Muscle Strength and Exercise Kinetics in COPD Patients With a Normal Fat-Free Mass Index Are Comparable to Control Subjects*

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**Study objective:** This study was designed to investigate the extent of clinical muscle dysfunction in stable patients with COPD who were attending an out-patient pulmonary clinic compared with that of age-matched control subjects without COPD.

**Design and subjects:** Respiratory muscle and hand grip strength, steady-state O₂ kinetics, and body composition were measured in 32 patients with COPD (19 women) [mean (± SD) FEV₁, 38 ± 11% predicted] and 36 age-matched control subjects (13 women).

**Results:** Measurements of handgrip force (mean, 97 ± 32% vs 106 ± 26% predicted, respectively), maximal expiratory pressure (mean, 57 ± 33% vs 61 ± 22% predicted, respectively), steady-state O₂ kinetics (mean, 72 ± 34 s vs 78 ± 37 s, respectively) and steady-state CO₂ kinetics (mean, 77 ± 38 s vs 65 ± 32 s, respectively) at submaximal exercise were similar in patients and control subjects. All the subjects, except for one female COPD patient, had a normal fat-free mass index (FFMI), although on average the FFMI was lower in male patients (19.8 ± 2.8) than in male control subjects (23.0 ± 2.8; p < 0.01).

**Conclusions:** In patients with COPD who were attending a regular outpatient pulmonary clinic, there was no evidence of reduced upper extremity and expiratory muscle strength or prolonged O₂ and CO₂ kinetics during isowork submaximal cardiopulmonary exercise compared to healthy, age-matched control subjects. Also, a normal body composition was found in nearly all COPD patients. This argues against the existence of a clinically significant systemic myopathy in most stable patients with severe COPD and normal FFMI. *(CHEST 2003; 124:75–82)*

**Key words:** COPD; exercise kinetics; muscle strength; nutrition

**Abbreviations:** AT = anaerobic threshold; BMI = body mass index; CS = citrate synthetase; DLCO = diffusing capacity of the lung for carbon monoxide; FFM = fat-free mass; FFMI = fat-free mass index; HADH = 3-hydroxyacyl-CoA dehydrogenase; Pe,max = maximal expiratory pressure; Pi,max = maximal inspiratory pressure; τ = time constant; V₂CO₂ = carbon dioxide uptake; V₂O₂ = oxygen uptake; Wmax = maximal workload

Impaired exercise tolerance is common in patients with COPD. The impairment cannot be explained by ventilatory limitations and/or decreased diffusion capacity alone. Also, peripheral muscle dysfunction may play an important role, especially in patients with evidence of malnutrition.¹

The peripheral muscle abnormalities in COPD patients include atrophy, weakness, morphologic changes, and altered metabolic capacity. Bernard et al² found an average 30% decrease in thigh cross-sectional area in patients with moderate-to-severe COPD compared with age-matched healthy subjects. The loss of muscle mass was associated with weakness; however, the ratio of quadriceps strength to mid-thigh cross-sectional area was similar, sug-

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suggesting that atrophy is the major cause of the weakness. The morphologic changes in these patients were a reduction in type 1 muscle fibers with a reciprocal increase in type 2b fibers. These changes are consistent with a morphologic explanation for the physiologic observation of early fatigue during exercise.

In line with this finding, low activity for the oxidative enzymes citrate synthetase (CS) and 3-hydroxyacyl-CoA dehydrogenase (HADH) was shown in needle biopsy specimens of the vastus lateralis muscle of patients with COPD. At rest, there is a low intracellular pH, reduced phosphocreatine and adenosine triphosphate content as well as increased lactate content. During exercise, a greater decline in muscle intracellular pH and phosphocreatine/inorganic phosphate ratio was observed, even in patients with no reduction in peripheral oxygen delivery. This suggests that the altered muscle metabolism during exercise could be related to poor oxidative capacity and/or abnormal metabolic regulation. The nature of these observations remains controversial. However, due to the finding of elevated levels of inflammatory cytokines in many patients with COPD, it has become attractive to postulate the presence of a “systemic” myopathy in many patients with COPD.

Several observations argue against the presence of a systemic myopathy. First, not all muscles are affected to the same extent. Bernard and coworkers have shown that the strength of the upper extremities was relatively preserved compared with that of the lower extremities. Biopsy specimens from the diaphragms of patients with COPD were undergoing lung volume-reduction surgery showed an increase in fatigue-resistant fibers such as the slow isoforms of the myosin light and heavy chains I compared with those from control subjects. More recently, Gea and coworkers have demonstrated similar fiber compositions and mitochondrial content of CS, phosphofructokinase, and lactate dehydrogenase in the deltoid muscle of patients with COPD compared with those in control subjects, even though the former manifested the characteristic decrease in leg ergometry performance.

The difference between structure and function among different muscle groups could result from the difference in activity levels due to the demand placed on each muscle group. The upper limb muscles perform activities of daily life, and the diaphragm bears the increased work of breathing. Also, the fact that the oxidative capacity and the mitochondrial content of CS and HADH, as well as the anaerobic threshold (AT) improve after training supports the importance of deconditioning.

The results of studies on muscle function are difficult to compare for the following several reasons: small number of patients and control subjects, patient selection, such as the inclusion of patients receiving rehabilitation; comparison of older patients with younger control subjects; and O2 kinetics studied at high and different work rates or in a subgroup of hypoxemic COPD patients.

In addition, the data available on respiratory muscle function in COPD patients is also controversial. Maximal inspiratory pressure (Pimax) values often are reported to be lower due to hyperinflation. Maximal expiratory pressure (Pmax) values are usually normal, but decreased pressures are described in patients with COPD in whom systemic effects on muscle function have been suggested.

Therefore, the aim of our study was to investigate whether there was clinically significant evidence of generalized muscle dysfunction in a large group of outpatients with stable COPD. To achieve this aim, we compared noninvasive muscle strength parameters, steady-state oxygen and CO2 kinetics, and body composition in COPD patients with those in age-matched control subjects without COPD.

**Materials and Methods**

**Subjects**

We studied 68 subjects (36 men), of whom 32 had COPD and 36 were control subjects. The study was approved by the Institutional Review Board of St. Elizabeth’s Medical Center. All patients signed the informed consent form. COPD was defined using the standards of the American Thoracic Society. The inclusion criteria for this group were as follows: FEV1 < 55% predicted; age > 55 years; and stable disease after receiving medical treatment for at least 6 months. Exclusion criteria were as follows: chest or lung surgery; myocardial infarction within 6 months of study; ventilatory dependency; malignancy; congestive heart failure; hepatic cirrhosis; end-stage renal disease; and a history of psychiatric or neurologic illness that interfered with participation in the study. Patients were recruited from our outpatient pulmonary clinic. Control subjects were recruited by advertisement. Inclusion criteria were FEV1 and/or FEV1/FVC ratio of > 70% of the predicted value and age > 55 years. The exclusion criteria were the same as those for the COPD patients.

**Measurements**

**Pulmonary Function Testing:** Spirometry was performed with a dry seal spirometer (SensorMedics; Yorba Linda, CA) according to American Thoracic Society recommendations. Functional residual capacity was measured by body plethysmograph in COPD patients and by N2 uptake by helium dilution in control subjects.
Exercise Testing: Exercise testing was performed on a cycle ergometer while breathing room air (Vmax 29; SensorMedics). Minute ventilation, oxygen uptake (VO2) and carbon dioxide output (VCO2) were measured breath by breath. Heart rate was monitored by a 12-lead ECG. Subjects started with a 2-min resting period breathing through the mouthpiece. Then they started pedaling at a rate of 60 cycles per minute and a constant load of 9 W for 4 min to reach a steady state. After that, an incremental maximal exercise test was performed, increasing the workload by 16 W every minute until exhaustion to determine the maximal workload (Wmax), maximal VO2 and the AT by the V-slope method. To characterize the kinetic behavior of VO2 and VCO2 during phase II of steady-state exercise, the average response data for all subjects were fit by a least squares gradient algorithm to a first-order monoexponential model. The time constant (τ) [ie, the time to reach 63% of the steady-state response] was subsequently computed. At the end, all subjects were asked for the reason why they stopped the exercise (eg, leg fatigue, shortness of breath, both, or other).

Measurements of Muscle Strength: Pimax and Pemax were measured at residual volume and total lung capacity, respectively, according to the method described by Black and Hyatt. Handgrip was measured with a hand dynamometer (Jamar; Asimow Engineering Co; Santa Monica, CA). Three measurements were used to average the strength for the right and left hands.

Nutritional Evaluation

Height, weight, and body mass index (BMI) were obtained. A normal BMI was defined as 21–25, underweight was defined as a BMI of < 21, and overweight was defined as a BMI of > 25. An estimate of the fat-free mass (FFM) was made by bioelectrical impedance measuring reactance and resistance (RJL Quantum Systems, Inc; Harper, Clinton Township, MI) as described by Lukaski et al. An FFM index (FFMI) of ≤ 16 kg/m² for men and ≤ 15 kg/m² for women was defined as depletion.

Statistical Analysis

The data are expressed as the mean ± SD. The t test for independent samples was used to compare the two groups. The Fisher exact test was used to analyze the female/male distribution in both groups and the reasons for stopping the exercise test. Forward multiple regression analysis was performed to predict the VO2max in patients with COPD. A p value of < 0.05 was considered to be significant. The data were analyzed using a statistical software package (Statistica; Statsoft, Inc; Tulsa, OK).

Table 1—Control Subject and Patient Characteristics*

<table>
<thead>
<tr>
<th>Variable</th>
<th>COPD Patients (n = 32)</th>
<th>Control Subjects (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, No.</td>
<td>Female 19</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Male 13</td>
<td>23</td>
</tr>
<tr>
<td>Age, yr</td>
<td>66 (8)</td>
<td>63 (7)</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.67 (0.09)</td>
<td>1.71 (0.1)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72.7 (15.1)</td>
<td>81.6 (20.5)</td>
</tr>
<tr>
<td>BMI</td>
<td>25.9 (5.3)</td>
<td>27.5 (5.3)</td>
</tr>
<tr>
<td>FEV1_L</td>
<td>0.97 (0.29)</td>
<td>2.58 (0.50)</td>
</tr>
<tr>
<td>% predicted</td>
<td>38 (11)</td>
<td>80 (13)</td>
</tr>
<tr>
<td>FEV1/FVC, %</td>
<td>48 (10)</td>
<td>75 (6)</td>
</tr>
<tr>
<td>FRC, % predicted</td>
<td>161 (49)</td>
<td>97 (17)</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>122 (20)</td>
<td>96 (13)</td>
</tr>
<tr>
<td>DLco, % predicted</td>
<td>67 (20)</td>
<td>95 (18)</td>
</tr>
</tbody>
</table>

*Values given as mean (SD) unless otherwise indicated.

Pulmonary Function

As expected (Table 1), the patients with COPD were obstructed (ie, mean FEV1, 38 ± 11% predicted), had increased static lung volumes, and had decreased diffusion capacity.

Exercise Testing

In three patients with COPD, the exercise was not performed due to technical difficulties. These patients were similar in all parameters to the patients included in the analysis. Table 2 shows a difference in VO2 max, AT, and Wmax between patients and control subjects. The reason for discontinuing exercise differed between control subjects, who stopped mainly because of leg fatigue, and COPD patients, the majority of whom stopped because of dyspnea (p < 0.01 [Fisher exact test]). However, O2 and CO2 kinetics were not different between the groups (Fig 1). We could not determine AT in 17 patients and 4 control subjects.

Muscle Strength Measurements

The functional muscle measurements are shown in Table 3. The Pimax was lower in patients than in control subjects. The Pemax, handgrip strength, and the percentage of FFM of total body weight were the same in both groups. Respiratory muscle strength, handgrip strength, and FFM also were analyzed by gender. All COPD patients except one woman had significant (p = 0.09). Age did not differ between the groups. For both groups, the BMI was above normal.

RESULTS

General Characteristics

The characteristics of the patients and control subjects are shown in Table 1. The COPD patients were using the following medications: inhaled long-acting or short-acting β-agonists, 19 patients; inhaled anticholinergic agents, 16 patients; inhaled steroids, 13 patients; oral theophylline, 9 patients; and oral steroids (prednisone, 5, 8, and 15 mg), 3 patients. More women were included in the COPD group, however, this difference was not statistically signifi-
normal FFMI values. The FFM as well as the FFMI were lower in male patients with COPD compared to female patients with COPD. The handgrip strength did not differ between men and women in both groups.

Correlations

Correlations between exercise parameters and FEV₁, diffusing capacity of the lung for carbon monoxide (DLCO), FFMI, handgrip strength, and respiratory muscle strength in the COPD group are shown in Table 4. Significant correlations were found between exercise parameters and FFMI, FEV₁, DLCO, and Pemax. The result of the forward multiple regression analysis is shown in Table 5. The FFMI and DLCO explained 45% of the variance in VO₂max and can be modeled using the following regression equation:

\[
\dot{V}O_2_{\text{max}} (L/min) = -0.77 + 0.72 \text{FFMI} \\
+ 0.003 \text{DLCO (pred)}
\]

The correlation between the absolute FFM and handgrip strength in the COPD group was 0.53 (p < 0.01) [Fig 2].

Discussion

This study demonstrated that stable patients with COPD who attended a regular outpatient clinic have similar handgrip strength, Pemax values, and O₂ and CO₂ kinetics at submaximal exercise compared to age-matched control subjects. Furthermore, the normal values for FFMI and the similar values for BMI in both groups suggest that there is no overall malnutrition in the majority of stable outpatients with COPD, and that therefore malnutrition cannot be a major contributor to decreased exercise performance. As has been shown before, inspiratory muscle strength was lower in COPD patients.

The exercise tolerance of patients with COPD is decreased compared to that of healthy subjects. The reason for this is complex and involves changes in lung mechanics, cardiopulmonary interactions, central reflexes, and peripheral skeletal muscle performance. The patients reported here had severe airflow limitation and increased lung volumes. Given these mechanical limitations, it is not surprising that they had decreased exercise capacity compared to control subjects. Most patients (59%) complained that dyspnea was the main reason for stopping the exercise. This is different from the situation with control subjects, who stopped exercising primarily because of leg fatigue (69%). In the most frequently cited study,26 most patients with COPD stopped exercising because of leg fatigue. However, in that report patients with a wide range of airflow limitations were studied, thereby including many patients with mild and moderate COPD who more closely resemble healthy individuals. In contrast, our patients had more severe airflow limitation and were more representative of those patients in whom the findings of muscle biopsy specimen tests and physiologic studies have suggested the presence of peripheral muscle abnormalities.2–6,12 It is possible that the
lower inspiratory pressures, coupled with the inability to increase ventilation, contribute to dyspnea at peak exercise.\textsuperscript{27}

We further explored the function of the peripheral muscles in patients and control subjects. Surprisingly, at identical submaximal exercise load the kinetics for O\textsubscript{2} and CO\textsubscript{2} were similar in both groups (Table 2, Fig 1). This contrasts with the results reported by Nery et al,\textsuperscript{13} who showed prolonged O\textsubscript{2} kinetics in patients with COPD (56 s) compared to healthy subjects (39 s). However, the number of subjects in that study was small (six healthy subjects and nine COPD patients), the workload was high for patients with COPD (40 W to compare absolute work rate) and dissimilar (COPD patients, 40 W; control subjects, 70 W) to compare the relative work rates using 80% of the control subjects at the AT. In addition, the subjects were younger (control subjects, 53 years of age; COPD patients, 58 years of age) than our patients. Our results also differ from those of Palange et al\textsuperscript{14} who showed a longer \(\tau\) V\textsubscript{O2} in COPD patients (116 s) compared to control subjects (49 s). However, the nine COPD patients in that study were all hypoxemic, and only six control subjects were used. In addition, exercise was performed at different loads (patients with COPD, 24 W; control subjects, 50 W). We believe that the larger number of patients and appropriate age-matched control subjects reported on here are the most likely explanations for the observed differences among the studies. In addition, we offered the same workload to both groups. Although the actual work rate was low, this level was chosen because it was the highest workload tolerated by patients with the most severe disease, thereby allowing for isowork comparisons.

The controversy over the presence and role of a specific myopathy in exercise limitations can be extended to the cellular level. The results of muscle biopsy studies evaluating oxidative and glycolytic enzymes are conflicting. Maltais et al\textsuperscript{4} showed that the activity of oxidative enzymes was lower while that of glycolytic enzymes did not differ between patients with COPD and control subjects. This is in contrast with the findings of Jakobsson et al\textsuperscript{28} who found higher levels of phosphofructokinase and lactate dehydrogenase, but also lower levels of oxidative

\begin{figure}
\centering
\includegraphics{figure1.png}
\caption{The time taken by O\textsubscript{2} and CO\textsubscript{2} to reach 63\% of the steady state (\(\tau\)) was similar in patients with COPD and control subjects.}
\end{figure}

\begin{table}
\centering
\caption{Correlation Coefficients Between Exercise Parameters, Pulmonary Function Tests, FFMI, Handgrip Strength, and Respiratory Muscle Strength in Patients With COPD\textsuperscript{a}}
\begin{tabular}{lcccccc}
\hline
Variables & FEV\textsubscript{1}, \% Predicted & DL\textsubscript{CO}, \% Predicted & FFMI, kg/m\textsuperscript{2} & Handgrip Strength, \% Predicted & P\textsubbox{max}, \% Predicted & P\textsubbox{max}, \% Predicted \\
\hline
V\textsubscript{O2,max} & 0.25 & 0.33 & 0.65\textdagger & 0.12 & 0.12 & 0.23 \\
L/min & 0.44\ddagger & 0.52\ddagger & 0.28 & -0.08 & 0.40\dagger & 0.51\dagger \\
W\textsubscript{max}, W & 0.16 & 0.20 & 0.34 & 0.11 & 0.20 & 0.19 \\
\hline
\textsuperscript{a}V\textsubscript{O2,max} = maximal V\textsubscript{O2}.
\textsuperscript{\dagger}p < 0.001.
\textsuperscript{\ddagger}p < 0.05.
\textsuperscript{\dagger}p < 0.01.
\end{tabular}
\end{table}
enzymes, although the decrease of HADH did not reach significance in COPD patients. In a couple of studies using tibialis anterior or deltoidus muscle biopsy specimens, no differences in oxidative and glycolytic enzyme capacities were found between COPD patients, with and without prednisolone use, and healthy control subjects.\textsuperscript{10,29} Furthermore, Levine et al\textsuperscript{9} showed that in patients with severe COPD, there was an increase of slow-twitch, heavy-chain 1 fibers and a decrease of fast myosin, heavy-chain type 2A and 2B fibers in the diaphragm of patients with severe COPD compared to those in control subjects.\textsuperscript{3} In contrast, an increase of type 2B fibers was seen in quadriceps muscle biopsy specimens from patients with COPD.\textsuperscript{3} The differences among the studies are difficult to explain. The results seem to indicate that, if present, the myopathy may not be expressed equally across different muscle groups, with arm muscles and diaphragm better preserved, perhaps reflecting their continuous use despite disease progression.

To gain further insight into the clinical relevance of the muscle dysfunction, we extended our observations to other muscle groups. We found that $P_{\text{tmax}}$ was similar in patients and control subjects. This is in agreement with other reports.\textsuperscript{15} However, it might be decreased in other patients with COPD in whom systemic effects on muscle strength may be present.\textsuperscript{16} $P_{\text{tmax}}$ was lower in patients compared with control subjects in another report,\textsuperscript{15} most likely due to lung hyperinflation.\textsuperscript{30}

The handgrip strength did not differ between healthy subjects and patients with COPD. This is in contrast with the results of Engelen et al.\textsuperscript{31} But, in the latter study, 20\% of the COPD patients were nutritionally depleted. It is not surprising that a lower handgrip strength was found in that malnourished group. In our study, male COPD patients had a lower FFMI than did control subjects, but in all men the FFMI was normal (ie, $>16$ kg/m$^2$). The BMI and FFMI values of our COPD patients were in the same range as the BMI and FFMI of the healthy volunteers in the study of Engelen et al.\textsuperscript{31} However, we observed a correlation between FFM and handgrip strength ($r = 0.53$). Gosselink et al\textsuperscript{32} found reduced handgrip strength in COPD patients, but those findings were not compared to those of healthy, age-matched control subjects, and no body composition measurements were performed. Bernard et al\textsuperscript{2} compared the strength of different peripheral muscles such as the quadriceps, the pectoralis major, and the latissimus dorsi. The strength was lower in COPD patients, but, after correcting the strength of the quadriceps femoris for cross-sectional area, the difference disappeared. All of these findings taken together suggest that handgrip

![Figure 2: Correlation between handgrip strength and FFM in patients with COPD.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21996/)
strength is normal in those patients in whom FFM is preserved. In those patients in whom FFM decreases (such as in some of our men with COPD), the handgrip force may be affected. This finding underlines the importance of not simply relying on the body weight or the BMI of the patient. It also may be helpful to measure the FFM with relatively simple tools such as bioimpedance and/or handgrip strength.

The importance of overall muscle mass also is shown by the evaluation of the different factors that helped to explain the exercise capacity (VO₂ max). Using multiple logistic regression (Table 5), 45% of the variance in VO₂ max was explained by a combination of FFMI and diffusion capacity. These results further expand and support those of Baarends et al., who were able to explain 53% of the variance in maximal VO₂ by a model combining the FFMI and the DLCO. Our findings support the schematic concept proposed by Baarends et al., who suggested that patients with COPD should be evaluated for their body mass composition. The small but important group of patients with a decreased FFM then could be targeted for specific therapy such as nutrition, targeted exercise, and/or anabolic steroids.

An important limitation of our study might be that we did not measure quadriceps strength, because most morphologic studies were performed on the quadriceps femoris muscle. However, even if we had found a decreased quadriceps strength in COPD patients, a systemic myopathy is still unlikely because of the preserved handgrip and expiratory muscle strength and O₂ kinetics. Furthermore, Serres et al. reported no differences in quadriceps strength between COPD patients and age-matched control subjects, thus supporting our findings. Bernard and coworkers, who described lower quadriceps strength in COPD patients, observed that after correction for the cross-sectional area this difference disappeared. Finally, Engelen et al. also described a lower quadriceps strength, but this disappeared after correction for FFM. Therefore, the lack of measurement of quadriceps strength, as desirable as it would have been, does not affect our observations. It also could be argued that the study was not powered to detect a difference in some of the variables explored. However, the number of patients and control subjects evaluated in our study was three times larger than that of the positive studies frequently cited. In addition, assuming the same mean value for O₂ and CO₂ kinetics, > 200 patients would have been needed to detect a 10% difference. The clinical relevance of a statistical difference that requires > 200 patients to be demonstrated might be questionable.

In summary, we conclude that there is no clinical evidence of reduced expiratory muscle strength or upper extremity muscle strength in COPD patients with normal FFMI values. These findings and the fact that the O₂ and CO₂ kinetics for lower extremity exercise did not differ between patients and matched control subjects suggest that a systemic myopathy is unlikely in most patients with COPD and a preserved muscle mass. Our findings support the schematic concept that patients with COPD should be evaluated for their body mass composition beyond the BMI. The small but important group of patients with a decreased FFM then could be targeted for specific therapy such as nutrition, targeted exercise, and/or anabolic steroids.

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