groups.

Peripheral \(D_2O\), Lower-Limb Metabolism, and Blood-Lactate Concentration During Exercise

Resting and exercise values for \(P_{O_2}\), \(P_{O_2}\), \(S_{A_02}\), venous \(O_2\) saturation (\(S_{V_02}\)), arteriovenous \(O_2\) content difference \((C(a-v)_{O_2})\), \(D_{O_2leg}\), \(V_{O_2leg}\), \(V_{CO_2leg}\), and single-leg respiratory quotient (\(R_{Qleg}\)) are shown in Table 3. Resting and exercise values for \(P_{O_2}\) and \(S_{O_2}\) were significantly lower in COPD patients than in normal subjects (all \(P < 0.001\)), whereas \(P_{O_2}\) and \(S_{V_02}\) were similar in both groups during submaximal exercise. In both groups, the beginning of exercise was accompanied by a reduction in \(P_{O_2}\), which remained stable afterward. In contrast, \(S_{V_02}\) decreased progressively during exercise and reached nadir values of 24 ± 3% and 28 ± 3% at peak exercise in normal subjects and in COPD patients, respectively (\(P > 0.05\)).

As a result of lower \(S_{A_02}\), the \(D_{O_2leg}\) tended to be smaller in COPD patients during submaximal level (all \(P > 0.11\)). In contrast, \(D_{O_2leg}\) was markedly lower in COPD patients compared with normal subjects at peak exercise (\(P < 0.0001\)). \((C(a-v)_{O_2})\) was preserved in COPD patients, as indicated by the small and nonsignificant differences in \((C(a-v)_{O_2})\) between both groups during submaximal exercise. \(V_{CO_2leg}\) was no different at rest in the two groups and tended to be smaller in COPD patients during submaximal exercise (at 60 W: 408 ± 87 vs. 333 ± 86 ml/min in normal and in COPD patients, respectively; \(P = 0.14\)). Because the \(V_{CO_2leg}\) was almost identical for both groups, the leg respiratory coefficient (\(R_{Qleg}\)) was greater in COPD patients than in normal subjects during submaximal exercise, although this difference reached statistical significance only at 60 W (1.21 ± 0.05 vs. 1.04 ± 0.06, respectively; \(P < 0.05\)). As a reflection of a higher exercise work rate achieved in normal subjects, \(Q_{leg}\), \(V_{O_2leg}\), and \(V_{CO_2leg}\) were greater in these individuals at maximal exercise (\(P < 0.005\)).

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**Table 2. Response to maximal exercise**

<table>
<thead>
<tr>
<th></th>
<th>Normal Subjects</th>
<th>COPD Patients</th>
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<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Peak (V_{O2}), l/min</td>
<td>2.6 ± 0.2</td>
<td>1.1 ± 0.1*</td>
</tr>
<tr>
<td>Peak (V_{CO2}), l/min</td>
<td>2.9 ± 0.2</td>
<td>1.1 ± 0.1*</td>
</tr>
<tr>
<td>Peak work rate, W</td>
<td>168 ± 15</td>
<td>63 ± 5*</td>
</tr>
<tr>
<td>Peak heart rate</td>
<td></td>
<td></td>
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<tr>
<td>Beats/min</td>
<td>165 ± 3</td>
<td>136 ± 7*</td>
</tr>
<tr>
<td>%Predicted maximum</td>
<td>92 ± 2</td>
<td>77 ± 4*</td>
</tr>
<tr>
<td>Peak (V_e), l/min</td>
<td>115 ± 9</td>
<td>42 ± 3*</td>
</tr>
<tr>
<td>Peak (V_e/MMV), %</td>
<td>87 ± 4</td>
<td>111 ± 8†</td>
</tr>
<tr>
<td>Peak Borg score</td>
<td></td>
<td></td>
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<tr>
<td>Dyspnea</td>
<td>6.2 ± 0.8</td>
<td>7.3 ± 0.7</td>
</tr>
<tr>
<td>Leg fatigue</td>
<td>6.5 ± 1.1</td>
<td>7.4 ± 0.6</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects. \(V_{CO2}\), \(V_{O2}\) consumption; \(V_{CO2}\), \(V_{O2}\) excretion; \(V_e\), minute ventilation; MVV, maximal voluntary ventilation; predicted maximal heart rate = 210 – 0.66-age. *\(P < 0.001\); †\(P < 0.05\).

**Table 3. Lower limb hemodynamic and metabolic responses at rest and during exercise at various intensities in normal subjects and in patients with COPD**

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>COPD</th>
<th>Normal</th>
<th>COPD</th>
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<th>COPD</th>
<th>Normal</th>
<th>COPD</th>
<th>Normal</th>
<th>COPD</th>
<th>Normal</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Q_{leg}), l/min</td>
<td>0.43 ± 0.06</td>
<td>0.44 ± 0.04</td>
<td>2.19 ± 0.20</td>
<td>1.85 ± 0.17</td>
<td>2.64 ± 0.18</td>
<td>2.47 ± 0.19</td>
<td>3.08 ± 0.19</td>
<td>2.72 ± 0.23</td>
<td>5.71 ± 0.45</td>
<td>2.54 ± 0.15*</td>
<td></td>
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<tr>
<td>(P_{A02}), Torr</td>
<td>107 ± 4</td>
<td>74 ± 4*</td>
<td>97 ± 3</td>
<td>70 ± 5*</td>
<td>102 ± 2</td>
<td>71 ± 6*</td>
<td>99 ± 2</td>
<td>68 ± 5*</td>
<td>96 ± 5</td>
<td>66 ± 4*</td>
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<td></td>
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<tr>
<td>(P_{V02}), Torr</td>
<td>26 ± 1</td>
<td>24 ± 2</td>
<td>23 ± 1</td>
<td>23 ± 2</td>
<td>24 ± 1</td>
<td>24 ± 2</td>
<td>24 ± 1</td>
<td>24 ± 2</td>
<td>23 ± 2</td>
<td>24 ± 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(S_{A02}), Torr</td>
<td>98 ± 1</td>
<td>95 ± 1*</td>
<td>98 ± 1</td>
<td>93 ± 1*</td>
<td>99 ± 1</td>
<td>92 ± 2*</td>
<td>98 ± 1</td>
<td>90 ± 2*</td>
<td>98 ± 1</td>
<td>90 ± 2*</td>
<td></td>
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<tr>
<td>(S_{V02}), Torr</td>
<td>43 ± 3</td>
<td>37 ± 4</td>
<td>34 ± 2</td>
<td>30 ± 2</td>
<td>31 ± 3</td>
<td>30 ± 3</td>
<td>33 ± 3</td>
<td>31 ± 3</td>
<td>24 ± 3</td>
<td>28 ± 3</td>
<td></td>
<td></td>
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<tr>
<td>((C(a-v)_{O2})), ml/100 ml</td>
<td>11.3 ± 0.5</td>
<td>12.0 ± 0.7</td>
<td>13.0 ± 0.5</td>
<td>13.1 ± 0.5</td>
<td>13.8 ± 0.7</td>
<td>12.8 ± 0.5</td>
<td>13.3 ± 0.7</td>
<td>12.5 ± 0.5</td>
<td>15.0 ± 0.7</td>
<td>12.7 ± 0.6*</td>
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<tr>
<td>(D_{O2leg}), ml/min</td>
<td>86 ± 13</td>
<td>85 ± 6</td>
<td>453 ± 43</td>
<td>355 ± 80</td>
<td>527 ± 41</td>
<td>470 ± 37</td>
<td>614 ± 42</td>
<td>512 ± 46</td>
<td>1135 ± 94</td>
<td>475 ± 35*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(V_{O2leg}), ml/min</td>
<td>47 ± 6</td>
<td>52 ± 5</td>
<td>284 ± 27</td>
<td>242 ± 23</td>
<td>362 ± 31</td>
<td>317 ± 30</td>
<td>408 ± 33</td>
<td>333 ± 38</td>
<td>870 ± 97</td>
<td>324 ± 28*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(V_{CO2leg}), ml/min</td>
<td>45 ± 7</td>
<td>40 ± 4</td>
<td>282 ± 40</td>
<td>270 ± 25</td>
<td>379 ± 44</td>
<td>364 ± 41</td>
<td>428 ± 46</td>
<td>400 ± 44</td>
<td>1021 ± 94</td>
<td>400 ± 40*</td>
<td></td>
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</tr>
<tr>
<td>(R_{Qleg})</td>
<td>0.96 ± 0.08</td>
<td>0.78 ± 0.06</td>
<td>0.98 ± 0.08</td>
<td>1.12 ± 0.06</td>
<td>1.04 ± 0.08</td>
<td>1.14 ± 0.03</td>
<td>1.04 ± 0.06</td>
<td>1.21 ± 0.05*</td>
<td>1.20 ± 0.05</td>
<td>1.23 ± 0.04</td>
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<td></td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects; \(Q_{leg}\), single-leg blood flow; \(P_{A02}\), arterial partial pressure of \(O_2\); \(P_{V02}\), venous partial pressure of \(O_2\); \(S_{A02}\), arterial \(O_2\) saturation; \(S_{V02}\), venous \(O_2\) saturation; \((C(a-v)_{O2})\), arteriovenous \(O_2\) content difference; \(D_{O2leg}\), single-leg \(O_2\) transport; \(V_{O2leg}\), single-leg \(O_2\) consumption; \(V_{CO2leg}\), single-leg \(CO_2\) consumption; \(R_{Qleg}\), single-leg respiratory quotient. All comparisons are COPD patients vs. normal subjects at same exercise work rate. *\(P < 0.001\); †\(P < 0.05\).
The relationship between the individual values of D˙O2leg and venous lactate concentration obtained at an identical work rate (40 W) is depicted in Fig. 2. This exercise level was chosen because it was the highest achieved by all participants. For a given D˙O2leg, venous lactate concentration varied considerably among subjects.

Femoral Venous Blood Gases and Acid-Base Status During Exercise

The time course of changes in arterial and venous values for pH, P CO2, and standard HCO3 during exercise is shown in Fig. 3. The decline in arterial and venous pH is faster in COPD patients than in normal subjects (P < 0.0005), with lower pH at each submaximal exercise level (P < 0.05 at 20 W, and P < 0.001 at 40 and 60 W). This was caused by CO2 accumulation and metabolic acidosis, as indicated by a faster increase in P CO2 and a steeper decrease in standard HCO3 in arterial and femoral blood in COPD patients compared with normal subjects (P < 0.005). At end of exercise, arterial and venous pH were similar in both groups, averaging 7.31 ± 0.02 and 7.27 ± 0.01, and 7.16 ± 0.02 and 7.14 ± 0.01 in normal subjects and in COPD patients, respectively (P > 0.05), despite a much lower peak-exercise work rate achieved in the latter group. The relationship between venous pH at 40 W and the VO2peak is shown in Fig. 4. A significant positive correlation was found between these two parameters (r = 0.91, P < 0.0001). Not shown in Fig. 4 is a similar observation made at 20 W (r = 0.84, P < 0.0001).

DISCUSSION

In this study, we evaluated energy metabolism of the lower limb and hemodynamics responses during leg-cycle exercise in patients with severe COPD and in age-matched normal subjects. There were striking differences in metabolism and acid-base status of the blood draining the active peripheral muscles in the COPD group compared with the normal control group. These differences could not be explained by changes in peripheral D O2. Despite a much lower maximal-exercise capacity in COPD patients, similarities between end-exercise RQleg, lactate release, and venous pH in both groups indicate a maximal or near-maximal peripheral muscle activation in COPD patients. This finding contrasts the traditional view regarding exercise physiology in patients with severe COPD. That view states that these individuals cannot tolerate sufficient exercise intensity to activate their peripheral muscles (2).

Peripheral Perfusion and D O2

At a given level of exercise, Q leg and D O2leg were preserved in COPD patients compared with normal subjects, although the values tended to be smaller in the former group. This difference, however, did not reach statistical significance, possibly because of the relatively small number of subjects included in this
study. The finding that the rise in peripheral blood flow is normal or slightly reduced in these patients is consistent with previous studies on central hemodynamics during exercise in COPD patients. These studies have shown a normal cardiac output/V_{O2} relationship\(^\text{(9)}\). It also indicates that, in COPD, the increase in cardiac output during cycle exercise is appropriately directed to the lower limbs. It is possible, however, that, in some patients with clinically evident cor pulmonale or in those who develop right ventricular dysfunction during exercise\(^\text{(23)}\), inadequate increase in cardiac output and consequently in Q_{leg} during exercise may be important in limiting exercise in those individuals.

**Lactate Release and Metabolism in Lower Limb During Exercise in Patients with COPD**

Excessive arterial blood lactate accumulation during exercise in COPD patients was related to an increased lactate release in the lower limb. This indicates that the decrease in lactate degradation by organs, such as the liver or noncontracting skeletal muscles, is not the primary mechanism accounting for the increase in lactate concentration in COPD. The increased lactate release probably reflects an accelerated lactate production, although reduced lactate uptake by the muscles of the lower limb\(^\text{(30)}\) may have contributed to the increase in lactate release.

The increase in lactate release and the higher venous P_{CO2} and RQ_{leg} found at submaximal exercise in COPD patients suggest that the energy sources for muscle contraction are different in these patients compared with normal subjects; i.e., there is a higher glycolytic activity in the former. These results are in line with previous studies that used \textsuperscript{31}P-NMR to demonstrate greater decline in intracellular pH and in PCr/(PCr + P_i) ratio during exercise in patients with COPD\(^\text{(18, 24)}\). These data and the present study indicate an impaired oxidative phosphorylation and ATP resynthesis, with early activation of anaerobic glycolysis within the con-

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**Fig. 3.** Arterial (A) and venous (B) pH, arterial P_{CO2} (P_{A\text{CO}_2}, C), and venous P_{CO2} (P_{V\text{CO}_2}, D), arterial (E) and venous (F) standard (st) bicarbonates during submaximal (open symbols) and peak (closed symbols) exercise in COPD patients (○ and ⃝) and in normal subjects (□ and ▼). Peak exercise values represent an average of all peak values obtained in each subject in both groups. In contrast to submaximal values, they were not obtained at an identical work rate. During submaximal exercise, arterial and venous blood acidosis was more profound in COPD patients because of greater P_{CO2} and metabolic acidosis. At maximal exercise, arterial and venous pH values were similar in both groups. *P < 0.05; †P < 0.001; ‡P < 0.01.

**Fig. 4.** Relationship between venous pH at 40 W and peak O_{2} uptake (V_{O2,peak}). ●, Normal subjects; ○, COPD patients. A significant relationship was found between these 2 parameters (r = 0.91, P < 0.0001).
trating muscles in patients with COPD. A number of factors may contribute to this altered muscle metabolic activity, including a decreased DO2 and a less-efficient oxidative metabolism. Similarities in Q˙leg, O2 extraction, and PvO2 for a given exercise level, and the large variability of blood lactate concentrations for a given DO2leg (Fig. 2) suggest that the altered energy metabolism in COPD cannot be accounted for by poor perfusion and oxygenation of the contracting muscles. Because these metabolic abnormalities are not explained by a reduction in DO2 and extraction, a possible explanation for this finding is an intrinsic muscle abnormality or an altered metabolic regulation of muscle in COPD (26). This contention is further supported by a study indicating poor skeletal muscle oxidative capacity in these patients (22), and by the relationship described between the increase in arterial lactate during exercise and skeletal muscle oxidative capacity in normal subjects (14), patients with COPD (22) and those with chronic heart failure (33). A shift toward a more pronounced anerobic glycolysis can also occur in a state of cellular hypoxia. There is evidence, both in normal subjects exposed to environment with low PO2 (12) and in COPD patients (24), that chronic hypoxia could modify significantly the cellular oxidative metabolism. In our patients, this explanation is less likely, because their resting PaO2 was not markedly reduced, ranging between 62 and 97 Torr, and their Qleg and DO2 were preserved at rest and during exercise. However, normal or slightly decreased daytime PaO2 and peripheral DO2 at rest or during exercise do not completely rule out chronic intracellular hypoxia. Oxygen desaturation may occur repeatedly during sleep in patients with severe COPD, and the degree of cellular hypoxia may be underestimated from the resting daytime PaO2. Qleg and O2 can also be directed toward nonmuscular tissue and not to the contracting muscle. This is unlikely, because it has been shown that the rise in Qleg during exercise is closely related to skeletal muscle blood flow (27). Intracellular hypoxia could also result from a mismatch between DO2 and the metabolic requirements within the contracting muscle (36). This would occur if the vasoregulation were abnormal during exercise in COPD, although the preserved O2 extraction does not support this contention. Finally, a block to O2 diffusion from the extracellular space to the mitochondria could explain intracellular hypoxia despite preserved DO2 and O2 extraction. These issues could not be resolved by the present study, and in this regard monitoring of intramuscular PO2 would be helpful.

Femoral Venous Blood Gases and Acid-Base Status During Exercise

The venous blood pH and PCO2 at rest and during exercise were used to estimate the corresponding end-capillary values and to provide some indication of the metabolic milieu to which the muscle cells are exposed (31). Because of greater PCO2 and lactic acidosis, the decline in venous pH was much faster in COPD patients than in normal subjects. Considering the level of exercise, this acidosis is definitely abnormal and may be involved in further worsening of skeletal muscle function during exercise. Studies have indicated that intracellular acidosis may adversely influence muscle contractility and be involved in the development of muscle fatigue and, consequently, may be involved in exercise tolerance (13, 20). The correlation between venous pH at 40 W and the VO2peak is in accordance with these notions, and it can be hypothesized that early muscle acidosis may be involved in exercise termination. However, the relationship between venous pH and VO2peak must be interpreted cautiously. Previous studies have indicated that changes in muscle pH may be dissociated from those of VO2peak (19). This suggests that the link between these two variables is more complex than a one-to-one causal relationship.

Methodological Considerations

In the present investigation, Qleg was measured with the bolus injection method. This technique has been used successfully by several investigators, and the present results obtained are remarkably similar to those reported after using paired electromagnetic flow probes or the dye-dilution technique (16, 35, 37). Resting and exercise values for Qleg and VO2leg obtained in our normal subjects are comparable to those reported in previous studies; therefore, we are confident about their validity (16, 35, 37). However, because Qleg and blood-gas measurements were not simultaneous and were probably obtained before reaching a steady state, a small error in VO2leg calculation can be expected. The magnitude of this error can be estimated by looking at the changes in total body VO2 that occurred between minutes 2 and 3 of the exercise step, assuming that most of the changes in VO2 during this period originated in the lower limbs and that C(a-v)O2 was relatively stable. At 60 W, the increase in total body VO2 from minute 2 to 3, averaged 23 ml/min in normal subjects and 54 ml/min in COPD patients. At this exercise level, this amounts to an underestimation in VO2leg of 3 and 8% in normal subjects and COPD patients, respectively. Because the magnitude of this error is greater in COPD patients, the actual differences in VO2leg values for a given work rate between the two groups would be even smaller than those reported in this study.

Clinical Implications

The present results point to skeletal muscle dysfunction as being responsible for the early lactic acidosis onset in COPD. However, the discussion regarding the causes of the muscle abnormalities can only be speculative. Several muscle changes found in COPD, including reductions in muscle mass, in strength, and in mitochondrial enzyme activities, and the excessive lactic acidosis during exercise are consistent with the effects of chronic inactivity and the resulting muscle deconditioning (4). The improvement in skeletal muscle oxidative
capacity in COPD patients that occurs with 12 wk of endurance training is also consistent with this interpretation (21). In that study, however, the decreases in enzyme activities were not completely corrected. This suggests that the training duration was not sufficiently long or that other contributing factors, such as malnutrition or chronic hypoxia (even if mild), may have played a role in altering the skeletal muscle function in COPD patients.

Accordingly, the observed differences in muscle metabolism between COPD patients and normal subjects can probably be explained largely by the different fitness level of the two groups. Although the fitness level of the control group could be considered normal, with a mean V\textsubscript{O\textsubscript{2peak}} within 1 SD of the reported mean value for normally active men of this age group (25), it was above the average value for individuals of this age group \[V\textsubscript{O\textsubscript{2peak}} < 70\% \text{ above the predicted value of J} \text{ones (15)}\]. Despite this limitation of the present study, we believe that differences in lactate response would have persisted, even if a group of less-fit subjects (i.e., V\textsubscript{O\textsubscript{2peak}} \approx 100\% predicted value) had been used for comparison. 1) The difference in lactate concentration in the blood draining the active muscles between normal subjects and COPD patients was substantial. 2) There was no overlap of blood lactate concentration between the two groups at submaximal exercise level despite the fact that one normal subject had a V\textsubscript{O\textsubscript{2peak}} value 102\% of that predicted.

In COPD patients, the end-exercise \(V_e\) was greater than the calculated maximal voluntary ventilation, whereas the peak heart rate was smaller than the calculated maximal voluntary ventilation, \(V\textsubscript{O\textsubscript{2peak}}\). In addition, oxygen desaturation, whereas the peak heart rate was smaller than the calculated maximal voluntary ventilation, \(V\textsubscript{O\textsubscript{2peak}}\), may have played a role in altering the skeletal muscle function in COPD patients.

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