Quadriceps Fatigability after Single Muscle Exercise in Patients with Chronic Obstructive Pulmonary Disease

M. Jeffery Mador, Omer Deniz, Ajay Aggarwal, and Thomas J. Kufel

Division of Pulmonary, Critical Care, and Sleep Medicine, State University of New York at Buffalo; and the Veterans Affairs Western New York Healthcare System, Buffalo, New York

The purpose of this study was to compare quadriceps fatigability in patients with varying severity of chronic obstructive pulmonary disease with age-matched control subjects. Ten healthy control subjects, 8 patients with severe disease (FEV_1 less than 35% predicted), and 11 patients with mild to moderate disease were studied. The FEV_1 was 1.75 ± 0.13 L (SE), 50.4 ± 2.9% of predicted in the mild to moderate group, and 0.87 ± 0.06 L, 25.9 ± 1.9% of predicted in the severe group. Quadriceps fatigue was quantified by the reduction in potentiated twitch force after a potentially fatiguing task. All subjects performed three sets of 10 maximum voluntary contractions of the right quadriceps muscle. Quadriceps maximum voluntary contraction force was 58.3 ± 3.3 kg for the healthy older group, 49.0 ± 4.2 kg in the mild to moderate group, and 44.3 ± 4.7 kg in the severe group. The fall in potentiated twitch force after exercise was significantly greater in the patients with severe disease than in the healthy control subjects. In conclusion, the quadriceps in patients with severe chronic obstructive pulmonary disease are more fatigable than those in age- and sex-matched healthy control subjects.

Keywords: lung disease, obstructive; skeletal muscle; muscle fatigue; quadriceps

Skeletal muscle dysfunction is common in patients with chronic obstructive pulmonary disease (COPD) and tends to preferentially involve the proximal lower limb muscles (1–3). Muscle atrophy (2), muscle weakness (2–4), reduced muscle endurance (5), reduced oxidative metabolism (6–8), reduced muscle capillarity (9), and a change in muscle fiber type (reduced proportion of type 1 fibers) (10, 11) have all been observed in the quadriceps muscle of patients with COPD. These changes should all increase the fatigability of the quadriceps muscle. In a prior study, we showed that for the same duration and intensity of cycle exercise, patients with COPD displayed significantly greater quadriceps fatigue than matched control subjects (12). However, the difference between groups in that study could be entirely due to the differing effects of whole-body exercise in patients with COPD and healthy control subjects and to a reduction in muscle mass and strength in the patients with COPD compared with the healthy control subjects. These potential mechanisms can be eliminated by examining quadriceps fatigability during single muscle exercise (eliminating whole-body exercise effects) and by normalizing the fatigue protocol for the subject's maximal strength (eliminating the effect of differences in muscle strength and mass). We hypothesized that quadriceps fatigability would be increased in patients with COPD during single muscle exercise when the fatigue protocol was normalized for differences in strength. We further hypothesized that this difference would be greater in patients with more severe COPD.

Recently, it has been shown that fatigue of the quadriceps muscle can be detected with serial measurements of quadriceps twitch force (TwQ) during magnetic stimulation of the femoral nerve (13). A reduction in TwQ after the fatiguing task provides a quantitative estimate of the degree of contractile fatigue elicited by the task (14). Accordingly, we measured TwQ before and after a series of maximum voluntary contractions (MVCs) in patients with mild to moderate COPD, patients with severe COPD, and matched control subjects. A significantly greater reduction in TwQ after the fatiguing task in the patients with COPD compared with the healthy control subjects would support our hypothesis.

METHODS

Subjects

Eight patients with severe COPD, 11 patients with mild to moderate COPD, and 10 age-matched control subjects were studied. All subjects were male. Anthropomorphic characteristics and smoking history are summarized in Table 1. Pulmonary function was measured using standard techniques according to American Thoracic Society recommendations. Diffusing capacity was measured by the single breath technique. Pulmonary function measurements are shown in Table 2. COPD was classified according to the American Thoracic Society guidelines (15). Severe COPD was defined as an FEV_1 of less than 35% (stage III). Mild to moderate COPD was defined as an FEV_1 of 35% or more but less than 70% (stages I and II disease). The study was approved by the appropriate institutional review boards, and written informed consent was obtained from all subjects.

Healthy control subjects were identified by reviewing a list of all patients followed in the primary care outpatient clinics at the Buffalo Veterans Affairs Medical Center (VAMC). Patient charts were screened until 10 healthy subjects were identified who agreed to participate in the study. Active or past smoking was not an exclusion criterion; however, all normal subjects had screening pulmonary function testing, and subjects with abnormal values were excluded. In addition, the healthy control subjects underwent a screening history, physical examination, medication review, and resting electrocardiogram to exclude significant underlying disease.

Patients with COPD were identified from prospective review of pulmonary function tests performed at the Buffalo VAMC over a 3-month period. Patients who had pulmonary function tests within the prescribed range were screened for comorbidities and clinical stability. Twenty-two patients were identified. Two declined to participate, and one had a significant comorbidity that was missed on initial screening. All subjects had never previously participated in studies of muscle function.

Twitch Measurements

The femoral nerve was magnetically stimulated with a magnetic stimulator (Magstim 200; Magstim Co. Ltd., Whitland, Dyfed, Wales) using a 70-mm figure-of-eight coil (16). In some of the patients, magnetic

(*Received in original form February 6, 2002; accepted in final form April 9, 2003*)

Correspondence and requests for reprints should be addressed to M. Jeffery Mador, M.D., Division of Pulmonary, Critical Care and Sleep Medicine, Section 111S, State University of New York at Buffalo, Veterans Administration Medical Center, 3495 Bailey Avenue, Buffalo, New York 14215. E-mail: mador@acsu.buffalo.edu

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

Am J Respir Crit Care Med Vol 168. pp 102–108, 2003
Originally Published in Press as DOI: 10.1164/rccm.200202-080OC on April 10, 2003
Internet address: www.atsjournals.org

TABLE 1. PATIENT DEMOGRAPHICS

	Severe COPD	Mild to Moderate COPD	Healthy Control Subjects
Age, yr	68.3 ± 3.6	69.8 ± 2.0	67.2 ± 1.4
Height, cm	174 ± 2	178 ± 2	177 ± 2
Weight, kg	70 ± 4	82 ± 5*	85 ± 2*
BMI, kg/m^2	23.1 ± 1.1	25.8 ± 1.0	27.1 ± 0.8*
Current/former smokers	3/5	6/5	2/5
Smoking pack years	77 ± 11	59 ± 9	23 ± 7*†

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease.

Data expressed as mean ± SE.

* Significant difference from patients with severe COPD.

† Significant difference from patients with mild to moderate disease.

stimulation of the femoral nerve elicited a large shock artifact that obscured the compound motor action potential (M wave). However, with careful positioning of the recording electrodes and ground, M waves were obtained in eight healthy control subjects, four of the patients with severe COPD, and seven of the patients with mild to moderate COPD. We measured both the unpotentiated TwQ (TwQu) and the potentiated TwQ (TwQp) as previously described (14, 16, 17). Unpotentiated and potentiated twitches were obtained before and 10, 30, and 60 minutes after the fatigue protocol. After a vigorous voluntary contraction, the subsequent twitch is significantly increased in size (twitch potentiation) (18). Recent studies have suggested that the potentiated twitch is more sensitive at detecting fatigue than the unpotentiated twitch, particularly when the amount of fatigue is small (14, 19).

To determine the degree to which our subjects could voluntarily activate their quadriceps muscle, twitches were obtained during the last two MVC maneuvers of each set of measurements. Superimposed twitches were compared with potentiated twitches to determine the percent activation during the MVC maneuver (100-superimposed twitch/potentiated twitch × 100) (20).

All twitches were obtained at 100% of stimulator output. Twitch force and quadriceps electromyogram (EMG) were digitized and stored on disk using Windaq software (Dataq Instruments Inc., Akron, OH) at a sampling rate of 1,000 Hz.

Fatigue Protocol

Subjects performed 3 sets of 10 MVCs. Each set was separated by a 3-minute rest. The subject maintained each MVC for 5 seconds followed by a 5-second rest. Subjects received verbal and visual feedback to assist the subject in maintaining the correct rhythm. To evaluate for central fatigue, twitches were obtained during the last three contractions of each run. Twitches were obtained during the contraction (superimposed twitch) and just before the next contraction. The force signal was digitized and stored on disc, and the average mean and peak force were calculated for each set of MVCs. The percentage activation during the fatigue protocol appeared to differ between groups, although this difference was not statistically significant. Accordingly, the MVCs were adjusted for the percentage activation to provide an estimate of the force that would have been obtained if activation had been complete in all subjects. A schematic for the experimental protocol is provided in Figure 1.

Data Analysis

Changes in variables over time and between groups were analyzed by repeated-measures analysis of variance. If the F value was significant, Fisher's least significant difference was employed to determine where the differences lay. Correlations between continuous variables were made using simple linear regression. Data are expressed as mean ± SE. An expanded methods section providing further details on subject characteristics and quadriceps measurements is available in the online supplement.

RESULTS

Patient demographics are shown in Table 1. Patients with severe COPD had a lower body weight and body mass index than patients with mild to moderate disease and the healthy control subjects. The patient's pulmonary function tests are shown in Table 2. Body mass index was significantly correlated with the FEV_1 ($r = 0.53$, $p < 0.0035$).

Peak and mean force during the fatiguing task are shown in Figures 2A and 2B. Peak and mean forces were adjusted for percentage activation. Peak and mean forces fell progressively with each set of contractions for all groups. The fall in peak force during the fatiguing task was significantly greater in the patients with severe disease compared with the healthy control subjects ($p = 0.04$). The fall in mean force during the fatiguing task was significantly greater in the patients with severe disease than in the patients with mild to moderate disease ($p = 0.0128$) or the healthy control subjects ($p = 0.0045$). The percentage activation at baseline and during each set of contractions is shown in Figure 2C. The percentage activation did not change significantly during the course of the fatiguing task, indicating that the fall in force was not due to a reduction in effort; that is, there was no evidence of central fatigue. The duty cycle was similar in all three patient groups. TwQp during the fatiguing task expressed as a percentage of the baseline value is shown in Figure 2D. TwQp fell during the fatiguing task in all groups. TwQp decreased during the fatiguing task to a greater extent in the patients with severe disease compared with the healthy control subjects ($p < 0.04$). The fall in TwQp during the fatiguing task in the patients with mild to moderate disease was intermediate between these two groups and was not significantly different from either group.

The degree to which force fell during the fatigue protocol was significantly affected by the ability of the subjects to activate their quadriceps muscle during the protocol (Figure 3). Those

TABLE 2. PULMONARY FUNCTION

	Severe		Mild to Moderate		Healthy	
	Actual	Predicted	Actual	Predicted	Actual	Predicted
FEV_1, L	0.87 ± 0.06	26 ± 2	1.75 ± 0.13*	53 ± 3*	3.04 ± 0.11*†	87 ± 3*†
FVC, L	2.11 ± 0.12	49 ± 3	3.18 ± 0.25*	70 ± 4*	3.93 ± 0.16*†	88 ± 3*†
FEV_1/FVC	37 ± 2		54 ± 2*		76 ± 1*†	
RV, L	4.19 ± 0.38	184 ± 22	3.31 ± 0.18	137 ± 9*	2.45 ± 0.22*†	103 ± 8*†
TLC, L	6.54 ± 0.43	97 ± 6	6.55 ± 0.28	94 ± 4	6.32 ± 0.29	92 ± 3
D_{LCO}, ml/min/mm Hg	12.8 ± 1.5	50 ± 5	15.8 ± 1.9	59 ± 6	29.0 ± 1.5*†	109 ± 6*†
D_{LCO}/V_A	4.47 ± 0.25		2.91 ± 0.38*		2.64 ± 0.32*	

Definition of abbreviations: D_{LCO} = diffusing capacity; RV = residual volume, TLC = total lung capacity.

* Significant difference from patients with severe COPD.

† Significant difference from patients with mild to moderate COPD.

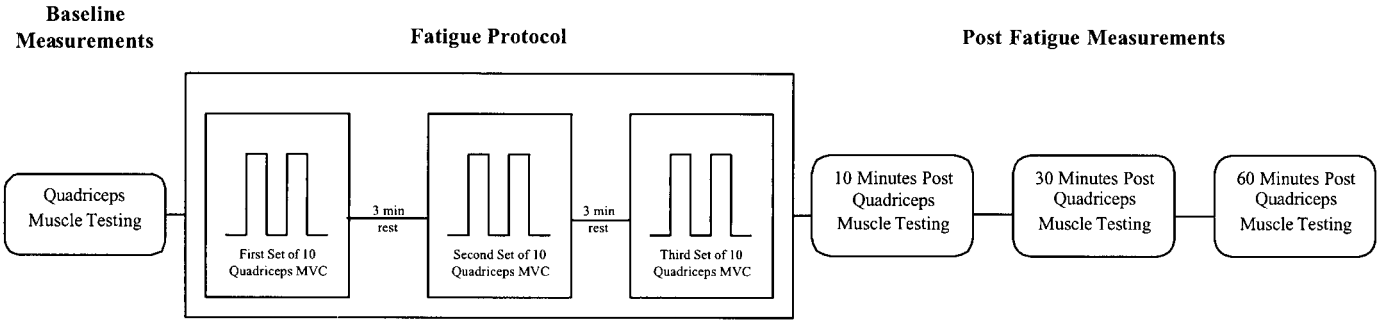

Figure 1. Schematic of experimental protocol.

subjects who were able to activate their quadriceps muscle the most during the protocol had the greatest force loss. Although differences between groups were not statistically significant, the severe group appeared to activate their quadriceps to a slightly greater extent during the fatigue protocol (Figure 2C). In addition, the effect of differences in activation differed between groups. The regression between percentage activation and fall in force was tighter (higher correlation coefficient) with a higher slope in the patients with severe COPD compared with the healthy older subjects. Differences in activation could potentially explain the differences that we observed between groups. Accordingly, we used group-specific linear regression equations to adjust the force lost during the fatigue protocol to that that would have occurred had every subject maximally activated their quadriceps muscle throughout the fatiguing protocol. Differences in activation between groups accounted for only 2.1% of the total difference between the healthy older subjects and patients with severe COPD for the adjusted peak MVC during the fatigue run, 19.7% of the total difference for the adjusted mean MVC during the fatigue run, and the total difference was actually increased by 2.4% for TwQp during the fatigue run. All of the previously observed statistical differences remained when the data were corrected for percentage activation.

The TwQu results are shown in Figure 4A. TwQu fell after exercise in all groups, but the magnitude of the fall varied significantly between groups. The fall in TwQu after exercise was significantly greater in the patients with severe disease than in the healthy control subjects ($p = 0.0045$). The fall in TwQu after exercise in the patients with mild to moderate disease fell between that observed in the healthy control subjects and the patients with severe disease. The difference between the mild to moderate group and the severe group approached statistical significance ($p = 0.07$). TwQp results are shown in Figure 4B. TwQp fell significantly after exercise in all groups. The fall in TwQp after exercise was significantly greater in the patients with severe disease than in the patients with mild to moderate disease ($p = 0.05$) or the healthy control subjects ($p < 0.04$). The fall in TwQp after exercise was not significantly different in the patients with mild to moderate disease compared with the healthy control subjects. The correlation between the degree of activation during the load and the fall in TwQu and TwQp after loading did not reach statistical significance in the healthy control subjects ($r = -0.139$ and 0.048, respectively), and thus, these data were not corrected for percentage activation.

At baseline, the MVC of patients with severe disease was significantly lower, 44.3 ± 4.7 kg, than in the healthy control subjects, 58.3 ± 3.3 kg ($p < 0.03$). The MVC of patients with mild to moderate disease, 49.0 ± 4.2 kg, was intermediate between these two groups and was not significantly different from either group. MVC results are shown in Figure 4C. The MVCs were adjusted to correct for differences in activation between subjects. Specifically, the MVCs were adjusted to provide an estimate of the MVC that would have occurred if activation had been complete. The fall in MVC after exercise was significantly greater in the patients with severe disease than in the patients with mild to moderate disease ($p = 0.01$) or the healthy control subjects ($p < 0.006$). The fall in MVC after exercise was not significantly different in the patients with mild to moderate disease compared with the healthy control subjects.

The adjusted MVC for the patients with severe disease was 81.6% of that obtained in the mild to moderate group and 71.7% of that obtained in the healthy control subjects. The corrected MVC at baseline correlated with the FEV_1 ($r = 0.47$, $p < 0.01$) and the body mass index ($r = 0.46$, $p = 0.011$). Quadriceps M waves were not significantly different from baseline at any time after exercise in any group.

To address whether there was a dose–response relationship between the severity of COPD and the degree of quadriceps fatigability, that is, whether the degree of quadriceps fatigability increased with increasing severity of disease, linear regression was performed with FEV_1 as the independent variable and the change in the various fatigue indices as the dependent variable. There were significant albeit relatively weak negative correlations between the FEV_1 (percentage predicted) and all of the fatigue indices: TwQu ($r = 0.57$, $p < 0.0015$; Figure 5), TwQp ($r = 0.41$, $p < 0.03$), adjusted MVC ($r = 0.43$, $p < 0.02$), TwQp during load ($r = 0.45$, $p < 0.02$), adjusted MVC during load ($r = 0.42$, $p < 0.03$), and mean MVC during load ($r = 0.42$, $p < 0.025$). All of these correlations, however, became nonsignificant when the normal subjects were not included in the analysis.

DISCUSSION

The major finding of this study is that subjects with severe COPD demonstrated increased quadriceps fatigability compared with healthy control subjects. Quadriceps fatigability in subjects with mild to moderate disease appeared to be intermediate between the healthy age-matched control subjects and the subjects with severe disease.

Skeletal Muscle Endurance in COPD

Patients with COPD have reduced muscle mass and decreased strength in proportion to the reduction in muscle mass (2). However, assessment of muscle endurance in patients with COPD has been relatively limited. Three studies have examined skeletal muscle endurance in patients with COPD compared with control subjects (5, 21, 22). One study showed reduced quadriceps endurance in patients with COPD (5), whereas another did not

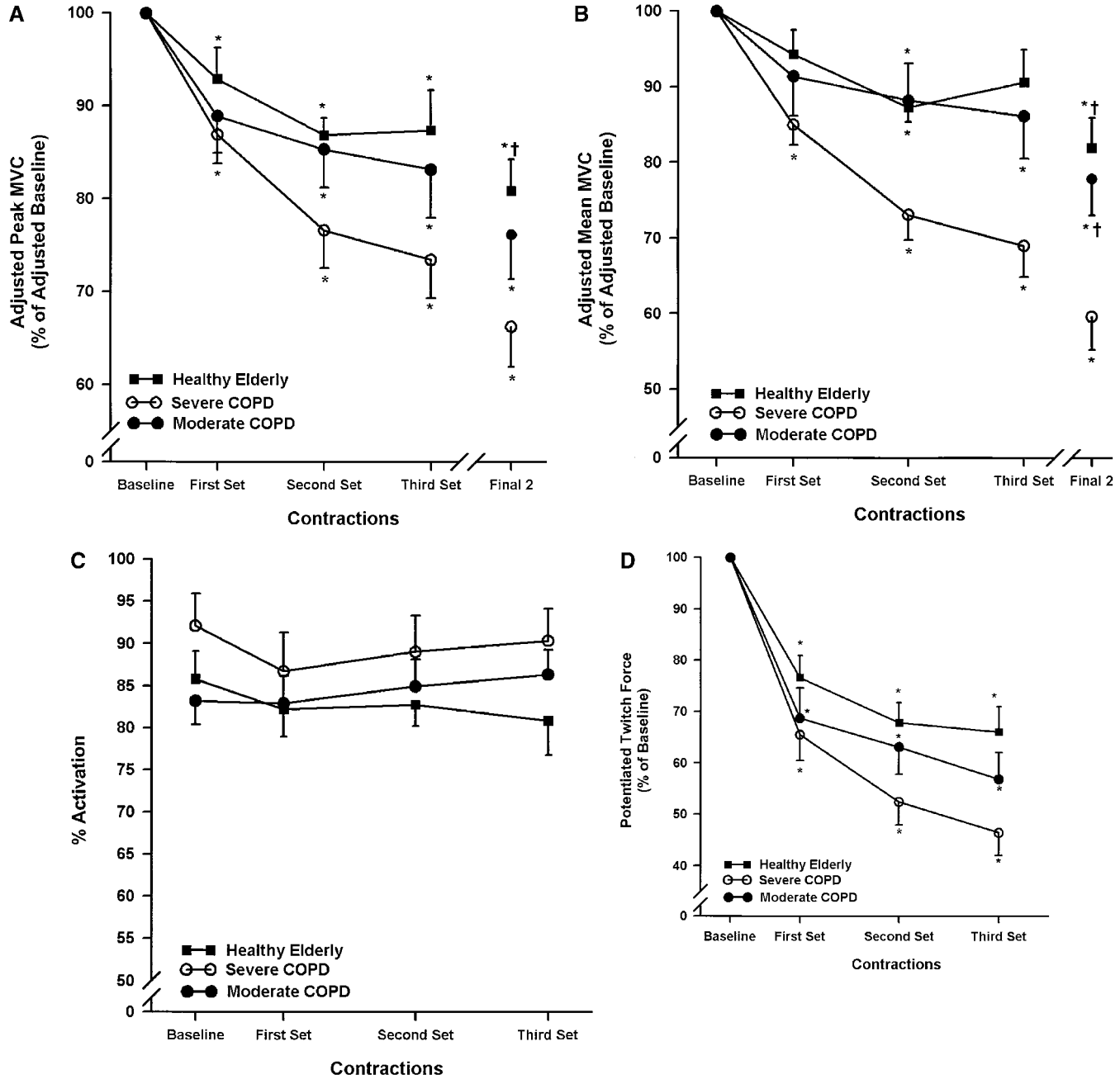

Figure 2. Peak force (*A*), mean force (*B*), percentage activation (*C*), and potentiated twitch force (*D*) at baseline and during the fatiguing task in the healthy older subjects (*closed squares*) and in the subjects with severe (*open circles*) and mild to moderate (*closed circles*) COPD. Peak and mean force were adjusted to correct for differences in activation between subjects. The average force for the first, second, and third sets of contractions and the average of the last two contractions of the third set are shown expressed as a percentage of baseline. The baseline peak and mean force were also adjusted for the percentage activation during the baseline maneuvers. Superimposed twitches were obtained during the last three contractions of each set. Superimposed twitches expressed as a percentage of the potentiated twitch were used to calculate the percent activation. *Significant difference from baseline. †Significantly different from subjects with severe COPD. The fall in peak, mean, and the potentiated twitch force during the fatiguing task was significantly greater in the subjects with severe disease than in the healthy control subjects. The fall in mean force was significantly greater in the patients with severe COPD than the patients with mild to moderate COPD. The percentage activation did not change significantly from baseline during the course of the fatiguing task, indicating that the fall in force was not due to a reduction in effort; that is, there was no evidence of central fatigue.

(21). The last study showed a modest reduction in elbow flexors endurance in patients with COPD (22). The measures of endurance were effort dependent, possibly accounting for the divergent results. In this study, we measured quadriceps fatigability using effort-independent methods: twitch measurements and fall in MVC force with measurement of the degree of activation during the MVC maneuver. We clearly showed that quadriceps fatigability was increased in subjects with severe COPD. Because fatigability is a measure of the endurance properties of a muscle, this finding suggests that quadriceps endurance is decreased in patients with severe COPD.

In a prior study, we showed that after cycle exercise at the

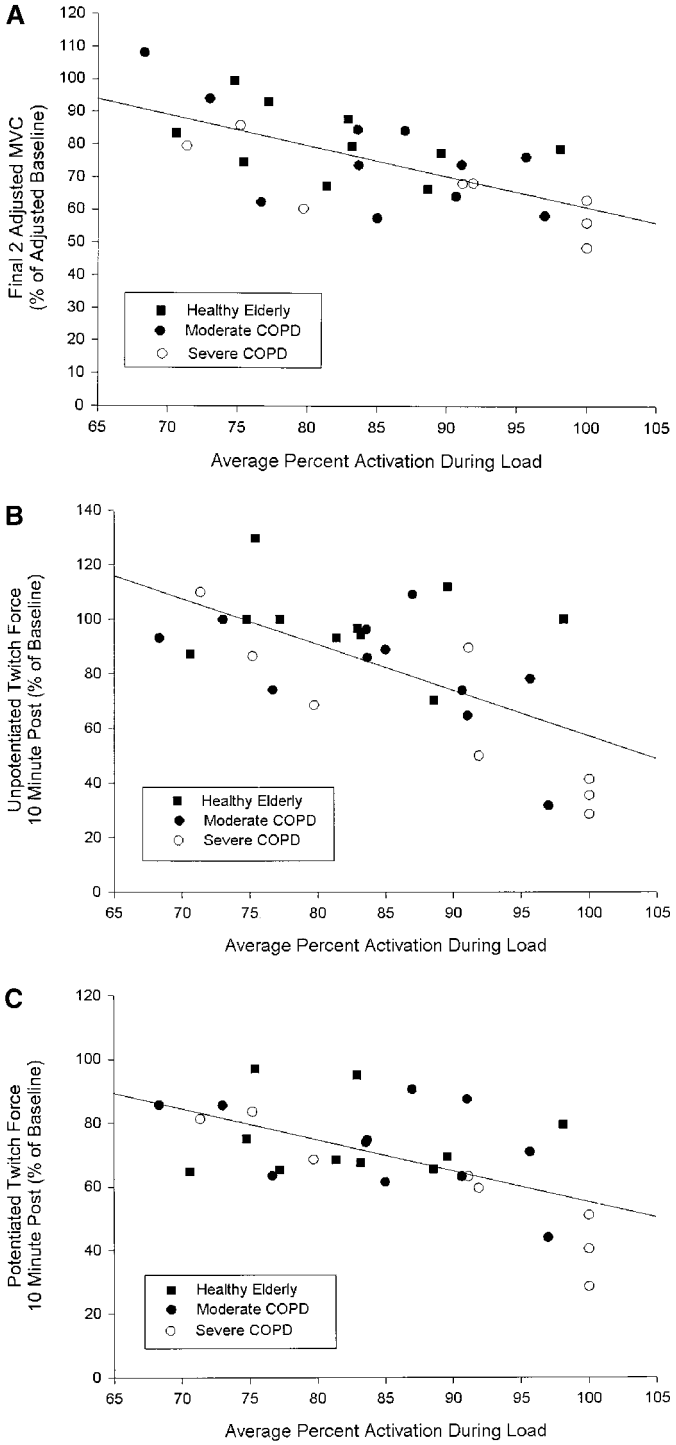

Figure 3. Relationship between the degree of activation during the fatigue protocol and the amount of peak force lost during the protocol (*A*) and the fall in the unpotentiated (*B*) and the potentiated (*C*) twitch force after the fatigue protocol. Significant relationships were found. The better able the subject was to activate their quadriceps during the fatigue protocol, the greater the force loss.

same absolute exercise intensity and for a similar duration, patients with COPD displayed significantly greater contractile fatigue of the quadriceps muscle than age-matched healthy older subjects (12). In that study, the increased quadriceps fatigability could be secondary to a reduced muscle mass, to limitations in oxygen delivery to the leg muscles during cycle exercise, or to differences in the neurohumeral response to whole-body exercise in patients with COPD compared with healthy control subjects (23). In that study, although the subjects were matched for the same absolute intensity, the patients with COPD exercised at a higher relative intensity (as a percentage of their maximum), which could also alter the neurohumeral and circulatory response to exercise. In this study, we performed single muscle exercise so that a plateau in leg blood flow (possibly caused by competition for blood flow with the ventilatory muscles) or differences in neurohumeral response would not be a factor (23). Furthermore, by normalizing the exercise task to the patient's MVC, differences in strength or muscle mass will no longer influence the degree of fatigue elicited.

In this study, there were differences in the ability of subjects to voluntarily activate their quadriceps muscle. Those subjects who were better able to activate their muscle not surprisingly displayed greater fatigue during and after the fatigue protocol. Although differences between groups were not statistically significant, subjects with severe disease appeared better able to activate their quadriceps muscle (Figure 2C). This difference in activation had only a trivial effect on the differences that we observed between the subjects with severe COPD and the healthy control subjects. When we corrected for this difference in activation, the difference between the subjects with severe disease and the healthy control subjects persisted.

Impairments in oxidative enzyme capacity (6, 7), shifts in fiber type proportions with a decrease in type 1 and an increase in type 2b more fatigable fibers (10, 11), reduced muscle capillarity (9), and nuclear magnetic spectroscopy data consistent with impaired oxidative metabolism (8) have all been demonstrated in the quadriceps muscle of patients with COPD. If these changes were of sufficient magnitude, they would clearly be expected to increase muscle fatigability. Why these changes occur in patients with COPD is an area of intense research interest. Most patients with severe COPD are greater than 60 years old and are relatively inactive, and our patients were no exception. Deconditioning and an accentuation of the normal aging process are of obvious importance mechanistically (1). Nevertheless, there is increasing evidence that systemic inflammation and oxidative stress from COPD itself play a role (24). In a hamster model of emphysema, the level of activity was rigorously controlled (25). Hind limb muscle oxidative capacity was reduced in the emphysematous hamsters compared with a control group, despite no difference in activity level between groups. Physical activity can be crudely estimated in patients, and it would be of considerable interest to see whether the increased quadriceps fatigability that we observed in patients with severe COPD would still be observed if the level of physical activity was carefully matched between the patients and the control group.

Differences between COPD Patients

Subjects with severe disease clearly demonstrated increased quadriceps fatigability compared with the healthy control subjects. Subjects with more moderate disease had visual changes in the fatigue indices either between the severe and healthy control groups; TwQu before and after load, peak adjusted MVC and TwQp during load or similar to the healthy control subjects; TwQp and MVC before and after load, mean MVC during load. However, there were no significant differences between the healthy older subjects and the subjects with mild to moderate disease in any of the fatigue indices. Differences between the subjects with severe and mild to moderate disease were observed for some of the indices, and this is supportive of a dose–response relationship. Furthermore, when FEV_1 is treated as a continuous rather than nominal variable and the degree of fatigue compared

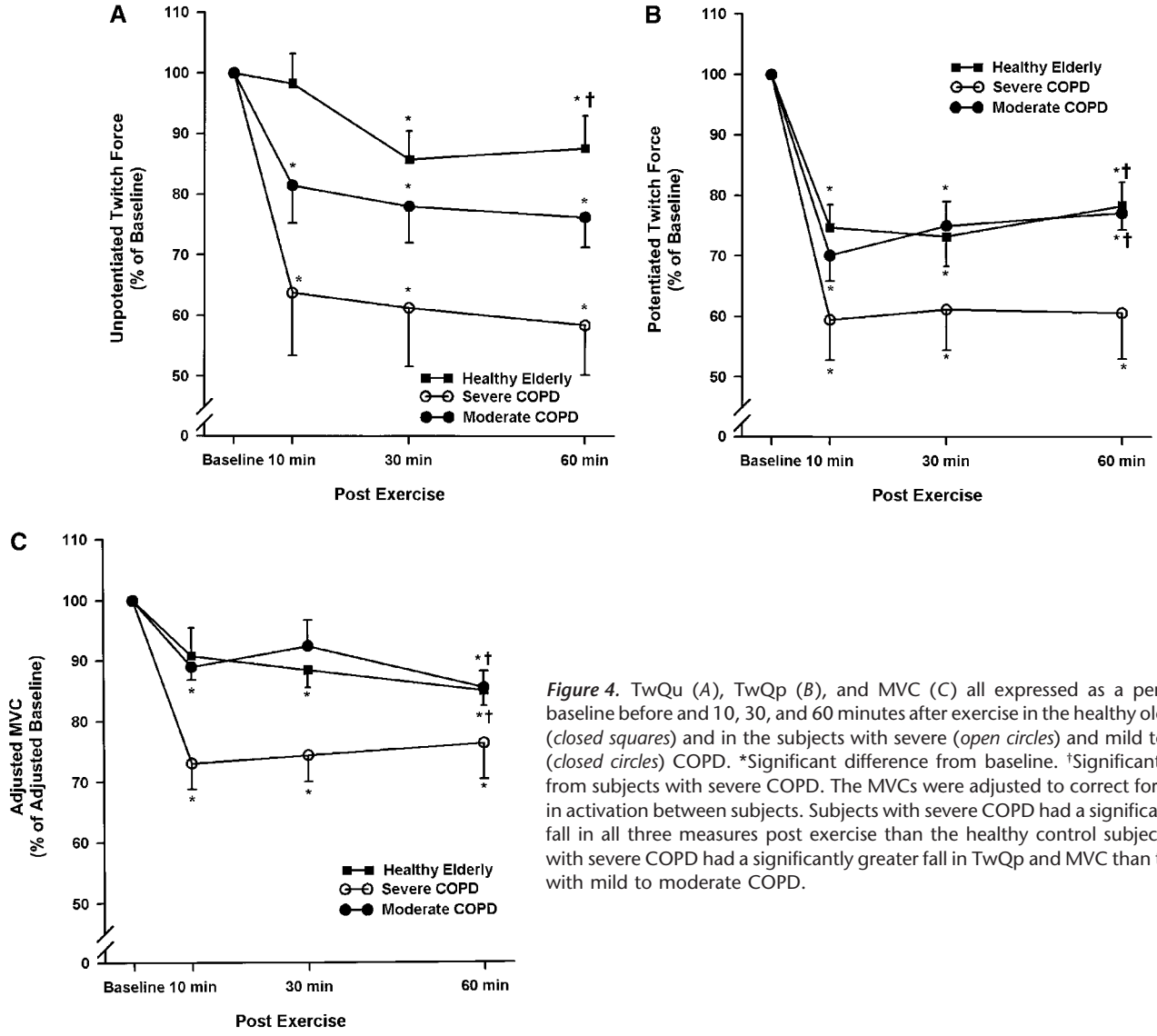

Figure 4. TwQu (*A*), TwQp (*B*), and MVC (*C*) all expressed as a percentage of baseline before and 10, 30, and 60 minutes after exercise in the healthy older subjects (*closed squares*) and in the subjects with severe (*open circles*) and mild to moderate (*closed circles*) COPD. *Significant difference from baseline. †Significantly different from subjects with severe COPD. The MVCs were adjusted to correct for differences in activation between subjects. Subjects with severe COPD had a significantly greater fall in all three measures post exercise than the healthy control subjects. Subjects with severe COPD had a significantly greater fall in TwQp and MVC than the subjects with mild to moderate COPD.

across all subjects, weak but significant correlations between the FEV_1 and the degree of quadriceps fatigability were observed for every one of the fatigue indices, clearly supporting a dose–response relationship. Thus, our data provide support that patients with milder disease are also affected but to a lesser extent than those with more severe disease, but this area requires further investigation in a larger cohort of subjects.

Our subjects with severe COPD had a significantly lower body weight than the subjects with mild to moderate disease or the healthy control subjects. However, only two subjects with severe disease were significantly underweight, defined as a body weight of less than 90% of ideal body weight. Patients with COPD can have significant muscle atrophy despite maintenance of normal body weight (26). In this study, subjects with severe COPD had a quadriceps-adjusted MVC that was 72% of the healthy control subjects. Because reductions in strength are felt to be solely due to reductions in muscle mass in patients with COPD (2), our subjects with severe COPD must have had some degree of muscle atrophy. Our subjects with mild to moderate disease did not have a significantly reduced corrected MVC, but it was lower than the control group (88% of the control value), suggesting that some muscle atrophy was present. Further study is required to determine how common it is for patients with milder COPD to have significant muscle weakness or atrophy.

Serres and colleagues have observed a reduction in quadriceps endurance with no difference in muscle strength in a group of patients with COPD compared with age-matched control subjects (5). Thus, it appears possible to have an impairment in endurance in patients who do not display muscle weakness or atrophy. How commonly the endurance properties of the quadriceps are impaired in patients with COPD who do not display any muscle atrophy or muscle weakness also needs to be determined.

Were Our Quantitative Indices of Fatigue Valid?

In this study, we used TwQ during and after the fatiguing task and the percentage fall in peak and mean MVC force during the fatiguing task as our indices to quantify fatigue. Ideally, fatigue should be assessed by obtaining a force frequency curve before and after the potentially fatiguing task. Clearly, tetanic stimulation of the quadriceps muscle is not feasible in unanesthetized human subjects. Polkey and colleagues have shown that TwQ can provide a reasonable estimate of the degree of contractile fatigue elicited by a potentially fatiguing task (13). Similarly, measuring the fall in MVC force during a fatiguing task, when the degree of muscle activation during the MVC is monitored,

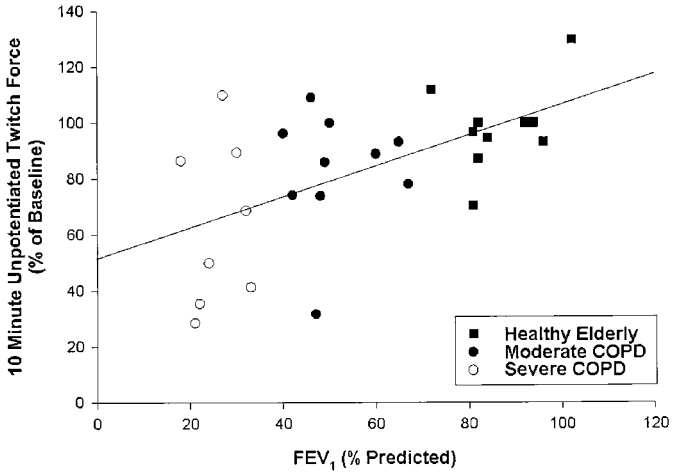

Figure 5. Relationship between FEV_1 as a percentage of the predicted value and TwQu as a percentage of the baseline value. The degree of fatigue increased (greater fall in TwQu at 10 minutes after exercise) as the FEV_1 decreased ($r = 0.57$, $p < 0.0015$).

is a well-accepted method for quantifying contractile fatigue (27). In this study, regardless of the index used, the results were the same. TwQu, TwQp during and after the fatiguing task, and the percentage fall in peak and mean force during the fatiguing task all showed a significant difference between subjects with severe disease and healthy control subjects.

Limitations of the Study

We studied only male subjects, as the Veteran population is overwhelmingly male. Although there are no studies that suggest that female subjects would behave differently, it would be important to study female subjects in future studies. We included smokers and past smokers in our control group. If we had included only nonsmokers, our control subjects might have been "healthier," and their exercise performance could potentially have been better accentuating the differences between groups. We showed that quadriceps fatigability is greater in patients with COPD compared with healthy control subjects. However, this study did not address whether this increased quadriceps fatigability would interfere with normal activities of daily living. Thus, the clinical significance of this finding remains to be determined. In conclusion, patients with severe COPD have increased quadriceps fatigability when compared with age-matched control subjects.

References

1. Mador MJ, Bozkanat E. Skeletal muscle dysfunction in COPD. *Respir Res* 2001;2:216–224.
2. 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.
3. Gosselink R, Troosters T, Decramer M. Distribution of muscle weakness in patients with stable chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2000;20:353–360.
4. Gosselink R, Troosters T, DeCramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. *Am J Respir Crit Care Med* 1996;153:976–980.
5. Serres I, Gautier V, Varray A, Prefaut C. Impaired skeletal muscle endurance related to physical inactivity and altered lung function in COPD patients. *Chest* 1998;113:900–905.
6. Jakobsson P, Jorfeldt L, Henriksson J. Metabolic enzyme activity in the quadriceps femoris muscle in patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;151:374–377.
7. Maltais F, Simard AA, Simard C, Jobin J, Desgagnes 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.
8. Sala E, Roca J, Marrades RM, Alonso J, Gonzalez de Suso JM, Moreno A, Barbera JA, Nadal J, de Jover L, Rodriguez-Roisin R, *et al.* Effects of endurance training on skeletal muscle bioenergetics in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;159: 1726–1734.
9. Jobin J, Maltais F, Doyon JF, LeBlanc P, Simard PM, Simard AA, Simard C. Chronic obstructive pulmonary disease capillarity and fiber-type characteristics of skeletal muscle. *J Cardiopulm Rehabil* 1998;18: 432–437.
10. 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 patients with chronic obstructive pulmonary disease. *Med Sci Sports Exerc* 1998;30:1467–1474.
11. Maltais F, Sullivan MJ, LeBlanc P, Duscha BD, Schachat FH, Simard C, Blank JM, Jobin J. Altered expression of myosin heavy chain in the vastus lateralis muscle in patients with COPD. *Eur Respir J* 1999; 13:850–854.
12. Mador MJ, Bozkanat E, Kufel TJ. Quadriceps fatigue after cycle exercise in patients with chronic obstructive pulmonary disease compared with healthy controls. *Chest* 2003;123:1104–1111.
13. 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.
14. Kufel TJ, Pineda LA, Mador MJ. Comparison of potentiated and unpotentiated twitches as an index of contractile fatigue. *Muscle Nerve* 2002; 25:438–444.
15. Standards for the Diagnosis and Care of Patients with Chronic Obstructive Pulmonary Disease: ATS statement: definitions, epidemiology, pathophysiology, diagnosis, and staging. *Am J Respir Crit Care Med* 1995; 152:S78–S83.
16. Mador MJ, Kufel TJ, Pineda LA, Steinwald A, Aggarwal A, Upadhyay AM, Khan MA. Effect of pulmonary rehabilitation on quadriceps fatigability during exercise. *Am J Respir Crit Care Med* 2001;163:930–935.
17. Mador MJ, Kufel TJ, Pineda LA. Quadriceps and diaphragmatic function following exhaustive cycle exercise in the healthy elderly. *Am J Respir Crit Care Med* 2000;162:1760–1766.
18. Mador MJ, Magalang UJ, Kufel TJ. Twitch potentiation following voluntary diaphragmatic contraction. *Am J Respir Crit Care Med* 1994;149: 739–743.
19. Laghi F, Topeli A, Tobin MJ. Does resistive loading decrease diaphragmatic contractility before task failure. *J Appl Physiol* 1998;85:1103–1112.
20. Bellemare F, Bigland-Ritchie B. Central components of diaphragmatic fatigue assessed by phrenic nerve stimulation. *J Appl Physiol* 1987;62: 1307–1316.
21. Zattara-Hartmann MC, Badier M, Guillot C, Tomei C, Jammes Y. Maximal force and endurance to fatigue of respiratory and skeletal muscles in chronic hypoxemic patients: the effects of oxygen breathing. *Muscle Nerve* 1995;18:495–502.
22. Newell SZ, McKenzie DK, Gandevia SC. Inspiratory and skeletal muscle strength and endurance and diaphragmatic activation in patients with chronic airflow limitation. *Thorax* 1989;44:903–912.
23. Simon M, LeBlanc P, Jobin J, Desmeules M, Sullivan MJ, Maltais F. Limitation of lower limb VO_2 during cycling exercise in COPD patients. *J Appl Physiol* 2001;90:1013–1019.
24. Debigare R, Cote CH, Maltais F. Peripheral muscle wasting in chronic obstructive pulmonary disease: clinical relevance and mechanisms. *Am J Respir Crit Care Med* 2001;164:1712–1717.
25. Mattson JP, Poole DC. Pulmonary emphysema decreases hamster skeletal muscle oxidative enzyme capacity. *J Appl Physiol* 1998;84:1573–1580.
26. Schols AMWJ, Soeters PB, Dingemans AMC, Mostert R, Frantzen PJ, Wouters EFM. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis* 1993;147:1151–1156.
27. Bigland-Ritchie B, Furbush F, Woods JJ. Fatigue of intermittent submaximal voluntary contractions: central and peripheral factors. *J Appl Physiol* 1986;61:421–429.