Impact of preinduced quadriceps fatigue on exercise response in chronic obstructive pulmonary disease and healthy subjects

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Gagnon P, Saey D, Vivodtzev I, Laviolette L, Mainguy V, Milot J, Provencher S, Maltais F. Impact of preinduced quadriceps fatigue on exercise response in chronic obstructive pulmonary disease and healthy subjects. J Appl Physiol 107: 832–840, 2009. First published July 2, 2009; doi:10.1152/japplphysiol.91546.2008.—Exercise intolerance in chronic obstructive pulmonary disease (COPD) results from a complex interaction between central (ventilatory) and peripheral (limb muscles) components of exercise limitation. The purpose of this study was to evaluate the influence of quadriceps muscle fatigue on exercise tolerance and ventilatory response during constant-workrate cycling exercise testing (CWT) in patients with COPD and healthy subjects. Fifteen patients with COPD and nine age-matched healthy subjects performed, 7 days apart, two CWTs up to exhaustion at 80% of their predetermined maximal work capacity. In a randomized order, one test was performed with preinduced quadriceps fatigue and the other in a fresh state. Quadriceps fatigue was produced by electrostimulation-induced contractions and quantified by maximal voluntary contraction and potentiated twitch force (TwQmax). Endurance time and ventilatory response during CWT were compared between fatigued and fresh state. Endurance time significantly decreased in the fatigued state compared with the fresh condition in COPD (356 ± 69 s vs. 294 ± 45 s; P < 0.05) and controls (450 ± 74 s vs. 340 ± 45 s, P < 0.05). Controls showed significantly higher ventilation and end-exercise dyspnea scores in the fatigued condition, whereas, in COPD, fatigue did not influence ventilation or dyspnea during exercise. The degree of ventilatory limitation, as expressed by the \(\text{Ve/Vmax} \) ratio, was similar in both conditions in patients with COPD. We conclude that it is possible to induce quadriceps fatigue by local electrostimulation-induced contractions. Our findings demonstrate that peripheral muscle fatigue is an additional important factor, besides intense dyspnea, that limits exercise tolerance in COPD.

quadriceps muscle fatigue; exercise tolerance; ventilatory response; electrostimulation

EXERCISE INTOLERANCE IS ASSOCIATED with poor quality of life (16) and increased mortality (28) in patients with chronic obstructive pulmonary disease (COPD). Even though ventilatory limitation is the primary defect in these patients, it is well recognized that extrapulmonary factors contribute to exercise intolerance (14). Among these, it has been argued that peripheral muscle dysfunction, a well-characterized phenomenon in COPD (20), may have significant impact on exercise tolerance (10, 12, 21). Hence, exercise limitation in COPD could be schematized as a complex interaction between a central (ventilatory limitation) and a peripheral component (leg fatigue) (29).

In recent years, the influence of increased work of breathing on peripheral muscle fatigue at exercise has been documented in healthy subjects. During strenuous exercise, peripheral vasconstriction associated with the high demand for respiratory muscle blood flow appears to compromise locomotor muscle perfusion (7, 13) and consequently enhance muscle fatigue (34). This blood redistribution phenomenon in favor of the respiratory muscles may also occur in COPD (37). Conversely, events taking place within the lower limb muscles may influence the central component of exercise limitation. For example, the accumulation of metabolic byproducts such as lactate and inorganic phosphates in the contracting and fatiguing muscles may impact on the cardiorespiratory responses by stimulating group III and IV muscle afferents (22).

The contribution of limb muscles to exercise intolerance in COPD is mostly supported by correlative observation (10, 12, 21), whereas direct evidence linking limb muscle dysfunction to reduced exercise tolerance in COPD is lacking. One approach to address this issue is to compare the whole body exercise responses between a fresh state and a fatigued state, when a certain group of muscles has been prefatigued. This particular approach has been used to highlight the contribution of respiratory muscle fatigue to exercise intolerance in healthy subjects (18, 39, 43). In this investigation, we planned to quantify the impact of preinduced quadriceps fatigue on a subsequent cycling exercise in healthy subjects and patients with COPD. To pinpoint the impact of fatigue of a specific muscle group, we first tested the hypothesis that it would be possible to fatigue the quadriceps in a noneffort-dependent manner by inducing repeated muscle contractions with neuromuscular electrical stimulation (NMES). We then hypothesized that the induction of peripheral muscle fatigue before exercise would reduce exercise duration via an exaggerated ventilatory response, in healthy subjects and in patients with COPD. To this end, healthy subjects and patients with COPD performed a constant-workrate cycling exercise (CWT) that was preceded or not by the induction of fatigue of the quadriceps. The physiological responses during the two exercise conditions were then compared.

MATERIALS AND METHODS

Subjects

Patients with COPD (postbronchodilator forced expiratory volume in 1 s (FEV1) <80% predicted and FEV1/forced vital capacity (FVC) <0.7) were recruited to participate in this study during a stable phase of the disease. Healthy sedentary age-matched subjects with normal spirometry (FEV1 ≥80% predicted and FEV1/FVC ≥0.7) served as controls. In both groups, subjects were excluded if they presented any medical condition, other than COPD, likely to influence muscle and exercise testing (i.e., cardiovascular, neurological, musculoskeletal,
Femoral nerve [potentiated twitch force (TwQpot)]. In a randomized vol-
untary contraction (MVC) and magnetic stimulation of the quadriceps force measured and baseline quadriceps force was
quantified during maximally braked ergocycle (Quinton Corival 400; A-H Robins, Seattle, WA) and connected to the respiratory circuit through a mouthpiece.

**Study Design**

Study participation included three visits. During the first visit, anthropometric measurements, pulmonary function testing, and symptom-limited incremental exercise test were completed. The subsequent two visits (Fig. 1) were completed 7 days apart and consisted in performing one CWT up to exhaustion at 80% of the predetermined maximal workrate. Before CWT, FEV1 and inspiratory capacity were measured and baseline quadriceps force was quantified during maximal voluntary contraction (MVC) and magnetic stimulation of the femoral nerve [potentiated twitch force (TwQpot)]. In a randomized order, one CWT was performed with (fatigue state) and the other without (fresh state) preinduced quadriceps fatigue. Quadriceps fatigue was produced by repeated contractions of the quadriceps induced by an electrostimulation protocol. Fatigue was then quantified by measuring the change in quadriceps force 10 min after the electrostimulation protocol. Quadriceps force was measured again 10 min after CWT to quantify force loss produced during cycling. Subjects were asked to avoid alcohol, caffeine, and heavy meals 3 h before the visit and high intensity physical activity for at least 24 h before testing. Patients with COPD were instructed to take their usual medication throughout the study. Finally, the last two experimental visits were conducted at the same time of the day.

**Pulmonary Function Testing**

Standard pulmonary function tests, including spirometry, lung volumes, and diffusion capacity (DLco) were obtained during the initial visit, according to previously described guidelines (4) and related to predicted normal values (32). Spirometry was also performed before each CWT. Maximum voluntary ventilation (MVV) was estimated by multiplying FEV1 by 35 (9).

**Exercise Testing**

Incremental exercise testing. Subjects were seated on an electrically braked ergocycle (Quinton Corival 400; A-H Robins, Seattle, WA) and connected to the respiratory circuit through a mouthpiece. The exercise circuit consisted of a pneumotachograph. 

O2 and CO2 analyzers, and mixing chamber (Sensor Medics; Vmax Legacy, Yorba Linda, CA). After 5 min of rest, a progressive stepwise exercise test was performed up to the individual maximal capacity. Each exercise step lasted 1 min, and increments of 10 and 15 W were used in COPD and healthy subjects, respectively. Minute ventilation (Ve), oxygen uptake (Vo2), and CO2 excretion (Vaco2) were measured at rest and during exercise on a breath-by-breath basis.

**Fatigued condition**

TwQpot
MVC
Fatigue Protocol
CWT
Randomized order
7 days apart

**Fresh condition**

TwQpot
MVC
CWT

CWT. CWTs were performed until exhaustion at a working intensity corresponding to 80% of the peak workrate achieved during the incremental exercise test. The CWT was preceded by a 1-min unloaded warm-up period. Patients were instructed to pedal at a cadence of 60 revolution/min, and standardized encouragements were provided during exercise. Subjects were connected to the exercise circuit through a mouthpiece and wore a noseclip during the test. Vo2, Vaco2 were measured at rest and during exercise on a breath-by-breath basis. Heart rate (HR) was monitored by an electrocardiograph (Cardiosoft program-Corina, Milwaukee, WI) and blood pressure by an automated blood pressure monitor (Quinton 410; Quinton, Bothell, WA) at rest, at 2-min intervals during exercise, and at end of exercise. Oxygen pulse saturation (SpO2) was measured by a pulse oximeter (OSM2 Hexoximeter; Radiometer, Copenhagen, Denmark). The perception of dyspnea and leg fatigue was assessed at 2-min intervals during exercise using the modified 10-point Borg scale (6). Changes in operational lung volumes during exercise were derived from measurements of dynamic inspiratory capacity as previously reported (25). Inspiratory capacity was measured at rest, at 2-min intervals during exercise, and at end of exercise. In the fatigued state, CWT started 30 min after the end of the quadriceps muscle fatigue protocol. We introduced a fixed delay between the end of the fatigue protocol and the start of the exercise test to standardize the procedures across all participants while allowing sufficient time to measure the strength of the quadriceps and the inspiratory capacity. A technician unaware of the fatigue or fresh state of the participants was asked to supervise the CWT.

**Fatigue Protocol**

A 50-min NMES protocol was used to fatigue the quadriceps. Subjects were seated in a recumbent chair (N-K 330 Exercise Table; N-K Products, Elsinore, CA) with 90° knee flexion and ankles attached to a strain gauge (Hewlett-Packard, Houston, TX). The strain gauge was systematically adjusted perpendicularly to the leg, and the position was maintained throughout the protocol. The strain gauge signal was amplified (Model 8811A amplifiers; Hewlett-Packard), transformed by an analog transducer (Biopac, Goleta, CA), and linked to a computer for data analysis. Carbon electrodes (Empi StimCare Specialty Electrodes; Empi, St. Paul, MN) were applied on the surface of each quadriceps. Cathodes were placed on vastus lateralis and vastus medialis motor points while anode was proximally located on the surface of the vastus intermedius. The protocol was delivered on both quadriceps simultaneously using an electrostimulator (CEFAR RehabH260; Medical AB, Malmo, Sweden). It was preceded by a 5-min warm-up period consisting of continuous stimulation at 5-Hz pulse width for 300-μs pulse duration. Intermittent stimulations were then applied for 50 min using 10-s stimulation periods at 50 Hz for 400 μs interspaced with 12-s periods of stimulation at 5 Hz for 400 μs. Duty cycle was 45%. The intensity of the stimulus was progressively increased throughout the protocol to obtain the highest tolerable stimulation. Symmetrical biphasic squared-pulsed current was used,
and visible contractions were seen in every subject. Force developed by the quadriceps throughout the protocol was recorded at 4-min intervals by a strain gauge (Hewlett-Packard).

**Quadriceps Strength Measurements**

Quadriceps TwQ pot of the dominant leg was measured by supramaximal magnetic stimulation of the femoral nerve while subjects were positioned as in the fatigue protocol. A commercial magnetic stimulator was used to stimulate the femoral nerve while subjects were seated. The quadriceps (35). Patients who did not tolerate the NMES fatigue protocol or did not reach this predefined fatigue criteria were excluded from the study.

The time course of quadriceps fatigue after the electrostimulation protocol was characterized in four controls and four patients with COPD during a subsequent visit. In these individuals, we reproduced the same NMES procedures used previously. Quadriceps TwQ pot and MVC were obtained at rest and 10, 30, 60, and 120 min after the fatigue protocol. During this time frame, single (1 Hz) unpotentiated twitch (TwQ unpot) and paired TwQ unpot stimuli measured at 10, 50, and 100 Hz were obtained. The stimulus obtained at 1 Hz (single TwQ unpot(t1)) was digitally subtracted from the paired responses to obtain the averaged second stimulus (t2) (30, 46). The results of t2 at 10 Hz (t210Hz) and at 100 Hz (t2100Hz) were then reported as a ratio to determine t210:100. This ratio has recently been validated on the quadriceps muscle (42). Ve and HR were measured by a portable device (Jaeger Oxycon Mobile; VIASYS Healthcare, Yorba Linda, CA) at rest and during the electrostimulation protocol.

**Table 1. Subject’s characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 9)</th>
<th>COPD (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>71 ± 2</td>
<td>67 ± 2</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>(8/1)</td>
<td>(15/0)</td>
</tr>
<tr>
<td>Body Mass Index, kg/m²</td>
<td>28 ± 1.0</td>
<td>24 ± 0.5</td>
</tr>
<tr>
<td>Voorips Score</td>
<td>7.6 ± 0.6</td>
<td>6.5 ± 0.5</td>
</tr>
<tr>
<td>FEV1, l</td>
<td>2.63 ± 0.14</td>
<td>1.19 ± 0.08†</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>102 ± 4</td>
<td>44 ± 3†</td>
</tr>
<tr>
<td>FVC, l</td>
<td>3.61 ± 0.21</td>
<td>2.99 ± 0.15*</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>97 ± 3</td>
<td>78 ± 3†</td>
</tr>
<tr>
<td>FRC, % predicted</td>
<td>88 ± 10</td>
<td>138 ± 11*</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>92 ± 5</td>
<td>109 ± 6*</td>
</tr>
<tr>
<td>DlCO, % predicted</td>
<td>96 ± 7</td>
<td>56 ± 3*</td>
</tr>
<tr>
<td>Wmax, watts</td>
<td>142 ± 7</td>
<td>82 ± 6†</td>
</tr>
<tr>
<td>VO2peak, l/min</td>
<td>1.93 ± 0.12</td>
<td>1.35 ± 0.10*</td>
</tr>
<tr>
<td>TwQpeak, kg</td>
<td>9.9 ± 0.9</td>
<td>11.0 ± 0.8</td>
</tr>
<tr>
<td>MVC, kg</td>
<td>46.4 ± 2.4</td>
<td>35.7 ± 2.5*</td>
</tr>
</tbody>
</table>

Values are mean ± SE. COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; FRC, functional residual capacity; TLC, total lung capacity; DlCO, diffusion capacity; Wmax, maximal workload; VO2peak, peak oxygen consumption; TwQpot, mean potentiated quadriceps twitch force obtained at baseline on the fresh and fatigue testing days; MVC, mean maximal voluntary contraction obtained at baseline on the fresh and fatigue testing days. *P < 0.05; †P < 0.001.

**Physical Activity Score**

The level of physical activity in daily living was assessed by a questionnaire previously developed by Baecke and colleagues (5), adapted further for elderly subjects (45), and previously used in COPD (36). The Voorips questionnaire attributes a score for household, sports, and leisure time activities, and a score below 9 points is considered to represent a sedentary lifestyle.

**Statistical Analysis**

All results are expressed as means ± SE. In each group, Ve, VO2, VCO2, Ve/VCO2, partial pressure of end-tidal carbon dioxide (PteCO2), HR, tidal volume (VT), and breathing frequency (B) were compared at rest between the two conditions using a paired t-test. The exercise-induced changes for the same parameters were compared during exercise using a mixed repeated ANOVA, allowing us to evaluate and compare the time course of different variables between both groups and conditions. Unpaired t-test was used to compare intergroup differences at rest, isotime (i.e., at the same absolute time), and at peak exercise. Before and after NMES fatigue protocol, muscle force (MVC and TwQ pot) was compared using paired t-test within groups and unpaired t-test between groups. One hundred percent isotime was defined as the latest exercise time that was reached during the two conditions. Endurance time was defined as the duration of the CWT excluding the warm-up period. Pearson correlations were performed to examine the association between nonrepeated measures. A statistical level of significance of 0.05 was used for all analysis.

**RESULTS**

**Subjects**

We initially tested 11 control subjects and 19 patients with COPD. Of this population, one healthy man and three patients...
with COPD (1 man; 2 women) were excluded from the study because of NMES intolerance. In addition, one healthy man and one man with COPD were excluded from the present investigation because they did not meet our a priori fatigue criteria. Thus 78% of control subjects and 79% of patients with COPD initially enrolled in testing successfully completed the study. Characteristics of studied subjects are presented in Table 1. The two groups had similar age and physical activity questionnaire scores consistent with a sedentary life style. Patients with COPD showed moderate to severe airflow obstruction according to GOLD standards (33). MVC, peak power output ($W_{peak}$), and peak $V\dot{O}_2$ were reduced in patients with COPD compared with controls.

**Quadriceps Muscle Fatigue**

MVC and $TwQ_{pot}$ at baseline were similar between the fatigued and fresh testing conditions: MVC, 46.6 ± 2.5 vs. 46.2 ± 2.6 kg and 35.8 ± 2.5 vs. 35.6 ± 2.5 kg in healthy subjects and COPD, respectively; $TwQ_{pot}$, 10.1 ± 1.1 vs. 9.7 ± 0.7 kg and 11.2 ± 0.8 vs. 10.9 ± 0.7 kg in healthy subjects and COPD, respectively.

The time courses of electrostimulation intensity and force production during the NMES protocol are depicted in Fig. 2. Electrostimulation intensity was progressively increased throughout the protocol, in an attempt to deliver the highest tolerable stimulation. Healthy controls tended to tolerate higher stimulation intensities than patients with COPD, but this difference did not reach statistical significance. During the protocol, the quadriceps force output remained relatively stable and was similar in both groups amounting to 7.6 ± 1.3% MVC in healthy controls and 7.8 ± 0.3% MVC in patients with COPD ($P > 0.05$).

Loss of quadriceps force following the NMES fatigue protocol is presented in Fig. 3. As illustrated, the $TwQ_{pot}$ drop from baseline values was similar in healthy controls (35 ± 5% of baseline values) and patients with COPD (30 ± 3% of baseline values), whereas MVC reduction was more pronounced in controls than in patients with COPD (25 ± 2% vs. 17 ± 2% of baseline values, $P < 0.05$). The fall in MVC correlated with that of $TwQ_{pot}$ in all the subjects ($r = 0.47, P = 0.02$). The fall in MVC also correlated with the intensity of electrostimulation ($r = 0.54, P = 0.006$).

The time course of fatigue following the electrostimulation protocol tested in four controls and four patients with COPD is presented in Fig. 4. The fall in $TwQ_{pot}$ and MVC was maintained up to 120 min postelectrostimulation. The fall in $TwQ_{unpot}$ 10 and 120 min postelectrostimulation was similar across all magnetic stimulation frequencies in both groups (data not shown). As a result, $t_{210:100}$ remained constant from baseline (controls, 0.72 ± 0.02; COPD, 0.79 ± 0.03) to 10 min, 30 min, 60 min, and 120 min postelectrostimulation. $V\dot{E}$ and HR increased minimally during the whole electrostimulation protocol for healthy controls and COPD; mean $\Delta V\dot{E}$ through NMES protocol was 2.3 ± 0.1 l/min ($P = 0.06$) and 1.7 ± 0.3 l/min ($P = 0.18$), whereas mean $\Delta HR$ was 5.9 ± 0.5 beat/min ($P = 0.04$) and 4.5 ± 0.9 beat/min ($P = 0.42$), for controls and patients with COPD, respectively.

**Effect of Fatigue on Endurance Time, Ventilatory Response, and Physiological Parameters During Exercise**

Both groups showed a significant decrease in endurance time in the fatigued compared with the fresh condition that amounted 109 ± 38 s ($P < 0.05$) and 61 ± 28 s ($P < 0.05$) in controls and COPD, respectively (Fig. 5). Healthy controls showed significantly higher ventilation during exercise (Fig. 6) in the fatigued condition, whereas fatigue did not increase ventilation during exercise in COPD. The $V\dot{E}/MVV$ ratio at end of exercise reached a value >1 in patients with COPD both in the fatigued and fresh states, indicating the absence of ventilatory reserve on both exercise testing conditions (Table 2).

In both groups, no differences were found in $V\dot{O}_2$, $V\dot{CO}_2$, $V\dot{E}/V\dot{CO}_2$, $P_{ETCO}_2$, and HR comparisons at isotime points.

![Fig. 3. Fall in MVC and $TwQ_{pot}$ for the control (open bars) and the COPD group (solid bars) 10 min after the NMES fatigue protocol. Values are expressed in percents of baseline values. *$P < 0.01$ compared with baseline values; †$P < 0.05$ control group vs. COPD group.](http://jap.physiology.org/)

![Fig. 4. Time course of MVC (A) and $TwQ_{pot}$ (B) after NMES fatigue protocol in 4 control subjects (A) and 4 patients with COPD (B). Values are expressed as percent of baseline values and reported at rest, 10, 30, 60, and 120 min after the fatigue protocol. *$P < 0.05$ compared with baseline measures.](http://jap.physiology.org/)
between the fatigued and fresh states (Table 2). At rest and peak exercise, systolic blood pressure, diastolic blood pressure, and SpO2 were comparable between the two conditions in both groups (Table 2). Finally, quadriceps fatigue did not result in any changes of the breathing pattern (Table 2). Patients with COPD experienced a fall in inspiratory capacity during exercise that was not significantly modified by the preinduction of muscle fatigue (Table 2). No correlation was found between the level of fatigue and the magnitude of decrease in endurance time.

Dyspnea and leg fatigue Borg score at 1 min, isotime, and peak exercise are presented in Fig. 7. In controls, leg fatigue scores at isotime were higher in the fatigued condition compared with the fresh condition, while dyspnea was significantly higher at peak exercise in the fatigued condition. Consistent with these findings, 56% of controls reported dyspnea as the main exercise-limiting symptom when fatigued compared with 22% in the fresh state (P < 0.07). In patients with COPD, symptom perception during exercise was not significantly modified by the presence of quadriceps fatigue.

The loss in MVC produced by CWT itself tended to be smaller when performed in the fatigued condition compared with the fresh state (Fig. 8); this was true for both groups. The fall in TwQpot during CWT was also smaller in the fatigued state compared with the fresh state in patients with COPD, whereas no difference was found in control subjects.

DISCUSSION

The present study investigated the impact of quadriceps muscle fatigue on the tolerance to CWT and the ventilatory response during exercise in healthy subjects and patients with COPD. This study represents the first to directly evaluate the influence of preinduced quadriceps muscle fatigue during exercise in patients with COPD. We were able to induce fatigue of the quadriceps that persisted for at least 120 min. This fatigue was present across a range of paired magnetic stimulation frequencies (1–100 Hz), suggesting that we were able to induce a global fatigue of the quadriceps resembling the physiological situation when fatigue is induced by repeated voluntary contractions.

Preinduced leg fatigue has been shown to reduce exercise performance during a subsequent cycling exercise in young athletes (1). In that study, however, lower limb fatigue was induced by a bout of high-intensity cycling exercise, and it is possible that central fatigue, or other systemic effects of whole body exercise possibly occurring during the prefatigue cycling exercise trial, may have contributed to the reduction in performance during the subsequent exercise period. Our results extend the observations of this study by using a muscle-specific fatiguing protocol in a different study population. Our fatiguing protocol, by its virtue of specifically fatiguing the quadriceps and minimizing cardiorespiratory stimulation, provides further evidence that quadriceps fatigue is an important determinant of exercise performance. We also show that this important effect of quadriceps fatigue is not limited to athletes but also applies to older and nontrained healthy subjects. Our study also highlights that peripheral muscle fatigue, as induced in the present study, was an additional important factor, besides ventilatory limitation and dyspnea, that restricted exercise tolerance in COPD. This information is relevant considering that, although we and others have argued about the role of limb muscle dysfunction on exercise intolerance in COPD (12, 35), this topic is still a matter of debate (27).

Mechanisms of Reduced Exercise Tolerance With Muscle Fatigue

The reduction in exercise tolerance observed in the fatigued state supports a role for peripheral muscle fatigue in exercise intolerance in healthy subjects and patients with COPD. Although our study does not allow drawing a definitive conclusion on the nature of the link between muscle fatigue and reduced exercise tolerance, we can speculate on this issue. We found in healthy controls that quadriceps fatigue was associated with greater ventilatory demand and higher dyspnea perception. The similar Vt/VCO2 ratio between the fresh and
Table 2. Isotime and peak physiological response during constant workrate exercise tests

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 9)</th>
<th>COPD (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fresh</td>
<td>Fatigued</td>
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<tr>
<td>Isotime Comparisons</td>
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<td></td>
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<tr>
<td>( V_{\dot{E}} ), l/min 0%</td>
<td>18.9 ± 0.9</td>
<td>22.4 ± 1.3</td>
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<tr>
<td>25%</td>
<td>43.9 ± 3.6</td>
<td>46.2 ± 5.6</td>
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<tr>
<td>50%</td>
<td>56.7 ± 3.6</td>
<td>64.2 ± 4.1</td>
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<tr>
<td>75%</td>
<td>67.9 ± 3.2</td>
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<tr>
<td>100%</td>
<td>73.8 ± 3.8</td>
<td>81.5 ± 5.1*</td>
</tr>
<tr>
<td>Peak</td>
<td>80.0 ± 1.4</td>
<td>—</td>
</tr>
<tr>
<td>( V_{\dot{E}}/MVV, % ) 0%</td>
<td>22 ± 1</td>
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</tr>
<tr>
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<td>50 ± 4</td>
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<tr>
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<td>( V_{\dot{IC}} ), l/min 0%</td>
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<td>Peak</td>
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<td>( V_{\dot{CO}<em>2}/V</em>{\dot{O}_2} ) 0%</td>
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<tr>
<td>100%</td>
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<td>33.9 ± 1.6</td>
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<tr>
<td>Peak</td>
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<td>( P_{\dot{O}<em>2}/P</em>{\dot{CO}_2} ), mmHg 0%</td>
<td>36.0 ± 0.5</td>
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<td>38.8 ± 1.0</td>
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<td>75%</td>
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<td>100%</td>
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<td>Peak</td>
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<td>( V_{\dot{T}} ), l/min 0%</td>
<td>0.89 ± 0.07</td>
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<td>1.60 ± 0.11</td>
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<tr>
<td>50%</td>
<td>2.06 ± 0.16</td>
<td>2.09 ± 0.16</td>
</tr>
<tr>
<td>75%</td>
<td>2.11 ± 0.19</td>
<td>2.14 ± 0.16</td>
</tr>
<tr>
<td>100%</td>
<td>2.09 ± 0.17</td>
<td>2.15 ± 0.17</td>
</tr>
<tr>
<td>Peak</td>
<td>2.05 ± 0.19</td>
<td>—</td>
</tr>
<tr>
<td>( B_0 ), breath/min 0%</td>
<td>23 ± 2</td>
<td>23 ± 2</td>
</tr>
<tr>
<td>25%</td>
<td>27 ± 1</td>
<td>28 ± 2</td>
</tr>
<tr>
<td>50%</td>
<td>30 ± 2</td>
<td>32 ± 3</td>
</tr>
<tr>
<td>75%</td>
<td>34 ± 4</td>
<td>35 ± 3</td>
</tr>
<tr>
<td>100%</td>
<td>36 ± 2</td>
<td>39 ± 3</td>
</tr>
<tr>
<td>Peak</td>
<td>42 ± 3</td>
<td>—</td>
</tr>
<tr>
<td>HR, beat/min 0%</td>
<td>84 ± 3</td>
<td>83 ± 4</td>
</tr>
<tr>
<td>25%</td>
<td>113 ± 6</td>
<td>114 ± 6</td>
</tr>
<tr>
<td>50%</td>
<td>127 ± 7</td>
<td>129 ± 7</td>
</tr>
<tr>
<td>75%</td>
<td>137 ± 6</td>
<td>139 ± 7</td>
</tr>
<tr>
<td>100%</td>
<td>142 ± 7</td>
<td>143 ± 8</td>
</tr>
<tr>
<td>Peak</td>
<td>146 ± 7</td>
<td>—</td>
</tr>
</tbody>
</table>

Values are mean ± SE. \( V_{\dot{E}} \), ventilation; MVV, maximal voluntary ventilation; \( V_{\dot{O}_2} \), oxygen uptake; \( V_{\dot{CO}_2} \), carbon dioxide output; \( P_{\dot{O}_2}/P_{\dot{CO}_2} \), partial pressure of end-tidal carbon dioxide; \( V_{\dot{T}} \), tidal volume; \( B_0 \), breathing frequency; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; IC, inspiratory capacity. \( *P < 0.05 \) compared with the nonfatigued condition within groups.

fatigued exercise suggests that the increase in ventilation observed in the fatigued state was metabolically driven, perhaps in relationship with acidosis, lactate, and inorganic phosphate accumulation in the fatigued muscles.

The influence of quadriceps muscle fatigue on the exercise tolerance seemed to be modulated differently in patients with COPD in whom the reduction of exercise tolerance following quadriceps fatigue was not related to a higher ventilatory response nor worsened dynamic hyperinflation.

The absence of increased cardiac and blood pressure responses during exercise in the fatigued state both in healthy controls and in patients with COPD also suggest that the enhanced metaboreflex is not the main mechanism through which exercise tolerance was reduced in the fatigued state in both study populations. In fact, others’ and our data suggest that peripheral fatigue may, by itself, be the limiting factor preventing further exercise to continue. Compelling evidence supports that peripheral muscle fatigue during exercise is highly regulated (1–3). This theory stipulates that feedback signals originating in the fatigued muscles inhibit motor cortical output, thus preventing subsequent locomotor recruitment and the development of dangerous and potentially irreversible fatigue (2). The smaller degree of quadriceps fatigue reached when CWT was performed in the fatigued state compared with the fresh state is consistent with this theory. In patients with COPD developing contractile fatigue of the quadriceps during cycling exercise, acute bronchodilation had no positive effects on exercise duration (35). In fact, these individuals actually stopped exercising at the same level of quadriceps fatigue (within 5%), regardless of whether they received a placebo or a bronchodilator before exercise. Together, these observations support the contention that quadriceps fatigue during exercise is tightly regulated in patients with COPD. These observations are also in line with the notion that the central nervous system integrates information originating from the peripheral muscles to determine the duration of exercise and the degree of muscle fatigue (3, 24).

**Methodological Considerations**

The use of NMES to induce fatigue of the quadriceps is attractive because it has limited impact on ventilation and HR (40). Another interesting feature of this modality is that it is independent from motivation and effort. The occurrence of
quadriceps fatigue after NMES was objectively quantified by measuring the fall in the strength of the quadriceps during magnetic stimulation of the femoral nerve (TwQpot) and MVC. The fall in both measures of strength was large and beyond measurement variability (35), confirming that we were able to fatigue the quadriceps with NMES. The persisting fall in quadriceps strength for 120 min suggests that muscle fatigue was present throughout the exercise period. There was greater fall in MVC in healthy controls after the electrostimulation protocol compared with patients with COPD. Tolerability to greater stimulation intensities in healthy controls may have contributed to the greater fall in MVC observed in this group as suggested by the correlation between the magnitude of fall in MVC during the electrostimulation protocol and stimulation intensity.

The absence of sham fatigue protocol before exercise when performed in the fresh state is a potential methodological limitation of our study. We felt that it would not have been possible to blind our subjects to the study intervention despite using a sham procedure. Electrostimulation is uncomfortable and easily perceived so that the active and the sham stimulation protocols would have been easily distinguished by the participants. To minimize the impact of this limitation, a technician blinded to the study intervention was asked to supervise the endurance exercise tests. Also, subjects were naive to the precise objectives and primary outcomes of the study.

The force reduction in MVC and TwQpot after the NMES fatigue protocol was similar to those reported by Mador and colleagues after a quadriceps fatiguing task in patients with COPD (19). Although the study was not designed to precisely determine the type of fatigue induced, the fall in TwQpot after the NMES fatigue protocol persisted for at least 120 min, reflecting low-frequency fatigue (8, 17). Fatigue induced by the NMES protocol was present at low and high frequencies as indicated by the similar fall in quadriceps force at 1, 10, 50, and 100 Hz and by the stable t210:100 values for up to 120 min post-NMES. A potential explanation for these observations could be the stimulation frequency of 50 Hz used in the electrostimulation protocol, representing a cutting point between high- and low-stimulation frequency (44). This specific stimulation frequency was chosen because it is reasonably close to physiological discharge frequency observed during voluntary muscular contractions (10–40 Hz) (11, 38).

Despite obvious strengths, our electrostimulation fatigue protocol may not exactly reproduce what is seen with other
fatiguing protocols involving voluntary or magnetically induced muscle contractions (38, 40). The fall in quadriceps force observed in the study participants may also appear unexpectedly high considering the relatively modest force output that was generated during the electrostimulation protocol (7–8% MVC). For a similar muscle force output during the fatiguing protocol, electrostimulation appears to elicit greater muscle fatigue compared with voluntary contractions (40). The magnitude of the fall in TwQpot was also larger with our electrostimulation protocol than what has been reported with repeated magnetic-stimulated muscle contractions (38). The differences in the magnitude of the fall in force between electrostimulation and other types of fatigue protocols could be related to the pattern of muscle fiber recruitment during electrostimulation and to the prolonged duration of our fatigue protocol.

During neuromuscular electrostimulation, fiber recruitment initially takes place on the surface of the muscle. Eventually, superficial fibers will fatigue as reflected by a progressive reduction in torque production unless stimulation intensity is increased and allowed to maintain the contraction of the fatigued fibers and to recruit additional and deeper motor units (23). It is thus conceivable that the progressive increase in stimulation intensities during our 50-min electrostimulation protocol (Fig. 2) resulted in the recruitment and fatigue of a large portion of the quadriceps fibers, thus explaining the relatively large fall in TwQpot and MVC. This statement is supported by a study that used positron emission tomography scanning to quantify thigh blood flow during an electrostimulation protocol (41). Assuming that muscle blood flow indirectly reflects contractile activity, it was demonstrated that ~60% of the surface of the thigh was solicited during electrostimulation that generated a force output corresponding to 10% of the MVC (41). On the basis of these concepts, we submitted that our 50-min protocol was sufficient to allow the recruitment and eventually the fatigue of a substantial portion of the quadriceps fibers, despite a modest force output generated during electrostimulation.

It was of critical importance to ensure that quadriceps strength had returned to fresh state when patients were evaluated at the third visit. The 7-day period between the two CWTs was likely sufficient as evidenced by the fact that strength of the quadriceps at baseline was similar between visits. We did not assess the reproducibility of endurance time to CWT in the present study. Nevertheless, a large database of more than 450 patients with COPD demonstrated that the endurance time was highly reproducible (26). That study showed a small learning effect on the second trial (33 s). However, the randomized cross-over study design of our study should have counterweighted this potential bias.

We conclude that it is possible to induce quadriceps muscle fatigue by NMES and that this particular fatigue is a factor, among others, that contributes to limited exercise tolerance in patients with COPD and healthy subjects. Although the mechanisms underlying these observations could not be completely resolved, this study adds another layer of evidence pointing toward a peripheral component of exercise limitation in COPD. Interventional studies manipulating the magnitude of the afferent signals originating from the peripheral fatiguing muscles could be instrumental in clarifying the mechanisms of reduced exercise tolerance after the induction of muscle fatigue in COPD.

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