Limb Muscle Dysfunction in COPD: Effects of Muscle Wasting and Exercise Training

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ABSTRACT

FRANSSEN, F. M. E., R. BROEKHUIZEN, P. P. JANSSEN, E. F. M. WOUTERS, and A. M. W. J. SCHOLS. Limb Muscle Dysfunction in COPD: Effects of Muscle Wasting and Exercise Training. *Med. Sci. Sports Exerc.*, Vol. 37, No. 1, pp. 2–9, 2005. **Purpose:** Lower-limb muscle weakness has often been reported in COPD, and contributes to exercise intolerance. Controversial information is available regarding upper-limb muscle adaptations and the influence of muscle wasting on muscle weakness. We investigated leg and arm muscle function in 59 stable COPD patients (GOLD stage III) with preserved fat-free mass (FFM) and in 28 patients with reduced FFM relative to age- and sex-matched healthy control subjects and studied the effects of 8 wk of whole-body exercise training. **Methods:** FFM was measured with bioelectrical impedance analysis. Isokinetic quadriceps (F-leg) and biceps strength (F-arm), as well as quadriceps (E-leg) and biceps endurance (E-arm) were determined with a Biodex dynamometer. Exercise training consisted of cycle ergometry, treadmill walking, weight training, and gymnastics during 5 $d \cdot wk^{-1}$. **Results:** F-leg (76.2 ± 3.6 vs 118.2 ± 6.3 N·m, $P < 0.001$) and F-arm (25.6 ± 1.3 vs 38.1 ± 2.1 N·m, $P < 0.001$) were significantly and similarly reduced in the COPD patient group compared with controls. Also, E-leg (−2.13 ± 0.12 vs −1.61 ± 0.11, $P < 0.01$), but not E-arm (−2.72 ± 0.11 and −2.47 ± 0.13 NS), was decreased in patients. F-leg (62.4 ± 4.3 vs 82.8 ± 4.7 N·m, $P < 0.01$), but not F-arm or muscle endurance, was reduced in FFM-depleted compared with non-FFM–depleted patients. Whereas after training F-leg and E-leg significantly increased by 20% in the whole COPD group, biceps muscle function remained unchanged. **Conclusion:** Lower- and upper-limb muscle dysfunction was observed in COPD patients, irrespective of the presence of FFM depletion. Generalized muscle weakness suggests systemic muscular involvement, although the preserved arm endurance and the poor response of arm performance to exercise training is indicative for intrinsic differences in muscular adaptations between leg and arm muscles. **Key Words:** CHRONIC OBSTRUCTIVE PULMONARY DISEASE, FAT-FREE MASS, MUSCLE STRENGTH, MUSCLE ENDURANCE, LOWER AND UPPER LIMBS, PULMONARY REHABILITATION

Skeletal muscle weakness of the lower extremities is frequently observed in patients with chronic obstructive pulmonary disease (COPD), and contributes to exercise limitation (14,15), impaired health status (29), and increased use of health care services (8). Peripheral muscle dysfunction in COPD has been related to muscle wasting of the extremities (9), whereas the contribution of abnormalities in quadriceps muscle morphology (31) and energy metabolism (20) has not yet been elucidated. Recently, it was suggested that peripheral muscle dysfunction is absent in COPD patients with normal muscle mass, assessed by fat-free mass (FFM) (16), thus emphasizing the role of nutritional depletion in the etiology of muscle dysfunction. Muscle weakness can be approached as loss of muscle strength, muscle endurance, or a combination of these. Muscle strength is defined as the capacity of the muscle to develop maximal force, whereas endurance is the capacity of the muscle to sustain mechanical output during (a series of) loaded contraction(s).

Although several studies reported lower-limb muscle impairment in COPD, little and conflicting information is available on the function of other peripheral muscle groups, especially of the upper limbs. In addition, the relative distribution of muscle weakness between different muscle groups remains unclear. Insight in the pattern of muscular dysfunction in COPD would contribute to a better understanding of underlying local or systemic pathophysiology, such as inactivity and deconditioning, malnutrition, sys-

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temic inflammation, hypoxemia, and use of systemic corticosteroids. Some studies reported a relative preservation of strength of upper-limb muscles (2,14), whereas others found a similar degree of muscle weakness for lower and upper limbs, however, with differences between proximal and distal arm muscle groups (13).

Although muscle endurance was less frequently studied in COPD, both normal (22) as well as decreased values for lower (5,6,28) and upper extremities (32) were described. In one study, a relative preservation of muscle endurance of the upper limb was reported in comparison with the lower limb (5), whereas in another study a combination of impaired arm muscle endurance and normal leg muscle endurance was described (32). Differences in the muscle function testing equipment, protocols, and measured muscle groups together with heterogeneity in studied COPD groups probably contribute to divergent results. Therefore, the first purpose of the present study was to carefully study and compare muscle strength and endurance of the proximal lower and upper limbs in severe COPD patients relative to healthy subjects. Strength and endurance were measured in a single testing protocol, which was identical for lower- and upper-limb muscle function assessment, and the same dynamometer was used for leg and arm. To gain more insight in the mechanism and clinical implications of muscle dysfunction in COPD, this study additionally explored functional differences between muscle groups of lower and upper extremities in COPD patients with a preserved muscle mass and patients with a reduced muscle mass. Finally, this study investigated the effects of 8 wk of exercise training, consisting of a combination of whole-body endurance training and strength training of lower and upper extremities, on leg and arm muscle function in the COPD group.

METHODS

Subjects. Eighty-seven patients with moderate to severe COPD (1) and 35 age-matched healthy volunteers were studied at baseline. All patients were in clinically stable condition and were consecutively recruited on admission to the pulmonary rehabilitation center Hornerheide, where they participated in an intensive inpatient pulmonary rehabilitation program. Patients exhibiting an increase in $FEV_1 > 10\%$ of baseline after inhalation of a β_2-agonist were excluded. Other exclusion criteria were recent surgery and chronic diseases, such as malignant disorders, clinically apparent heart failure, gastrointestinal abnormalities and insulin dependent diabetes mellitus. Within the COPD population, 28 subjects fulfilled the criteria for depletion of FFM (7), whereas the FFM of the other 59 patients was in the normal range. The control group was recruited from an advertisement in a local newspaper for baseline comparison of body composition and muscle function. Controls did not participate in the exercise training program. Written informed consent was obtained from all subjects and the ethical review board of the University Hospital Maastricht approved the study.

Pulmonary function. Lung function testing included forced spirometry and assessment of lung volumes by whole-body plethysmography (Masterlab, Jaeger, Würzburg, Germany). FEV_1 and forced vital capacity (FVC) were calculated from the flow-volume curves. The highest values of at least three measurements were used. Diffusing capacity for carbon monoxide (DL_{CO}) was measured by the single breath method (Masterlab, Jaeger, Würzburg, Germany). Instruments were calibrated $2\times\ d^{-1}$. All values obtained were expressed as a percentage of reference values (26). Arterial blood gas analysis was performed in all patients at rest (ABL 330, Radiometer, Copenhagen, Denmark).

Anthropometric measurements. Besides body weight and height, FFM was measured by bioelectrical impedance analysis at a frequency of 50 kHz (Xitron 4000b, Xitron technologies, San Diego, CA). Resistance was measured in supine position at the right side as described by Lukaski (19). A patient specific regression equation, described by Schols et al. (27), was used to calculate FFM in COPD subjects. FFM index was calculated as the ratio of FFM to height in meters squared.

Peripheral muscle function. Isokinetic muscle strength and endurance of the dominant knee extensor (quadriceps) and elbow flexor (biceps) muscles were measured using a dynamometer (Biodex System II, Biodex Corporation, Shirley, New York, U.S.). During leg muscle function testing, 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 secured 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. To assess arm muscle function, equipment was reinstalled and subjects sat upright on a chair in front of the dynamometer with their backs towards it. The shoulder of the dominant arm was placed in 90° abduction. The upper arm was supported and fixed with a belt in the horizontal plane on an adjustable stand. The ventral side of the forearm was placed in the frontal plane. The handgrip of the lever arm was held by the subjects. The lateral epicondyle of the humerus was used as the axis of elbow rotation and was visually aligned with axis of rotation of the dynamometer. Subjects were instructed to keep their contralateral hand on their thigh.

The isokinetic testing protocol consisted of 15 sequential volitional maximal contractions at an angular velocity of $90°\cdot s^{-1}$. Maximal isokinetic strength was defined as the highest peak torque (N·m) in this series of 15 (Fig. 1). To determine isokinetic muscle endurance, the peak torques of the successive contractions were expressed as a percentage of the highest value. The first contraction was excluded from analysis. A linear curve was fitted through the calculated points. The slope of this curve, indicating the proportional decline in peak torque per contraction, was used as a measure for muscle endurance (Fig. 1). A more negative slope indicated lower muscle endurance or

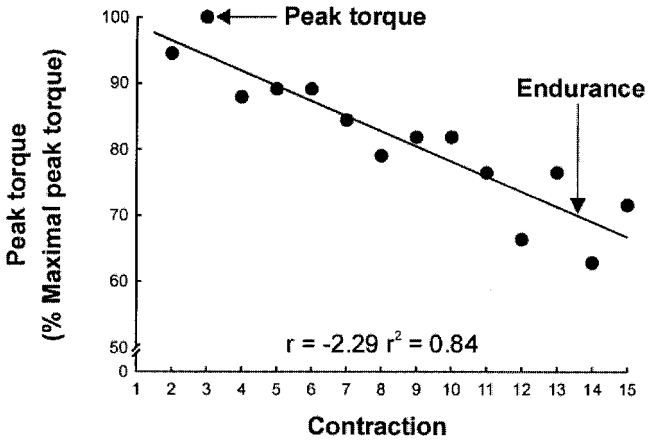

FIGURE 1—Methodology of muscle function testing. Maximal isokinetic strength was defined as the highest peak torque in a series of 15 maximal isokinetic contractions. The slope of the linear curve through the successive relative peak torques (r) was used as measure for muscle endurance. See Methods section for details.

increased muscle fatigue. Series in which the slope was ascending or in which the curve had a $R^2 < 0.209$ were excluded. The R^2 value of 0.209 is based on the critical value of the Pearson's correlation coefficient at a one-tailed *P* value of 0.10 and 13 degrees of freedom. For comparison of lower- and upper-limb muscle function, strength and endurance were also expressed as a percentage of the mean values obtained in the control group.

In addition to the isokinetic muscle function assessment and for comparison with other studies on muscle function in COPD, isometric handgrip force was measured with a hydraulic hand dynamometer (Jamar, Sammons Preston Rolyan, Jackson, IL). The average value of maximal force of left and right hand during a series of three maneuvers was used for analysis.

Exercise capacity. For characterization of the COPD patient group in terms of whole-body exercise tolerance, exercise capacity was assessed by progressive incremental exercise testing on an electrically braked cycle ergometer (Corival 400, Lode, Groningen, The Netherlands). During the entire exercise test, expired gases were investigated using breath by breath analysis through a breathing mask (Oxycon Beta, Jaeger, Würzburg, Germany). After 2 min of rest and 1 min of unloaded cycling, power was increased by 10 W every minute in patients. In control subjects, the load was increased with 15–25 W every minute, depending on relative fitness of the subject, so as to lead to fatigue in 10–12 min. None of the subjects knew the exercise load and all were encouraged to cycle at 60 rpm until exhaustion.

Study design. Inclusion, medical examination, and baseline measurements of pulmonary function, body composition, peripheral muscle function, and exercise performance in COPD patients were performed within the first 2 wk after admission to the pulmonary rehabilitation center. This period also allowed for familiarization with the various procedures in order to avoid learning effects. After two weeks, all patients participated in a comprehensive inpatient 8-wk respiratory rehabilitation program consisting of exercise training during 5 $d \cdot wk^{-1}$, education, and (when appropriate) psychosocial and behavioral intervention. During their stay in the rehabilitation center, a standardized weight maintaining diet was offered to weight stable patients that were not eligible for nutritional supplementation (7). All subjects in the FFM-depleted group and 11 patients with preserved FFM but low body weight or weight loss received standardized nutritional support during rehabilitation (Respifor, Royal Numico NV, Amsterdam, The Netherlands; $3\times$ d^{-1}, 564 kcal; 20% energy protein, 60% energy carbohydrate, 20% energy fat). The physical exercise training program consisted of a combination of endurance and strength exercise training. Submaximal cycle ergometry was performed $2\times$ d^{-1} for 20 min. Initial load was set at 50–60% of baseline peak work rate. 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 $min \cdot d^{-1}$ 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 arm exercise training sessions, consisting of 10×1 min of unsupported arm 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 patients' muscular performance by a team of experienced physiotherapists.

Control subjects visited the pulmonary rehabilitation center on two successive days. On the first day, a medical examination was performed and body composition and respiratory function were assessed. Furthermore, the controls practiced on the Biodex dynamometer with an exercise therapist to become familiar with the apparatus and minimize learning effects. On the second day, the actual muscle function measurement and maximal bicycle ergometry were performed.

Statistical analysis. Results are expressed as mean ± standard error of the mean (SEM). Statistical analysis on baseline differences between patients and controls was performed using an unpaired Student's *t*-test. One-way analysis of variance (ANOVA) was used to determine differences between FFM-depleted, non-FFM–depleted patients and controls. LSD multiple comparison test was used as post hoc test. The Student's paired *t*-test for dependent samples was used to test for differences in relative muscle strength and endurance between the lower and upper limbs in COPD patients. Pearson's correlation analysis was performed in the patient group in order to investigate linear relationship between variables of body composition and muscle function. Changes in muscle function between baseline and week eight were tested with Student's paired *t*-test in the whole group of COPD patients. Because of the limited number of paired observations in especially the FFM-depleted group, due to strict methodological criteria (as described in the section about peripheral muscle function measurement), the

latter analysis was not performed for both COPD subgroups separately. All P values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics. At baseline, sex distribution, age, and height were comparable in non-FFM–depleted COPD patients, FFM-depleted patients, and controls (Table 1). Body weight was significantly lower in patients compared with controls, and in depleted compared with nondepleted patients, resulting in a reduced BMI in the patient group compared with controls (22.4 ± 0.4 vs 26.3 ± 0.4 kg·m^{-2}, $P < 0.001$) and in FFM-depleted versus non-FFM–depleted COPD. The reduced body weight was mainly the result of a decreased FFM in both patient groups, but a decreased fat mass also contributed to the lower body weight in the depleted patient group. Patients were characterized by severe airflow obstruction with hyperinflation and a reduced diffusing capacity for carbon monoxide (GOLD stage III). Despite comparable spirometry and blood gases, diffusing capacity for carbon monoxide was lower in FFM-depleted patients compared with nondepleted patients. Exercise capacity, measured with cycle ergometry, was markedly impaired in patients compared with controls ($\dot{V}O_{2max}$: 961 ± 37 vs 2134 ± 124 mL·min^{-1}, $P < 0.001$). Although exercise performance was lower in FFM-depleted patients compared with nondepleted patients, statistical significance was not reached.

Muscle strength. Isokinetic strength of the dominant quadriceps (76.2 ± 3.6 vs 118.2 ± 6.3 N·m, $P < 0.001$) and biceps (25.6 ± 1.3 vs 38.1 ± 2.1 N·m, $P < 0.001$) muscles was significantly reduced in COPD patients compared with controls. Mean quadriceps and biceps strength of patients were 65 ± 3% and 67 ± 3% (NS) of the mean control value, indicating that lower- and upper-proximal limb muscle strength were equally affected. As shown in Figure 2, quadriceps and biceps strength was significantly reduced in both non-FFM–depleted as well as FFM-depleted patients. Furthermore, quadriceps strength was significantly lower in FFM-depleted compared with nondepleted patients, whereas biceps strength was comparable in both patient groups. Also after correcting for FFM, quadriceps (1.57 ± 0.06 vs 2.00 ± 0.07 N·m·kg^{-2}) and biceps muscle strength (0.53 ± 0.02 vs 0.64 ± 0.02 N·m·kg^{-2}) were significantly reduced in COPD patients compared with controls. However, the difference in quadriceps strength between depleted and nondepleted patients disappeared after correction for FFM (1.54 ± 0.09 and 1.58 ± 0.07 N·m·kg^{-2}, respectively, NS).

Handgrip strength was significantly lower in COPD patients than in controls (33.2 ± 0.9 vs 40.7 ± 2.4 kg, $P < 0.01$). As shown in Table 1, both FFM-depleted as well as nondepleted patients had decreased handgrip strength, with no difference between these two groups.

Muscle endurance. Quadriceps muscle endurance was significantly reduced in COPD patients, and both subgroups compared with controls (proportional decline in peak torque per contraction: −2.13 ± 0.12 vs −1.61 ± 0.11, $P < 0.01$), and was 80 ± 7% of the mean control value. Lower-limb endurance was comparable in FFM-depleted and non-FFM–depleted patients, as indicated in Figure 2. Biceps muscle endurance was 10 ± 4% lower in patients than in controls (−2.72 ± 0.11 and −2.47 ± 0.13, respectively), but the difference was not statistically significant. Also, there was no statistically significant difference in upper-limb muscle endurance between non-FFM–depleted and FFM-depleted patients.

Correlation analysis. On bivariate correlation analysis in the COPD group, quadriceps strength ($r = 0.43$, $P < 0.001$), biceps strength ($r = 0.47$, $P < 0.001$), and handgrip force ($r = 0.40$, $P < 0.001$) correlated strongly with FFMI, whereas quadriceps and biceps muscle endurance were not related to FFMI. Lower- ($r = 0.534$, $P < 0.001$) and upper-extremity strength ($r = 0.612$, $P < 0.001$) correlated strongly with $\dot{V}O_{2max}$. Skeletal muscle function was not related to parameters of pulmonary function.

Effects of exercise training. After the exercise training program, both strength as well as endurance of the quadriceps muscle increased with 20% in the COPD patient group ($P < 0.01$), whereas biceps muscle function did not significantly change (Fig. 3). Body weight (+1.8 ± 0.3 kg, $P < 0.001$) and FFM (+1.5 ± 0.3 kg, $P < 0.001$) significantly increased after the pulmonary rehabilitation program, whereas FM remained unchanged (+0.34 ± 0.2 kg). Peak cycling work rate (+15 ± 2 W, $P < 0.001$) and $\dot{V}O_{2max}$ (+137 ± 26 mL·min^{-1}, $P < 0.001$) also improved significantly, indicating an enhanced exercise capacity in patients.

TABLE 1. Baseline characteristics of the study groups (mean ± SEM).

	Controls (N = 35)	Non-FFM–Depleted COPD (N = 59)	FFM-Depleted COPD (N = 28)
Male/female (N)	24/11	41/18	18/10
Age (yr)	62 ± 1	63 ± 1	62 ± 2
Body composition			
Height (cm)	172.2 ± 1.6	169.9 ± 1.0	168.3 ± 1.5
Weight (kg)	78.3 ± 2.0	69.6 ± 1.4#	53.6 ± 1.6#**
BMI (kg·m^{-2})	26.3 ± 0.4	24.1 ± 0.4#	18.9 ± 0.4#**
FFM (kg)	59.0 ± 1.9	51.1 ± 1.0#	40.7 ± 1.0#**
FFMI (kg·m^{-2})	19.8 ± 0.4	17.7 ± 0.2#	14.3 ± 0.2#**
FM (kg)	19.4 ± 1.2	18.5 ± 0.9	12.9 ± 0.9#**
FMI (kg·m^{-2})	6.6 ± 0.4	6.4 ± 0.3	4.6 ± 0.3#**
Lung function			
FEV_1 (%predicted)	111 ± 3	37 ± 2#	31 ± 3#
FVC (%predicted)	116 ± 3	76 ± 3#	70 ± 3#
DL_{CO} (%predicted)	112 ± 3	53 ± 3#	39 ± 3#*
P_aO_2 (kPa)	—	9.3 ± 0.2	9.3 ± 0.3
P_aCO_2 (kPa)	—	5.4 ± 0.1	5.7 ± 0.2
Functional capacity			
Peak work rate/FFM (W·kg^{-1})	3.4 ± 0.1	1.2 ± 0.1#	1.3 ± 0.1#
$\dot{V}O_{2max}$/FFM (mL·kg^{-1}·min^{-1})	36.4 ± 1.2	19.2 ± 0.8#	21.9 ± 1.3#
Handgrip force (kg)	40.7 ± 2.4	33.9 ± 1.3#	31.8 ± 1.5#

BMI, body mass index; FFM, fat-free mass, assessed by bioelectrical impedance analysis; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; DL_{CO}, diffusing capacity for carbon monoxide. P_aO_2, arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension; $\dot{V}O_{2max}$, maximal oxygen consumption.

Significance of differences between patients and controls is indicated as: # $P < 0.001$. Significant differences between FFM-depleted and non-FFM–depleted patients are shown as: ** $P < 0.001$ and * $P < 0.05$.

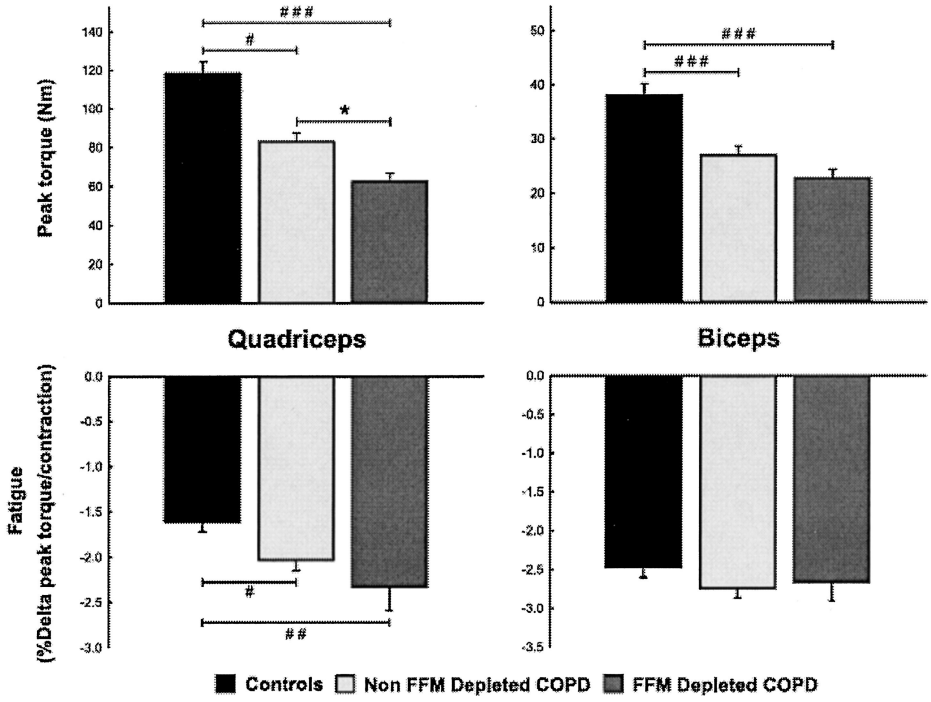

FIGURE 2—Baseline muscle strength (expressed as peak torque) and fatigue (expressed as proportional decline in peak torque per contraction) of the lower and upper extremities in controls, non-FFM–depleted COPD patients, and FFM-depleted COPD patients (mean ± SEM). Quadriceps and biceps muscle strength were significantly reduced in both patient groups compared with controls. Quadriceps muscle strength was significantly lower in FFM-depleted than in non-FFM–depleted patients. Quadriceps fatigue, but not biceps fatigue, was significantly higher in both patient groups than in controls, whereas fatigue was comparable in subgroups of COPD. ### $P < 0.001$; ## $P < 0.01$; # $P < 0.05$ vs controls; * $P < 0.05$ vs non-FFM–depleted COPD.

DISCUSSION

The results of the present study can be summarized as follows. First, a reduced skeletal muscle function of the lower and upper limbs was observed in COPD patients. Quadriceps and biceps muscle strength were comparably affected, whereas the loss of muscle endurance was restricted to the lower extremities. Also, quadriceps strength was more impaired in FFM-depleted patients compared with non-FFM–depleted patients, whereas biceps strength and peripheral muscle endurance were comparable in these groups. Finally, enhanced quadriceps muscle function was observed after 8 wk of intensive whole-body exercise training, whereas biceps muscle function was unchanged.

Reduced muscle strength of the lower and upper extremities was previously reported in COPD (2,13,14,21) and was confirmed here. However, the relative involvement of the different muscle groups remains controversial. In this study, isokinetic muscle strength of quadriceps and biceps muscles was equally affected, indicating generalized muscle weakness. This result is not consistent with reports of a relatively preserved arm function in COPD (2,14,21). Bernard et al. (2) reported a proportionally greater reduction in isokinetic

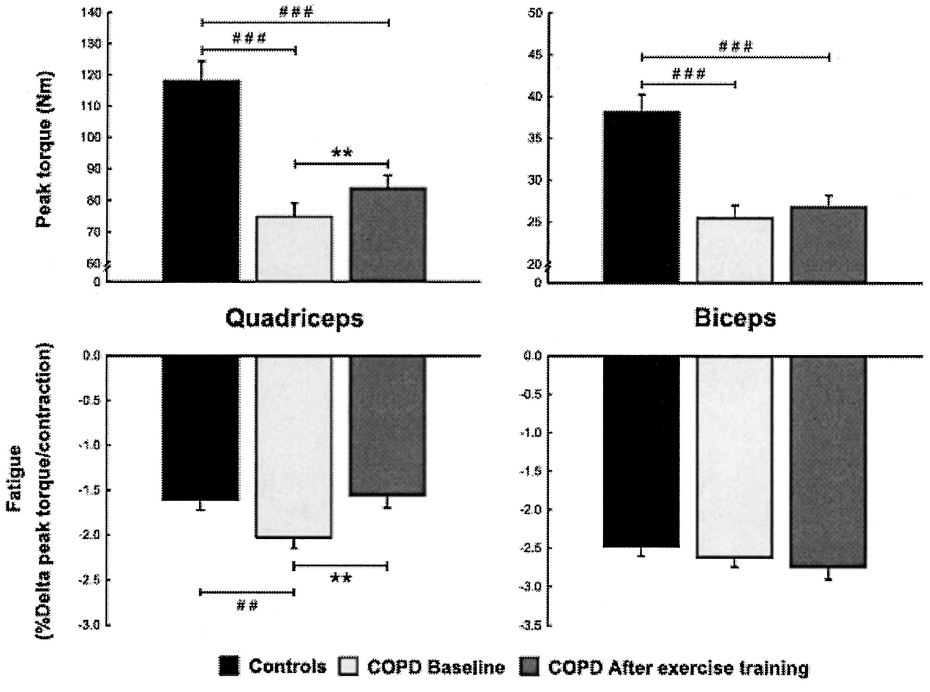

FIGURE 3—Muscle strength (expressed as peak torque) and fatigue (expressed as proportional decline in peak torque per contraction) of the lower and upper extremities in COPD before and after 8 wk of whole-body exercise training in comparison with the baseline control group (mean ± SEM). The increase in strength and reduction in fatigue of the quadriceps muscle during training was statistically significant. Biceps muscle function did not change during 8 wk of exercise training. ### $P < 0.001$; ## $P < 0.01$ vs controls; ** $P < 0.01$ vs baseline.

quadriceps strength than that of pectoralis major and latissimus dorsi muscles in 34 normal-weight COPD patients compared with controls. In addition, Gosselink et al. (14) observed lower relative values for isometric quadriceps strength, compared with handgrip force in 41 COPD patients, related to reference values. However, in another study, the same authors (13) described a similar extent of weakness for quadriceps and arm muscles. In that study, isometric strength of proximal arm muscles was more affected than that of distal arm muscles. In a recent study of nonvolitional muscle strength by Man et al. (21), quadriceps strength was substantially reduced in COPD, whereas strength of adductor pollicis muscle and diaphragm were normal. For several reasons, it is difficult to compare the results of the various studies. First, quadriceps muscle strength was used as a measure for lower-limb muscle function in all studies, but numerous muscle groups of the upper limbs were investigated. Differences in the intensity of recruitment of shoulder girdle muscles, proximal arm muscle groups, and distal and hand muscle groups during activities of daily living may account for various degrees of conditioning of these muscle groups and thus for relative differences in the observed degree of muscle weakness. Furthermore, the muscles of the shoulder girdle are additionally stimulated in COPD patients, because they act as accessory inspiratory muscles when ventilatory demands increase (24). Also, methods and equipment for muscle function testing differed, not only between studies, but also between lower and upper extremity in the same study (14). Furthermore, both isokinetic protocols, in which the velocity of muscle contraction is constant, as well as isometric protocols, in which muscle fiber length and joint angle are constant, were used. Finally, heterogeneity regarding age, sex, severity of disease, and body composition of the studied COPD patients might have contributed to the conflicting results. The present study in severe COPD patients, using the same isokinetic protocol and equipment for quadriceps and biceps muscle function testing, showed that lower- and upper-extremity strength were equally affected, which is indicative of the presence of generalized proximal muscle weakness in COPD.

This is the first study that explored differences in muscle weakness between subgroups of COPD patients with preserved and reduced FFM, independent of body weight. Lower-extremity muscle strength was more impaired in FFM-depleted patients than in patients with a preserved muscle mass. After correcting for the difference in FFM between the groups, quadriceps strength was comparable, suggesting that muscle mass is the main cause of the variation in the degree of muscle weakness observed within the COPD group. It is, however, important to note that significant muscle dysfunction of lower and upper extremities was present not only in COPD patients with a reduced FFM, but also in patients with a preserved FFM. This observation is in contradiction to the results of a recent study by Heijdra et al. (16), who reported normal values for expiratory and handgrip muscle strength in COPD GOLD stage III outpatients with a normal FFM index, and concluded that a clinically significant systemic myopathy is absent in this subset of patients. Quadriceps and biceps muscle function was not assessed. The present results, however, indicate that although muscle mass is an important determinant of muscle strength, the occurrence of muscle dysfunction is not limited to a subset of FFM-depleted COPD patients, but is already present in patients with preserved muscle mass. Others also observed muscle dysfunction in normal-weight COPD patients with a milder degree of airflow obstruction (5). Because muscle dysfunction contributes to exercise intolerance (14,15) and reduced quality of life (29), specific therapies aimed at enhancing muscular performance, such as exercise training and nutritional and anabolic interventions, should not be limited beforehand to the subset of cachectic COPD patients. Unlike quadriceps strength, biceps muscle strength was not different between cachectic patients and those with normal FFM. Because loss of muscle mass is strongly related to muscle weakness, comparable biceps strength in the two subgroups suggests that the additional muscular atrophy in cachectic patients is mainly restricted to the lower-limb muscles. Among other factors, chronic underuse of locomotor muscles of the lower extremities is probably important in the development of this additional atrophy. Although this study included detailed measurements of body composition, the regional distribution of muscle mass was not assessed.

The ratio of muscle strength to whole-body FFM was reduced in COPD patients compared with controls. Also, differences in muscle strength between patients with preserved and reduced FFM disappeared after correcting for FFM. This observation is in agreement with a study by Engelen et al. (9), who reported lower values for muscle function per kilogram of whole-body FFM in COPD, compared with controls. In contrast, muscle function per kilogram of extremity FFM was comparable in patients and controls in that study. In addition, a normal ratio of quadriceps strength to quadriceps muscle cross-sectional area was reported in COPD (2). These combined results indicate a relative redistribution of FFM in COPD with preservation of trunk FFM and predominant loss of extremity muscle mass.

In accordance with previous publications (5,6,28), impaired quadriceps muscle endurance was perceived in this study. The observation of a comparable muscular endurance in COPD patients with normal and reduced FFM is new. In agreement with this observation, muscle mass, assessed by FFM, was not related to muscle endurance in the COPD group or in controls. This suggests that intrinsic muscular abnormalities are involved in increased skeletal muscle fatigue in COPD. These abnormalities include alterations in muscle substrate and energy metabolism and altered fiber type distribution (11). Although a causal relationship between morphological or metabolic alterations in skeletal muscle and muscle function has not been shown in COPD, a role for increased exercise-induced muscle oxidative stress in the development of decreased quadriceps endurance was recently suggested (6). Contrary to lower-extremity endurance, upper-limb muscle endurance was comparable in COPD patients and controls, suggesting that this component

of upper-extremity muscle function is preserved. This finding is supported by the study of Clark et al. (5). Despite a reduced quadriceps endurance and impaired strength for lower and upper limbs, sustained isokinetic arm function was normal in a group of normal weight mild COPD patients. In addition to the normal upper-limb muscle endurance in the present study, preserved values for arm mechanical efficiency and peak arm exercise capacity were recently reported in a comparable group of COPD patients (10). These combined observations might very well be related to an uneven distribution of intrinsic alternations, such as changes in percentage Type I muscle fibers and oxidative capacity, in peripheral skeletal muscles between the leg and arm in COPD patients (12).

The efficacy of exercise training as part of a respiratory rehabilitation program in improving functional exercise capacity in COPD is well established (4,17). In the present group of patients with baseline muscle weakness, 8 wk of whole-body exercise training resulted in improvements in quadriceps strength and endurance by 20% and an increase of 16% in maximal oxygen uptake. These improvements very likely resulted from the combination of highly intensive aerobic cycling and treadmill training, which formed the major components of the physical training program, and lower-limb strengthening exercises. Significant crossover training effects between strength and endurance training were previously described and the combination of these training modalities seems an optimal strategy for COPD patients (25,30). Considerable increases in quadriceps strength after aerobic training (3,23,25) and improvements in endurance performance after resistance training (30) were reported. The results of the present study confirm that muscle dysfunction in COPD is remediable with aimed therapy and that the applied methodology for measuring strength and endurance can be used to evaluate the outcome of rehabilitation. In contrast to lower-extremity performance, biceps muscle weakness, which was determined with identical methodology at baseline, was not repelled during the rehabilitation period. The lack of a training effect is probably related to intensity and specificity of the exercise training. Although subjects participated in daily unsupported arm exercises, gymnastics involving arm activities, and individualized upper-limb resistance training, the training stimulus to the muscle groups of the upper limbs may have been insufficient. Furthermore, specificity of training effects for trained muscle groups in COPD was earlier demonstrated by Lake et al. (18). Upper-limb exercises resulted in improved arm performance, whereas lower-limb training increased walking distance. No crossover training benefits were seen between arms and legs. As mentioned before, lower-extremity endurance training was the main component of the exercise program. Baseline preservation of upper-extremity muscular structure, metabolism, and endurance capacity may also have contributed to the lack of response of arm function to the offered comprehensive training program.

Clinical implications. This study showed that muscular dysfunction of lower and upper extremities occurs in both cachectic COPD patients as well as patients with a relatively normal body composition. Loss of muscle mass is a main contributor to muscle weakness, but the loss of muscle endurance and the reduced strength per kilogram muscle mass suggest that other factors are also important. Limiting specific therapies aimed at enhancing muscle function or exercise tolerance to patients with a reduced FFM, would result in an undertreatment of the group of patients with functional impairments despite a normal body composition. Therefore, screening of COPD patients for such therapies should include not only assessments of body mass index and FFM, but also measurements of muscle function. Furthermore, the results of muscle function testing in this study indicate that strength and endurance are distinct and independent components of muscle function, which should ideally both be determined when assessing muscle performance in clinical and scientific setting in COPD. Whereas the equal distribution of strength loss between lower and upper extremities is indicative for a systemic muscle involvement, the normal endurance component of muscle function of the upper limb suggests structural and metabolic differences between leg and arm in COPD.

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