Reduced Mechanical Efficiency in Chronic Obstructive Pulmonary Disease but Normal Peak $\dot{V}O_2$ with Small Muscle Mass Exercise

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We studied six patients with chronic obstructive pulmonary disease (COPD) (FEV_1 = 1.1 ± 0.2 L, 32% of predicted) and six age- and activity level–matched control subjects while performing both maximal bicycle exercise and single leg knee-extensor exercise. Arterial and femoral venous blood sampling, thermodilution blood flow measurements, and needle biopsies allowed the assessment of muscle oxygen supply, utilization, and structure. Maximal work rates and single leg $\dot{V}o_2$max (control subjects = 0.63 ± 0.1; patients with COPD = 0.37 ± 0.1 L/minute) were significantly greater in the control group during bicycle exercise. During knee-extensor exercise this difference in $\dot{V}o_2$max disappeared, whereas maximal work capacity was reduced (flywheel resistance: control subjects = 923 ± 198; patients with COPD = 612 ± 81 g) revealing a significantly reduced mechanical efficiency (work per unit oxygen consumed) with COPD. The patients had an elevated number of less efficient type II muscle fibers, whereas muscle fiber cross-sectional areas, capillarity, and mitochondrial volume density were not different between the groups. Therefore, although metabolic capacity *per se* is unchanged, fiber type differences associated with COPD may account for the reduced muscular mechanical efficiency that becomes clearly apparent during knee-extensor exercise, when muscle function is no longer overshadowed by the decrement in lung function.

Keywords: lung disease; oxygen consumption; blood flow; fiber type; quadriceps

Although researchers have recently focused their attention on the potential involvement of skeletal muscle in the pathophysiology of chronic obstructive pulmonary disease (COPD) (1–5), there is currently no accord on this matter (6). An issue that has clouded conclusions is the difference between skeletal muscle dysfunction and disuse (7). Certainly, patients with COPD experience locomotor muscle disuse, promoted by the dyspnea that accompanies exercise in this condition. However, should simply deconditioned skeletal muscle be considered dysfunctional? The tendency to answer yes to this question has been promoted by studies that magnify the differences in COPD skeletal muscle by comparisons with relatively physically active control subjects (1, 7–9). Thus, the selection of appropriately inactive control subjects becomes an essential component of the experimental design of research focused on the assessment of skeletal muscle function and COPD.

Additional support for the concept of dysfunctional muscle in COPD has been provided by the regular use of whole body exercise, such as cycling, to evaluate muscle function (1, 3, 10). The use of a large muscle mass exercise paradigm, in patients with COPD, may shroud peripheral muscle limitations by the attainment of a patient's reduced ventilation ceiling, before truly taxing the locomotor muscles. Ideally, to study muscle function itself in COPD, the amount of muscle recruited should be small enough that the patient can achieve maximal muscular work before the influence of central ventilatory limitations.

The single leg knee-extensor exercise model (11), allows the measurement of oxygen (O_2) supply and $\dot{V}O_2$ to a known mass of active muscle (12) under conditions of limited ventilatory demand and thus is an ideal exercise paradigm with which to study the skeletal muscle of patients with COPD (13). The ability to monitor muscle O_2 supply in this paradigm is essential because without this metabolic differences may be the consequence of either intrinsic muscle dysfunction or the normal response of healthy (even if detrained) muscle to reduced O_2 supply.

Consequently, this study was designed to assess skeletal muscle function in patients with COPD during both cycle and single leg knee-extensor exercise in comparison with that of healthy control subjects that were well matched, both in terms of physical activity and physical characteristics. The purpose of this study was to test the following hypotheses: (*1*) during cycle exercise the skeletal muscle of patients with COPD will appear dysfunctional in comparison with that of control subjects in terms of maximal work rate, muscle blood flow, and $\dot{V}O_2$, whereas (*2*) during single leg knee-extensor exercise the skeletal muscle of patients with COPD will have a more similar physiologic response to that of the control subjects. This work has been previously published in abstract form (14).

METHODS

Subjects

Six patients with COPD (FEV_1 = 1.1 ± 0.2, 32 ± 5% predicted) (15) and six healthy age-, weight-, and activity-matched control subjects volunteered according to the University of California San Diego, Human Research Protection Program requirements. Control subjects were determined to be sedentary, and the majority of the patients with COPD had completed the University of California San Diego Pulmonary Rehabilitation Program (within 8–24 months) but did not differ from the control subjects in terms of current physical activity (16–18). Subject characteristics are presented in Table 1.

Exercise Models

Two exercise modalities were employed in this study, the first being conventional bicycle ergometry performed on an electrically braked bike (Excalibur; Quinton Instruments Co., Gröningen, Holland). Cadence was self-selected, but for most subjects fell between 60 and 80 rpm. The second exercise paradigm was knee-extensor exercise, which limits muscular work to the quadriceps of one leg (11, 12, 19). This was

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TABLE 1. SUBJECT CHARACTERISTICS

	Control Subjects	Patients with COPD
Number of subjects	6	6
Age, yr	65.4 ± 4.3	64.0 ± 3.6
Height, cm	171.2 ± 3.4	179.4 ± 4.8
Weight, kg	81.7 ± 6.3	82.5 ± 11.2
Body mass index, kg/m^2	28.2 ± 1.1	25.6 ± 1.7
Quadriceps mass, kg	2.0 ± 0.1	1.8 ± 0.2
Leg muscle mass, kg	7 ± 0.2	6.3 ± 0.3
FEV_1, L, % predicted	3.1 ± 0.3	1.1 ± 0.2
	(106 ± 4.0)	(32.4 ± 4.6)*
FVC, L, % predicted	4.0 ± 0.4	3.1 ± 0.4
	(102.6 ± 0.4)	(70.9 ± 4.3)*
FEV_1/FVC, %	77.8 ± 1.3	33.6 ± 3.2*
Resting arterial HbO_2, %	97.0 ± 0.3	95.2 ± 0.6*
Resting arterial P_{O_2}, mm Hg	97.7 ± 2	87.4 ± 3*
Arterial [Hb], g/dl	14.0 ± 1	14.5 ± 0.4
Number of prior steroid users	0	2

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; [Hb] = hemoglobin concentration; HbO_2 = oxyhemoglobin.

Percent predicted values derived from Crapo and coworkers (15).

Leg muscle mass estimate based on 3.5 times the measured quadriceps muscle mass (63).

* Significantly different from control subjects.

performed with subjects reclined on a padded chair with the knee-extensor exercise ergometer placed in front of them (illustrated in Reference 20) (*see* online supplement).

Experimental Protocol

Within 1 week of preliminary familiarization studies, subjects returned to the laboratory where two catheters (radial artery and left femoral vein) and a thermocouple (left femoral vein) were emplaced using the sterile technique as previously reported (19, 21) (*see* online supplement). Blood samples were taken from the arterial and femoral venous catheters to quantify arterial–venous O_2 concentration differences.

After the catheterization procedures, two bouts of graded exercise were performed: (*1*) conventional cycle exercise and (*2*) single leg knee-extensor exercise. The order of these exercise bouts across subjects was balanced to avoid potential ordering effects. For each exercise bout, the work rate was increased from an unweighted warm-up to the previously determined maximum work rate with a minimum of three work levels. Data were obtained at each level after the attainment of steady-state exercise (2–4 minutes depending on the exercise intensity). Each exercise bout was completed in 8 to 12 minutes. $\dot{V}_E$, pulmonary $\dot{V}_{O_2}$, and $\dot{V}_{CO_2}$, were calculated by a commercially available software package (Consentius Technologies, Salt Lake, UT) integrated with a Perkin-Elmer MGA 1,100 mass spectrometer, a gas mixing chamber, and a Fleisch pneumotachograph #3 (Hans-Rudolph, Kansas City, Missouri) (19).

Blood Analyses

P_{O_2}, P_{CO_2}, pH, O_2 saturation, and hemoglobin concentration ([Hb]) were measured on an IL 1306 blood gas analyzer and IL 482 CO-oximeter (Instrumentation Laboratories, Lexington, MA.). O_2 concentration was calculated as 1.39 ml O_2 × [Hb] g/100 ml × measured O_2 saturation (fraction) + 0.003 ml O_2/100 ml of blood × measured P_{O_2} (mm Hg). Arterial–venous [O_2] difference was calculated from the difference in radial artery and femoral venous O_2 concentration. This difference was then divided by arterial concentration to give O_2 extraction.

Muscle Biopsy

A percutaneous needle biopsy of vastus lateralis muscle was obtained at approximately 3.5 cm of depth, 15 cm proximal to the knee, and slightly distal to the ventral midline of the muscle in four patients with COPD and four control subjects. The muscle samples from each biopsy were either immediately frozen in liquid nitrogen and stored at −80°C for subsequent histochemical, citrate synthase activity and myoglobin concentration analyses or immersion-fixed in glutaraldehyde fixative (6.25% glutaraldehyde solution in 0.1 M sodium cacodylate buffer; total osmolarity, 1,100 mOsm; pH 7.4) for processing for electron microscopy and morphometry. Details of these specific methodologies are available in the online supplement.

Thigh Volume Measurement

Using thigh length, circumference, and skinfold measurements, thigh volume was calculated to allow an estimate of quadriceps femoris muscle mass (22, 23).

Statistical Analyses

Analysis of variance and a Tukey *post hoc* analysis were used to determine differences across a series of work intensities. At maximal exercise, variables were tested for a significant difference between the groups by repeated measures *t* test. All statistics were performed using a commercially available software package (Graph Pad, San Diego, CA). All data are presented as means ± SE. The p value was set at 0.05 or less.

RESULTS

Muscle Biopsy Data

The anthropometric measurement of quadriceps muscle mass revealed no difference between patients with COPD and control subjects (Table 1). The muscle characteristics determined using needle biopsy samples are presented in Table 2. There were significant differences in the proportions of muscle fiber type, with patients with COPD exhibiting reduced proportion of type I fibers (Figure 1). The elevated proportion of type II fibers in patients with COPD was evident in both type IIA and type IIX, but the greatest difference was apparent in the type IIX fibers that were approximately 2.5 times as numerous (expressed as a percentage of fibers) compared with control subjects. Patients with COPD did not reveal altered capillarity when expressed as capillary density, capillary fiber ratio, or number capillaries around a fiber. Mitochondrial volume density and cross-sectional area were relatively low in both groups (24) but were not different between patients with COPD and control subjects. It should be noted that these mitochondrial measurements are not fiber type–specific and therefore represent an average for all fibers. Muscle fiber cross-sectional area was not different between the two groups. There was no difference in [myoglobin] between patients with COPD and control subjects, with both groups falling within the previously reported range for this and other techniques used on human tissue (25).

Bicycle Exercise

The major physiologic variables recorded during cycle exercise are reported in Table E1 (*see* online supplement). In terms of

TABLE 2. VASTUS LATERALIS MUSCLE CHARACTERISTICS

	Control Subjects	Patients with COPD
% Area of type I fibers	50 ± 7	21 ± 6*
% Area of type II fibers	50 ± 7	79 ± 6*
% Area of type IIA fibers	36 ± 12	42 ± 4*
% Area of type IIX fibers	16 ± 6	39 ± 2*
Capillary density, capillaries/mm^2	343 ± 8	335 ± 14
Capillary-to-fiber ratio	1.01 ± 0.04	1.07 ± 0.11
Number of capillaries around a fiber	2.7 ± 0.2	2.6 ± 0.2
Mitochondrial volume density, %	3.7 ± 0.2	3.6 ± 0.2
Fiber cross-sectional area, μm^2	2958 ± 90	3201 ± 290
Citrate synthase activity, μmol/min/g tissue	12.1 ± 1.1	12.4 ± 1.4
Myoglobin, mg/g wet weight	7.4 ± 0.9	7.3 ± 1.0

Number of subjects per group = 4, with the exception of % area of type IIA and IIX fibers (3 per group) and citrate synthase activity (n = 5 per group).

* Significantly different from control subjects.

maximum work rate the control subjects achieved a 128% greater work rate than the patients with COPD. As expected, leg $\dot{V}O_2$max and maximal leg blood flow were significantly attenuated in the patients with COPD because of the large reduction in maximal work rate. Indices of arterial O_2 availability such as arterial Hb saturation, arterial Po_2, and arterial O_2 concentration (Ca_{O_2}) were reduced throughout exercise in the patients with COPD when compared with control subjects. However, leg blood flow at a given work rate was higher in the patients with COPD. This resulted in a tendency for greater O_2 delivery at a given work rate to the muscle of patients compared with that of the control subjects. This submaximal leg blood flow was also accompanied by a significantly elevated vascular conductance (at a given work rate) in the patients with COPD. Throughout the progressive exercise test, O_2 extraction was slightly, but significantly attenuated in the patients in comparison with that of the control subjects, whereas both leg $\dot{V}O_2$ and pulmonary $\dot{V}O_2$ tended to be elevated but without statistically significant differences. Measures of metabolic stress such as arterial and venous pH and venous lactate outflow revealed similar responses to the submaximal work rates in both patients and control subjects without significant differences. Heart rate was the same at a given work rate in both groups, and thus the patient's maximal heart rate was attenuated when compared with that of the control subjects. Perceived breathlessness was accelerated in the patients with COPD, whereas the assessment of muscle fatigue indicated similar muscular distress at the limited work rates achieved.

Single Leg Knee-Extensor Exercise

The major physiologic variables recorded during knee-extensor exercise are reported in Table E2 (*see* online supplement). Using this exercise modality, the control subjects achieved a 50% greater maximum work rate than the patients with COPD. However, unlike bicycle exercise, leg $\dot{V}O_2$max and maximal leg blood flow were not attenuated in the patients with COPD despite the difference in maximal work rate. Ca_{O_2} was not lower throughout exercise in the patients with COPD when compared with control subjects. Leg blood flow for a given work rate was again elevated in the patients with COPD and again resulted in a greater O_2 delivery to the muscle of patients at a given work rate in comparison with that of control subjects. In this exercise modality, the elevated submaximal leg blood flow was not clearly accompanied by a significantly elevated vascular conductance in the patients. Throughout exercise, O_2 extraction was again significantly attenuated in the patients in comparison with the control subjects whereas leg $\dot{V}O_2$ was elevated. As during cycle exercise, measures of metabolic stress such as arterial and venous pH and venous lactate outflow revealed very similar responses to the submaximal work rates in both patients and control subjects. Heart rate was the same at a given work rate in both groups, and thus the patient's maximal heart rate was attenuated when compared with that of the control subjects. Subjective assessment of muscle fatigue indicated greater muscular distress at a given work rate in the patients, but maximum levels were equal in both groups. Although perceived breathlessness was accelerated in the patients at a given work rate, the maximal level was not different between groups.

Summary Comparison between Cycle and Single Leg Knee-Extensor Exercise

The disparity in maximal work rate between patients with COPD and control subjects was greatly reduced during single leg knee-extensor exercise when compared with cycle exercise. Unlike cycle exercise, during maximal knee-extensor exercise patients were able to attain the same leg $\dot{V}O_2$max as the control subjects. However, an apparent difference in mechanical efficiency, evident to a lesser degree during cycling, but clearly demonstrated during knee-extension exercise, resulted in an attenuated maximum knee-extension work rate for the patients with COPD compared with the control subjects. Leg blood flow for a given work rate was elevated in the patients with COPD compared with the control subjects during both exercise paradigms. As Ca_{O_2} was not severely compromised in the patients, this resulted in an elevated O_2 delivery to the exercising muscle at each work rate in each exercise paradigm. Subjectively, the patients indicated that they were less breathless during maximal knee-extensor exercise compared with cycling, and both groups indicated that maximal muscle fatigue was attained at the end of the knee-extensor exercise study, whereas only the control subjects achieved severe muscle fatigue during cycle exercise.

DISCUSSION

This study reveals significant differences in both skeletal muscle structure and function between activity and anthropometrically matched control subjects and patients with severe COPD. Functionally, the current data indicate that patients with COPD have a tendency for inefficient work economy in skeletal muscle, demonstrated even during cycle exercise, but more clearly during knee-extensor exercise (when the muscles are truly taxed in isolation from the limited pulmonary function). Structurally, the patients with COPD revealed a much greater proportion of type II muscle fibers, most apparent in the form of type IIX. This unique approach of tilting the balance from central to peripheral limitation (bike to knee-extensor exercise comparison) and the clear differences found in muscle structure suggest that the mechanical inefficiency in patients with COPD may be a direct result of an increased percentage of inefficient type II muscle fibers. As a consequence of the small sample size and the relatively constrained features of these patients (minimal muscle wasting, nonhypoxemic, etc.), it is important not to generalize these findings to the whole diverse population of patients with COPD.

Fiber Type, and Fiber Type Energetics

Patients with moderate to severe COPD consistently demonstrate an increase in the proportion of type II fibers, assessed either histochemically (26, 27) (Figure 1) or by the expression of myosin heavy chain isoforms (28, 29). This is the opposite of changes in fiber type associated with healthy aging (30). The cause of this unexpected fiber type composition may be the result of extended or intermittent exposure to conditions of reduced O_2 availability (31) or a consequence of disuse (32, 33). In the current study considerable effort was made to find control subjects who exhibited a similar level of activity as the patients with COPD (who for this population were relatively active). Consequently, although possible (34), it is unlikely based on subject selection criteria that disuse alone can account for the greater number of type II fibers in the patient group. In addition, if disuse were a major factor, concomitant changes such as reductions in fiber size, capillary-to-fiber ratio and mitochondrial density that were not observed (Table 2), would be expected. The patients in the current study experienced only mild hypoxia at rest (Pa_{O_2} = 87 mm Hg) (Table 1) that increased only slightly (Pa_{O_2} = 78 mm Hg) at maximal cycle exercise (Table E1 in the online supplement), despite exhibiting quite severe symptoms of COPD (Table 1). Hence, although the concomitant elevation in the proportion of type IIA fibers with the more typical increase in type IIB fibers is not identical to the previously reported effects of hypoxia (35), these data support the concept that hypoxia itself (albeit mild

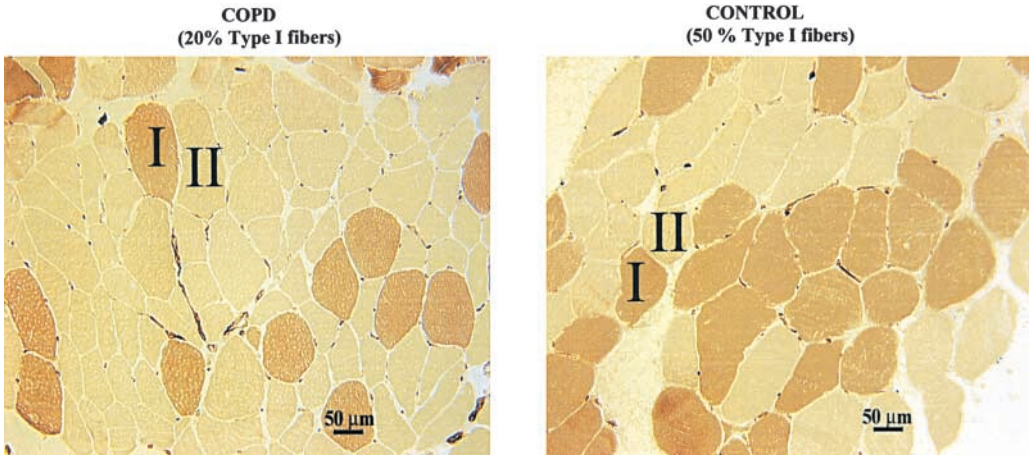

Figure 1. Light micrographs of histochemical sections stained for both capillaries and fiber type in patients with chronic obstructive pulmonary disease (COPD) and control subjects.

in this case) may induce the observed shift in fiber type exhibited by these patients (31).

The economy of constant muscular work is, beyond a threshold, inversely related to exercise intensity (36). Therefore, there is an apparent excess O_2 cost for a given amount of work during high-intensity muscular contraction, the mechanism for which is not clearly understood (37). As exercise intensity and or rate of force development increases there is a growing reliance on type II muscle fibers that has been proposed to lead to less efficient muscular work (38). There are convincing data at both the *in vitro* (39, 40) and *in vivo* (36, 38) levels that the energetic cost of force production is fiber type–specific. The mechanisms associated with a greater cost of developing tension with fast-twitch fibers (type II) may include: lower chemical-to-mechanical coupling efficiency and the adenosine triphosphatase (ATPase)–driven calcium pump whose activity is 5 to 10 times faster in the type II compared with type I fibers (39, 40). However, proportionality between maximum shortening velocities, ATPase activities (41), and between the energy cost of tension development in the extensor digitorum longus (type II) and soleus (type I) suggest that the faster actomyosin turnover is the most likely mechanism (42). Regardless of mechanism, it is apparent that fiber type differences in these patients with COPD may explain the difference in mechanical efficiency observed here during exercise. It should be recognized that, although such a mechanical inefficiency has been documented previously in a COPD study with a similar catheter-based approach to interrogate the muscle itself (10) and not simply assessing the whole body response to exercise, there are certainly many other investigations that have failed to reveal such a finding (6).

O_2 Transport and $\dot{V}o_2$

Several studies have reported that exercise tolerance is improved by O_2 supplementation in patients with COPD (13, 43, 44). Recognizing the impact of reducing hypoxemia in COPD and evidence of an elevated O_2 cost of breathing (45), which may steal blood from the limb muscles (13, 46), it had been suggested that O_2 delivery to the exercising muscle of patients with COPD may be compromised (1). However, the current data and the few other studies that have directly assessed blood flow, O_2 delivery, and O_2 uptake across the exercising muscle of patients with COPD, indicate that at an absolute submaximal work rate these parameters appear to be well preserved or even increased (Tables E1 and E2 in online supplement, Figures 2 and 3) (1, 10). Healthy subjects have also been documented to increase muscle blood flow to compensate for reductions in Ca_{O_2} (47). However, the increase in muscle blood flow and even O_2 delivery in the

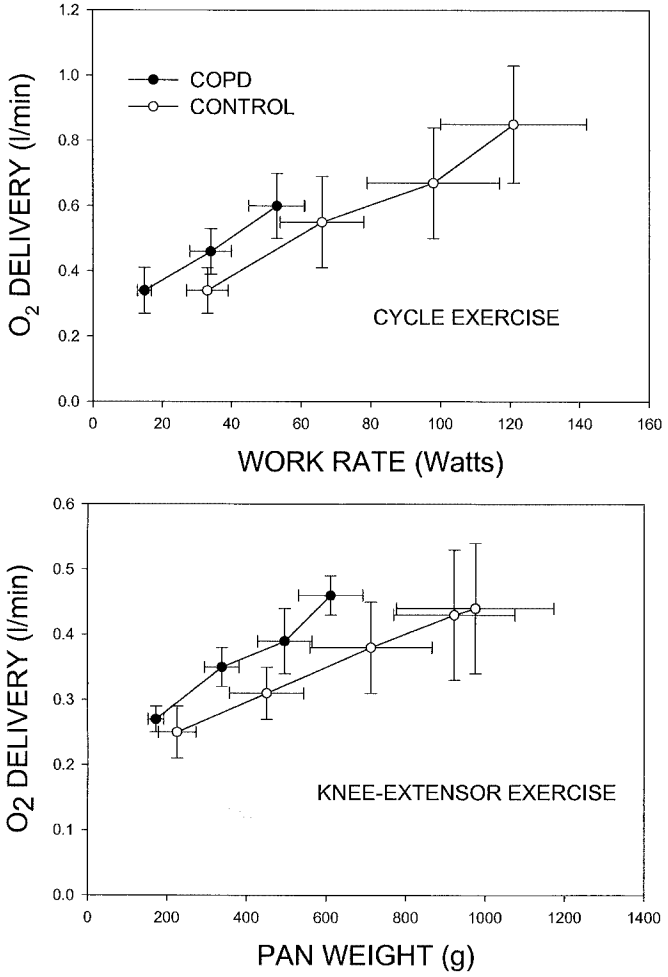

Figure 2. The relationship between oxygen (O_2) delivery to the exercising muscles and work rate in patients with COPD and control subjects during both cycle exercise (*upper panel*) and single leg knee-extensor exercise (*lower panel*).

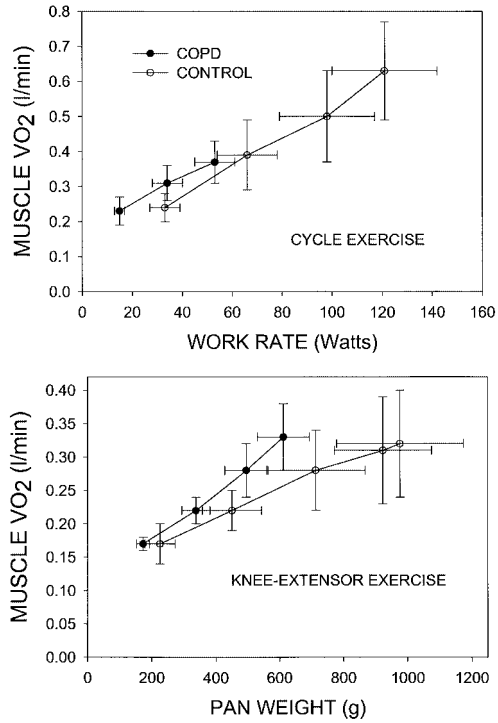

Figure 3. The relationship between muscle $\dot{V}O_2$ and work rate in patients with COPD and control subjects during both cycle exercise (*upper panel*) and single leg knee-extensor exercise (*lower panel*).

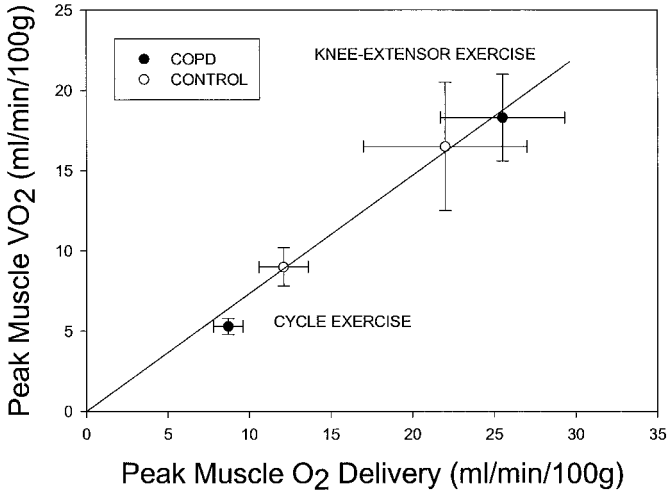

Figure 4. Similar relationship between peak muscle $\dot{V}O_2$ and O_2 delivery in patients with COPD and control subjects during cycle exercise and single knee-extensor exercise. Note that the much larger active muscle mass assumed for cycle exercise ($\sim$ 7 kg) results in a low $\dot{V}O_2$ per 100 g of tissue in comparison with the knee-extensor exercise (active muscle mass $\sim$ 2 kg).

current patients goes beyond a compensation for reduced Ca_{O_2}, which was somewhat mild during cycle exercise (Table E1 in the online supplement) and not significant during knee-extensor exercise (Table E2 in the online supplement), but appears to more likely linked to the increased metabolic demand of their type II rich muscle.

It has previously been demonstrated, noninvasively, that moving from cycle exercise to isolated single leg knee-extensor exercise resulted in a large increase in the amount of maximal work (per unit of muscle mass) of the quadriceps in patients with COPD (13). This was interpreted as evidence of a metabolic reserve capacity in these patients, as has been previously recognized in normal healthy subjects (48). The current data afford the opportunity to go beyond the work rate per unit of muscle achieved in the whole body exercise and the isolated muscle and to examine the relationship between O_2 delivery and $\dot{V}O_2$ during the two exercise modalities in both patients with COPD and matched control subjects (Figure 4). Figure 4 illustrates the finding that a large increase in O_2 delivery can be used to support a proportional increase in $\dot{V}_{O_2}$ in both groups. This finding supports the concept that patients with COPD have a significant metabolic reserve capacity that is only evident when their muscles are somewhat freed from the constraints of the cardiopulmonary system. It is important to note that this interpretation of the data does not take into account the apparent mechanical inefficiency exhibited by these patients, as already recognized and attributed to fiber type changes. Thus, although these patients with COPD appear to have a large metabolic reserve capacity, this does not appear to directly translate a proportional increase in muscular work capacity. It is also interesting to note that the slope of this relationship between O_2 delivery and $\dot{V}O_2$ is similar to that previously reported for the transition between cycle and knee-extensor exercise in well-trained healthy subjects (48). This suggests that similarly across well-trained young, healthy old, and patients with COPD, skeletal muscle has the ability to consume more O_2 as O_2 demand and delivery are enhanced by switching from an exercise paradigm that is less centrally limited.

Myoglobin has been suggested to be important in O_2 transport from blood to muscle cells (49) and has previously been reported to be reduced in patients with COPD (50). The current data (Table 2) are at the high end of the range of myoglobin concentration previously reported in humans of 4 to 8 mg/g of wet muscle (50, 51) but were not different between control subjects and patients. It was previously reported that older subjects, who tend to have a greater predominance of type I fibers than young control subjects, had a small (10%) increase in myoglobin concentration compared with their young counterparts (53). The current data are quite different from the previous findings because neither did the aged control subjects ($\sim$ 65 years) demonstrate a convincing relative increase in type I fibers nor did the patients with COPD reveal a decreased myoglobin concentration despite muscle fiber type changes in the appropriate direction (an increased proportion of type II fibers). Based on studies of diving mammals exposed to long periods of hypoxia (52, 53), in which the intramuscular myoglobin concentration is elevated, it could be hypothesized that patients with COPD may adaptively increase their myoglobin concentration in response to their resting and exercise-induced hypoxemia (Table 2, and Tables E1 and E2 in the online supplement). However, the power of exercise training (54) and inactivity (55) in other animal species suggest that any changes in myoglobin concentration due to hypoxemia may be offset by inactivity in the COPD population.

Skeletal Muscle Capillarity

Typically, the assessment of capillarity in patients with COPD has revealed rarefaction (26, 56). In the current study, we failed to find a difference in capillarity between patients with COPD and control subjects (Table 2). Not only was the capillarity remarkably similar, but comparing the four patients with COPD with eight normal healthy control subjects (four of the current control subjects and four additional control subjects, not matched for age, activity, etc.) showed the same relationship between

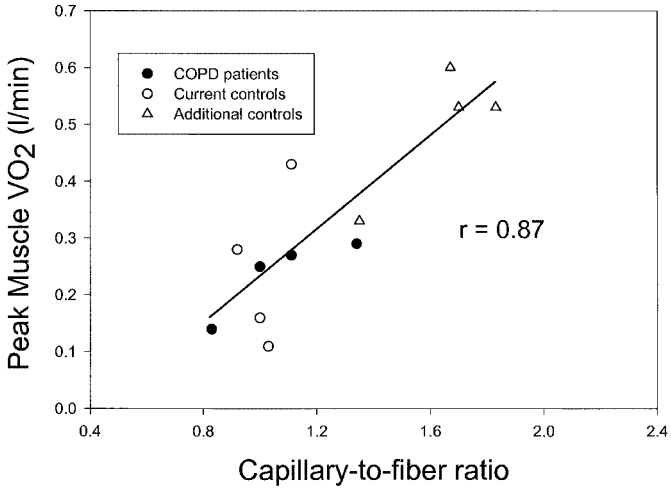

Figure 5. The relationship between peak muscle $\dot{V}O_2$ during single knee-extensor exercise and capillary-to-fiber ratio for patients with COPD and healthy but inactive control subjects. Four additional control subjects, somewhat more physically active and not age matched (53 ± 3 years), who were studied during a chronic heart failure study in our laboratories, have been included to widen the scope of the data and facilitate the regression analysis.

peak muscle $\dot{V}O_2$ (during knee-extensor exercise) and capillary-to-fiber ratio (Figure 5). This finding supports the concept that despite age and health status differences, the structural capacity to transport O_2 may be of primary importance in determining maximal O_2 flux (57, 58) and that this relationship is intact in patients with COPD. The capillary network is relatively plastic and is consequently altered by exercise and inactivity (59). Although this is not the only research that failed to identify a difference in capillarity between patients with COPD and control subjects (56), a possible explanation for this finding is that a significant effort went into matching the physical activity levels of relatively active patients with COPD (most had recently partaken in the University of California San Diego Pulmonary Rehabilitation Program) with inactive control subjects.

Metabolic Capacity

The current findings that citrate synthase activity and mitochondrial volume are not different between control subjects and patients with COPD (Table 2) are both internally consistent and indicative of a similar metabolic capacity in the two groups. This is supported by the almost identical skeletal muscle $\dot{V}O_2$max achieved during knee-extensor exercise in the control subjects and patients with COPD, albeit with different work efficiencies as discussed (Figure 3). Prior investigations have reported diminished oxidative enzymes (27, 60), such as citrate synthase activity, in patients with COPD. The relatively low and similar values in both groups for both citrate synthase activity and mitochondrial volume suggest that the matching of patients and control subjects in the current research was, based on these exercise sensitive criteria (61, 62), very good. However, it is somewhat surprising that these data are so similar in view of the relative paucity of type I muscle fibers in the patients with COPD (Table 2), expected to be rich in mitochondria. This fall in type I muscle fibers and the potential reduction in mitochondrial volume was somewhat tempered by the rise in type IIA fibers that still have a large oxidative capacity relative to the type IIB fibers. It is also possible that an adaptive process associated with the fiber type changes has altered the mitochondrial volume typically associated with each fiber type in the patients with COPD. Along the same theme, it is interesting to note that despite the significant differences in muscle fiber type, there was no apparent difference in arterial or venous blood pH at the same absolute work rates or at maximal exercise. Venous lactate outflow levels were similar at submaximal workloads but were higher at maximal exercise in the control subjects, accompanying the greater work rate achieved by this group. Again, these data indicate that a given work rate was similar in terms of relative metabolic stress between these two groups.

Disuse, Dysfunction, and Myopathy

Here it is important to clearly define the terms often used to debate issues of muscle function in patients with COPD: disuse being a reduction in muscle use, dysfunction being abnormal or impaired function, and myopathy being a disease of muscle. Continuing to recognize the importance of appropriate control data and within the confines of these definitions, the current data offer some support for the concept that patients with COPD experience a form of myopathy and dysfunction. The elevation in type II fibers and the resultant reduction in mechanical efficiency during muscular work could certainly be considered a destructive process (myopathy) or abnormal or impaired function (dysfunction). However, the current data also reveal similarities in mitochondrial enzyme activities, metabolic scope, metabolic response in terms of lactate production and blood pH, fiber size, and structure–function relationships in the patients with COPD when compared with activity-matched control subjects. Had the patient data been compared with more active individuals, many of these variables may have appeared abnormal and could have easily been classified as the result of muscle disuse. Therefore, it may be concluded that patients with COPD demonstrate limited myopathic or dysfunctional changes in skeletal muscle when compared with appropriate control subjects.

In summary, this research documents a mechanical inefficiency in small subset of patients with COPD that becomes clearly evident when skeletal muscle is studied in isolation from central limitations. Accompanying and perhaps responsible for this altered mechanical efficiency in these patients is a substantial increase in the number of type II muscle fibers. Despite these differences the skeletal muscle of patients with COPD revealed a similar maximal metabolic capacity, mitochondrial density, citrate synthase activity, capillarity, a normal relationship between capillarity and maximal metabolic capacity, and, like the control subjects, the capacity to use more O_2 with a change in exercise paradigm that allows greater O_2 delivery per unit of muscle. Thus, it must be concluded that although there are apparent differences in the skeletal muscle of patients with COPD, which may to some extent be described as dysfunction or even a myopathy, these differences do not impact all aspects of muscle function and structure.

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