REDUCED MECHANICAL EFFICIENCY IN COPD, BUT NORMAL PEAK VO\textsubscript{2} WITH SMALL MUSCLE MASS EXERCISE

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ABSTRACT:

We studied 6 patients with COPD (FEV1 = 1.1 ± 0.2 L, 32% of predicted) and 6 age and activity level matched controls 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 O2 supply, utilization and structure. Maximal work rates and single leg maximal oxygen consumption (controls = 0.63 ± 0.1; COPD = 0.37 ± 0.1 l/min) were significantly greater in the control group during bicycle exercise. During knee-extensor exercise this difference in maximal oxygen consumption disappeared, while maximal work capacity was reduced (flywheel resistance: controls = 923 ± 198; COPD = 612 ± 81 g) revealing a significantly reduced mechanical efficiency (work per unit O2 consumed) with COPD. The patients had an elevated number of less efficient Type II muscle fibers while 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 is no longer overshadowed by the decrement in lung function.

Word Count 200

KEY WORDS: lung disease, Oxygen consumption, blood flow, fiber type, quadriceps
INTRODUCTION:

Although researchers have recently focused their attention on the potential involvement of skeletal muscle in the pathophysiology of COPD (7, 28, 32, 35, 41) there is currently no accord on this matter (1). An issue that has clouded conclusions is the difference between skeletal muscle dysfunction and disuse (52). 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 (32, 33, 52, 67). Thus, the selection of appropriately inactive controls 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 (32, 35, 64). The use of a large muscle mass exercise paradigm, in COPD patients, 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 (3), allows the measurement of O2 supply and utilization to a known mass of active muscle (53) under conditions of limited ventilatory demand, and thus is an ideal exercise paradigm with which to study the skeletal muscle of patients with COPD (59). The ability to monitor muscle O2 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\textsubscript{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 to 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 to controls in
terms of maximal work rate, muscle blood flow, and VO\textsubscript{2}, while 2) during single leg knee-
extensor exercise the skeletal muscle of patients with COPD will have a more similar
physiological response to that of the control subjects. This work has been previously published in
abstract form (51).
METHODS:

Subjects: Six patients with COPD (FEV₁ = 1.1 ±0.2, 32 ± 5% predicted ) and six healthy age, weight and activity matched controls volunteered according to the University of California San Diego, Human Research Protection Program requirements. Controls were determined to be sedentary and the majority of the COPD patients had completed the UCSD Pulmonary Rehabilitation Program (within 8-24 months), but did not differ from the controls in terms of current physical activity (13, 23, 70). 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 Company, Holland). Cadence was self selected, but for most subjects fell between 60-80 revolutions per minute. The second exercise paradigm was knee-extensor exercise, that limits muscular work to the quadriceps of one leg (3, 53, 58), this was performed with subjects reclined on a padded chair with the knee-extensor exercise ergometer placed in front of them (illustrated in Reference (57)) (see online supplement).

Experimental protocol: Within 1 wk 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 sterile technique as previously reported (49, 58)(see online supplement). Blood samples were taken from the arterial and femoral venous catheters to quantify arterial-venous O₂ concentration differences.

Following 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 3 work levels. Data were obtained at each level following the attainment of steady state exercise (2-4 mins depending upon the exercise intensity). Each exercise bout was completed in 8-12 minutes. Minute ventilation, pulmonary VO$_2$, and VCO$_2$, were calculated by a commercially available software package (Consentius Technologies, Salt Lake, UT) integrated with a Perkin-Elmer MGA 1100 mass spectrometer, a gas mixing chamber, and a Fleisch pneumotachograph #3 (Hans-Rudolph)(58).

**Blood analyses:** PO$_2$, PCO$_2$, 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$_2$ x [Hb] g/100ml x measured O$_2$ saturation (fraction) + 0.003 ml O$_2$/100 ml of blood x measured PO$_2$ (mmHg). Arterial-venous [O$_2$] difference was calculated from the difference in radial artery and femoral venous oxygen 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 mid-line of the muscle in four COPD patients and four controls. 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 0.1M sodium cacodylate buffer; total osmolarity, 1100 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 (4, 26).

**Statistical Analyses:** ANOVA and a Tukey Post Hoc analysis were utilized 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 COPD patients and controls (Table 1). The muscle characteristics determined on needle biopsy samples are presented in Table 2. There were significant differences in the proportions of muscle fiber type, with the COPD patients exhibiting reduced proportion of Type I fibers. The elevated proportion of Type II fibers in the COPD patients was evident in both Type IIA and Type IIX, but the greatest difference was apparent in the Type IIX fibers that were ~2.5 times as numerous (expressed as a percentage of fibers) compared to controls. The COPD patients did not reveal altered capillarity when expressed as capillary density, capillary fiber ratio, or number capillaries around a fiber. Mitochondrial volume density and CSA were relatively low in both groups (20), but were not different between the COPD patients and controls. It should be noted that these mitochondrial measurements are not fiber type specific and therefore represents an average for all fibers. Muscle fiber cross-sectional area was not different between the two groups. There was no difference in [myoglobin] between the COPD patients and controls, with both groups falling within the previously reported range for this and other techniques used on human tissue (50).

**Bicycle exercise:** The major physiological variables recorded during cycle exercise are reported in Table E1 (in online repository). In terms of maximum work rate the control subjects achieved a 128 % greater work rate than the patients with COPD. As expected leg VO.$\text{max}$ 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 oxygen availability such as arterial Hb saturation, arterial PO$_2$, and CaO$_2$ were reduced throughout exercise in the patients with COPD when compared to controls. However, the elevated 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 to controls. 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 to the controls while both leg $VO_2$ and pulmonary $VO_2$ tended to be elevated, but without statistically significant differences. Measures of metabolic stress such as arterial and venous pH and venous lactate out flow revealed similar responses to the submaximal work rates in both patients and controls 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 to the controls. Perceived breathlessness was accelerated in the patients with COPD, while the assessment of muscle fatigue indicated similar muscular distress at the limited work rates achieved.

**Single leg-knee extensor exercise:** The major physiological variables recorded during knee-extensor exercise are reported in Table E2 (in online respository). Using this exercise modality the control subjects achieved a 50% greater maximum work rate than the patients with COPD. However, unlike bicycle exercise leg $VO_{2\text{max}}$ and maximal leg blood flow were not attenuated in the patients with COPD despite the difference in maximal work rate. $CaO_2$ was not lower throughout exercise in the patients with COPD when compared to controls. 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 to controls. 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, test $O_2$ extraction was again significantly attenuated in the patients in comparison to the controls while
leg VO$_2$ was elevated. As during cycle exercise, measures of metabolic stress such as arterial and venous pH and venous lactate out flow revealed very similar responses to the submaximal work rates in both patients and controls. 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 to the controls. 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 to cycle exercise. Unlike cycle exercise, during maximal knee-extensor exercise patients were able to attain the same leg VO$_{2\text{max}}$ as the controls. 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 to the controls. Leg blood flow for a given work rate was elevated in the patients with COPD compared to the controls subjects during both exercise paradigms. As CaO$_2$ was not 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, while only the controls 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 controls and patients with severe COPD. Functionally, the current data indicate that COPD patients 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, non hypoxemic etc.), it is important not to generalize these findings to the whole diverse population of COPD patients.

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 (24, 25) or by the expression of myosin heavy chain isoforms (37, 65). This is the opposite of changes in fiber type associated with healthy aging (29). The cause of this unexpected fiber type composition may be the result of extended or intermittent exposure to conditions of reduced O2 availability (22) or a consequence of disuse (2, 71). In the current study considerable effort was made to find control subjects who exhibited a similar level of activity as the COPD patients (who for this population were relatively active). Consequently, although possible (5), 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. Additionally, 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 (\( \text{PaO}_2 = 87 \ \text{mmHg} \)) (Table 1) that increased only slightly (\( \text{PaO}_2 = 78 \ \text{mmHg} \)) at maximal cycle exercise (Table E1, in online repository), 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 (8), these data support the concept that hypoxia itself (albeit mild in this case) may induce the observed shift in fiber type exhibited by these patients (22).

The economy of constant muscular work is, beyond a threshold, inversely related to exercise intensity (21). Therefore, there is an apparent excess \( \text{O}_2 \) cost for a given amount of work during high intensity muscular contraction, the mechanism for which is not clearly understood (48). As exercise intensity and or rate of force development increases there is a growing reliance upon type II muscle fibers that has been proposed to lead to less efficient muscular work (10). There are convincing data at both the in \textit{in vitro} (15, 73) and \textit{in vivo} (10, 21) level 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 ATPase driven calcium pump whose activity is five to ten times faster in the Type II compared to Type I fibers (15, 73). However, proportionality between maximum shortening velocities, ATPase activities (6), 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 (12). Regardless of mechanism, it is
apparent that fiber type differences in these COPD patients 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 (64) and not simply assessing the whole body response to exercise, there are certainly many other investigations that have failed to reveal such a finding (1).

**Oxygen transport and utilization:** Several studies have reported that exercise tolerance is improved by O₂ supplementation in patients with COPD (36, 44, 60). Recognizing the impact of reducing hypoxemia in COPD and evidence of an elevated O₂ cost of breathing (31), which may steal blood from the limb muscles (17, 60) it had been suggested that O₂ delivery to the exercising muscle of patients with COPD may be compromised (32). However, the current data and the few other studies that have directly assessed blood flow, O₂ delivery and O₂ uptake across the exercising muscle of COPD patients, indicate that at an absolute submaximal work rate these parameters appear to be well preserved or even increased (Tables E1 and E2 in online repository, Figures 1 and 2)(32, 64). Healthy subjects have also been documented to increase muscle blood flow to compensate for reductions in CaO₂ (16). However the increase in muscle blood flow and even O₂ delivery in the current patients goes beyond a compensation for reduced CaO₂, which was somewhat mild during cycle exercise (Table E1, in online respository) and not significant during knee-extensor exercise (Table E2, in online respository), but appears to more likely linked to the increased metabolic demand of their Type II rich muscle.

It has previously been demonstrated, non-invasively, 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 (60). This was
interpreted as evidence of a metabolic reserve capacity in these patients, as has been previously recognized in normal healthy subjects (55). 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 O₂ delivery and O₂ utilization during the two exercise modalities in both COPD patients and matched controls (Figure 4). Figure 4 illustrates the finding that a large increase in O₂ delivery can be utilized to support a proportional increase in O₂ consumption 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 COPD patients appear to have a large metabolic reserve capacity this appears to not directly translate a proportional increase in muscular work capacity. It is also interesting to note that the slope of this relationship between O₂ delivery and utilization is similar to that previously reported for the transition between cycle and knee-extensor exercise in well trained healthy subjects (54), suggesting that similarly across well trained young, healthy old, and patients with COPD, skeletal muscle has the ability to consume more O₂ as O₂ demand and delivery are enhanced by switching from an exercise paradigm that is less centrally limited.

Myoglobin has been suggested to be important in O₂ transport from blood to muscle cells (56) and has previously been reported to be reduced in patients with COPD (42). The current data (Table 2) are at the high end of the range of myoglobin concentration previously reported in humans of 4-8 mg/g of wet muscle (42, 43), but were not different between controls and patients. It was previously reported that older subjects, who tend to have a greater predominance of Type I
fibers than young controls, had a small (10%) increase in myoglobin concentration compared with their young counterparts (43). The current data are quite different from the previous findings as the aged controls (≈65 yrs) did not 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 upon studies of diving mammals exposed to long periods of hypoxia (9, 27), in which the intramuscular myoglobin concentration is elevated, it could be hypothesized that COPD patients may adaptively increase their myoglobin concentration in response to their resting and exercise induced hypoxemia (Table 2, and Tables E1 and E2 in online repository). However, the power of exercise training (47) and inactivity (46) 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 COPD patients has revealed rarefaction (25, 74). In the current study several we failed to find a difference in capillarity between the COPD patients and controls (Table 2). Not only was the capillarity remarkably similar, but comparing the 4 COPD patients with 8 normal healthy controls (4 of the current controls and 4 additional controls, not matched for age, activity etc.) showed the same relationship between peak muscle VO₂ (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 O₂ may be of primary importance in determining maximal O₂ flux (39, 40) and that this relationship is intact in patients with COPD. The capillary network is relatively plastic and is consequently altered by exercise and inactivity (61). Although this is not the only research that failed to identify a difference in capillarity between COPD patients and
controls (74), a possible explanation for this finding is that a significant effort went into matching the physical activity levels of relatively active COPD patients (most had recently partaken in the UCSD Pulmonary Rehabilitation Program) with inactive control subjects.

**Metabolic capacity:** The current findings that citrate synthase activity and mitochondrial volume are not different between controls and COPD patients (Table 2) are both internally consistent and indicative of similar metabolic capacity in the two groups. This is supported by the almost identical skeletal muscle VO2max achieved during knee-extensor exercise in the controls and patients with COPD, albeit with different work efficiencies as discussed (Figure 1). Prior investigations have reported diminished oxidative enzymes (24, 34), 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 controls in the current research was, based on these exercise sensitive criteria (19, 30), 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 COPD patients (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 controls,
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; 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 COPD
patients 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 COPD patients 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 COPD patients demonstrate limited
myopathic or dysfunctional changes in skeletal muscle when compared with appropriate controls.

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 COPD patients revealed a similar maximal
metabolic capacity, mitochondrial density, citrate synthase activity, capillarity, a normal relationship between capillarity and maximal metabolic capacity and, like the controls, the capacity to utilize more O\textsubscript{2} with a change in exercise paradigm that allows greater O\textsubscript{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.
ACKNOWLEDGEMENTS:

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REFERENCES:


Figure Legends:

**Figure 1.** The relationship between 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 2.** The relationship between muscle VO$_2$ 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 3.** Light micrographs of histochemical sections stained for both capillaries and fiber type in COPD and control subjects.

**Figure 4.** Similar relationship between peak muscle VO$_2$ and O$_2$ delivery in patients with COPD and control subjects during cycle exercise and single knee-extensor exercise. Note: The much larger active muscle mass assumed for cycle exercise (7kg) results in a low VO$_2$ per 100g of tissue in comparison to the knee-extensor exercise (active muscle mass ≈ 2 kg).

**Figure 5.** The relationship between muscle VO$_{2\text{max}}$ during single knee-extensor exercise and capillary-to-fiber ratio for patients with COPD and healthy, but inactive controls. 4 additional controls, somewhat more physically active and not age matched (53 ± 3 yrs), 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.
Table 1: Subject characteristics.

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<thead>
<tr>
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<th>COPD</th>
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<tbody>
<tr>
<td><strong>Number of subjects</strong></td>
<td>6</td>
<td>6</td>
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<tr>
<td>Age (years)</td>
<td>65.4 ± 4.3</td>
<td>64.0 ± 3.6</td>
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<tr>
<td>Height (cm)</td>
<td>171.2 ± 3.4</td>
<td>179.4 ± 4.8</td>
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<tr>
<td>Weight (kg)</td>
<td>81.7 ± 6.3</td>
<td>82.5 ± 11.2</td>
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<tr>
<td>Body mass index (kg/m²)</td>
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<td>25.6 ± 1.7</td>
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<tr>
<td>Quadriceps mass (kg)</td>
<td>2.0 ± 0.1</td>
<td>1.8 ± 0.2</td>
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<tr>
<td>Leg muscle mass (kg)</td>
<td>6.3 ± 0.3</td>
<td>7 kg ± 0.2</td>
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<tr>
<td>FEV₁ (liters) (% predicted)</td>
<td>3.1 ± 0.3 (106 ± 4.0)</td>
<td>1.1 ± 0.2 (32.4 ± 4.6) *</td>
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<td>FVC (liters) (% predicted)</td>
<td>4.0 ± 0.4 (102.6 ± 0.4)</td>
<td>3.1 ± 0.4 (70.9 ± 4.3) *</td>
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<td>FEV₁/FVC (%)</td>
<td>77.8 ± 1.3</td>
<td>33.6 ± 3.2 *</td>
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<td>Resting arterial HbO₂ (%)</td>
<td>97.0 ± 0.3</td>
<td>95.2 ± 0.6 *</td>
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<td>Resting arterial PO₂ (mmHg)</td>
<td>97.7 ± 2</td>
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<td>Arterial [Hb] (g/dl)</td>
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<td>Number of prior steroid users</td>
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* significantly different from controls; % predicted derived from Crapo et al. (11); Leg muscle mass estimate based upon 3.5 times the measured quadriceps muscle mass (14).
Table 2: Vastus Lateralis muscle characteristics.

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<tr>
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<tbody>
<tr>
<td>% area of type I fibers</td>
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<td>21 ± 6 *</td>
</tr>
<tr>
<td>% area of type II fibers</td>
<td>50 ± 7</td>
<td>79 ± 6 *</td>
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<tr>
<td>% area of type IIA fibers</td>
<td>36 ± 12</td>
<td>42 ± 4 *</td>
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<tr>
<td>% area of type IIX fibers</td>
<td>16 ± 6</td>
<td>39 ± 2 *</td>
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<tr>
<td>Capillary density (capillaries/mm²)</td>
<td>343 ± 8</td>
<td>335 ± 14</td>
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<tr>
<td>Capillary-to-fiber ratio</td>
<td>1.01 ± 0.04</td>
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<td>Number of capillaries around a fiber</td>
<td>2.7 ± 0.2</td>
<td>2.6 ± 0.2</td>
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<td>3.7 ± 0.2</td>
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<tr>
<td>Fiber cross-sectional area (µm²)</td>
<td>2958 ± 90</td>
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<td>Citrate synthase activity (µmol/min/g tissue)</td>
<td>12.1 ± 1.1</td>
<td>12.4 ± 1.4</td>
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<tr>
<td>[myoglobin] (mg/g wet weight)</td>
<td>7.4 ± 0.9</td>
<td>7.3 ± 1.0</td>
</tr>
</tbody>
</table>

* significantly different from controls. 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).
Figure 1:
Figure 2:

**Cycle Exercise**
- **Muscle VO2 (l/min)** vs. **Work Rate (Watts)**
- COPD vs. Control

**Knee-Extensor Exercise**
- **Muscle VO2 (l/min)** vs. **Pan Weight (g)**
- COPD vs. Control
Figure 3.

COPD  
(20% Type I fibers)

CONTROL  
(50% Type I fibers)
Figure 4.

Peak Muscle VO₂ (ml/min/100g)

Peak Muscle O₂ Delivery (ml/min/100g)

- COPD
- CONTROL

KNEE-EXTENSOR EXERCISE

CYCLE EXERCISE
Figure 5.

![Graph showing the relationship between Capillary-to-fiber ratio and Peak Muscle VO\textsubscript{2} (l/min). The graph includes data points for COPD patients, current controls, and additional controls. The Pearson correlation coefficient, r, is 0.87.]
ONLINE DATA SUPPLEMENT

REDUCED MECHANICAL EFFICIENCY IN COPD,
BUT NORMAL PEAK VO$_2$ WITH SMALL MUSCLE MASS EXERCISE

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          Luke J. Haseler
          Sundar R.D. Mudaliar
          Robert Henry
          Andrew L. Ries
          Odile D. Mathieu-Costello
          Peter D. Wagner
METHODS:

Subjects: Six patients with severe COPD (FEV\(_1\) = 1.1 ±0.2, 32 ± 5% predicted) and six healthy age, weight and activity matched controls volunteered to participate in this study. Health histories and physical examinations were completed and written informed consent was obtained according to the University of California San Diego, Human Subjects Committee requirements. Each subject’s daily physical activity was assessed using a modified Minnesota Leisure Time Physical Activity Questionnaire that correlates well with exercise testing results (13, 23, 70) and all controls were determined to have no previous history of physical training or recreational sport and no regular or occasional physical exercise above that required for daily activities. The majority of the COPD patients had completed the UCSD Pulmonary Rehabilitation Program, but did not differ from the controls in terms of current physical activity. The 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 Company, Holland). Cadence was self selected, but for most subjects fell between 60-80 revolutions per minute. The second exercise paradigm was KE for which subjects reclined on a padded chair with the KE ergometer placed in front of them (illustrated in Reference (57)). The resistance to knee-extension was provided via a fiberglass bar attached to the crank of the ergometer and to a specially designed heel and shin brace worn by the subject. Work rate was prescribed and measured as a percentage of the maximum resistance (weight (g), resisting the fly-wheel turning) at the end of the preliminary KE graded maximal test. A fixed rate of sixty dynamic contractions of the knee-extensor muscles per minute were performed. Contractions of the quadriceps muscle group caused the lower part of the leg to extend from approximately 90 to
170° flexion. The momentum of the flywheel returned the relaxed leg to the start position without knee flexor contraction. Subject reports, force tracings, electromyography, and T2 weighted magnetic resonance imaging (3, 53, 58) support the conclusion that active contractions are limited to the quadriceps muscles during this exercise modality.

**Preliminary tests:** Subjects performed a minimum of two training bouts on both the cycle ergometer and the KE ergometer to ensure familiarity with the exercise modalities. Within these practice periods subjects performed two graded maximal exercise tests on each ergometer (work rate increased according to individual capability) and a simulated final experiment adhering to the planned protocol, but without any vascular catheterization. Minute ventilation, pulmonary VO$_2$, and VCO$_2$, were calculated by a commercially available software package (Consentius Technologies, Salt Lake, UT) integrated with a Perkin-Elmer MGA 1100 mass spectrometer, a gas mixing chamber, and a Fleisch pneumotachograph #3 (Hans-Rudolph)(58).

**Experimental protocol:** Within 1 wk of the preliminary studies, subjects returned to the laboratory in the morning where two catheters (radial artery and left femoral vein) and a thermocouple (left femoral vein) were emplaced using sterile technique as previously reported (49, 58). During exercise, iced saline was infused at a constant rate through the femoral venous catheter at flow rates sufficient to decrease blood temperature at the thermocouple by $\approx$1°C. Infusions were continued for 15-20 s until femoral vein temperature had stabilized at its new lower value. Saline injection rate was measured by weight change in a reservoir bag suspended from a force transducer that was calibrated before and after each experiment. The calculation of blood flow was performed on thermal balance principles as detailed by Andersen and Saltin (4). Blood samples were taken from the arterial and femoral venous catheters to quantify arterial-venous O$_2$ concentration differences.
Following 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. This was followed by further 5% increases in work rate as tolerated to ensure a true maximum was achieved. Data were obtained at each level following the attainment of steady state exercise (2-4 mins depending upon the exercise intensity). Each exercise bout was completed in 8-12 minutes. The sequence of events at each work rate was as follows: 1) 3 ml arterial and femoral venous blood samples were first taken and femoral vein blood flow was then measured. This sequence was repeated to yield duplicate measurements of all variables.

**Blood analyses:** PO$_2$, PCO$_2$, 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.). Between each sample, electrodes were calibrated and demonstrated acceptable reproducibility (SD of repeated determinations: PO$_2$ and PCO$_2$, 1.5 mmHg; pH, 0.003). O$_2$ concentration was calculated as 1.39 ml O$_2$ x [Hb] g/100ml x measured oxyhemoglobin fraction + 0.003 ml O$_2$/100 ml of blood x measured PO$_2$ (mmHg). Arterial-venous [O$_2$] difference was calculated from the difference in radial artery and femoral venous oxygen 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 mid-line of the muscle in four COPD patients and four controls. The 5 mm diameter biopsy needle was attached to sterile tubing and a syringe to apply a negative pressure to assist in the
muscle sample collection (18). Local anesthetic (1% xylocaine) was applied in a circle around the tissue surrounding the biopsy site, to avoid tissue edema and muscle fiber ultrastructural alterations induced by infiltration of anesthetic into the biopsy site itself (66). The muscle samples from each biopsy were either immediately frozen in isopentane cooled to -140°C in liquid nitrogen and stored at -80°C for subsequent histochemical and biochemical analyses, or immersion-fixed in glutaraldehyde fixative (6.25% glutaraldehyde solution in 0.1M sodium cacodylate buffer; total osmolarity, 1100 mOsm; pH 7.4) for processing for electron microscopy and morphometry.

Citrate synthase activity (CSA). The CSA activity was determined spectrophotometrically at 30°C, in a Milton Roy model 21D spectrophotometer by the method of Srere (69). Briefly, the muscle tissue was homogenized in an ice bath using a glass Konte Duall tissue grinder mounted on a variable speed drill. The homogenate was diluted in an EDTA and EGTA phosphate buffer to a known concentration, and spectrophotometry performed in a TRIS buffer. The Acetyl CoA reagent was in the form of a sodium salt. The homogenate from each sample was aliquotted into three duplicate samples and assayed in triplicate. The coefficient of variation of CSA across triplicates of the same sample was 0.1%.

Myoglobin concentration: The myoglobin assay utilized was that previously reported by Reynafarje (50). The muscle tissue was cleaned of fat and connective tissue, weighed and homogenized. A phosphate buffer, 0.04M at pH 6.6 was added in the proportion of 19.25 ml/g tissue and this was then homogenized for 30 second periods until no solid particles were discernible. The resulting homogenate was then centrifuged at 28000 g for 50 minutes. From the clear supernatant a 3 ml sample was transferred to a small test tube where pure CO was passed through it. After 8 minutes the flow of gas was interrupted and a pinch of dry dithionate was
added to ensure the complete reduction of the pigments. The equilibrated solution was transferred to a cuvette and the optical density read at 538 and 568 µm in a Milton Roy model 21D spectrophotometer. The difference in optical density at 538 and 568 µm was multiplied by the factor 117.3 with the resulting value representing myoglobin per gram of wet muscle tissue (50).

**Histochemistry:** Eight µm-thick transverse sections were cut at -24°C on a cryostat (Jung-Reichert Cryocut 1800) and kept at -20°C until histochemical processing, which was performed within a week of sectioning. After 5 min fixation in a Guth and Samaha fixative at room temperature, sections were incubated at 37°C for 1 hr in lead (Pb)-ATPase staining medium to simultaneously stain for fiber types I and II and capillaries (63). Fiber types I, IIA and IIX (68) were identified by metachromatic histochemical staining (45) of adjacent sections from each tissue block.

**Tissue preparation for microscopy:** The glutaraldehyde-fixed samples were completely cut into thin longitudinal strips and processed for electron microscopy as described previously (38). From each biopsy, four blocks were cut into 1µm-thick transverse sections with an LKB Ultrotome III and stained with 0.1% aqueous Toluidine Blue solution. The angles of sectioning used to provide the transverse sections were determined as described previously (38). Ultrathin sections (50-70nm) were cut transversely to the muscle fiber axis from each block and were contrasted with uranyl acetate and bismuth subnitrate (62). Electron micrographs for morphometry were taken on 70 mm films with a Zeiss 10 electron microscope.

**Morphometry:** The relative cross-sectional area and number of type I and type II fibers was estimated by point-counting using an eyepiece square grid test A100 (72) on histochemical sections examined at a magnification of 250x with a light microscope. On average, 8.3 ± 0.9
fields, randomly selected by systematic random sampling were measured, yielding 201 ± 21 fiber profiles in each sample. Capillary density (i.e. capillary number per fiber cross-sectional area), capillary-to-fiber ratio (i.e. capillary number per fiber number), capillary number around a fiber and fiber cross-sectional area were measured by point-counting on 1µm-thick sections examined at a magnification of 400x with a light microscope. On average, 6.4 ± 0.6 fields were measured per sample, yielding 89 ± 12 fiber profiles for each biopsy. The volume density of mitochondria, myofibrils and lipid droplets per volume of muscle fiber was estimated by point-counting at a final magnification of 49,000 x on 20 fields obtained by systematic random sampling on one ultrathin transverse section from each block (total 80 fields/biopsy). A microfilm reader (Documator DL2, Jenoptic, Jena, Germany) was used to project contact prints of electron micrographs on a 144-point square grid. All morphometric measurements were performed in a blinded fashion, and the order of samples was randomized.

Thigh Volume Measurement: Using thigh length, circumference and skinfold measurements, thigh volume was calculated to allow an estimate of quadriceps femoris muscle mass, as utilized by Andersen and Saltin and others (4, 26). It should be recognized that this calculation of muscle mass and the consequent normalizing of blood flow and O₂ assume that this is the only muscle mass involved in the knee-extensor exercise, an assumption recently verified in the KE human exercise model (53).

Statistical Analyses: ANOVA and a Tukey Post Hoc analysis was utilized 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). Variables were considered significantly different when the p-value was 0.05 or less.
REFERENCES:


Table E1: Major physiological variables measured during incremental cycle exercise

<table>
<thead>
<tr>
<th>Work rate (Watts)</th>
<th>COPD Control</th>
<th>15 ± 2</th>
<th>34 ± 6</th>
<th>53 ± 8#</th>
<th>66 ± 12</th>
<th>98 ± 19</th>
<th>121 ± 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of maximum work rate</td>
<td>COPD Control</td>
<td>30 ± 1</td>
<td>64 ± 3</td>
<td>100</td>
<td>53 ± 2</td>
<td>80 ± 2</td>
<td>100</td>
</tr>
<tr>
<td>Arterial Hb saturation (%)</td>
<td>COPD Control</td>
<td>94 ± 1*</td>
<td>94 ± 1*</td>
<td>93 ± 2*#</td>
<td>97 ±</td>
<td>97 ± 1</td>
<td>97 ± 0.1</td>
</tr>
<tr>
<td>CaO₂ (ml O₂ /100 ml)</td>
<td>COPD Control</td>
<td>19.0 ± 1.5*</td>
<td>19.0 ± 1.5*</td>
<td>19.1 ± 1.4*#</td>
<td>20.0 ± 0.4</td>
<td>20.2 ± 0.3</td>
<td>20.5 ± 0.4</td>
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<tr>
<td>CvO₂ (ml O₂ /100 ml)</td>
<td>COPD Control</td>
<td>6.0 ± 0.8</td>
<td>5.6 ± 0.9</td>
<td>6.7 ± 1.0#</td>
<td>5.8 ± 0.4</td>
<td>5.3 ± 0.3</td>
<td>5.2 ± 0.4</td>
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<tr>
<td>Leg PaO₂ (mmHg)</td>
<td>COPD Control</td>
<td>79 ± 7*</td>
<td>80 ± 8*</td>
<td>78 ± 7*#</td>
<td>105 ± 2</td>
<td>109 ± 1</td>
<td>115 ± 3</td>
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<tr>
<td>Leg PvO₂ (mmHg)</td>
<td>COPD Control</td>
<td>21 ± 1</td>
<td>22 ± 2</td>
<td>25 ± 2</td>
<td>23 ± 1</td>
<td>22 ± 1</td>
<td>24 ± 1</td>
</tr>
<tr>
<td>Leg blood flow (l/min)</td>
<td>COPD Control</td>
<td>1.8 ± 0.3*</td>
<td>2.5 ± 0.5*</td>
<td>3.2 ± 0.6*#</td>
<td>2.7 ± 0.7</td>
<td>3.4 ± 0.9</td>
<td>4.1 ± 0.8</td>
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<tr>
<td>Leg O₂ delivery (l/min)</td>
<td>COPD Control</td>
<td>0.34 ± 0.1*</td>
<td>0.46 ± 0.1*</td>
<td>0.61 ± 0.1*#</td>
<td>0.55 ± 0.1</td>
<td>0.67 ± 0.2</td>
<td>0.85 ± 0.2</td>
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<tr>
<td>Leg O₂ extraction</td>
<td>COPD Control</td>
<td>69 ± 2*</td>
<td>69 ± 3*</td>
<td>62 ± 3</td>
<td>71 ± 2</td>
<td>74 ± 1</td>
<td>74 ± 2</td>
</tr>
<tr>
<td>Leg VO₂ (l/min)</td>
<td>COPD Control</td>
<td>0.23 ± 0.04*</td>
<td>0.31 ± 0.05*</td>
<td>0.37 ± 0.06*#</td>
<td>0.39 ± 0.10</td>
<td>0.50 ± 0.13</td>
<td>0.63 ± 0.14</td>
</tr>
<tr>
<td>Leg vascular conductance (ml/min/mmHg)</td>
<td>COPD Control</td>
<td>16.2 ± 2.7*</td>
<td>23.9 ± 5.4*</td>
<td>27.8 ± 5.7*#</td>
<td>24.8 ± 6.6</td>
<td>29.7 ± 7.5</td>
<td>33.8 ± 6.8</td>
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<tr>
<td>Arterial pH</td>
<td>COPD Control</td>
<td>7.42 ± 0.01</td>
<td>7.40 ± 0.01</td>
<td>7.36 ± 0.01</td>
<td>7.37 ± 0.01</td>
<td>7.35 ± 0.02</td>
<td>7.32 ± 0.02</td>
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<tr>
<td>Venous pH</td>
<td>COPD Control</td>
<td>7.34 ± 0.00</td>
<td>7.30 ± 0.01</td>
<td>7.24 ± 0.02</td>
<td>7.25 ± 0.02</td>
<td>7.20 ± 0.02</td>
<td>7.15 ± 0.02</td>
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<tr>
<td>Venous lactate outflow (mmol/min)</td>
<td>COPD Control</td>
<td>0.4 ± 0.1</td>
<td>0.7 ± 0.21</td>
<td>1.3 ± 0.4#</td>
<td>1.9 ± 0.9</td>
<td>3.0 ± 1.4</td>
<td>4.4 ± 2.1</td>
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<tr>
<td>Pulmonary VO₂ (l/min)</td>
<td>COPD Control</td>
<td>0.8 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>1.2 ± 0.1#</td>
<td>1.2 ± 0.1</td>
<td>1.5 ± 0.1</td>
<td>1.7 ± 0.1</td>
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<tr>
<td>Pulmonary Ve (l/min)</td>
<td>COPD Control</td>
<td>25 ± 20</td>
<td>31 ± 3</td>
<td>39 ± 3</td>
<td>45 ± 3</td>
<td>60 ± 4</td>
<td>72 ± 6</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>COPD Control</td>
<td>89 ± 5</td>
<td>97 ± 6</td>
<td>111 ± 7#</td>
<td>112 ± 11</td>
<td>122 ± 11</td>
<td>147 ± 14</td>
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<tr>
<td>Perceived muscle fatigue</td>
<td>COPD Control</td>
<td>2 ± 1</td>
<td>4 ± 1</td>
<td>6 ± 2#</td>
<td>6 ± 1</td>
<td>8 ± 2</td>
<td>9 ± 2</td>
</tr>
<tr>
<td>Perceived breathlessness</td>
<td>COPD Control</td>
<td>3 ± 1*</td>
<td>7 ± 2*</td>
<td>10 ± 0*</td>
<td>3 ± 1</td>
<td>5 ± 2</td>
<td>9 ± 2</td>
</tr>
</tbody>
</table>
* significantly different relationship from controls across work rates. # significantly different from controls at maximal exercise.
Table E2: Major physiological variables measured during single leg knee-extensor exercise

<table>
<thead>
<tr>
<th>Variable</th>
<th>COPD Control</th>
<th>Control</th>
<th>COPD Control</th>
<th>Control</th>
<th>COPD Control</th>
<th>Control</th>
<th>COPD Control</th>
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<th>COPD Control</th>
<th>Control</th>
<th>COPD Control</th>
<th>Control</th>
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</thead>
<tbody>
<tr>
<td>Fly wheel Resistance (g)</td>
<td>173 ± 20</td>
<td>338 ± 44</td>
<td>496 ± 68</td>
<td>612 ± 81</td>
<td>836 ± 195</td>
<td>923 ±</td>
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<tr>
<td>Percentage of maximum work rate</td>
<td>29 ± 1</td>
<td>55 ± 3</td>
<td>83 ± 2</td>
<td>100</td>
<td>90 ± 0</td>
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<tr>
<td>Arterial Hb saturation (%)</td>
<td>95 ± 1</td>
<td>95 ± 1</td>
<td>94 ± 1</td>
<td>95 ± 1</td>
<td>97 ± 0</td>
<td>97 ± 0</td>
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<tr>
<td>CaO₂ (ml O₂ /100 ml)</td>
<td>18.7 ± 1.5</td>
<td>18.6 ± 1.5</td>
<td>17.7 ± 1.6</td>
<td>18.4 ± 1.4</td>
<td>18.5 ± 0.6</td>
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<td>CvO₂ (ml O₂ /100 ml)</td>
<td>6.9 ± 0.5</td>
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<td>5.2 ± 0.6</td>
<td>5.4 ±</td>
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<tr>
<td>Leg PaO₂ (mmHg)</td>
<td>82 ± 5*</td>
<td>85 ± 6*</td>
<td>82 ± 7*</td>
<td>86 ± 6*#</td>
<td>101 ± 2</td>
<td>103 ±</td>
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<tr>
<td>Leg PfO₂ (mmHg)</td>
<td>25 ± 1</td>
<td>25 ± 1</td>
<td>24 ± 2</td>
<td>26 ± 2</td>
<td>23 ± 1</td>
<td>24 ±</td>
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<tr>
<td>Leg VO₂ (l/min)</td>
<td>1.5 ± 0.2*</td>
<td>1.9 ± 0.2*</td>
<td>2.2 ± 0.2*</td>
<td>2.8 ± 0.4*</td>
<td>2.1 ± 0.4</td>
<td>2.5 ±</td>
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<td>Leg O₂ delivery (l/min)</td>
<td>0.27 ± 0.03*</td>
<td>0.35 ± 0.03*</td>
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<td>0.43 ± 0.1</td>
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<td>Leg O₂ extraction</td>
<td>63 ± 1*</td>
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<td>68 ± 2*</td>
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<td>72 ± 3</td>
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<tr>
<td>Leg VO₂ (l/min)</td>
<td>0.17 ± 0.01*</td>
<td>0.22 ± 0.02*</td>
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<td>0.31 ± 0.08</td>
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<td>Leg vascular conductance</td>
<td>13.8 ± 2.0</td>
<td>16.6 ± 1.8</td>
<td>16.3 ± 1.0</td>
<td>20.7 ± 1.8</td>
<td>21.4 ± 4.6</td>
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<td>Arterial pH</td>
<td>7.42 ± 0.01</td>
<td>7.41 ± 0.01</td>
<td>7.40 ± 0.00</td>
<td>7.39 ± 0.00</td>
<td>7.38 ± 0.01</td>
<td>7.38 ±</td>
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<tr>
<td>Venous pH</td>
<td>7.31 ± 0.01</td>
<td>7.28 ± 0.01</td>
<td>7.25 ± 0.01</td>
<td>7.22 ± 0.03</td>
<td>7.19 ± 0.0</td>
<td>7.21 ±</td>
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<tr>
<td>Venous lactate outflow (mmol/min)</td>
<td>0.5 ± 0.3</td>
<td>0.8 ± 0.2</td>
<td>1.2 ± 0.4</td>
<td>2.2 ± 0.5 #</td>
<td>2.9 ± 1.3</td>
<td>3.8 ±</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>89 ± 3</td>
<td>93 ± 2</td>
<td>96 ± 2</td>
<td>96 ± 2</td>
<td>104 ± 10</td>
<td>108 ±</td>
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<tr>
<td>Perceived muscle fatigue</td>
<td>3 ± 1*</td>
<td>5 ± 2*</td>
<td>8 ± 1*</td>
<td>10 ± 0.5*</td>
<td>8 ± 2</td>
<td>10 ±</td>
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<td></td>
</tr>
<tr>
<td>Perceived breathlessness</td>
<td>1 ± 0*</td>
<td>2 ± 1*</td>
<td>4 ± 1*</td>
<td>6 ± 1*</td>
<td>5 ± 1</td>
<td>6 ±</td>
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</table>

* significantly different relationship from controls across work rates. # significantly different from controls at maximal exercise.