

Contractile Fatigue, Muscle Morphometry, and Blood Lactate in Chronic Obstructive Pulmonary Disease

Didier Saey, Annie Michaud, Annabelle Couillard, Claude H. Côté, M. Jeffery Mador, Pierre LeBlanc, Jean Jobin, and François Maltais

Centre de recherche, Hôpital Laval, Institut Universitaire de Cardiologie et de Pneumologie de l'Université Laval; Centre de recherche du CHUQ pavillon CHUL, Université Laval, Québec, Canada; Laboratoire de Physiologie des Interactions, Hôpital Arnaud de Villeneuve, Montpellier, France; and Pulmonary, Critical Care, and Sleep Medicine, State University of New York at Buffalo and the Buffalo VAMC, Buffalo, New York

We hypothesized that patients with chronic obstructive pulmonary disease developing contractile fatigue of the quadriceps during cycle exercise may have characteristic metabolic and muscle features that could increase their susceptibility to fatigue, thus differentiating them from those who do not develop fatigue. We examined, in 32 patients, the fiber-type proportion, enzymatic activities, and capillary density in the vastus lateralis and the arterial blood lactate level during constant work-rate cycling exercise. Contractile fatigue was defined as a postexercise fall in quadriceps twitch force greater than 15% of resting values. Twenty-two patients developed contractile fatigue after exercise. No significant differences were found between fatiguers and nonfatiguers for the endurance time, fiber-type proportion, and oxidative enzyme activities. The lactate dehydrogenase activity was significantly higher ($p < 0.05$) and muscle capillarization significantly reduced in fatiguers ($p < 0.05$). Compared with nonfatiguers, the arterial lactate level during exercise was significantly higher in fatiguers ($p < 0.001$). A significant relationship was found between the fall in quadriceps twitch force and lactate dehydrogenase activity, capillary/fiber ratio, and blood lactate level. We conclude that changes in muscle enzymatic profile and capillarization with a greater reliance on glycolytic metabolism during exercise are associated with contractile fatigue in patients with chronic obstructive pulmonary disease.

Keywords: COPD; exertion; fatigue; muscle

A role for lower limb muscles in limiting exercise in chronic obstructive pulmonary disease (COPD) has been proposed based on the inverse relationship between the perception of leg fatigue during cycling exercise and exercise tolerance (1) and on the development of leg fatigue during exercise (2) in a significant proportion of patients with this disease. Moreover, we recently reported that the exercise response to bronchodilation can be modulated by the presence of contractile leg fatigue, thus providing additional support to the hypothesis that peripheral muscle dysfunction may influence exercise tolerance in COPD (3).

In healthy subjects, muscle fatigue is attributed to various mechanisms ranging from poor central command output to an altered interaction between contractile proteins (4). It is also

well accepted that metabolic changes in the muscle, such as lactate accumulation and phosphocreatine depletion (5), limitations in muscle energy supply (6), and structural and metabolic disorganization of contractile proteins (7), can all be involved in the development of contractile muscle fatigue. In COPD, reported muscle changes that could be associated with fatigue include reduction in the proportion of the more fatigue-resistant slow-twitch fibers (8–11) and modifications in muscle energy metabolism (12–14), leading to increased lactate accumulation and premature muscle acidosis (15–17). Because of its clinical relevance, it is important to elucidate the mechanisms and the impact of leg fatigue in patients with COPD.

One interesting question is why contractile fatigue, defined as a reversible postexercise fall in quadriceps strength, is only found in approximately 50% of patients with COPD (3, 18). Two possibilities could be considered: either the peripheral muscle of individuals with contractile fatigue shows intrinsic susceptibility to fatigue or some patients stop exercise before the occurrence of contractile fatigue for various reasons, such as intolerable dyspnea, ventilatory limitation, central fatigue, and poor motivation.

On the basis of the previously reported peripheral muscle changes in patients with COPD, we hypothesized that the susceptibility to develop contractile muscle fatigue in these individuals could be linked to the typical skeletal muscle adaptations found in this disease, leading to higher reliance on anaerobic glycolysis, greater blood lactate accumulation, and early acidosis during exercise.

Accordingly, the objective of this study was to compare the fiber-type distribution, the enzymatic profile and the capillarity density of the vastus lateralis, and the blood lactate kinetics during constant work-rate cycling exercise between patients with COPD, with and without exercise-induced contractile leg fatigue.

Some of the results of this study have been reported previously in the form of an abstract (19).

METHODS

Subjects

Thirty-two sedentary men with spirometric evidence of chronic airflow limitation volunteered to participate in this study. The diagnosis of COPD was based on spirometry showing moderate to severe irreversible airflow obstruction (postbronchodilator $FEV_1 < 60\%$ predicted value, and $FEV_1/FVC < 70\%$) (20) and current or past smoking history (> 20 packs/year). Subjects were stable at the time of the study, and none suffered from cardiovascular, neurologic, skeletal muscle, or any other condition that could alter their capacity to perform the exercise test. No patients were on long-term oxygen therapy, nor did they receive oxygen during exercise. None of the subjects had been involved in a rehabilitation program before their participation in this study. The research protocol was approved by the institutional ethics committee, and a signed, informed consent was obtained from each subject. Eighteen of these subjects were the object of a previous report (3).

Study Design and Methods

After reviewing their medical history and familiarization with the study procedures, subjects filled out a physical activity questionnaire (21).

(Received in original form August 3, 2004; accepted in final form February 15, 2005)

Supported by La Fondation J.D. Bégin de la Chaire de Pneumologie de l'Université Laval, the Réseau Provincial de Recherche en Adaptation-Réadaptation, and CIHR grant MOP-53135. D.S. is recipient of a Ph.D. training award of Fonds de la Recherche en Santé du Québec. F.M. is a research scholar of the Fonds de la Recherche en Santé du Québec.

Correspondence and requests for reprints should be addressed to Dr. François Maltais, M.D., Centre de Pneumologie, Hôpital Laval, 2725 Chemin Ste-Foy, Ste-Foy, PQ, G1V 4G5 Canada. E-mail: francois.maltais@med.ulaval.ca

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 171, pp 1109–1115, 2005

Originally Published in Press as DOI: 10.1164/rccm.200408-1005OC on February 25, 2005

Internet address: www.atsjournals.org

Anthropometric measurements, pulmonary function testing, a computed tomography of the mid thigh, a percutaneous biopsy of the vastus lateralis muscle of the dominant leg, and a symptom-limited incremental cycle exercise test were then obtained. Within 1 week, subjects returned to the laboratory for a submaximal constant work-rate cycling exercise performed at 80% of their peak work rate. To standardize the procedures, patients were asked to withdraw from short-acting β_2 -agonists (6 hours), long-acting β_2 -agonists (12 hours), short-acting anticholinergics (6 hours), and theophyllines (24 hours) before the visit. Ipratropium bromide, 500 μg , was nebulized 1 to 1.5 hours before the exercise test. A cannula was placed in a radial artery to obtain blood samples at rest and during the constant work-rate cycling exercise. The quadriceps force was measured at rest, using first elicited contraction with magnetic stimulation of the femoral nerve and then during maximum voluntary contractions as previously described (3). FEV₁ was then measured, and the submaximal exercise was performed until exhaustion. Finally, quadriceps twitch force was measured again at 10, 20, and 30 minutes postexercise, whereas maximal voluntary contractions were performed 10 and 30 minutes after exercise. A detailed description of the methodology involved can be found in the online supplement.

Statistical Analysis

Results are reported as mean \pm SD. A statistical level of significance of 0.05 was used for all analyses. The duration of constant work-rate exercise was defined as the endurance time. On the basis of our previous works (2, 3), a greater than 15% decrease in quadriceps twitch force 10 minutes after exercise was considered as a true physiologic signal indicating contractile fatigue. On the basis of this definition of contractile fatigue, it was decided *a priori* to divide the study population into fatiguers (patients in whom a $>$ 15% decrease in quadriceps twitch force 10 minutes after exercise was observed) and nonfatiguers. An unpaired *t* test or a Mann-Whitney rank sum test, when normality was not obtained, was used to compare age, body mass index, lung function, endurance time, arterial lactate, maximal voluntary contraction, mid-thigh muscle cross-sectional area, and morphometric and enzymatic muscle characteristics between fatiguers and nonfatiguers. Possible correlations between the fall of quadriceps twitch force after exercise and arterial lactate, lactate dehydrogenase activity, muscle capillarization, and endurance time were evaluated using a Pearson correlation. The data were analyzed using the statistical package Sygmatat 1.0 (Jandel Scientific, San Rafael, CA).

RESULTS

Study Population

Subjects' characteristics are presented in Table 1. On average, patients had moderate to severe airflow obstruction and a low or moderate level of physical activity. Compared with healthy subjects previously studied in our laboratory, patients had a reduced mid thigh muscle cross-sectional area (10). Twenty-two patients demonstrated a more than 15% fall in quadriceps twitch force 10 minutes after exercise and were considered as fatiguers. Fatiguers and nonfatiguers could not be differentiated on the basis of their age, body mass index, level of physical activity, resting lung function, mid thigh muscle cross-sectional area, maximal voluntary contraction, and resting arterial blood gases. The physiologic response to incremental exercise testing is shown in Table 2. A peak respiratory exchange ratio greater than 1, the absence of ventilatory reserve at peak exercise ($\dot{V}_E/\text{maximum voluntary ventilation} > 100\%$), and a high symptom score indicated that maximum exercise intensity was reached by the patients (22). Apart from the perception of leg fatigue, which was significantly lower in nonfatiguers, the response to incremental exercise was similar between the two groups.

Quadriceps Muscle Fatigue

The time course of quadriceps twitch force and maximal voluntary contraction for fatiguers and nonfatiguers after exercise is illustrated in Figure 1. In fatiguers, the fall of quadriceps twitch

TABLE 1. SUBJECTS' CHARACTERISTICS

	Fatiguers (n = 22)	Nonfatiguers (n = 10)
Age, yr	65 \pm 8	63 \pm 9
BMI, kg/m ²	28 \pm 5	28 \pm 4
PA score	6.8 \pm 4.0	7.8 \pm 3.3
FEV ₁ , L	1.18 \pm 0.41	1.12 \pm 0.42
FEV ₁ , % predicted	43 \pm 14	39 \pm 15
FVC, L	2.66 \pm 1.28	2.49 \pm 0.92
FEV ₁ /FVC	46 \pm 10	45 \pm 6
DL _{CO} , % predicted	82 \pm 20	68 \pm 22
IC, % predicted	58 \pm 15	57 \pm 19
TLC, % predicted	114 \pm 16	118 \pm 10
RV, % predicted	173 \pm 45	185 \pm 56
MTCSA, cm ²	84 \pm 11	85 \pm 14
MVC, kg	44 \pm 10	45 \pm 9
Sa _{O₂} , %	97 \pm 2	96 \pm 2
Po ₂ , mm Hg	88 \pm 14	78 \pm 12
Pco ₂ , mm Hg	40 \pm 6	40 \pm 6

Definition of abbreviations: BMI = body mass index; DL_{CO} = diffusion capacity; IC = inspiratory capacity; MTCSA = mid thigh muscle cross-sectional area; MVC = maximum voluntary contraction; PA score = physical activity score; RV = residual volume; TLC = total lung capacity.

Values are means \pm SD.

force persisted up to 30 minutes postexercise, suggesting a low-frequency fatigue, a type of fatigue that is manifested preferentially at low frequencies of stimulation and characterized by a slow rate of recovery (23). This quadriceps twitch force decrease was accompanied by a significant and persistent fall of maximal voluntary contraction. In nonfatiguers, the reduction in maximal voluntary contraction occurring after exercise was smaller than in fatiguers, and this fall was no longer significant 30 minutes postexercise. The actual percentage of fall in quadriceps twitch force and maximal voluntary contraction after exercise can be found in the online supplement.

Muscle Structure and Enzymatic Activities

Because of the insufficiency of muscle tissue, lactate dehydrogenase activity could be obtained in 28 patients and muscle capillarization in 31 patients. As shown in Table 3, there was no significant difference between fatiguers and nonfatiguers for the fiber-type distribution, fiber cross-sectional areas, and the oxidative enzyme activities of the vastus lateralis. The lactate dehydrogenase enzyme activity, the lactate dehydrogenase/citrate synthase, and lactate dehydrogenase/3-hydroxyl CoA dehydrogenase enzymatic ratios

TABLE 2. PEAK PHYSIOLOGIC RESPONSES DURING INCREMENTAL EXERCISE

	Fatiguers (n = 22)	Nonfatiguers (n = 10)
\dot{V}_{O_2} , L/min	1.20 \pm 0.33	1.11 \pm 0.32
Work rate, W	100 \pm 30	89 \pm 33
Heart rate, beat/min	141 \pm 15	133 \pm 18
\dot{V}_E , L/min	50.0 \pm 15.8	47.9 \pm 11.0
\dot{V}_E/MVV	1.11 \pm 0.40	1.25 \pm 0.24
RER	1.11 \pm 0.08	1.10 \pm 0.06
Sa _{O₂}	95 \pm 4	94 \pm 4
Dyspnea Borg score	7.6 \pm 2.1	7.1 \pm 2.1
Leg fatigue Borg score	7.4 \pm 2.0	5.6 \pm 2.5*

Definition of abbreviations: MVV = maximum voluntary ventilation; RER = respiratory exchange ratio.

Values are means \pm SD.

*p < 0.05 compared to fatiguers (unpaired *t* test).

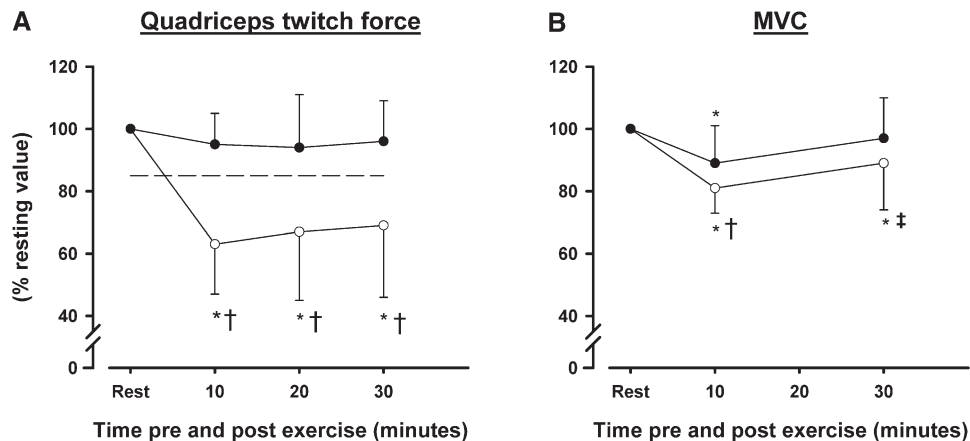


Figure 1. (A) Quadriceps twitch force and (B) maximal voluntary contraction (MVC) expressed in % resting values at rest, and 10, 20, and 30 minutes post-exercise. Mean values and their SD for fatiguers (open circles) and nonfatiguers (closed circles) are represented. The dashed line indicates the fatigue threshold. **p* < 0.05 versus resting values; †*p* < 0.05 versus nonfatiguers; ‡*p* = 0.064 versus nonfatiguers.

were significantly higher in fatiguers compared with nonfatiguers (*p* < 0.05). These discriminating enzymatic ratios provide useful indication about the preferential enzymatic pathway in the muscle (24). Muscle capillarization was lower in fatiguers compared with nonfatiguers as indicated by a significantly lower capillary/fiber ratio (1.5 ± 0.5 vs. 2.0 ± 0.4 , *p* < 0.05), a significantly smaller capillary contact/fiber ratio for type I and IIa fibers (*p* < 0.05; Figure 2A), and by a tendency for lower capillary contacts/fiber cross-sectional area for all fiber types (*p* = 0.06–0.08; Figure 2B).

Response to Submaximal Exercise

The physiologic response to submaximal exercise is presented in Table 4. No significant difference was found between fatiguers and nonfatiguers for endurance time, heart rate, \dot{V}_E , and $\dot{V}O_2$ responses at end-exercise. Compared with nonfatiguers, the response to submaximal exercise in fatiguers was characterized by a greater blood lactate accumulation and more profound

metabolic acidosis (Table 4). Mild exercise-induced desaturation was found in five fatiguers (end-exercise Sa_{O_2} of 89, 89, 88, 89, and 86%, respectively) and in two nonfatiguers (end-exercise Sa_{O_2} of 89 and 83%).

The perception of leg fatigue was greater during submaximal exercise and at end-exercise in fatiguers compared with nonfatiguers (Figure 3). The pattern of symptom limitation was different between the two groups (fatiguers: leg fatigue, 9%; dyspnea, 27%; both, 64%; nonfatiguers: leg fatigue, 0%; dyspnea, 60%; both, 40%), but this difference did not reach statistical significance. There was a statistically significant correlation between the fall in quadriceps twitch force at 10 minutes postexercise and the Borg leg fatigue score at end-exercise (*r* = 0.541, *p* = 0.002).

TABLE 3. MORPHOMETRIC AND ENZYMATIC ACTIVITIES OF THE VASTUS LATERALIS

	Fatiguers (n = 22)	Nonfatiguers (n = 10)
Fiber-type distribution, %		
Type I	35 ± 10	34 ± 15
Type IIa	44 ± 13	39 ± 14
Type IIx	20 ± 11	27 ± 11
Fiber surface, μm ²		
Type I	6,895 ± 2,082	7,065 ± 1,917
Type IIa	5,992 ± 1,885	6,294 ± 1,859
Type IIx	4,999 ± 2,054	4,042 ± 1,162
Oxidative enzymes, μmol/min/g muscle		
CS	12.37 ± 1.97	13.45 ± 2.89
HADH	5.12 ± 1.62	5.44 ± 2.75
Glycolytic enzymes, μmol/min/g muscle		
LDH	109.05 ± 48.17	72.75 ± 20.06*
PFK	64.98 ± 11.98	68.67 ± 19.63
HK	0.78 ± 0.37	0.77 ± 0.19
Enzymatic ratio		
LDH/HADH	24.03 ± 12.50	14.12 ± 5.61*
LDH/CS	9.27 ± 4.19	5.49 ± 1.52*

Definition of abbreviations: CS = citrate synthase; HADH = 3-hydroxyl CoA dehydrogenase; HK = hexokinase; LDH = lactate dehydrogenase; PFK = phosphofructokinase.

Values are means ± SD.

**p* < 0.05 compared to fatiguers (unpaired *t* test).

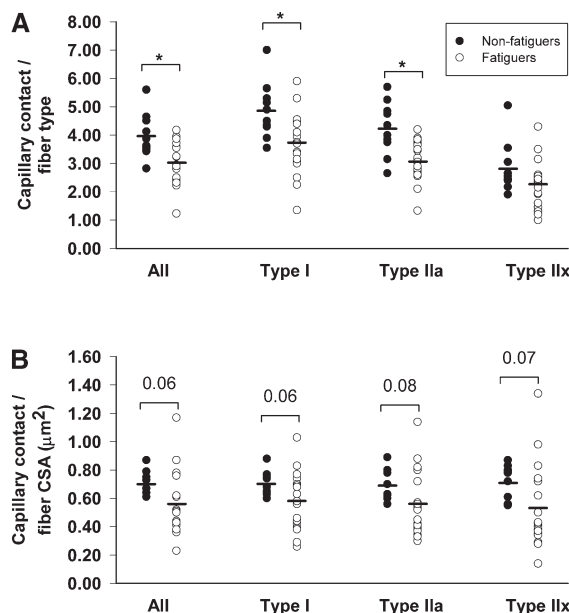


Figure 2. Individual values for capillary contact/fiber ratio (A) and capillary contact/fiber cross-sectional area (CSA) ratio (B) of all the different fiber types of the vastus lateralis in fatiguers (closed circles) and in nonfatiguers (open circles) obtained in 31 patients. The horizontal bars represent the mean values. **p* < 0.05 versus fatiguers. The capillary contact/fiber ratio for type I and type IIa was significantly lower in fatiguers compared with nonfatiguers, whereas the capillary contact/fiber CSA for type I, IIa, and IIx tended to be lower (*p* < 0.08) in fatiguers compared with nonfatiguers.

TABLE 4. PHYSIOLOGIC AND BLOOD GASES RESPONSE TO SUBMAXIMAL EXERCISE

	Fatiguers (n = 22)	Nonfatiguers (n = 10)
Endurance time, s	412 ± 164	387 ± 282
Heart rate, beat/min		
Rest	76 ± 15	74 ± 15
End-exercise	132 ± 18	132 ± 19
VO ₂ , L/min		
Rest	0.21 ± 0.12	0.28 ± 0.07
End-exercise	1.10 ± 0.34	1.04 ± 0.24
RER		
End-exercise	1.11 ± 0.08	1.03 ± 0.08 [†]
VE, L/min		
Rest	12.4 ± 3.7	13.5 ± 2.3
End-exercise	48.7 ± 17.1	42.8 ± 12.2
VE/MVV		
End-exercise	1.06 ± 0.21	1.03 ± 0.18
Symptoms		
Dyspnea	7.9 ± 2.0	7.3 ± 2.2
Leg fatigue	7.6 ± 2.0	5.3 ± 2.8 [†]
Blood gases		
Sa _{o2} , %		
Rest	97 ± 2	96 ± 2
End-exercise	94 ± 4*	92 ± 4*
Po ₂ , mm Hg		
Rest	87.1 ± 14.8	78.3 ± 11.6
End-exercise	82.0 ± 14.0	66.3 ± 8.8* [†]
pH		
Rest	7.45 ± 0.12	7.42 ± 0.03
End-exercise	7.27 ± 0.06*	7.33 ± 0.04* [†]
Pco ₂ , mm Hg		
Rest	40.0 ± 5.6	40.2 ± 5.6
End-exercise	45.2 ± 8.9*	44.8 ± 6.2*
Hco ₃ standard, mmol/L		
Rest	26.2 ± 2.4	25.9 ± 1.9
End-exercise	20.1 ± 3.7*	22.0 ± 3.4
Arterial lactate, mmol/L		
Rest	0.97 ± 0.49	0.88 ± 0.32
End-exercise	8.90 ± 3.13*	5.54 ± 2.50* [†]

Definition of abbreviations: Hco₃ = bicarbonate; MVV: maximum voluntary ventilation; RER = respiratory exchange ratio.

Values are means ± SD.

*p < 0.05 compared with baseline or rest.

[†]p < 0.05 compared with fatiguers (unpaired t test).

The arterial lactate kinetics obtained in 31 patients (an arterial cannula could not be inserted) during exercise for both groups is depicted in Figure 4. The arterial lactate level was significantly higher at end-exercise in fatiguers compared with

nonfatiguers (8.90 ± 3.13 vs. 5.54 ± 2.50 mmol/L, p < 0.001) and at each time point during submaximal exercise and recovery.

There was a significant correlation between the fall in quadriceps twitch force 10 minutes postexercise expressed in percentage of resting value and arterial lactate level at end-exercise (Figure 5A), lactate dehydrogenase activity (Figure 5B), and capillary-to-fiber ratio (Figure 5C; r = 0.44, p = 0.01; r = 0.46, p = 0.01; and r = 0.471, p = 0.007, respectively): that is, a high arterial lactate level at end-exercise, an elevated lactate dehydrogenase activity, and a smaller muscle capillarization predicted a large fall in quadriceps twitch force after exercise. No relationship between arterial lactate level at end-exercise and endurance time was found (r = 0.04).

DISCUSSION

Although previous independent studies have established that patients with COPD have a poor peripheral muscle endurance (25), low muscle aerobic enzyme activities (16), reduced muscle capillarization (26), greater susceptibility to develop contractile fatigue (2), and early onset of lactic acidosis during exercise (15), all these findings were reported in different populations. The current investigation is the first to evaluate all these parameters within the same individuals, allowing the study of the possible interactions between them. More importantly, we demonstrate that the susceptibility to develop muscle fatigue during cycling exercise varies from one patient to another, indicating that the COPD population is not homogenous when it comes to understanding muscle fatigue. Our data support the notion that this difference in the susceptibility to develop muscle fatigue among patients with COPD may find its origin within the muscles themselves, because patients with greater susceptibility to muscle fatigue show morphometric and metabolic features consistent with preferential reliance on glycolytic metabolism during exercise.

Methodologic Considerations

Because supramaximal magnetic stimulation of the femoral nerve is nonvolitional and painless, it can be successfully used to detect contractile fatigue of the quadriceps (2, 3, 18, 27, 28). We elected to use the potentiated twitch technique as opposed to the unpotentiated twitch because it is more sensitive and represents a more reproducible index of contractile fatigue (3, 29, 30). Last, a fall in quadriceps twitch force of more than 15% was used to define contractile fatigue. The use of this threshold in the present study was justified by our previous validation studies showing that the variability of the quadriceps twitch force measurement was less than 15% (3). When quadriceps twitch force measurements are repeated over time within a single subject,

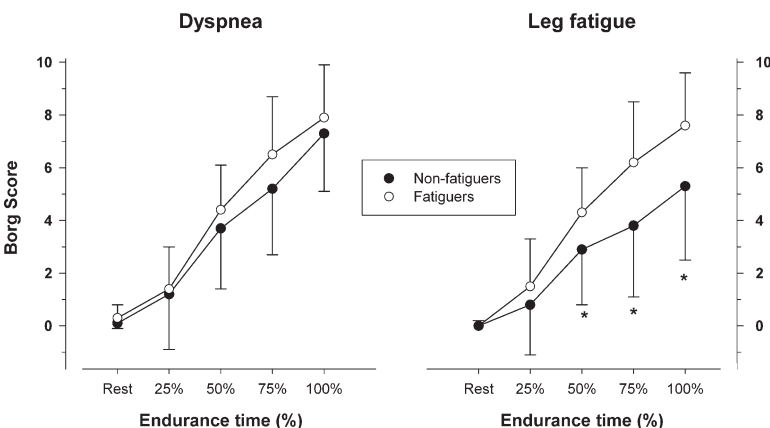


Figure 3. Time course for the Borg dyspnea and leg fatigue scores during constant work-rate exercise in fatiguers (open circles) and nonfatiguers (closed circles). Values are mean ± SD. Although there was no significant difference between the two groups for dyspnea during exercise, the perception of leg fatigue was significantly higher in fatiguers compared with nonfatiguers. *p < 0.05 versus fatiguers.

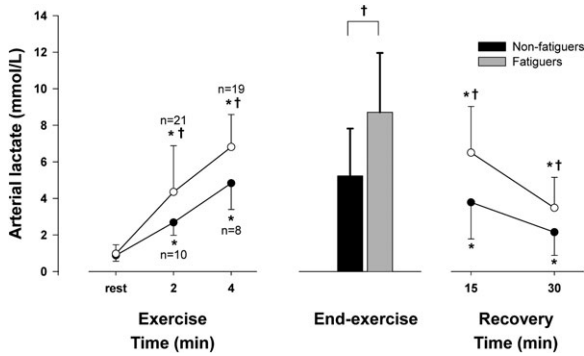


Figure 4. Arterial lactate concentration at rest, during exercise, and 15 and 30 minutes after a constant work-rate exercise in fatiguers (open circles and gray bar) and nonfatiguers (closed circles and black bar; mean \pm SD). Arterial lactate concentration was greater in fatiguers compared with nonfatiguers throughout the exercise and recovery periods. * $p < 0.05$ versus resting values; † $p < 0.05$ versus nonfatiguers.

the coefficient of variation is on average 6 to 8% (29). A 15% change in quadriceps twitch force therefore represents approximately twice the average variability and is thus highly unlikely to have occurred by chance alone.

Although our patients were categorized into fatiguers and nonfatiguers, the development of contractile fatigue is not an all-or-none phenomenon (30). This may explain, at least in part, the overlap in the enzymatic and morphologic muscle characteristics found between the two groups. Despite this, the differences found between the fatiguers and nonfatiguers in muscle enzymatic activities, lactate dehydrogenase activity and capillarization, as well as in blood lactate profile during exercise are consistent and physiologically plausible. The significant correla-

tions between the fall in quadriceps twitch force postexercise and blood lactate at end-exercise, lactate dehydrogenase activity, and capillary-to-fiber ratio also support the contribution of peripheral muscle changes to contractile fatigue. Taken together, these data are compelling in supporting the hypothesis that muscle changes are important in explaining individual variation in the susceptibility to develop muscle fatigue after cycling exercise in COPD.

Exercise in Fatiguers

In fatiguers, the combination of leg fatigue and dyspnea was the main symptomatic reason for exercise cessation. The exercise metabolic response in these individuals was characterized by a rapid increase in plasma lactate, which could reflect increased lactate production by the working muscles, reduced lactate clearance, or a combination of the two. Under the current conditions, we believe that the increased blood lactate originated from an augmented production by the leg muscles, as is the case when the rate of pyruvate production by the glycolytic pathway exceeds the rate of pyruvate oxidation by the mitochondria. The increased blood lactate in fatiguers is likely to originate from the contracting peripheral muscles because the respiratory muscles contribute only minimally to the increase in blood lactate during exercise in COPD (31). The observed relationship between plasma lactate level at end-exercise and the fall in quadriceps twitch force after exercise is also consistent with the peripheral origin of the elevated plasma lactate in fatiguers.

Despite the observation of a different muscle and metabolic profiles between fatiguers and nonfatiguers, we can only speculate on the existing link between elevated plasma lactate, reduced capillarization, and increased lactate dehydrogenase activity in fatiguers. One hypothesis is that a reduction in muscle capillarization and perfusion would lead to a preferential use of the glycolytic pathway and to an increased lactate production, a process resembling the situation observed in peripheral artery

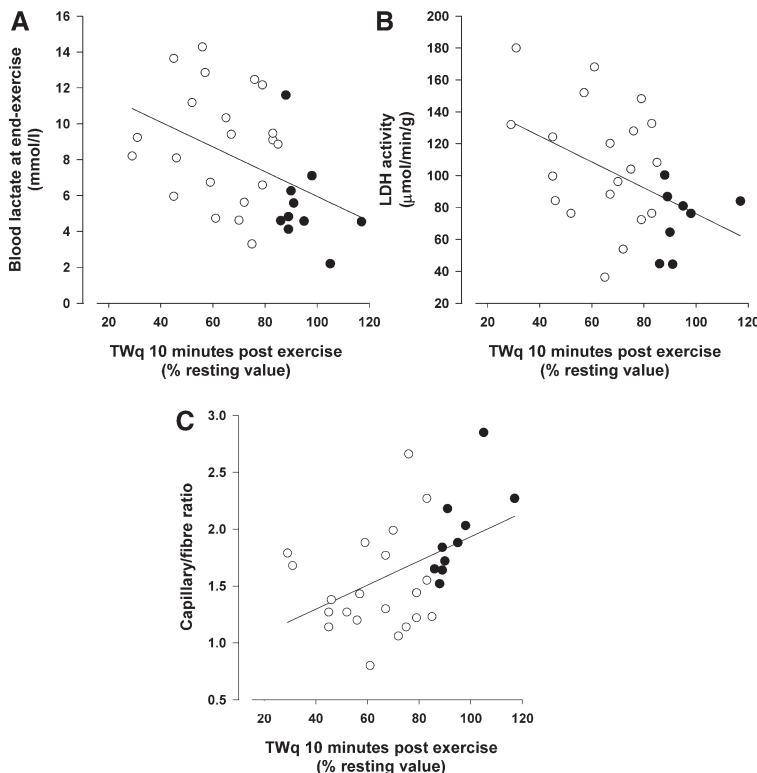


Figure 5. Relationship between change in the fall in quadriceps twitch force (TWq) 10 minutes postexercise expressed in % resting values and blood lactate at end-exercise (A; $n = 31$), muscle lactate dehydrogenase (LDH) activity (B; $n = 28$), and capillary/fiber ratio (C; $n = 31$). There was a significant correlation between the fall in TWq 10 minutes postexercise and the arterial lactate level at end-exercise ($r = 0.44$, $p = 0.01$), LDH activity ($r = 0.46$, $p = 0.01$), and the capillary/fiber ratio ($r = 0.471$, $p = 0.007$): that is, a high arterial lactate level at end-exercise, an elevated LDH activity, and a smaller muscle capillarization predicted a large fall in TWq after exercise.

disease (32). A reduced muscle capillarization in the presence of enhanced muscle lactate production could appear surprising knowing that lactate is a potential stimulus for angiogenesis (33, 34). Vascular endothelial growth factor is an important factor governing the angiogenic process by stimulating the capillary sprouting (33, 35). However, reduced vascular endothelial growth factor expression has been previously reported in the lung of patients with severe emphysema (36) and whether this could also be the case in the peripheral muscles of patients with greater susceptibility to contractile fatigue is unknown.

Fatigue and Exercise Limitation

In a study of 417 subjects, Killian and colleagues (22) found that dyspnea was the main symptom limiting exercise performance in only 26% of patient with COPD. The majority of patients were either limited by leg fatigue, or by a combination of the two symptoms. The finding of this initial study was further substantiated by the observation that contractile fatigue occurs after cycle exercise (2) and may contribute to exercise limitation in patients with COPD (3). In the present investigation, similar endurance time between fatiguers and nonfatiguers may apparently question the true contribution of leg fatigue to exercise intolerance. However, the fact that endurance time was similar between fatiguers and nonfatiguers does not mean that the same mechanisms of exercise intolerance were in play in the two groups. Although the relative contribution of the central and peripheral components of exercise intolerance within a single patient could not be sorted out, the data provided in the present study support the concept that the mechanisms underlying exercise intolerance were different between fatiguers and nonfatiguers and that leg fatigue was involved in the former group.

In the fatiguers, the sensation of leg fatigue was higher and the exercising muscles were weaker (because of fatigue) than in nonfatiguers, and it is not unreasonable to expect that this would influence exercise performance as suggested in our initial study about leg fatigue in COPD (3). This statement is supported by the significant correlation between the fall in twitch tension of the quadriceps and the perception of leg fatigue. The metabolic changes occurring in a fatiguing muscle leading to early acidosis will likely contribute to increased ventilatory requirement during exercise (15). Leg fatigue may also significantly contribute to increase the perception of dyspnea and the ventilatory requirements through the stimulation of metaboreceptors within the muscles (37). Stimulation of these receptors, a well-studied phenomenon in patients with chronic heart failure, is known to enhance ventilation during exercise. Therefore, in fatiguers, muscle fatigue and changes in peripheral muscle energy metabolism during exercise may contribute to overload the respiratory system and be a determinant in exercise cessation. The experience gained with pulmonary rehabilitation has also highlighted the contribution of peripheral muscle dysfunction to exercise intolerance in COPD. In fact, the improvement in peripheral muscle function represents the physiologic foundation for the better exercise tolerance after exercise training in COPD (38).

Potential Limitations

Although quadriceps capillarization and enzymatic profile and lactate responses to exercise were different between fatiguers and nonfatiguers, this finding does not necessarily imply that these muscle and metabolic changes had a causal relationship with leg fatigue. We acknowledge that the greater blood lactate accumulation is unlikely to be the direct cause of fatigue. This finding could rather indicate that fatiguers use different muscle energetic pathways during exercise compared with nonfatiguers, possibly leading to early muscle acidosis and to the accumulation of a variety of metabolic byproducts, such as lactate and inor-

ganic phosphate (39), that could be involved in the susceptibility to develop muscle fatigue.

Clinical Implication

The appreciation that the physiologic and metabolic responses to exercise are not uniform throughout the entire COPD population is likely to be clinically relevant. We have previously reported, for instance, that the exercise response to bronchodilation can be modulated by the presence of contractile fatigue (3). The ability to improve exercise tolerance and to adapt physiologically to exercise training could also be influenced by the occurrence or not of contractile fatigue during exercise. It can be speculated that subjects in whom cycle exercise is proximally limited by dyspnea would not be able to sufficiently activate their peripheral muscles during whole-body exercise training and thus would not derive great benefit from general physical reconditioning. In such patients, use of local muscle exercises as a training stimulus and emphasis on dyspnea control strategies would appear to be more physiologically appropriate. Conversely, aerobic training would seem to be perfectly suited to fatiguers in helping them to improve muscle capillarization.

Neural magnetic stimulation will remain an attractive research tool, but it is not practical to apply this tool in clinical practice, and it would be important to find simple surrogates for the assessment of contractile leg fatigue. Fatiguers and nonfatiguers could not be differentiated on the basis of their midhigh muscle cross-sectional area, suggesting that muscle fatigue is more related to the quality of the muscle rather than to its quantity. Although a significant correlation between the fall in quadriceps twitch force and the perception of leg fatigue was found ($r = 0.53$, $p = 0.001$), the strength of this association is not sufficient to discriminate subjects based on their symptom perception. Further work is needed in this area.

Conclusions

In summary, two different subsets of patients with COPD could be defined based on their susceptibility to leg fatigue. Compared with nonfatiguers, fatiguers could be characterized by a reduced muscle capillarization, greater lactate dehydrogenase activity, and higher arterial lactate level during exercise. A key message of the present study is that the degree of impairment in peripheral muscle function is not uniform in COPD, a phenomenon reflected by different degrees of susceptibility to contractile fatigue. As a corollary, it will be necessary to refine the physiologic evaluation of our patients with COPD to offer customized therapeutic interventions suiting the specific individual needs and to optimize their functional status.

Conflict of Interest Statement: D.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; C.H.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.J.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; P.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; J.J. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; F.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Acknowledgment: The authors acknowledge the help of Marthe Bélanger, Marie-Josée Breton, Brigitte Jean, and Josée Picard in accomplishing this study and of Eric Nadreau for his technical support during the exercise testing. They also thank Dr. Hélène Perrault and Dr. Frédéric Séries for helpful insight in the discussion of the data.

References

- Hamilton AL, Killian KJ, Summers E, Jones NL. Muscle strength, symptom intensity and exercise capacity in patients with cardiorespiratory disorders. *Am J Respir Crit Care Med* 1995;152:2021–2031.
- Mador MJ, Kufel TJ, Pineda L. Quadriceps fatigue after cycle exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;161:447–453.
- Saey D, Debigaré R, LeBlanc P, Mador MJ, Côté CH, Jobin J, Maltais F. Contractile leg fatigue after cycle exercise: a factor limiting exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003;168:425–430.
- Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. *Physiol Rev* 2001;81:1725–1789.
- Sahlin K. Metabolic factors in fatigue. *Sports Med* 1992;13:99–107.
- Sahlin K, Tonkonogi M, Soderlund K. Energy supply and muscle fatigue in humans. *Acta Physiol Scand* 1998;162:261–266.
- Westerblad H, Allen DG. Recent advances in the understanding of skeletal muscle fatigue. *Curr Opin Rheumatol* 2002;14:648–652.
- Gosker HR, Engelen MP, van Mameren H, van Dijk PJ, van der Vusse GJ, Wouters EF, Schols AM. Muscle fiber type IIX atrophy is involved in the loss of fat-free mass in chronic obstructive pulmonary disease. *Am J Clin Nutr* 2002;76:113–119.
- American Thoracic Society/European Respiratory Society. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;159(Suppl):S1–S40.
- Bernard S, Leblanc P, Whittom F, Carrier G, Jobin J, Belleau R, Maltais F. Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;158:629–634.
- Whittom F, Jobin J, Simard PM, Leblanc P, Simard C, Bernard S, Belleau R, Maltais F. Histochemical and morphological characteristics of the vastus lateralis muscle in COPD patients: comparison with normal subjects and effects of exercise training. *Med Sci Sports Exerc* 1998;30:1467–1474.
- Wuyam B, Payen JF, Levy P, Bensaidane H, Reutenauer H, Le Bas JF, Benabid AL. Metabolism and aerobic capacity of skeletal muscle in chronic respiratory failure related to chronic obstructive pulmonary disease. *Eur Respir J* 1992;5:157–162.
- Kutsuzawa T, Shioya S, Kurita D, Haida M, Ohta Y, Yamabayashi H. ³¹P-NMR study of skeletal muscle metabolism in patients with chronic respiratory impairment. *Am Rev Respir Dis* 1992;146:1019–1024.
- Maltais F, Leblanc P, Whittom F, Simard C, Marquis K, Belanger M, Breton MJ, Jobin J. Oxidative enzyme activities of the vastus lateralis muscle and the functional status in patients with COPD. *Thorax* 2000;55:848–853.
- Casaburi R, Patessio A, Ioli F, Zanaboni S, Donner CF, Wasserman K. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am Rev Respir Dis* 1991;143:9–18.
- Maltais F, Simard AA, Simard C, Jobin J, Desgagnés P, Leblanc P. Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD. *Am J Respir Crit Care Med* 1996;153:288–293.
- Allaire J, Maltais F, Doyon JF, Noel M, Leblanc P, Carrier G, Simard C, Jobin J. Peripheral muscle endurance and the oxidative profile of the quadriceps in patients with COPD. *Thorax* 2004;59:673–678.
- Mador MJ, Bozkanat E, Kufel TJ. Quadriceps fatigue after cycle exercise in patients with COPD compared with healthy control subjects. *Chest* 2003;123:1104–1111.
- Saey D, LeBlanc P, Debigaré R, Côté CH, Michaud A, Mador MJ, Maltais F. Quadriceps contractile fatigue in patients with COPD: histochemical and metabolism point of view [abstract]. *Am J Respir Crit Care Med* 2003;167:A962.
- American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;152(Suppl):S77–S120.
- Voorrips LE, Ravelli ACJ, Dongelmans PCA. A physical activity questionnaire for the elderly. *Med Sci Sports Exerc* 1991;8:974–979.
- Killian KJ, Leblanc P, Martin DH, Summers E, Jones NL, Campbell EJM. Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with airflow limitation. *Am Rev Respir Dis* 1992;146:935–940.
- Edwards RH, Hill DK, Jones DA, Merton PA. Fatigue of long duration in human skeletal muscle after exercise. *J Physiol* 1977;272:769–778.
- Green HJ, Sutton JR, Cymerman A, Young PM, Houston CS. Operation Everest II: adaptations in human skeletal muscle. *J Appl Physiol* 1989;66:2454–2461.
- Couillard A, Maltais F, Saey D, Debigaré R, Michaud A, Koechlin C, LeBlanc P, Prefaut C. Exercise-induced quadriceps oxidative stress and peripheral muscle dysfunction in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003;167:1664.
- Whittom F, Simard PM, Simard C, Leblanc P, Bernard S, Jobin J, Belleau R, Maltais F. Skeletal muscle capillarization in COPD: comparison with normal subjects and effects of endurance training. *Med Sci Sports Exerc* 1997;29:S104.
- Polkey MI, Kyroussis D, Hamnegard CH, Mills GH, Green M, Moxham J. Quadriceps strength and fatigue assessed by magnetic stimulation of the femoral nerve in man. *Muscle Nerve* 1996;19:549–555.
- Man WDC, Soliman MGG, Nikolettou D, Harris ML, Rafferty GF, Mustafa N, Polkey MI, Moxham J. Non-volitional assessment of skeletal muscle strength in patients with chronic obstructive pulmonary disease. *Thorax* 2003;58:665–669.
- Kufel TJ, Pineda LA, Mador MJ. Comparison of potentiated and unpotentiated twitches as an index of muscle fatigue. *Muscle Nerve* 2002;25:438–444.
- Laghi F, Topeli A, Tobin MJ. Does resistive loading decrease diaphragmatic contractility before task failure? *J Appl Physiol* 1998;85:1103–1112.
- Engelen MPKJ, Casaburi R, Rucker R, Carithers E. Contribution of the respiratory muscles to the lactic acidosis of heavy exercise in COPD. *Chest* 1995;108:1246–1251.
- Brass EP, Hiatt WR. Acquired skeletal muscle metabolic myopathy in atherosclerotic peripheral arterial disease. *Vasc Med* 2000;5:55–59.
- Burns PA, Wilson DJ. Angiogenesis mediated by metabolites is dependent on vascular endothelial growth factor (VEGF). *Angiogenesis* 2003;6:73–77.
- Trabold O, Wagner S, Wicke C, Scheuenstuhl H, Hussain MZ, Rosen N, Seremetiev A, Becker HD, Hunt TK. Lactate and oxygen constitute a fundamental regulatory mechanism in wound healing. *Wound Repair Regen* 2003;11:504–509.
- Forsythe JA, Jiang BH, Iyer NV, Agani F, Leung SW, Koos RD, Semenza GL. Activation of vascular endothelial growth factor gene transcription by hypoxia-inducible factor 1. *Mol Cell Biol* 1996;16:4604–4613.
- Kasahara Y, Tuder RM, Cool CD, Lynch DA, Flores SC, Voelkel NF. Endothelial cell death and decreased expression of vascular endothelial growth factor and vascular endothelial growth factor receptor 2 in emphysema. *Am J Respir Crit Care Med* 2001;163:737–744.
- Scott AC, Davies LC, Coats AJ, Piepoli M. Relationship of skeletal muscle metaboreceptors in the upper and lower limbs with the respiratory control in patients with heart failure. *Clin Sci (Lond)* 2002;102:23–30.
- Bernard S, Whittom F, Leblanc P, Jobin J, Belleau R, Bérubé C, Carrier G, Maltais F. Aerobic and strength training in patients with COPD. *Am J Respir Crit Care Med* 1999;159:896–901.
- Westerblad H, Allen DG, Lannergren J. Muscle fatigue: lactic acid or inorganic phosphate the major cause? *News Physiol Sci* 2002;17:17–21.