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Authors
ADAMI, ALESSANDRA
CORVINO, ROGERIO B
CALMELAT, ROBERT A
et al.

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Muscle Oxidative Capacity Is Reduced in Both Upper and Lower Limbs in COPD

ALESSANDRA ADAMI[1,2], ROGERIO B. CORVINO[2,3], ROBERT A. CALMELAT[2], JANOS PORSZASZ[2], RICHARD CASABURI[2], and HARRY B. ROSSITER[2,4]

[1]Department of Kinesiology, University of Rhode Island, Kingston, RI; [2]Rehabilitation Clinical Trials Center, Division of Respiratory and Critical Care Physiology and Medicine, The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, CA; [3]Human Performance Research Group, Center for Health and Exercise Science, UDESC, Florianópolis, SC, BRAZIL; [4]Faculty of Biological Sciences, University of Leeds, Leeds, UNITED KINGDOM

ABSTRACT

ADAMI, A., R. B. CORVINO, R. A. CALMELAT, J. PORSZASZ, R. CASABURI, and H. B. ROSSITER. Muscle Oxidative Capacity Is Reduced in Both Upper and Lower Limbs in COPD. *Med. Sci. Sports Exerc.*, Vol. 52, No. 10, pp. 2061–2068, 2020. **Introduction:** Skeletal muscle atrophy, weakness, mitochondrial loss, and dysfunction are characteristics of chronic obstructive pulmonary disease (COPD). It remains unclear whether muscle dysfunction occurs in both upper and lower limbs, because findings are inconsistent in the few studies where upper and lower limb muscle performance properties were compared within an individual. This study determined whether muscle oxidative capacity is low in upper and lower limbs of COPD patients compared with controls. **Methods:** Oxidative capacity of the forearm and medial *gastrocnemius* was measured using near-infrared spectroscopy to determine the muscle O_2 consumption recovery rate constant (k, min^{-1}) in 20 COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2/3/4, n = 7/7/6) and 20 smokers with normal spirometry (CON). Muscle k is linearly proportional to oxidative capacity. Steps per day and vector magnitude units per minute ($VMU \cdot min^{-1}$) were assessed using triaxial accelerometry. Differences between group and limb were assessed by two-way ANOVA. **Results:** There was a significant main effect of group (F = 11.2, η_p^2 = 0.13, P = 0.001): k was lower in both upper and lower limb muscles in COPD (1.01 ± 0.17 and 1.05 ± 0.24 min^{-1}) compared with CON (1.29 ± 0.49 and 1.54 ± 0.60 min^{-1}). There was no effect on k of limb (F = 1.8, η_p^2 = 0.02, P = 0.18) or group–limb interaction (P = 0.35). ($VMU \cdot min^{-1}$) was significantly lower in COPD (−38%; P = 0.042). Steps per day did not differ between COPD (4738 ± 3194) and CON (6372 ± 2107; P = 0.286), although the difference exceeded a clinically important threshold (>600–1100 steps per day). **Conclusions:** Compared with CON, muscle oxidative capacity was lower in COPD in both upper (−20%) and lower (−30%) limbs. These data suggest that mitochondrial loss in COPD is not isolated to locomotor muscles. **Key Words:** MITOCHONDRIA, NEAR-INFRARED SPECTROSCOPY, EXERCISE INTOLERANCE, OXYGEN CONSUMPTION, INACTIVITY, DYSPNEA

Address for correspondence: Harry B. Rossiter, Ph.D., Rehabilitation Clinical Trials Center, Division of Respiratory and Critical Care Physiology and Medicine, The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, 1124 W. Carson St., CDCRC Building, Torrance, CA 90502; E-mail: hrossiter@ucla.edu.
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Skeletal muscle dysfunction is one of the most important extrapulmonary manifestations impairing quality-of-life of patients with chronic obstructive pulmonary disease (COPD). Loss of muscle mass, strength and power, loss of type I (oxidative) muscle fibers, capillary rarefaction, mitochondrial loss, and mitochondrial dysfunction have each been identified and seem to progress with COPD severity (1–6).

Investigations of muscle dysfunction in COPD typically focus on locomotor muscles, especially of the quadriceps, because of their key role in ambulation, autonomy (7), and quality of life. However, prevalence and progression of disease-associated adaptations in upper limbs (UL) or trunk muscles are less well characterized. Muscle dysfunction isolated to the lower limbs (LL) within an individual implies causal mechanisms proximal to reduced locomotion, whereas dysfunction of both the UL and LL suggests a wider range of systemic mechanisms contributing to muscular impairments, for example, chronic

inflammation, oxidative stress, hypoxemia, nutrition, cigarette smoke, or other circulating variables (2,4,8–10).

Few studies, largely limited to functional performance measures (strength, endurance), have compared UL and LL muscles within individual COPD patients, and their findings are variable. Bernard et al. (11) found greater loss of strength in the LL than the UL of COPD patients compared with age-matched nonsmoking controls. Weakness and low isometric strength were found in both the UL and LL of COPD patients compared with age-matched healthy controls (12–14), but *biceps brachii* endurance was better preserved than in the *quadriceps* in a large study of COPD patients (13). These findings contrast smaller cohort studies by Miranda et al. (7) and Vilaró et al. (15), who showed that endurance and fatigability (7), and isometric strength (15) were more impaired in the UL than LL of COPD patients. Currently, there are no muscle biopsy studies comparing properties of arm and leg muscles within the same individuals. Therefore, the systemic or local cellular adaptations, which underlie strength or endurance deficits in COPD patients, are not known.

To address this, we determined UL (medial forearm) and LL (*gastrocnemius*) muscle oxidative capacity in moderate to very severe COPD patients compared with age-matched smokers with normal spirometry (CON). We used near-infrared spectroscopy (NIRS [1]) to determine noninvasively the recovery rate constant (k) of muscle oxygen consumption ($m\dot{V}O_2$ [16]) isolated from influences of circulatory or pulmonary function. $m\dot{V}O_2$ recovery k is directly proportional to muscle oxidative capacity measured in single muscle fibers ($r^2 = 0.77$ [17]). NIRS-based oxidative capacity assessment has been validated against magnetic resonance spectroscopy and biopsy in skeletal muscle (18,19). Based on previous reports of UL and LL muscle endurance in COPD patients (13), we hypothesized that, compared with CON, COPD patients would have a greater deficit in muscle oxidative capacity in the *gastrocnemius* than in the forearm.

MATERIALS AND METHODS

Participants

A group of current or former smokers with at least 10 pack-years of smoking history were enrolled: 20 moderate to very severe COPD patients (GOLD stages 2–4) and 20 age- and sex-matched participants with normal spirometry (CON; Table 1). Current or former smokers without COPD were selected as the appropriate comparator group for COPD patients with a smoking history. This attempts to isolate the effects of COPD on muscle oxidative capacity and control for the potential influence of smoking history. It is recognized that the control group in this study does not necessarily represent a "normal" or "healthy" condition. All participants were 45 to 90 yr old. Controls had prebronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ≥0.70 and $FEV_1 \geq 80\%$ predicted. COPD patients (postbronchodilator $FEV_1/FVC < 0.70$ and $FEV_1 < 80\%$ predicted) were in a stable state, with no exacerbation within previous 4 wk. Exclusion criteria were as follows: presence of significant disease other than COPD (a significant disease was defined as a disease, which may (i) put the patient at risk by participation; (ii) influence the results of the study, such as ischemic heart disease, chronic musculoskeletal, or renal disease; or (iii) limit the patient's ability comply with the protocol; active participation in pulmonary rehabilitation or participation in the past 18 months; and pregnancy in women. Participants were informed about study procedures and risks and gave written informed consent. The study was approved by the Human Subjects Committee of The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center (20403–01).

TABLE 1. Participant characteristics.

	COPD	CON	P
n	19	19	—
Age (yr)	64 (±9)	62 (±7)	0.44
Weight (kg)	72 (±17)	78 (±17)	0.23
Height (cm)	171 (±10)	170 (±10)	0.76
BMI ($kg \cdot m^{-2}$)	24 (±4)	27 (±4)	0.06
Sex (M/F)	14/5	14/5	—
Race (AA/NHW)	5/14	11/8	—
FVC (L)	3.1 (±0.9)	3.7 (±0.8)	**0.02**
FEV_1 (L)	1.6 (±0.8)	2.8 (±0.6)	**0.0001**
FEV_1/FVC (%)	47.3 (±15.2)	75.6 (±4.0)	**0.0001**
FEV_1 %pred	44.1 (±18.7)	97.1 (±12.1)	**0.0001**
Resting SpO_2 (%)	97 (±1.6)*	97 (±1.3)	0.39
Smoking history (ATS pack-years)	37 (±15)	38 (±19)	0.41
GOLD stage (2/3/4)	7/6/6	0/0/0	—

Data are mean (±SD). Bold font indicates significance at $P < 0.05$.
*Four COPD patients required nasal cannula O_2 during the visit (at 2 $L \cdot min^{-1}$).
AA, African American; F, female, M, male; NHW, non-Hispanic white; SpO_2, arterial oxygen saturation from finger pulse oximetry.

Measurements

Each participant visited the laboratory once, during which NIRS muscle and spirometry tests were performed. Participants completed symptom (COPD Assessment Test (CAT), modified Medical Research Council Dyspnea scale (mMRC)) and health-related quality of life (St. George's Respiratory Questionnaire (SGRQ); 36-item Short Form Health Survey (SF-36)) questionnaires. The SGRQ and SF-36 physical activity (PA)–related domains were used to evaluate daily PA. In addition, PA was objectively assessed in all COPD patients and six CON using 7-d triaxial accelerometry (Dynaport MoveMonitor; McRoberts BV, Den Haag, the Netherlands).

NIRS muscle oxidative capacity test. The nondominant forearm and medial *gastrocnemius* muscles were assessed using continuous-wave, spatially resolved spectroscopy NIRS (PortaMon; Artinis BV, NL). NIRS measures relative concentration of deoxygenated (HHb + Mb) and oxygenated ($HbO_2 + MbO_2$) hemoglobin and myoglobin within the muscle up to ~1.5 cm under the probe. From these measurements, relative changes in total hemoglobin and myoglobin ($THb = HHb + Mb + HbO_2 + MbO_2$) were calculated. Tissue saturation index (TSI; an index of tissue oxygen saturation) was calculated from these measurements.

With the participant supine on an exam bed, the belly of the calf and forearm muscles were identified. Palpation during a series of brief isometric muscle contractions was used to

optimize placement of the plastic-wrapped NIRS probe (1) longitudinally over a highly activated region of the medial forearm and medial *gastrocnemius*. The NIRS probe was then secured in position using an elastic bandage. A rapid-inflation pressure-cuff (SC12D; Hokanson, Bellevue, WA) was placed on the upper arm or proximal thigh on the same limb as the NIRS probe and attached to an electronically controlled rapid cuff inflator (E20; Hokanson). The participant was asked to relax and minimize UL or LL movement, except when instructed. Participants were familiarized with rapid cuff inflation and to the brief muscle contractions required in the protocol. Arterial occlusion pressure was determined for both limbs from a tolerated cuff pressure within the range of 175–275 mm Hg (mean, 221 ± 24 mm Hg (UL) and 218 ± 31 (LL) mm Hg) that resulted in a rise in HHb + Mb, a fall in HbO_2 + MbO_2, and stable THb signal over 15–20 s. Repeated dynamic muscle contractions were made at ~1 Hz by squeezing a foam tennis ball (forearm) or a plantar-flexion/relaxation against a light resistance (lower leg; hereafter referred to as muscle contractions).

Initially, participants lay at rest for 2–3 min to establish a stable baseline TSI. After this, ~10–15 s of light muscle contractions were performed to increase $m\dot{V}O_2$, and the limb was then subjected to arterial occlusion until a stable minimum TSI was reached or for 5 min (whichever occurred first). Cuff pressure was then released and the subsequent reactive reoxygenation was monitored until resting baseline was reestablished (typically ~8 min for UL and ~3.5 min for LL). This was used to determine an individualized muscle saturation physiological range (Fig. 1). Finally, two muscle oxidative capacity assessments were performed for each limb. Each consisted of 1) ~10- to 15-s muscle contractions to increase $m\dot{V}O_2$ and desaturate the muscle to ~50% of the physiological range (1) and 2) a series of intermittent arterial occlusions (5 occlusions for 5 s, 10 for 10 s, each separated by 5- to 20-s recovery; Fig. 1). Each of the assessments lasted ~6 min and was separated by ~2 min of rest. Participants were provided ~15 min between UL and LL testing. UL was always tested first. At the end of the procedure, the skinfold at the NIRS site was measured to estimate adipose tissue thickness (ATT; in millimeters; Table 1; Lange Skinfold Caliper; BetaTechnology Inc, Santa Cruz, CA).

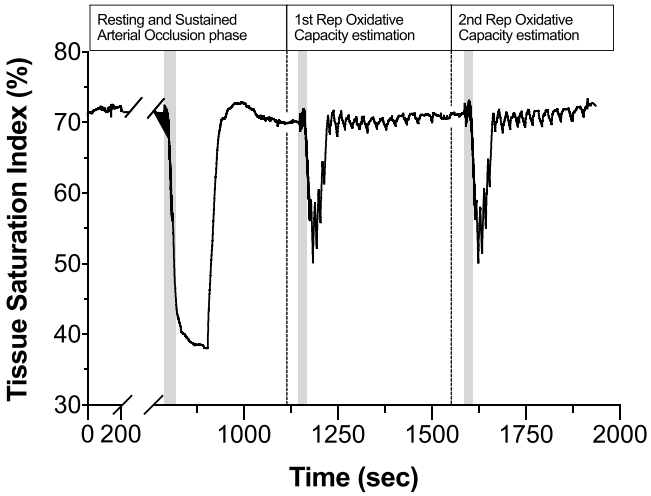

FIGURE 1—Changes in TSI during the NIRS muscle test. Three protocol phases are shown. The gray shading indicates muscle contractions, always preceded by a resting (i.e., baseline) phase. Data are from the medial *gastrocnemius* muscle of a control individual.

For each intermittent arterial occlusion during oxidative capacity tests, the linear rate of decline in TSI (desaturation in percent per second) was determined and a point value for relative $m\dot{V}O_2$ was reported. Because the rate of tissue deoxygenation during arterial occlusion is inversely proportional to $m\dot{V}O_2$, its value is reported as positive (in percent per second; Fig. 2). The primary study outcome was the exponential $m\dot{V}O_2$ recovery rate constant (k, min^{-1}), which was estimated using nonlinear least-squares regression (Fig. 2; OriginPro v8.6; OriginLab Co., Northampton, MA [1]). This protocol has strong test–retest reliability in smokers with and without COPD (intraclass correlation coefficient (ICC) ≥ 0.88) (1).

Pulse oximetry. Arterial oxygen saturation was estimated during resting phase at the beginning of testing using fingertip pulse oximetry (Rad-5 Pulse Oximeter MasimoSET®; Masimo Co., Irvine, CA).

Spirometry. Participants inhaled two puffs of metered-dose albuterol sulfate ~15 min before spirometric testing. Spirometry was performed in accordance with American Thoracic Society guidelines using a dual-beam Doppler ultrasound-based spirometer (EasyOne Pro; Ndd Medical, Zürich, Switzerland). FEV_1 and FVC were measured from the greatest FEV_1 and FVC from up to eight maximal expiratory maneuvers, where the greatest two measurements were within 150 mL.

PA by triaxial accelerometry. All COPD patients and 6 CON underwent 7 d of PA monitoring using triaxial accelerometry (Dynaport MoveMonitor; McRoberts BV). Each participant was instructed in the correct positioning of the monitor in small of the back and to adjust the elastic waistband to ensure the device was in contact with the body and comfortable. Participants were asked to wear the PA monitor for as long as possible during each 24-h period and to remove it only for bathing and swimming. The PA monitor was worn from the end of the study visit until 7 full days had elapsed. Data were processed using the manufacturer's protocols.

Daily PA measurements were accepted as valid if they met the criteria that the monitor was worn for at least 8 $h \cdot d^{-1}$ during waking hours (20) and for at least 5 $d \cdot wk^{-1}$ (not necessarily consecutive, without distinction between weekdays and weekends). Compliance with these conditions was ~94%. PA is reported as the mean number of steps per day (total accumulated during each 24-h period) and as the mean count of vector magnitude units per minute ($VMU \cdot min^{-1}$) during "daytime" hours between 8 AM and 11 PM. VMU is the vectorial sum of movements measured at 100 Hz from acceleration in the three orthogonal planes (sagittal, frontal, transversal) measured over a 1-min time period. The acceleration signal is converted to a digital representation and processed to obtain an "activity count," that is, VMU (for additional details, see, e.g., Van Hees et al. [21]).

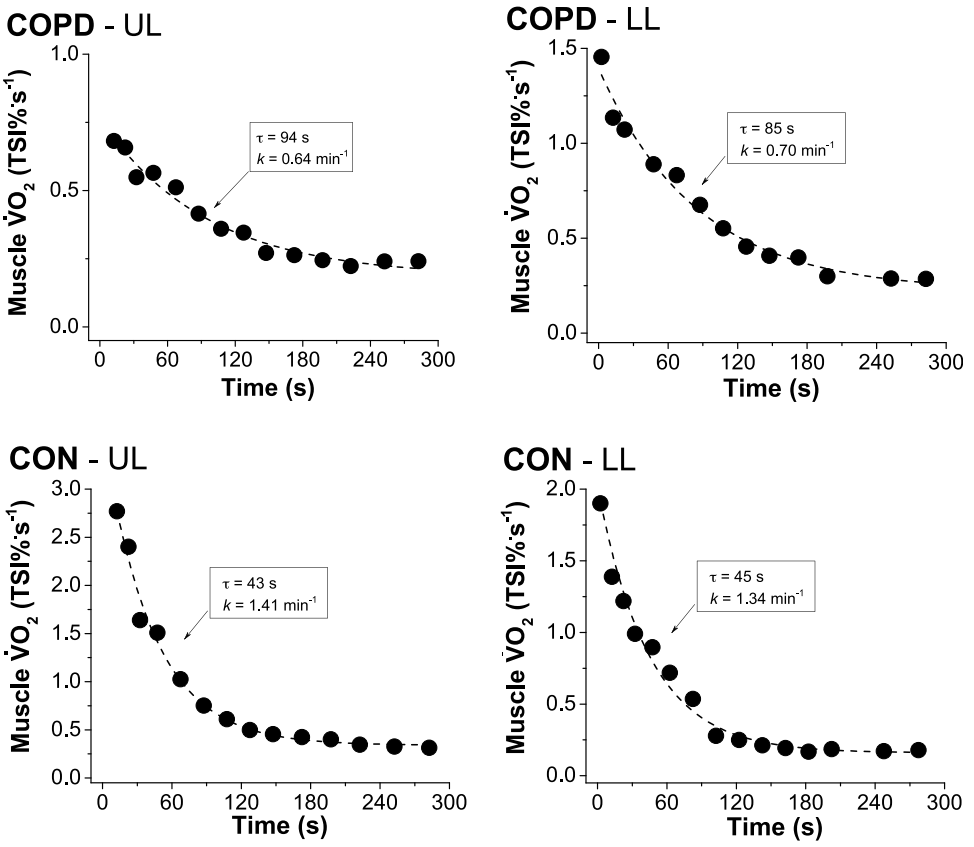

FIGURE 2—Representative COPD and CON responses for the muscle oxidative capacity assessments. m$\dot{V}O_2$ recovery after brief contractions is shown, with a monoexponential fit (dashed line), for the UL (medial forearm muscle, left) and LL (medial *gastrocnemius*, right). τ, m$\dot{V}O_2$ recovery time constant; *k*, m$\dot{V}O_2$ recovery rate constant ($k = (1/\tau).60$, min^{-1}).

Statistics. Coefficient of variation (CV) and ICC assessed within-subject test–retest reproducibility. Two-way ANOVA was used to identify *k* differences between group (COPD and CON) and limb (UL and LL). Associations were investigated by regression (Pearson). Significant differences were accepted at $P \leq 0.05$. Results are presented as mean ± SD, unless otherwise specified.

RESULTS

Participant characteristics. One COPD patient could not tolerate UL arterial occlusion, and therefore, the patient and the corresponding age- and sex-matched control were excluded from further analysis. Results are reported from 19 COPD and 19 CON. As intended, groups were matched by age and body characteristics (Table 1). Four COPD patients required nasal cannula O_2 during the visit (at 2 $L \cdot min^{-1}$).

Symptoms, PA, and quality of life. COPD patients had significantly greater CAT and mMRC scores than CON, confirming greater dyspnea in patients (Table 2). Significantly greater (worse) SGRQ total and subscale scores, and lesser SF-36 physical and general health component aggregate scores confirmed lower quality of life in COPD than CON (Table 2). COPD reported lower scores than CON in physical functioning and role-physical scales of SF-36 ($P < 0.001$), suggesting reduced capacity for performing daily and physical activities.

Triaxial accelerometry wearing compliance was met on 6 d (≥15 $h \cdot d^{-1}$) on average in both COPD and CON (Table 2B), except for one GOLD 1 patient who withdrew on day 2. Therefore, results are presented for six individuals in each group. The characteristics of the subgroup of six controls who undertook accelerometry assessment were: 5 men, 1 women; 56 ± 26 yr; 1.70 ± 0.60 m; 66.0 ± 32.5 kg; FEV_1,

TABLE 2. Symptoms and health-related quality of life questionnaire scores (A) and PA triaxial accelerometry monitoring (B).

		COPD	CON	*P*
A				
	CAT	16 [6–29]	5 [0–18]	**0.001**
	mMRC	2 [0–4]	0 [0–1]	**0.01**
	SGRQ score			
	Total	36 [11–73]	6 [0–48]	**0.0002**
	Active	48 [12–100]	12 [0–66]	**0.0001**
	Symptom	30 [0–56]	7 [0–48]	**0.005**
	Impacts	31 [0–80]	0 [0–39]	**0.001**
	SF-36 total score			
	Mental component summary	46 [35–63]	51 [33–61]	0.405
	Physical component summary	39 [22–55]	55 [34–62]	**0.0006**
	Physical functioning scale	38 [19–55]	53 [28–57]	**0.001**
	Role-physical scale	37 [18–57]	57 [35–57]	**0.0002**
	Body pain scale	55 [37–62]	62 [33–61]	0.64
	General health scale	39 [26–53]	46 [38–63]	**0.009**
B				
	Days of monitoring (*n*)	6.2 (±0.4)	6.0 (±0.0)	1.000
	Daytime VMU·min^{-1} (count)	300 (±170)	481 (±113)	**0.042**
	Steps per day (*n*)	4738 (±3194)	6372 (±2107)	0.286

A. Questionnaire scores are median [range min–max]. B. Data are mean (±SD). For SF-36, the mental and physical component summaries are aggregate scores. Bold font indicates significance at $P < 0.05$.

2.44 ± 1.13 L; and FVC, 3.20 ± 1.53 L. VMU·min^{-1} was significantly lower (P = 0.024) in COPD than CON. Although steps per day were not significantly different between COPD and CON (P = 0.286, Table 2B), the mean difference exceeded the clinically important difference established for COPD (600–1100 steps per day [22]).

UL and LL muscle oxidative capacity. Resting muscle TSI and ATT of the upper and lower extremities were not significantly different between COPD and CON (Table 3). There was no significant difference between the first and second k measurements within individuals for either limb; therefore, the average of the two repeated k values is reported. Test–retest reliability was high for UL and LL k values in both groups (COPD UL: CV = 3.8%, ICC = 0.96; LL: CV = 4.6%, ICC = 0.96; and CON UL: CV = 5.4%, ICC = 0.98; LL: CV = 4.5%, ICC = 0.98).

There was main effect of group on k (F = 11.2, η_p^2 = 0.13, P = 0.001) but not of limb (F = 1.8, η_p^2 = 0.02, P = 0.18). There was no group–limb interaction (P = 0.35). Compared with CON, COPD patients had significantly lower k in UL (~20%) and LL (~30%; Table 3, Fig. 3). There was no significant association between measures of PA (VMU·min^{-1}; steps per day) and k in the LL of COPD (r^2 = 0.06–0.13; P > 0.05) or CON (r^2 = 0.17–0.25; P > 0.05).

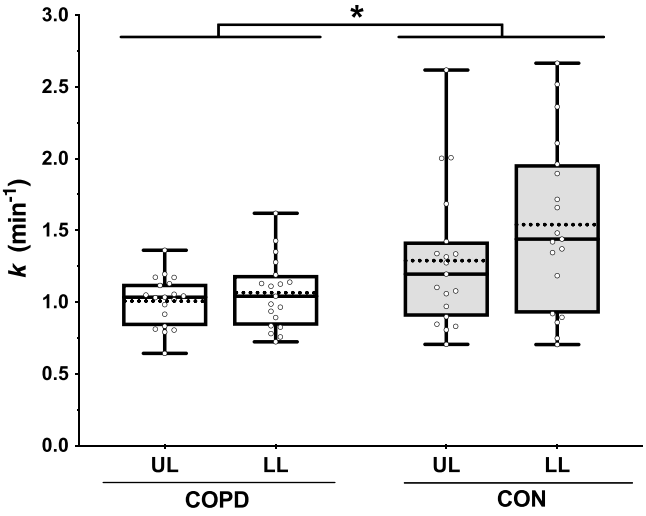

FIGURE 3—Median and interquartile ranges of medial forearm (UL) and medial *gastrocnemius* (LL) skeletal muscle VO_2 recovery rate constant (k) in the COPD and CON groups. Dotted line indicates the group mean. *Main effect of condition (COPD vs CON), $P \leq 0.001$.

DISCUSSION

This is the first study to determine skeletal muscle oxidative capacity in both upper and lower extremities of current or former smokers with or without COPD. Given the large volume of muscle biopsy data showing low muscle oxidative capacity in moderate to severe COPD patients, we hypothesized that LL muscle oxidative capacity would be more severely impaired, compared with matched smoker controls, than the UL. Contrary to our hypothesis, there was no interaction between group and limb for muscle k. We found that COPD patients had substantially lower muscle oxidative capacity (20%–30%) in both locomotor and forearm skeletal muscles compared with smokers without pulmonary obstruction (Table 3, Fig. 3). This deficit in muscle oxidative capacity in COPD was accompanied by a lower VMU·min^{-1} and clinically important (but not statistically significant) reduction in steps per day in COPD. However, there were only weak associations between k and PA (VMU·min^{-1} or steps per day) in the LL (r^2 = 0.06–0.25). Together, the findings of low oxidative capacity in UL and low oxidative capacity that was only weakly associated with activity in the LL, in COPD patients and controls well matched for smoking history, age, and sex, suggest a systemic deficit in muscle oxidative capacity in COPD patients that is not well explained by a low volume and/or intensity of PA alone.

TABLE 3. Skeletal muscle characteristics.

	COPD	CON	P
UL (R/L)	3/16	4/15	
Saturation (TSI) (%)	66 (±6)	67 (±7)	0.22
ATT (mm)	3.5 (±1.1)	4.1 (±2.2)	0.28
k (min^{-1})	1.01 (±0.17)	1.29 (±0.49)	**0.03**
LL (R/L)	18/1	16/3	
Saturation (TSI) (%)	67 (±4)	68 (±5)	0.23
ATT (mm)	4.5 (±2.8)	4.8 (±2.1)	0.77
k (min^{-1})	1.05 (±0.24)	1.54 (±0.60)	**0.002**

Data are mean (±SD). Bold font indicates significance at P < 0.05.
L, left. R, right.

UL and LL muscle oxidative capacity in COPD. The severity of the muscle oxidative capacity deficit in the LL of COPD patients (~20%–30%) is similar to reports from biopsy studies of the quadriceps (~10%–50%) (23). There is only one previous report of muscle biopsy analysis from the UL (deltoid) of 10 COPD patients, and this showed a trend (P = 0.07) for lower citrate synthase activity compared with controls (24). The ~20%–30% lower muscle oxidative capacity in COPD would likely translate into similar reduction in oxidative ATP synthesis in COPD (5,25–27), but could be affected further should mitochondrial uncoupling be increased (e.g., to mitigate oxidative stress).

In humans, the medial *gastrocnemius* has a greater expression of type I fibers than the forearm muscles (28,29), where muscle fiber characteristics favor acute strength and precision of movement over muscle endurance. Because of this, we anticipated that, overall, the LL muscles would have a greater oxidative capacity than the UL. However, we did not identify a statistical effect of limb, potentially because the study was underpowered for this comparison. The study was powered on the basis of anticipated differences of the primary outcome (k) between COPD and controls, and achieved a power ($1 - \beta$) of 0.89 to detect this large effect (Cohen's d = 1.07; G*power 3.1). Although there was a trend toward an effect of limb in controls (k = 1.54 ± 0.60 min^{-1} for LL vs k = 1.29 ± 0.49 min^{-1} for UL), the effect size was small (d = 0.46) and the power for this comparison was low ($1 - \beta$ = 0.28), suggesting the potential for type II error (false-negative interpretation). We estimate that 150 participants would be needed to determine with

a power of $1 - \beta = 0.8$ whether muscle oxidative capacity in middle-age smoker controls differed between UL and LL.

However, we were surprised that muscle oxidative capacity was very similar in UL and LL muscles in COPD and was lower in both muscles than even the UL muscles in controls. This highlights the severity of the profound loss of mitochondrial function in the ambulatory muscles of COPD patients, given that forearm muscles typically contain far more type II muscle fibers and are far more fatigable. It also suggests that a systemic mechanism may contribute strongly to whole-body mitochondrial loss in COPD (30).

Support for this concept can be found in the study by Rabinovich et al. (31), who reported that reduced mitochondrial density and function (coupling of oxidative phosphorylation) were strongly related to PaO_2 and early lactate release during exercise. Circulating cigarette smoke constituents (e.g., reactive aldehydes), oxidative stress and/or systemic inflammation, and cytokine expression may impair mitochondrial dynamics or biogenesis (4,32), or impair the neuromuscular junction (33), interrupting calcineurin signaling and other calcium-sensitive cellular mediators, each contributing to oxidative capacity loss in muscle. Although cigarette smoke constituents have been implicated in directly inhibiting oxidative phosphorylation (e.g., by inhibition of cytochrome c oxidase), studies to investigate this in humans have been inconsistent in their findings (32). In a previous NIRS study of 39 smokers without COPD, we were unable to identify a direct effect of current smoking on muscle oxidative capacity (34). However, the degree to which the loss of skeletal muscle oxidative capacity is pathological or a consequence of mitochondrial functional phenotype adaptations induced by muscle fiber switch and physical inactivity is still unclear (4,35).

Several studies have reported a preservation of type I fiber number, strength (24,36), or endurance (13) in UL muscles of COPD patients, suggesting that muscle structural alterations are not homogeneously distributed among different muscle groups in COPD (4,23). One interpretation of this is that reduced ambulation and consequent muscular deconditioning is a primary driver of the low oxidative muscle phenotype in the legs of COPD patients, whereas UL muscles may be better protected through engagement in activities of daily living. Although our PA data predominantly reflect activity of the LL muscles, overall our data do not support this proposal. Rather they suggest a systemic loss of the oxidative muscle phenotype in COPD (4,23,30,35,37).

Other structural changes, particularly loss of muscle mass, which is a strong predictor of mortality in COPD (4), have been implicated in reduced endurance (directly related to oxidative capacity) and strength in COPD patients. Franssen et al. (13) compared quadriceps and biceps brachii muscle strength and endurance in COPD patients with and without muscle mass depletion and found a significant reduction in strength only in the LL of those who had lost fat-free mass (FFM). However, the authors reported that this difference disappeared after correcting for FFM (13), suggesting that the loss of FFM contributes to muscle weakness in COPD, but other factors should be considered to explain endurance impairments in COPD. Although we did not assess muscle mass or FFM in our study, we sought stable COPD patients without recent exacerbations or uncontrolled weight loss in the previous 6 months, and body mass index (BMI) was not different from controls on average (24 ± 4 kg·m^{-2}). Although BMI is a crude index, six COPD patients in our study had BMI <21 kg·m^{-2} (range, 18.2–20.3 kg·m^{-2}; GOLD 2/3/4, $n = 2/3/1$), suggested as the lower limit of normal for chronic disease patients (4). Nevertheless, the mean k in this subgroup (UL, 0.91 ± 0.12 min^{-1}; LL, 1.05 ± 0.24 min^{-1}) was not significantly different from the COPD group as a whole, suggesting that low oxidative capacity is not a characteristic solely of underweight or undermuscled subjects. Our findings seem relevant to a general COPD population rather than those with overt weight loss or muscle weakness.

The levels of PA we found in our COPD patients were similar to those reported in the literature (38–40), whereas our smoker-controls were less active than reports for similar middle-age individuals (e.g., ~9000 steps per day; c.f. Table 2). The groups also differed in pulmonary function (by design), dyspnea, and self-reported physical functioning and quality of life (Table 2) and one objective measure of activity (VMU·min^{-1}), but were otherwise not different in smoking history, age, or sex. Although we also found no significant difference in steps per day between COPD and CON ($P = 0.286$), the mean difference (1634 steps per day; an effect size of $d = 0.60$) exceeded established clinical importance (600–1100 steps per day) that corresponds to a reduced risk of hospitalization (22) and morbidity. This suggests that PA is lower in COPD than in controls in our study by a clinically relevant magnitude, and it is likely that the study is underpowered to detect a statistically significant difference between COPD and controls in the secondary outcome of steps per day ($1 - \beta = 0.44$). Nevertheless, we found no association between objectively measured PA and k, suggesting that factors in addition to—or, perhaps, other than—PA are responsible for low oxidative capacity in muscles of COPD patients. Further study of a larger cohort is warranted to investigate this suggestion.

Study limitations. We used noninvasive assessment of muscle oxidative capacity to allow two muscle sites to be investigated. This assessment is reliable and has been validated against gold standard methods (biopsy and magnetic resonance spectroscopy). Nevertheless, this assessment is indirect and does not provide a detailed picture of intramyocyte signaling processes that contribute to mitochondrial loss. We did not assess muscle mass, FFM, muscle endurance, or strength in this study, to provide insight into how muscle oxidative capacity loss associates with muscle quantity or performance. This study was also relatively small, enrolling no more than seven subjects per each GOLD 2 to 4 category. Therefore, the study was not sufficiently powered to identify an effect of disease severity on UL and LL muscle oxidative capacity. The two NIRS-investigated sites are representative of skeletal muscles involved in daily activities (i.e., grasping or carrying for the forearm and locomotion for the *gastrocnemius*); the selection

of the muscle sites is limited by the NIRS-based technique, which requires the ability to implement repeated arterial occlusions (41). Therefore, a wider systemic assessment of respiratory abdominal or vertebral muscles is not possible with this method. We used accelerometry to provide an objective evaluation of the daily PA, which predominantly represents activity of the LL; therefore, UL activity remains unmeasured in our study.

Clinical implications and future perspectives. Low oxidative capacity in the locomotor muscle is associated with exercise intolerance and therefore may contribute to inactivity and poor quality of life and represents a strong therapeutic target (4,23). It is known that locomotor muscles respond well to endurance exercise training by increasing oxidative capacity, even in COPD patients (4,13). However, if muscle mitochondrial loss is systemic in COPD—and perhaps even not limited to the muscle tissues—then exercise training would be expected to ameliorate this deficit only in the muscles engaged by training, but not in a wider range of locations or tissues. Ameliorating systemic mitochondrial dysfunction may need additional, possibly pharmaceutical, therapies as an adjunct to exercise training in COPD patients. Systemic mitochondrial loss could contribute to immune system or liver dysfunction and cardiovascular disease, which are each prevalent in COPD patients. As such, the NIRS-based approach we used for this study may represent a relatively simple and noninvasive method to investigate the severity of systemic mitochondrial dysfunction and response to therapy. Future studies with a larger cohort are needed to identify whether severity of the pulmonary and/or PA impairments is associated with oxidative capacity loss of the UL and LL in COPD. Comprehensive evaluation of exercise capacity and isolated muscle structure and function is needed to identify the clinical correlates and physiological mediators underlying these observations.

CONCLUSIONS

We found that muscle oxidative capacity was low in both UL (forearm) and LL (medial *gastrocnemius*) muscles of moderate to very severe COPD patients compared with sex- and age-matched smokers with normal spirometry. Low oxidative capacity was not limited to the LL or to those with COPD. Low muscle oxidative capacity in COPD may contribute to the greater respiratory symptoms and reduced muscle endurance and quality of life in COPD patients. These data imply that low oxidative capacity in leg muscles of COPD patients may not solely relate to reduced ambulation and deconditioning, but that systemic factors, for example, inflammation or oxidative stress, are likely strong mediators loss of mitochondrial oxidative phenotype.

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The authors have no conflicts to declare. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The study results do not constitute endorsement by the American College of Sports Medicine. A. A. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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