Effects of Whole-Body Exercise Training on Body Composition and Functional Capacity in Normal-Weight Patients With COPD*

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Background: Skeletal muscle wasting is related to muscle dysfunction, exercise intolerance, and increased mortality risk in patients with COPD.

Study objectives: The aims of this study were to investigate the effects of whole-body exercise training on body composition in normal-weight patients with COPD, and to study the relationship between changes in body composition and functional capacity.

Setting and participants: Fifty patients with COPD (FEV1, 39% of predicted [SD, 16]) admitted to the pulmonary rehabilitation center at Hornerheide, and 36 healthy age-matched control subjects (for baseline comparison) were included.

Interventions: Patients participated in a standardized inpatient exercise training program consisting of daily submaximal cycle ergometry, treadmill walking, weight training, and gymnastics during 8 weeks.

Measurements: Fat-free mass (FFM) was measured by bioelectrical impedance analysis. None of the patients met the criteria for nutritional supplementation (body mass index < 21, or FFM index < 15 kg/m² in women and < 16 kg/m² in men). Exercise capacity was measured using incremental cycle ergometry. Isokinetic quadriceps strength was measured with a Biodex dynamometer (Biodex Medical Corporation; Shirley, NY).

Results: At baseline, patients were characterized by a significantly lower FFM than the control subjects. Age and FFM were independent predictors of skeletal muscle function and exercise capacity in patients. After rehabilitation, weight (72.4 ± 9.8 to 73.0 ± 9.4 kg, p < 0.05) significantly increased, as a result of increased FFM (52.4 ± 7.3 to 53.4 ± 7.7 kg, p < 0.05), while fat mass (20.0 ± 6.1 to 19.6 ± 5.7 kg) tended to decrease. Peak work rate (63 ± 29 to 84 ± 42 W, p < 0.001), maximal oxygen consumption (VO2max) [1,028 ± 307 to 1,229 ± 421 mL/min, p < 0.001], and isokinetic quadriceps strength (82.5 ± 36.4 to 90.3 ± 34.9 Newton-meters, p < 0.05) all improved. Changes in FFM were proportionally smaller than functional improvements, and were related to changes in VO2max (r = 0.361, p < 0.05), but not to other changes in functional capacity.

Conclusions: Intensive exercise training per se is able to induce an anabolic response in normal-weight patients with COPD classified into Global Initiative for Chronic Obstructive Lung Disease stages III-IV. Improvements in exercise performance and muscle function are proportionally larger than increases in FFM.

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Key words: aging; anabolic stimulation; body composition; COPD; exercise capacity; exercise training; fat-free mass; muscle strength

Abbreviations: BMI = body mass index; DLCO = diffusing capacity of the lung for carbon monoxide; FFM = fat-free mass; NS = not significant; VO2max = maximal oxygen consumption; Wmax = maximal work rate

Muscle wasting is a common systemic manifestation in patients with advanced COPD. Reductions in fat-free mass (FFM), as an indirect measure of muscle mass, may be a result of weight loss, but may also occur disproportionate to weight loss and in a substantial proportion of patients with a normal body weight.¹ ² Loss of muscle mass has been related to skeletal muscle dysfunction³ and exercise intolerance⁴ in these patients. Moreover, weight loss and skeletal muscle mass are strong predictors of mortality risk in COPD,⁵ ⁶ independent of the degree of airflow limitation.

Weight loss and muscle wasting have long been considered irreversible terminal events in the pro-
gression of COPD. However, in the last decades several investigators have challenged this concept and showed positive effects of anabolic interventions such as caloric supplementation as an integrated part of a pulmonary rehabilitation program and anabolic agents. One study,3 furthermore, showed that weight gain is associated with increased survival in these patients. Until now, most studies investigated body weight and body composition changes only in malnourished patients. Recently, however, the prognostic importance of weight change was also shown in normal-weight patients.7 and in another study6 muscle mass was even more closely related to survival than body weight in normal-weight patients with COPD. However, instead of caloric intervention, exercise is the first option in normal-weight, stable patients to increase muscle mass. Therefore, the first aim of the present study was to investigate if whole-body exercise per se is able to induce anabolism in these patients.

Based on the relationship between muscle wasting and functional capacity, it can be hypothesized that improvements in exercise capacity and muscle function after exercise training programs in COPD are related to changes in body composition. This relationship, however, is yet unclear in COPD, due to a lack of studies on the effects of exercise training in COPD that included detailed measurements of changes in body composition. Therefore, the second aim of this study was to investigate the relationship between changes in exercise performance, muscle function, and muscle mass.

**Materials and Methods**

**Participants**

The study group consisted of 50 patients with moderate-to-severe COPD* consecutively admitted to Asthma Center Hornerheide for an intensive inpatient pulmonary rehabilitation program. Baseline characteristics are presented in Table 1. For inclusion, FEV₁ had to be < 70% of the reference value and the increase in FEV₁ after inhalation of a β₂-agonist had to be < 10% of the reference value. None of the patients met the criteria for nutritional supplementation, which were defined as body mass index (BMI) ≤ 21 and/or FFM index ≤ 15 kg/m² (women) or ≤ 16 kg/m² (men). Patients in clinically unstable condition were excluded from participation in the study. Other exclusion criteria were malignancies, clinically apparent heart failure, renal, hepatic or GI abnormalities, insulin-dependent diabetes mellitus, inflammatory disease, and recent surgery. Patients were receiving one of the following pulmonary maintenance medications: inhaled β₂-adrenoceptor agonists and short-acting anticholinergics, 76%; anticholinergics by inhalation, 78%; combined inhalers of short-acting β₂-adrenoceptor agonists and short-acting anticholinergics, 18%; inhalation corticosteroids, 60%; combined inhalers of β₂-sympathomimetics and corticosteroids, 22%; and oral N-acetylcysteine, 66%. At the time of admission to the pulmonary rehabilitation center, 16% of patients were current smokers, 78% were ex-smokers, and 6% were nonsmokers. Smoking was not allowed during the entire rehabilitation period. Smoking history of the current smokers (52 ± 18 pack-years [± SD]) was significantly increased compared to that of ex-smokers (33 ± 20 pack-years, p < 0.05), while there were no significant differences in age, body composition, lung function, or functional capacity between these two groups. Also, the responses to exercise training were comparable in both groups.

Thirty-six, age-matched healthy volunteers were recruited from an advertisement in a local newspaper for baseline comparison of the study. Other exclusion criteria were malignancies, clinically apparent heart failure, renal, hepatic or GI abnormalities, insulin-dependent diabetes mellitus, inflammatory disease, and recent surgery. Patients were receiving the following pulmonary maintenance medications: inhaled short- and long-acting β₂-adrenoceptor agonists, 76%; anticholinergics by inhalation, 78%; combined inhalers of short-acting β₂-adrenoceptor agonists and short-acting anticholinergics, 18%; inhalation corticosteroids, 60%; combined inhalers of β₂-sympathomimetics and corticosteroids, 22%; and oral N-acetylcysteine, 66%. At the time of admission to the pulmonary rehabilitation center, 16% of patients were current smokers, 78% were ex-smokers, and 6% were nonsmokers. Smoking was not allowed during the entire rehabilitation period. Smoking history of the current smokers (52 ± 18 pack-years [± SD]) was significantly increased compared to that of ex-smokers (33 ± 20 pack-years, p < 0.05), while there were no significant differences in age, body composition, lung function, or functional capacity between these two groups. Also, the responses to exercise training were comparable in both groups.

**Study Design**

Patients were included within the first 2 weeks after admission to the pulmonary rehabilitation center. During this period,

**Table 1—Baseline Characteristics of the Study Groups**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Subjects</th>
<th>COPD Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (male/female), No.</td>
<td>36 (24/12)</td>
<td>50 (37/13)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>61 ± 6</td>
<td>64 ± 9</td>
</tr>
<tr>
<td>Height, cm</td>
<td>171.9 ± 9.3</td>
<td>169.9 ± 7.0</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78.4 ± 11.6</td>
<td>72.4 ± 9.7</td>
</tr>
<tr>
<td>BMI</td>
<td>26.4 ± 2.5</td>
<td>25.0 ± 2.8</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>58.7 ± 10.8</td>
<td>52.4 ± 7.1</td>
</tr>
<tr>
<td>FFM index, kg/m²</td>
<td>19.7 ± 2.1</td>
<td>18.1 ± 1.5</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>19.8 ± 7.4</td>
<td>20.0 ± 6.0</td>
</tr>
<tr>
<td>Pulmonary function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>111 ± 17</td>
<td>38 ± 16</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>116 ± 15</td>
<td>77 ± 20</td>
</tr>
<tr>
<td>Total lung capacity, % predicted</td>
<td>107 ± 10</td>
<td>113 ± 17</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>112 ± 17</td>
<td>56 ± 21</td>
</tr>
<tr>
<td>PaO₂, kPa</td>
<td>9.3 ± 1.1</td>
<td>3.4 ± 0.9</td>
</tr>
<tr>
<td>PaCO₂, kPa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional capacity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak work rate, W</td>
<td>198 ± 66</td>
<td>63 ± 29</td>
</tr>
<tr>
<td>VO₂max, mL/min</td>
<td>2.129 ± 0.68</td>
<td>1.028 ± 0.30</td>
</tr>
<tr>
<td>VO₂max/FFM, mL/kg/min</td>
<td>36.5 ± 6.5</td>
<td>19.3 ± 4.7</td>
</tr>
<tr>
<td>Quadriceps strength, Newton-meters</td>
<td>118 ± 37</td>
<td>83 ± 36</td>
</tr>
<tr>
<td>Quadriceps strength/FFM, Newton-meters/kg</td>
<td>2.00 ± 0.42</td>
<td>1.55 ± 0.57</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated. p < 0.05, vs control subjects. §p < 0.01, vs control subjects. †p < 0.001, vs control subjects.
Subjects underwent medical examination by a chest physician, and the baseline measurements of pulmonary function, body composition, exercise performance, and muscle function were performed. Furthermore, this 2-week period allowed for familiarization with the various procedures in order to avoid learning effects.

After 2 weeks, patients participated in a comprehensive inpatient respiratory rehabilitation program consisting of exercise training during 5 days, education, and (when appropriate) psychosocial and behavioral intervention. During their stay in the rehabilitation center, a standardized weight maintaining diet was offered to all patients. The aimed daily dietary protein intake was 60 to 80 g. No additional nutritional supplements or anabolic agents were used. The physical exercise training program consisted of a combination of endurance and strength exercise training. Submaximal cycle ergometry was performed for 20 min/d. Initial load was set at 50 to 60% of baseline maximal work rate (Wmax). Thereafter, training intensity was adapted to maintain the same relative training load during the intervention period under supervision of an exercise therapist. In addition, patients exercised on a treadmill for 20 min/d just below their symptom-limited rate. All patients participated in daily 30 min of gymnastics focused at either strength and endurance or mobilization and flexibility. Furthermore, patients attended daily unsupported arm exercise training sessions, consisting of 10 times 1 min of exercise, followed by 1 min of rest. Dynamic strength training exercises of the upper and lower extremities were incorporated in the program. Muscle groups, load, and number of repetitions were determined for each individual and were based on the experienced functional impairments in daily living and evaluation of the muscular performance by a team of experienced physiotherapists.

Assessments

Pulmonary Function: Lung function testing included forced spirometry and assessment of lung volumes by whole-body plethysmography (MasterLab; Jaeger; Wurzburg, Germany). FEV1 and FVC were calculated from the flow-volume curves. The highest values of at least three measurements were used. Maximal voluntary ventilation was indirectly estimated from FEV1. Diffusing capacity of the lung for carbon monoxide (DLCO) was measured by the single-breath method (Masterlab). Instruments were calibrated twice daily. All values obtained were expressed as a percentage of reference values. Arterial blood gas analysis was performed in all patients at rest (ABL 330; Radiometer; Copenhagen, Denmark).

Anthropometry: In patients with COPD, anthropometric measurements were performed on pulmonary rehabilitation program admission and after 2, 4, 6, and 8 weeks of exercise training. Body height was determined to the nearest 0.5 cm (WM 715; Lameris; Breukelen, the Netherlands) with subjects standing barefoot. Body weight was measured with a beam scale (SECA; Hamburg, Germany) without shoes and in light clothing to the nearest 0.1 kg. Body mass index (BMI) was calculated as the ratio of weight to height in meters squared. FFM was measured by bioelectrical impedance analysis at a frequency of 50 kHz (Xitron 4000h; Xitron Technologies; San Diego, CA). Resistance was measured in supine position at the right side as described by Lukaski et al. A patient specific regression equation, described by Schols et al., was used to calculate FFM in patients with COPD. FFM index was calculated as the ratio of FFM to height in meters squared.

Exercise Capacity: At baseline and after 8 weeks, all patients performed an incremental exercise test on an electrically braked cycle ergometer (Corival 400; Lode; Groningen, the Netherlands) under supervision of a chest physician. Before the start of the test, while seated on the cycle ergometer, ventilation characteristics at rest were analyzed during 2 min. During the entire exercise test, expired gases were investigated using breath-by-breath analysis through a breathing mask (Oxycon Beta; Jaeger). Heart rate, BP, and percutaneous oxygen saturation were monitored. After 1 min of unloaded cycling, power was increased in patients by 10 W every minute. In control subjects, the load was increased with 15 to 25 W every minute, so that the duration of the test was equal in patients and control subjects. None of the subjects knew the exercise load, and all were encouraged to cycle at 60 revolutions per minute until exhaustion.

Skeletal Muscle Strength: Isokinetic quadriceps strength of the dominant leg was measured using a Biodex dynamometer (Biodex Medical Corporation; Shirley, NY) before and after the training program. The testing protocol consisted of 15 sequential maximal voluntary contractions at an angular velocity of 90°/s. Quadriceps strength was defined as the highest peak torque in this series of 15. During the test, subjects were seated upright on the chair of the dynamometer with support of the back. At the level of the chest, pelvis, and thigh, subjects were restrained with straps. The hip joint was at an angle between 90° and 100° of flexion during testing. The lever arm was attached to the distal part of the tibia, and its axis of rotation was visually aligned with the anatomical axis of flexion of the knee joint. Subjects were instructed to keep their hands on their thighs during testing. In order to avoid learning effects, all subjects practiced on the dynamometer under supervision of a physiotherapist the day before the actual test.

Statistical Analysis

Results are expressed as mean ± SD, unless indicated otherwise. Statistical analysis on baseline differences between patients and control subjects was performed using an unpaired Student t test. Changes within the COPD group between baseline and week 8 were tested with a Student paired t test for dependent samples. A Pearson correlation analysis was performed in the patient group in order to investigate linear relationship between variables of (changes in) body composition and (changes in) exercise capacity and muscle function. Multiple stepwise regression analysis was used to identify independent predictors of exercise performance and quadriceps strength. All p values < 0.05 were considered statistically significant.

Results

Baseline characteristics of the study groups are presented in Table 1. Fifty patients (37 men and 13 women) met the selection criteria and were enrolled in the study. Mean age of the patients with COPD was 64 years. BMI averaged 25.0, and mean FFM index was 18.1 kg/m², which indicates that the patients had a normal body weight and FFM and were not eligible for nutritional supplementation. However, BMI of the patients was significantly reduced in comparison to the 36 age-matched control subjects, as a result of a 6.3-kg difference in FFM (p < 0.01), despite a comparable fat mass. On average, patients had moderate-to-severe airflow obstruction with hyperinflation and reduced DLCO. Group values for PaO2 and PaCO2 were within the normal limits. Six patients received long-term oxygen therapy.

At baseline, exercise capacity and quadriceps strength of patients were significantly reduced...
compared to control subjects. These differences in functional exercise capacity also existed after correction for FFM.

In bivariate correlation analysis in the COPD group, age, FFM, FEV₁, DLCO, and PaO₂ all significantly correlated with maximal oxygen consumption (VO₂max) and Wmax (data not shown). These parameters were entered in a stepwise regression model with VO₂max as dependent variable (Table 2). FFM alone accounted for 35% of the variation in VO₂max, and in combination with age and DLCO explained 56% of variation in VO₂max. FEV₁ and PaO₂ were excluded. When entering Wmax as dependent variable, FFM, age, FEV₁, and DLCO all individually contributed and explained 49% of variation. Furthermore, FFM and age of patients, but none of the variables of pulmonary function, were independently related to isokinetic quadriceps strength with a total adjusted $r^2$ of 0.50. FFM and age were not mutually correlated ($r = -0.024, p = 0.868$). Also, isokinetic quadriceps strength was related to VO₂max and Wmax ($r = 0.54$ and $r = 0.40$, respectively; $p < 0.01$) at baseline.

Changes in body composition after 8 weeks of exercise training are shown in Figure 1. After training, body weight increased as a result of an increase in FFM from 52.4 ± 7.3 to 53.4 ± 7.7 kg ($p < 0.05$). There was a slight decrease in fat mass by 0.4 kg (not significant [NS]). Forty-six percent and 58% of the gain in body weight and FFM, respectively, were achieved in the last 2 weeks of the intervention period. Exercise performance was significantly enhanced during the training period, as indicated by the 35% increase in peak work rate ($p < 0.001$) and 17% increase in VO₂max ($p < 0.001$; Fig 2, top left, A, and top right, B). The relative increase in Wmax was greater than the improvement in VO₂max ($p < 0.01$). Patients with COPD demonstrated a 30% improvement in quadriceps strength ($p < 0.05$), as shown in Figure 2 (bottom, C).

Changes in FFM correlated significantly with changes in VO₂max, but not with changes of Wmax or quadriceps strength (Fig 3). Changes in VO₂max and Wmax were mutually related ($r = 0.644, p < 0.001$). Changes in VO₂max, Wmax, or quadriceps strength were not related to age of the patients with COPD, ie, older patients showed a comparable anabolic response than younger patients (data not shown).

**Table 2—Results of Stepwise Regression Analysis for Baseline Exercise Capacity and Quadriceps Strength in Patients With COPD***

<table>
<thead>
<tr>
<th>Variables</th>
<th>VO₂max, mL/min</th>
<th>Wmax, W</th>
<th>Quadriceps Strength, Newton-Meters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>-0.37†</td>
<td>-0.43‡</td>
<td>-0.33†</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>0.55†</td>
<td>0.22‡</td>
<td>0.63†</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>NS</td>
<td>0.37‡</td>
<td>NS</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>0.33‡</td>
<td>0.25‡</td>
<td>NS</td>
</tr>
<tr>
<td>PaO₂₂</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Partial $r$ values are shown.
†$p < 0.01$.
‡$p < 0.001$.
§$p < 0.05$.

**Discussion**

The results of the present study indicated that intensive exercise training *per se* is able to induce an anabolic response in normal-weight patients with COPD. After 8 weeks of whole-body exercise training, body weight increased as a result of increased FFM, while body fat tended to decrease. Although exercise performance and muscle strength were strongly related to skeletal muscle mass at baseline, changes in functional capacity after the training program were only partially related to changes in body composition. Finally, it was shown that age is a predictor of baseline functional capacity in patients with COPD, independent of FFM and pulmonary function, but not of the response to rehabilitation.

**Exercise as Anabolic Stimulus**

Improvements in exercise performance, peripheral muscle function, and quality of life after exercise training in patients with COPD are well documented. However, the influence of exercise training *per se* on body composition has rarely been studied in COPD. In the present study, body weight and FFM increased in normal-weight patients after a balanced exercise training program of both endurance as well as strength training. This suggests that exercise training can act as an anabolic stimulus in these patients. These results are in accordance with a study by Bernard et al, who reported enhanced bilateral mid thigh muscle cross-sectional area, a measure of skeletal muscle mass, assessed by CT after 12 weeks of aerobic training combined with strength training in normal-weight patients with COPD. However, BMI did not change in their group. The changes in body composition reported in this study are similar to those reported after exercise conditioning in healthy elderly subjects. Besides improved muscle function, Frontera et al described 0.5-kg and 1.0-kg increases in body weight and FFM, respectively, after 12 weeks of strength training in untrained healthy older men. In general, the ability of exercise to induce changes in body weight, FFM, and fat mass is affected by various factors, including the type, intensity, frequency, and
Traditionally, whole-body endurance training played a central role in pulmonary rehabilitation. In order to reverse muscle weakness and increase muscle mass, however, resistance training might be more effective and various combined training regimens are currently being implemented in respiratory rehabilitation in patients with COPD. The results of this study confirm that a combination of whole-body exercise training and resistance training is effective in improving functional exercise capacity and muscle strength in patients with COPD.
of whole-body endurance training and strength training results in improved physiologic function, but may also increase FFM.

Clinical Implications of Muscle Wasting in Normal-Weight Patients With COPD

The results of this study in normal-weight patients are different from findings in depleted patients with COPD. Schols et al17 studied the effects of nutritional intervention vs placebo treatment embedded in the same pulmonary rehabilitation program in both depleted as well as nondepleted patients with COPD. Depleted patients who did not receive nutritional support showed no significant changes in body weight, FFM, or respiratory muscle function after 8 weeks of whole-body exercise training. In this group, FFM even tended to decrease by 0.6 kg. A subsequent study by Creutzberg et al18 showed that nutritional supplementation therapy implemented in a pulmonary rehabilitation program resulted in improved body composition, exercise performance, muscle function, and quality of life in depleted or weight-losing patients with COPD. The discrepancy in response to exercise training between depleted and nondepleted patients might be related to enhanced protein catabolism in depleted patients with COPD.19 In order to induce an anabolic response in depleted patients, extensive nutritional support, including caloric supplements and anabolic agents, is probably indicated, whereas this study shows that less intervening physiologic interventions are sufficient in normal-weight patients.

Although the patients with COPD in this study had a normal body weight and were not eligible for nutritional support, their BMI was significantly lower than that of the age-matched control subjects. This difference in body weight resulted from a significantly lower FFM in patients, despite a comparable fat mass. These baseline results once again indicate that loss of FFM may occur in normal-weight patients, and that nutritional assessment in patients with COPD should include measurements of both body weight and FFM.

Relationship Between Functional Improvements and Changes in Body Composition

In the present study, changes in functional capacity were only in part related to changes in FFM, although at baseline FFM was a strong predictor of cycling performance and quadriceps strength. Also, the increase in FFM (2%, p < 0.05) was insufficient to account for the increases in VO2max, Wmax, and strength. Despite the lack of correlation, the vast majority of patients showed enhanced functional capacity, FFM, or both (Fig 3). Several possible explanations may account for the absence of a direct relationship between improvements in muscle mass and functional capacity. In the present study, whole-body FFM was used as an indirect measure of muscle mass. Local increase in quadriceps muscle bulk as a result of exercise training was not assessed and may have been underestimated by the use of bioelectrical impedance analysis. It was previously reported that quadriceps muscle quantity and...
Determinants of Functional Capacity

FFM was strongly related to exercise capacity and muscle strength, which is in accordance with earlier studies. In the previously mentioned study of Bernard et al, quadriceps muscle mass was assessed before and after exercise training. Correlations between changes in quadriceps muscle cross-sectional area and functional improvements, however, were not mentioned. Low sensitivity of bioelectrical impedance analysis to detect local changes and redistributions in muscle mass probably plays a minor role in the nonexistence of a relationship between changes in muscle structure and functional capacity. In accordance with the present results, several investigations in healthy subjects showed that gains in muscle strength after resistance training were not related to local muscle hypertrophy, and that increments in strength were proportionally greater than increases in muscle bulk.

In addition to an increase in FFM, exercise training induces intrinsic alterations in skeletal muscle, such as increments in mitochondria or oxidative enzymes, which contribute to the improved physiologic function and may explain the lack of correlation between increased FFM and functional capacity. Furthermore, as a result of exercise training, patients with COPD might have developed the ability to increase motor-unit recruitment during exercise, and thereby performance might have increased more than muscle mass. Others also suggested a contribution of neurologic factors to functional improvements after training in elderly. Finally, decreased exertional dyspnea and anxiety to engage in exercise and increased motivation after pulmonary rehabilitation may also have contributed to the disproportionate gain in functional capacity, compared to FFM. In order to further investigate the possible mechanisms whereby functional capacity might be increased more than muscle mass, future studies are necessary. A prospective study consisting of a combination of local assessments of muscle mass, muscle biopsies, and nonvolitional strength measurements before and after an exercise training program would be able to discriminate between the mentioned factors.

Changes in FFM were positively related to changes in \( \text{V}O_2 \text{max} \), but not to changes in \( W_{\text{max}} \), although improvements in functional parameters were strongly correlated. The reason for this discrepancy is not readily apparent. The facts that muscle mass is the metabolically active tissue and that the effort to exercise influences peak work rate more than oxygen consumption probably contribute to this observation.

FFM was strongly related to exercise capacity and muscle strength, which is in accordance with earlier studies. In keeping with the conclusions of Hamilton et al, quadriceps strength was related to maximal work capacity. Loss of muscle mass and redistribution of fat mass with age have been demonstrated and are referred to as sarcopenia. Also, the normal aging process is accompanied by a decline in functional capacity. Frontera et al observed reduced muscle strength in 65- to 78-year-old men and women compared to younger subjects. When adjusted for FFM, estimated from hydrostatic weighing, age-related differences disappeared, indicating that loss of muscle mass is the most important determinant of age-related differences in skeletal muscle strength. Reduced muscle mass and strength also contribute to the decrease in maximal aerobic exercise capacity that occurs during aging. In the present cross-sectional study in 43- to 78-year-old patients with COPD, advanced age was negatively related to muscle function and exercise capacity. Moreover, stepwise regression analysis showed that the relationship between age and functional capacity was independent of the influence of FFM. Also, no mutual correlation was observed between FFM and age. These results suggest that age-related factors, other than loss of FFM, contribute to disability in patients with advanced COPD, and that the course of the aging process may be different in COPD compared with healthy subjects. Potential factors contributing to age-related functional impairment in COPD include changes in muscle morphology and energy metabolism and reduced activity of motor neurons. Larsson et al observed a selective atrophy of type II muscle fibers and a decreased proportion of type II fibers in biopsy specimens of the vastus lateralis muscle with increasing age in 51 healthy male subjects of different ages. In the same study, it was found that age, FFM, and type II fiber area were independent predictors of the age-related decline in strength. In accordance with these findings, a preferential muscle fiber type II atrophy was recently reported in vastus lateralis biopsy specimens of patients with COPD. Thus, muscular type II fiber atrophy may partially explain muscular weakness with increasing age, independent of the loss of lean body mass in COPD. Reduced oxidative capacity of vastus lateralis muscle has been reported in COPD and is related to peak exercise capacity. However, no major alterations in the activities of oxidative or glycolytic enzymes in skeletal muscles were described in relation to age in healthy subjects. Thus, it is unlikely that changes in muscle energy metabolism in COPD result from accelerated aging. Studies have shown that both the number and size of active motor units are affected during aging, but the prevalence and role of these and other neuropathic changes in age-related functional impairment in patients with COPD is unknown. Although advancing age was independently related...
with reduced functional capacity in COPD, the exact mechanism behind this observation remains unclear. The effects of the exercise training program on weight, FFM, and exercise performance were not related to age of the participants, indicating that the ability to adapt to an anabolic stimulus is maintained in older patients with COPD.

In conclusion, normal-weight patients with COPD classified into Global Initiative for Chronic Obstructive Lung Disease stages III-IV show an anabolic response to physical exercise training, which together with other training-induced adaptations contributes to functional improvements. The influence of changes in FFM on prognosis in normal-weight patients needs to be studied.

REFERENCES