Impaired Skeletal Muscle Endurance Related to Physical Inactivity and Altered Lung Function in COPD Patients*

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Study objective: The aims of this work were to determine (1) whether patients with COPD have impaired skeletal muscle performance (i.e., maximal strength and endurance) compared with healthy subjects, and (2) whether the level of physical activity, body composition, and lung function are related to skeletal muscle performance in COPD patients.

Methods: Seventeen COPD patients and eight healthy age-matched control subjects performed maximum voluntary contraction (MVC) of the quadriceps and an endurance test consisting of dynamic contractions of the quadriceps against 20% of MVC at an imposed regular pace until exhaustion. The endurance test duration determined the muscle “limit time” (Tlim). A score of physical activity (PA score) was obtained using an adapted physical activity questionnaire for the elderly, and body composition was measured by the bioelectrical impedance method. Symptom-limited oxygen uptake (Vo₂ sl) was also assessed in COPD patients using a maximal incremental exercise test.

Results: The results showed that Tlim and PA score were significantly decreased in COPD patients (p<0.05). Significant positive correlations were found in the COPD group between Tlim and the PA score (r=0.60; p<0.05), FEV₁ (r=0.52; p<0.05), and PaO₂ (r=0.63; p<0.05). The same results were found between the PA score and Vo₂ sl (r=0.57; p<0.05) and FEV₁ (r=0.63; p<0.05). Conclusion: These findings indicate impaired skeletal muscle endurance in COPD patients related to altered lung function and associated physical inactivity.

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Key words: body composition; COPD; deconditioning; endurance; physical activity questionnaire; skeletal muscle; strength

Abbreviations: FFM=fat-free mass; MVC=maximum voluntary contraction; PA=physical activity; Tlim=limit time; Vo₂=oxygen uptake; Vo₂ sl=symptom-limited oxygen uptake

Because exercise intolerance in patients with COPD appears to be due not only to pulmonary obstruction but also to a combination of several factors,1,2 consideration has been given recently to skeletal muscle function. Indeed, the reduced activity in the patient’s daily life due to dyspnea may lead to deconditioning, i.e., muscle function alteration.3,4 Investigations of skeletal muscle with nuclear magnetic resonance have shown abnormalities in muscle metabolism in these patients, indicating reduced oxidative capacity.5,6 Impaired muscle oxidative capacity suggests that skeletal muscle endurance is decreased,7 and such an alteration could explain the well-known leg fatigue described in these patients.8,9 A reduced maximal muscle strength was demonstrated in COPD patients and was found to be a significant contributor to work capacity limitation.8,9 However, to our knowledge, no data are yet available on skeletal muscle endurance and, for the assessment of peripheral muscle performance, isolated muscle strength alone is too limited. Moreover, although deconditioning has been suggested as an explicative factor of impaired skeletal muscle function and exercise capacity in COPD patients, the level of daily physical activity in these patients surprisingly has never been studied (to our knowl-

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nor has the possible relationships between this level and peripheral muscle performance.

The present study was thus undertaken to determine (1) whether patients with COPD have impaired skeletal muscle performance not only in terms of maximal strength but also in terms of endurance, compared with healthy subjects; and (2) whether the level of physical activity (PA), body composition, and lung function are related to skeletal muscle performance in COPD patients.

Materials and Methods

Subjects

Seventeen outpatient men with COPD (age, 62 years [SE, 2]) and eight healthy age-matched men (control group) were recruited to participate in this study. Each subject was informed of the purpose of the study and gave written consent. Patients were ex-smokers, had a clinical history consistent with COPD, and had spirometric evidence of bronchial obstruction; respiratory impairment ranged from moderate to severe according to the European Respiratory Society classification. At the time of the study, patients were in clinically stable condition with no recent infective exacerbation and were not smokers. All received inhaled treatment, including bronchodilators and corticoids. Subjects with cardiovascular limitation, metabolic abnormalities, or articular dysfunction were excluded from the study.

Material and Measurements

Lung Function and Blood Gas Assessment: Lung function studies were done using a whole body plethysmograph (Transmural Bodybox 2800; Sensormedics; Yorba Linda, Calif). Measurements included FVC and FEV1. Tiffenauer’s ratio (FEV1/FVC) was then calculated. The values obtained were compared with the normal values of Quanjer et al. Blood gas analyses were also performed in the COPD patients. Arterialized blood samples for PaO2 and PaCO2 were obtained at rest with the ear lobe micromethod (IL 1306; Milan, Italy).

Skeletal Muscle Performance Testing: We assessed maximum voluntary contraction (MVC) and endurance of the quadriceps for each leg using an exercise bench (Banc de Koch; Genin Medical; Les Angles, France). The apparatus for performing local muscle exercise consists of an ankle harness attached to nonelastic cord connected to a minimal friction system of ball-bearing pulleys and a dynamometer or adjustable weights (Fig 1). MVC was measured with a dynamometer. The exercise was performed with the subject in a sitting position at 90° knee and hip flexion. With arms crossed in front of the chest and position maintained, subjects performed three brief (4 s) maximal contractions, each separated by 1 min of rest. If maximal values of strength maintained 3 s as read on the dynamometer were reproducible (<5% of variability between values), the highest value of these three contractions was defined as MVC. Endurance of the quadriceps was then tested on the same exercise bench according to the technique of Monod and Scherrer. The exercise protocol consisted of extending one leg against weights corresponding to 20% of MVC with a pace of 12 movements per minute imposed with audio signal until exhaustion. The movement amplitude corresponded to the maximal extension of the leg and was identified before the start of the test. The duration of the movement was not imposed but it was required that subjects release muscles just after maximal extension, without maintaining static contraction or resisting when weights were set back. Thus, the active part of the movement was considered to be the load lift. The test was stopped when the subjects could no longer respect the movement amplitude or frequency two consecutive times despite verbal encouragement; duration was then recorded. This duration was called “limit time” (Tlim). Subjects performed these exercise tests for the two legs. The means of the two MVC and the two Tlim values (right and left muscle) were used for analysis.

Level of PA: PA was assessed by using a PA questionnaire adapted for the elderly. The questionnaire consisted of scores for household activities, sports activities, and other physically active leisure-time activities, together resulting in an overall PA score. Scores could not be obtained for three patients. One patient with depressive symptoms always responded that he had no activity. The two other patients could not quantify their physically active leisure time activities according to the questionnaire.

Nutritional Assessment: Body composition was assessed by the single-frequency bioelectrical impedance method. The measurement required subjects to present with an empty stomach. After 15 min of rest in supine position, resistance (ARC 50; Euguédia; Chambly, France) was measured on the right body side. Fat-free mass (FFM) was then calculated from height2/resistance and body weight using a patient-specific regression equation generated in 32 normal to underweight patients with COPD.

Exercise Tolerance: Exercise capacity was assessed in COPD patients by an incremental exercise test performed on a cycle ergometer (ERG 602; DIMEQ; Berlin, Germany). Patients breathed through a mouthpiece with a noseclip in place. Oxygen uptake (VO2) and carbon dioxide output were measured continuously using a mass spectrometer system (Metabolic Exercise Testing; Marquette Electronics; Milwaukee). A 12-lead ECG (Marquette Electronics) and pulse oximeter (Oxytal; Nihon Kohden Corporation; Tokyo, Japan) were monitored continuously during exercise testing. The exercise test was performed according to the individualized exercise test protocol used in our laboratory and defined as the following: first, the maximal
predicted work rate was calculated according to the equation of Jones et al.18 This maximal value was then adapted to the patient by multiplying it by FEV/FEV predicted. The 3-min warm up was conducted at 20% of this adapted maximal work rate. The work rate was then increased every minute. The increase rate was defined as 8% of the adapted maximal work rate in order to obtain the maximal work rate in about 10 min. This method usually results in a test duration of 5 to 12 min, which meets the exercise testing recommendations.19 In our study, to ensure that VO2 max was reached, three of the four following criteria had to be met: (1) stability of VO2 despite the increase in exercise intensity; (2) attainment of age-predicted maximal heart rate (210−0.65×age±10%); (3) respiratory exchange ratio >1.1; and (4) inability to maintain the required pedaling frequency (50 rpm) despite maximal effort and verbal encouragement. If one of the first three criteria was not observed, we considered that the maximal VO2 was symptom limited (VO2 sl).

Protocol: All the experiments were performed in the morning on 2 days for the COPD group and on 1 day for the control group. Spirometric and blood gas variables, and VO2 sl were measured in COPD patients on day 1. On day 2, spaced a week from day 1, the COPD group performed the other experiments such as the control group: subjects first underwent nutritional assessment between 8 and 9 AM. After breakfast, spirometric variables were measured for the control group. Subjects then were asked to respond to the questionnaire of physical activity. At the end of the morning, skeletal muscle performance was assessed.

Statistical Analysis

Statistical analysis was performed using statistical software (SigmaStat; Jandel Scientific; Erkrath, Germany). Statistical differences between the COPD and control groups were tested by an unpaired t test. If the equal variance test failed, we used a Mann-Whitney test. We analyzed relationships between skeletal muscle performance (MVC and Tlim) and PA score, FFM, FEV1, and PaO2 for COPD data using the Pearson correlation analysis, since the assumption of normal distribution was fulfilled for all the analyzed variables. Correlation analysis was also made between PA score and both VO2 sl and FEV1. Statistical significance was assumed for p<0.05. Values were expressed by their mean and with SE.

RESULTS

There were no significant differences between the COPD and control groups for anthropometric data (Table 1). Differences between the two groups could be observed for spirometric function and level of physical activity (Table 1).

Analysis of peripheral muscle performance showed no significant difference in MVC between the COPD group and the control group (22±1 kg vs 24±2 kg). In contrast, muscle endurance (Tlim) was significantly decreased in COPD patients compared with healthy subjects (Fig 2).

We found a significant relationship between MVC and FFM (r=0.57, p<0.05), Tlim and PA score (r=0.05) (Fig 3), Tlim and FEV1 (p<0.05) (Fig 4), and Tlim and PaO2 (p<0.05) (Table 2) in COPD patients. Significant correlations were also found between PA score and FEV1 (r=0.63, p<0.05), and VO2 sl (r=0.57, p<0.05), and between VO2 sl and MVC (r=0.59, p<0.05). No significant relationship was observed between VO2 sl and Tlim (r=0.31).

Table 1—Characteristics of Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>COPD (n=17)</th>
<th>Control (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>62±2</td>
<td>60±4</td>
</tr>
<tr>
<td>Height, cm</td>
<td>169±2</td>
<td>171±3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>71±4</td>
<td>77±3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25±1</td>
<td>26±1</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>54±2</td>
<td>61±2</td>
</tr>
<tr>
<td>FEV1, L</td>
<td>1.4±0.11</td>
<td>3.2±0.2</td>
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<tr>
<td>FEV1 % predicted</td>
<td>49±4</td>
<td>103±3</td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>53±3</td>
<td>78±5</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>78±2</td>
<td>78±2</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>39±1</td>
<td>–</td>
</tr>
<tr>
<td>PA score</td>
<td>5±1</td>
<td>10±2</td>
</tr>
</tbody>
</table>

*BMI= body mass index; values are expressed by their mean±SE.

1Significantly different from control value (p<0.001).

2Significantly different from control value (p<0.05).

FIGURE 2. Peripheral muscle endurance in COPD patients and control subjects. Values are expressed as mean (SE). Asterisk: significantly different from control value (p<0.05).

DISCUSSION

The major findings of this study are that (1) skeletal muscle endurance is impaired in COPD patients compared with healthy subjects; and that (2) skeletal muscle endurance is associated with level of daily physical activity and severity of airways obstruction. To study muscle endurance, we used local muscle exercise consisting of dynamic extension of the quadriceps at a regular pace. COPD patients performed a reduced number of contractions at a power output adapted from their own maximal...
strength. Since a subject’s motivation may determine attainment of maximal effort, the same investigator supervised the endurance test and gave the same encouragement to all subjects. Moreover, in a previous experiment consisting of repetitive tests with the same technique, Tlim was found to be highly reproducible since the correlation coefficients yielding Tlim and limit work were always >0.9.20 Furthermore, patients were not hypoxemic at rest and, during the incremental exercise test that involves a large part of the muscles, they did not present oxygen desaturation under 92%. It thus appears that during the endurance test involving one muscle group, the limiting factor cannot be oxygen availability, but rather the neuromuscular characteristics of the muscle.

Since deconditioning is a major problem often suggested as an explicative factor of exercise intolerance in patients, we thought it interesting to investigate the level of physical activity in our patients. Since our COPD population did not work because of age and/or pathology, we chose a questionnaire adapted for use in retired people with independent lifestyles.15 This questionnaire appears valid for COPD patients since we found a significant positive correlation between PA score and VO₂ sl. Patients had lower scores than the healthy subjects, who themselves had scores indicating sedentary lifestyles according to the questionnaire analysis.15 This result indicates a reduced level of daily physical activity in the patients and, to our knowledge, this is the first study of this variable in COPD patients.

Peripheral muscle weakness evidenced by reduced maximal strength of the quadriceps has been observed in COPD patients.8,9 However, skeletal muscle endurance assessment was not included in these studies. In the present work, we did not find maximal muscle strength to be significantly lower in patients compared with healthy subjects. This result, which contrasts with those of previous studies, could be surprising since the same muscular group, the quadriceps, was used for assessment of skeletal muscle performance. However, in the previous works, maximal quadriceps strength values in patients were compared with predicted values and not with those of a control group.

Our results showed that skeletal muscle endurance was decreased in COPD patients. A plausible explanation for this may be an abnormality of muscle metabolism. Indeed, the impaired muscle endurance is consistent with the metabolic changes commonly observed in skeletal muscle in COPD patients. Investigations of enzyme activities in the quadriceps femoris of these patients compared with those of control subjects demonstrated lower activity of an oxidative enzyme, the citrate synthase.21,22 Moreover, several earlier reports showed that during exercise, COPD subjects exhibited a higher inorganic phosphate-to-phosphocreatine ratio, which is an index of muscle oxidative capacity, and a lower intracellular pH than healthy control subjects.5,6 These results indicate impaired skeletal muscle aerobic capacity and suggest altered metabolic control with a metabolic shift toward dependence on lactic glycolysis. In a Tlim test, a rapid accumulation of metabolic byproducts in exercising muscle could be responsible for the decline of force and, therefore, could be responsible for muscular fatigue. For example, muscular fatigue has been attributed to in-
tracellular lactate accumulation, acidosis, or the increased concentration of inorganic phosphate.\(^{23,24}\) We investigated relationships between skeletal muscle performance and several variables (PA score, FFM, FEV\(_1\), and PaO\(_2\)) in COPD patients. Concerning skeletal muscle strength, we found a positive correlation between MVC and FFM. Since FFM is mainly composed of muscle cells, this result appears in agreement with the literature concerning maximal strength dependence on muscle cross-sectional area and anthropometric parameters.\(^{25}\) In contrast, no significant correlation was found between FFM and Tlim. This result indicates that the decreased muscle endurance was independent of the patient’s body composition. In agreement with this observation, an earlier study demonstrated that the altered oxidative muscle metabolism in COPD patients is not affected by their nutritional status.\(^{26}\)

An important mechanism of skeletal muscle alterations could be deconditioning. Indeed, the changes in skeletal muscle function described in COPD patients are the opposite of training and the same as the classic changes resulting from detraining.\(^{27,28}\) In agreement with a physical inactivity effect on skeletal muscle endurance, we found a significant relationship between Tlim and PA score. This result suggests that the level of PA is a determinant factor for muscle performance and, therefore, skeletal muscle alterations in COPD patients can be the result of deconditioning. We found skeletal muscle endurance also to be related to FEV\(_1\) and resting PaO\(_2\). Skeletal muscle function in relation to hypoxemia has been studied in COPD patients. Jakobsson et al.\(^{29}\) found significant correlations between muscle metabolite concentrations (glycogen, lactate, phosphocreatine) and PaO\(_2\). Moreover, Mannix et al.\(^{30}\) recently showed that the origin of adenosine triphosphate flux (oxidative phosphorylation or anaerobic glycolysis) in COPD patients is dependent on hypoxemia severity. The relations between Tlim and PaO\(_2\) and Tlim and FEV\(_1\) thus appear consistent with these findings, indicating the important role of altered lung function in limiting skeletal muscle function. Since FEV\(_1\) was also correlated with the patients’ scores, the reduced level of daily PA in the patients seems to be dependent on the severity of the disease. The interrelationships among Tlim, FEV\(_1\), and PA score suggest that these variables are cofactors that progress together, and this is in agreement with the secondary disease of deconditioning in patients described by the model of the dyspnea spiral.\(^{3,4}\) However, it is impossible to determine the respective parts of bronchial obstruction and deconditioning in altering skeletal muscle performance. Therefore, further studies matching healthy control subjects and COPD patients in terms of PA are needed to investigate the role of bronchial obstruction in altering skeletal muscle function.

In conclusion, our data demonstrated impaired skeletal muscle endurance in COPD patients that is associated with altered pulmonary function and reduced daily PA.

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