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Skeletal muscle power and fatigue at the tolerable limit of ramp-incremental exercise in COPD

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New and noteworthy

Chronic obstructive pulmonary disease (COPD) patients exhibit skeletal muscle abnormalities that contribute to high fatigability. Whether muscle fatigue is sufficient to limit whole-body exercise in COPD is unknown. Unlike controls, COPD patients are simultaneously highly fatigable and have a large muscle power reserve at the limit of whole-body exercise. COPD patients are more fatigable than controls, but this fatigue is insufficient to constrain locomotor power and define the limit of tolerance.

Abstract

Muscle fatigue (a reduced power for a given activation) is common following exercise in COPD. Whether muscle fatigue, and reduced maximal voluntary locomotor power, are sufficient to limit whole-body exercise in COPD is unknown. We hypothesized in COPD: 1) exercise is terminated with a locomotor muscle power reserve; 2) reduction in maximal locomotor power is related to ventilatory limitation; and 3) muscle fatigue at intolerance is less than age-matched controls. We used a rapid switch from hyperbolic to isokinetic cycling to measure the decline in peak isokinetic power at the limit of incremental exercise ('performance fatigue') in 13 COPD (FEV_1 49±17 %pred) and 12 controls. By establishing the baseline relationship between muscle activity and isokinetic power, we apportioned performance fatigue into the reduction in muscle activation and muscle fatigue. Peak isokinetic power at intolerance was ~130% of peak incremental power in controls (274±73 vs 212±84W, $p<0.05$), but ~260% in COPD (187±141 vs 72±34W, $p<0.05$) – greater than controls ($p<0.05$). Muscle fatigue as a fraction of baseline peak isokinetic power was not different in COPD vs controls (0.11±0.20 vs 0.19±0.11). Baseline to intolerance, the median frequency of maximal

isokinetic muscle activity was unchanged in COPD but reduced in controls (+4.3±11.6 vs -5.5±7.6%, $p<0.05$). Performance fatigue as a fraction of peak incremental power was greater in COPD vs controls and related to resting (FEV_1/FVC) and peak exercise ($\dot{V}_E/MVV$) pulmonary function ($r^2=0.47$, $r^2=0.55$, $p<0.05$). COPD patients are more fatigable than controls, but this fatigue is insufficient to constrain locomotor power and define exercise intolerance.

Abstract word count: 250 (250 max).

Abbreviations

AF, activation fatigue; $CI_{Difference}$, 95% confidence interval of the difference; EMG, electromyography; IC, inspiratory capacity; IRV, inspiratory reserve volume; MF, muscle fatigue; MVV, maximal voluntary ventilation; PF, performance fatigue; P_{iso}, isokinetic power

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by exertional shortness of breath and exercise intolerance consequent to airflow obstruction, gas exchange abnormalities, chronic inflammation, and skeletal muscle dysfunction. Lack of regular physical activity is common in COPD (40), worsens the cycle of deconditioning and exercise intolerance, and is associated with poor quality of life, frequent hospitalizations, and high mortality (20, 50, 52).

How COPD abnormalities interact to bring about the inability to maintain large-muscle-mass exercise such as walking or cycling (task failure or intolerance) is of major importance, and remain poorly understood. COPD patients exhibit more exercise-induced skeletal muscle fatigue (assessed by stimulated twitch force measurements) for a given absolute or normalized exercise task than age-matched controls (27, 28, 44): where the term ‘fatigue’ is defined in this paper as a loss in muscle force and/or shortening velocity that is recoverable with rest. Heightened fatigability in COPD is related to muscle capillary rarefaction, loss of oxidative capacity and reduced myofiber expression of type I myosin heavy chain (26, 45). Despite impairments in pulmonary function, many COPD patients still report leg fatigue as the major symptom limiting exercise performance (25). However, we do not know whether the reduction in available limb power (the product of average muscle force development and shortening velocity) actually defines the limit of tolerance in COPD. Do COPD patients reach limiting symptoms of breathlessness from hyperinflation (36) and low ventilatory reserve (35)

and/or leg fatigue (27, 28, 44) that are sufficient to produce a reduction in voluntary locomotor muscle power that limits performance?

Measurement of muscle power and fatigue is confounded by task-specificity, the dependence of power on contraction velocity, and the rapid recovery kinetics of fatigue. The technical requirements of transcranial or peripheral nerve stimulation, interpolated twitch, or maximal voluntary contraction generally limit the measurement of fatigue to tasks evoking single-joint isometric force. Attempts to make these measurements immediately after whole-body exercise (walking or cycling) are typically delayed by ~1-10 min from the point of task failure, at a time when substantial recovery has occurred (recovery half-time of ~30-60 s (10, 46)).

We developed a method to measure skeletal muscle power at the limit of tolerance during cycle ergometry using an instantaneous switch from cadence-independent cycling (hyperbolic) to isokinetic (constant velocity) cycling (10). This task-specific, velocity-controlled measurement can be implemented pseudo-instantaneously at the limit of tolerance. We use brief (<5 s) maximal effort isokinetic power (P_{iso}) measurements to quantify the total reduction, between baseline and intolerance, in voluntary isokinetic locomotor power (termed 'performance fatigue'). As a supplemental measurement, we use surface electromyography (EMG) to measure two major components of fatigue: 'activation fatigue' (the power deficit caused by the reduction in maximal isokinetic EMG activity), and 'muscle fatigue' (the loss of isokinetic power for a given EMG activity) (10).

Using this method we aimed to determine: 1) whether COPD patients possess a reserve in locomotor power at the limit of tolerance; 2) whether declining locomotor power during exercise is related to ventilatory limitation; and 3) whether COPD patients exhibit greater proportions of the 'muscle' or 'activation' components of fatigue compared with age-matched controls. We hoped that these findings would help us to identify whether patients are unable to 'access' available locomotor power due to their cardiopulmonary symptoms and dysfunction, and if so, what mechanisms underpin their exercise intolerance.

We hypothesized: 1) moderate to severe COPD patients exhibit a larger reserve in the capacity for maximal evocable power generation at the limit of tolerance than healthy age-matched controls; 2) performance fatigue in whole-body exercise in COPD is related to ventilatory limitation; and 3) COPD patients exhibit less muscle fatigue and greater activation fatigue compared to healthy controls in this large-muscle-mass exercise task. Our rationale was that pulmonary limitations in COPD constrain locomotor power through afferent feedback primarily affecting motor unit recruitment.

Materials and Methods

Participants

Thirteen stable COPD patients (FEV_1 <80% predicted; FEV_1/FVC <0.7), and 12 age- and sex-matched healthy controls with normal pulmonary function provided written informed consent (Table 1). The local institutional review board approved this study,

and all procedures complied with the latest revisions of the *Declaration of Helsinki* and *Belmont Report*. All participants were screened for cardiovascular disease with a resting ECG and a medical history was taken to exclude patients with a significant disease other than COPD. Some data from 4 of the 12 age-matched controls were reported in a previous paper detailing the method of fatigue and power measurement (10).

Pulmonary Function

In COPD patients, post-bronchodilator (albuterol sulfate; ProAir HFA, Teva Respiratory, North Wales, PA) spirometry, body plethysmography (RV, FRC, TLC), and diffusing capacity (D_LCO) measurements were performed (Vmax Encore with V62J Autobox, CareFusion, San Diego, CA) according to ATS/ERS guidelines (11, 21, 32, 33, 39). Healthy participants completed spirometry alone. Maximum voluntary ventilation (MVV) was calculated as FEV_1 x 40 (33).

Exercise Protocols

Participants completed two experimental phases: 1) short (<5 s) bouts of variable effort isokinetic cycling at 70 rpm to determine the relationship between muscle activity (EMG) and P_{iso} at baseline; and 2) a ramp-incremental exercise test, followed by a short (<5 s) maximal isokinetic effort at 70 rpm performed immediately at the limit of tolerance.

Baseline EMG-P_{iso}. Volunteers cycled on an ergometer (Excalibur Sport PFM, Lode, Groningen, NL) with pedaling rate constrained at 70 rpm (isokinetic). Participants gave 4 variable efforts at approximately 25%, 50%, 75% and 100% of maximum. Each effort

lasted ~3-5 s, and was separated by ~1-5 min of unloaded cycling. This process was repeated 2-3 times. Baseline P_{iso} is reported as the greatest mean power achieved over three consecutive isokinetic crank revolutions during a single repeat.

EMG-P_{iso} Following Ramp Exercise. Participants completed a ramp-incremental exercise test to the limit of tolerance (5-30 $W.min^{-1}$). Ramp rate was set to 5 $W.min^{-1}$ for COPD patients with FEV_1 <1.0 L, 10 $W.min^{-1}$ for all other COPD patients, and 15-30 $W.min^{-1}$ for controls based on a target ramp duration of 10 min and predicted $\dot{V}O_{2peak}$. During the unloaded and ramp phases, the ergometer power was cadence-independent (hyperbolic). The limit of tolerance was defined as being unable to maintain a pedaling cadence above 55 rpm, despite strong verbal encouragement. At the limit of tolerance, the ergometer was switched instantaneously to isokinetic mode at 70 rpm. As all resistance from the flywheel is removed, participants immediately accelerated pedaling cadence to the target of 70 rpm. Volunteers were strongly encouraged to give a maximal final effort for 4-5 revolutions (<5 s) before recovering at 0 W. This maneuver is similar to the baseline maximal isokinetic effort, with which the participants were well familiarized.

Ergometry

The computer-controlled electromagnetically-braked cycle ergometer (Excalibur Sport PFM, Lode BV, Groningen, NL) was instrumented with force transducers in the bottom bracket spindle. Left and right torque (Nm) was measured independently (peak force 2000 N, < 0.5 N resolution and measurement uncertainty of < 3%). Instantaneous

192 angular velocity of the crank (rad.s^{-1}) was measured with a resolution of 2° using three
193 independent sensors sampling in series (measurement uncertainty of < 1%). During
194 isokinetic efforts, power was calculated every 2° from torque and angular velocity
195 measurements. There was no systematic difference in the power production between
196 the left and right cranks. Therefore P_{iso} was calculated from power on right crank
197 averaged over 3 crank revolutions (5, 10), and was paired with an EMG datum from the
198 same leg (described below). Crank power data are reported as 2 times one-leg to allow
199 for direct comparison with power output measured at the flywheel (which, naturally,
200 averages contributions of both legs).
201
202 *Electromyography*
203 Surface EMG was measured in five muscles of the right leg: *vastus lateralis*, *rectus*
204 *femoris*, *vastus medialis*, *biceps femoris*, and *gastrocnemius lateralis*. Placement sites
205 were shaved, abraded with gauze, and cleaned with 70%vol. isopropyl alcohol. Wireless
206 transmitting Ag bipolar parallel-bar surface electrodes were placed over the muscle
207 belly according to Surface Electromyography for the Non-Invasive Assessment of
208 Muscles (SENIAM) recommendations (Trigno Wireless System, Delsys Inc., Boston,
209 MA). Electrodes were placed over: the *vastus lateralis*, 2/3^{rds} of the distance from the
210 anterior superior iliac spine to the lateral side of the patella; the *rectus femoris*, halfway
211 between the anterior superior iliac spine and the superior border of the patella; the
212 *vastus medialis*, 8/10^{ths} of the distance from the anterior superior iliac spine to the joint
213 space in front of the anterior border of the medial ligament; the *biceps femoris*, halfway
214 between the ischial tuberosity and lateral epicondyle of the tibia; and the *gastrocnemius*

215 *lateralis*, 1/3rd the distance between the head of the fibula and the calcaneus. The
216 longitudinal axis of the electrode was aligned parallel to the long axis of the muscle.
217
218 EMG signals were differentially amplified and sampled at 2 kHz with 16-bit resolution.
219 Each sensor had a signal bandwidth of 20-450 Hz and common mode rejection ratio of
220 >80 dB. During post-processing, signals were filtered with a second-order Butterworth
221 band-pass filter (3dB, 10-500 Hz) and smoothed via root mean square (RMS) with a
222 100 ms window. The peak voltage (μV; from the 100 ms RMS) during each crank
223 revolution was used to quantify of muscle activity. The earliest three consecutive
224 isokinetic crank revolutions that were appropriately constrained at 70 rpm were
225 identified in the output from the cycle ergometer, and the peak RMS EMG from these
226 were ensemble averaged for each muscle; these were typically the 2nd, 3rd, and 4th
227 crank revolutions after switching to isokinetic cycling. The RMS EMG values from the 5
228 muscles of the right leg were averaged to provide an EMG datum to pair with P_{iso}
229 produced at the crank from the same leg. Median frequency (MDF) was calculated from
230 the same three consecutive isokinetic crank revolutions as the RMS EMG using
231 EMGworks (Delsys Inc., Boston, MA), after first isolating the active muscle bursts from
232 the quiescent phase of each crank revolution. The relative change in isokinetic MDF
233 (ΔMDF, %) between baseline and incremental peak maximal efforts were analyzed for
234 each muscle independently and ensemble averaged. The muscle selection reflected the
235 weighted power contributions from knee extension/flexion and plantarflexion (14).
236

Fatigue Characterization

For characterization of the EMG-P_{iso} relationship the RMS EMG values were normalized to the visit maximum. The baseline linear relationship between power production and EMG activity (measurement of baseline EMG-P_{iso}) was characterized using least-squares regression. Measurements made at the limit of tolerance for ramp incremental exercise were used to calculate three fatigue measurements (each expressed in W). Performance fatigue was the reduction in P_{iso} (W) from the baseline (fatigue-free) maximum. The proportion of performance fatigue resulting from activation fatigue was calculated from the power equivalent of the reduction in RMS EMG activity, using the baseline linear regression between EMG and P_{iso} at 70rpm. Muscle fatigue was calculated from the balance (MF = PF – AF; with lower bounds constrained at 0 W), i.e. the deviation in power from the baseline EMG-P_{iso} relationship at the measured EMG value (for a graphical representation for these indices, see Figure 3). Maximal isokinetic ΔMDF was also calculated as an independent index of muscle fatigue (31). Performance fatigue as a fraction of ramp peak power was calculated as an index of fatigue normalized for the exercise task.

Cardiopulmonary Measurements

Respired gases and ventilation were measured breath-by-breath with a commercial metabolic measurement system (VMax Spectra, CareFusion, San Diego, CA USA). The system was calibrated immediately prior to each testing session. A 3 L syringe (Hans Rudolph Inc., Shawnee, KS, USA) was used to calibrate the mass flow sensor from ~0.2 to 8.0 $L.s^{-1}$, mimicking flow rates expected at rest and during exercise. The CO_2

and O_2 analyzers were calibrated using gases of known concentrations (O_2 26.0% and 16.0%; CO_2 0.0% and 4.0%). Inspiratory capacity (IC) was measured in COPD patients at rest in triplicate, and at 2 min intervals during the exercise protocol. Heart rate (HR) was measured from the 12-lead ECG (Cardiosoft, GE Healthcare, Little Chalfont, UK), and arterial O_2 saturation (Masimo Corp, Irvine, CA) was monitored throughout exercise. In COPD, at rest and every 2 min during exercise, dyspnea and leg effort were assessed using the modified Borg scale (CR-10) followed by an IC maneuver.

Statistical analyses

Means were compared, where appropriate, with t-tests, ANOVA, or mixed model ANOVA. Statistical significance was determined at $p<0.05$. Data are presented as mean±SD, and, where appropriate, the 95% confidence interval of the difference ($CI_{Difference}$) is included.

Results

At baseline, COPD patients generated a maximum P_{iso} of 350±162 W, which was less than controls (498±160 W, $p<0.05$). During the ramp-incremental test, COPD patients reached a peak power (hyperbolic power measured at the flywheel) of 72±34 W and $\dot{V}O_{2peak}$ was 1.2±0.4 L.min^{-1} (Table 1). Controls produced a peak ramp power of 212±84 W and $\dot{V}O_{2peak}$ was 2.6±0.9 L.min^{-1}, which were both greater than COPD (Table 1). COPD peak Borg CR10 scores were 5.7±2.4 for leg fatigue and 5.3±2.0 for breathlessness ($p=0.66$). At peak ramp, inspiratory reserve volume (IRV) in COPD was 0.4±0.3 L.

Comparison (group x time) of the peak power required at the end of the ramp-incremental and P_{iso} at the limit of tolerance revealed main effects of group ($F[1,23]=12.4$, $p<0.05$, $\eta^2=0.35$) and time ($F[1,23]=25.1$, $p<0.05$, $\eta^2=0.52$). In COPD, P_{iso} at the limit of tolerance was ~260% of ramp peak power (187±141 vs 72±34 W, $p<0.05$, Figure 1C and 1D). In controls, P_{iso} at the limit of tolerance was ~130% of ramp peak power (274±73 vs 212±84 W, $p<0.05$, Figure 1A and 1B). The power reserve relative to the ramp peak power was significantly greater in COPD vs controls ($p<0.05$).

Performance fatigue as a fraction of ramp peak power was greater in COPD than CON (2.4±1.1 vs 1.1±0.3, $p<0.05$, Figure 2A), and in COPD was strongly and negatively related to resting (FEV_1/FVC) and peak-exercise ($\dot{V}_E/MVV$) pulmonary function ($r^2=0.47$, $r^2=0.55$, $p<0.05$, Figure 2B and 2C). In controls there were no significant relationships between performance fatigue and pulmonary function.

The EMG-P_{iso} relationship was used to characterize activation and muscle fatigue at the limit of tolerance (Figure 3). Maximum evocable EMG activity at peak was significantly greater in controls vs COPD (81.0±10.2 vs 69.4±12.2% of baseline; $CI_{Difference}$ 2, 21 %; $p<0.05$; Figure 4A). Muscle fatigue was less in COPD vs controls (30±46 vs 94±72 W, $CI_{Difference}$ 12, 116 W, $p<0.05$; Figure 4B), but was not different when expressed as a fraction of baseline peak isokinetic power (0.11±0.20 vs 0.19±0.11, $p=0.3$, Figure 4C). In controls, maximum effort isokinetic MDF across the 5 leg muscles fell from 77.1±17.3 Hz at baseline to 72.3±16.9 Hz at peak ($p<0.05$). The significant decline in MDF

between baseline and peak was negatively correlated with MF in controls (r^2 = 0.46, p<0.01), and the decline was greater than COPD ($CI_{Difference}$ 1, 19 %; p<0.05; Figure 4D). In COPD, there was no change in MDF between baseline and peak (71.5±19.5 vs 73.4±15.1 Hz; p>0.05).

Overall, while performance fatigue was related to $\dot{V}_E$/MVV (r^2=0.24, p<0.05, Figure 5A), neither component alone of performance fatigue was correlated with $\dot{V}_E$/MVV (or IRV) at the limit of tolerance in COPD (Figure 5B and 5C).

Discussion

We aimed to determine whether the heightened muscle fatigue associated with COPD (26-28, 44, 45) limits tolerance during locomotor exercise. We found that COPD, unlike controls, were less able to voluntarily evoke maximal isokinetic muscle activity at the limit of ramp-incremental exercise, but nonetheless expressed a large reserve in short-term locomotor power. Despite this instantaneous power reserve, COPD had greater performance fatigue vs controls and this was correlated with poor pulmonary function and high peak exercise $\dot{V}_E$/MVV. Absolute muscle fatigue was less in COPD at the limit of tolerance and maximal effort isokinetic MDF in the locomotor muscles was unchanged from baseline, unlike in controls where it was reduced. To our surprise, maximal evocable isokinetic muscle activity and activation fatigue were not related to $\dot{V}_E$/MVV in COPD.

328 *Locomotor Power Reserve in COPD*

329 In agreement with our earlier studies (10, 16, 17), only a modest reserve in short-term
330 skeletal muscle power production was present at the limit of tolerance in controls. Thus,
331 the perceptual and physiological limits to exercise were closely matched. Conversely, a
332 large skeletal muscle power reserve was present immediately following the limit of
333 tolerance in COPD. Using a short isokinetic bout we showed that COPD patients were
334 capable of briefly producing ~260% of the power output required at the limit of
335 tolerance. Thus, maximal evocable power production is not the limiting factor for
336 exercise in COPD. While the patients are unlikely to be able to sustain this power much
337 beyond the 5 s of measurement, the power is substantially larger than the reserve in
338 healthy young or older adults (10, 17, 34) and is consistent with a reserve in metabolic
339 capacity of the locomotor muscles in COPD (43). While COPD patients have greater
340 performance fatigue, they possess a short-term capacity for power production that
341 exceeds the task requirement at the limit of tolerance – the utility of this capacity is
342 unknown. Without metabolic measurements of the intramuscular environment, we are
343 unable to determine how the energy requirements are met for this brief excursion of
344 locomotor power above the task requirement.

345

346 *Performance Fatigue, Pulmonary Function, and Ventilatory Limitation in COPD*

347 In controls and COPD, the P_{iso} achieved at the limit of tolerance was approximately half
348 of the baseline (fatigue-free) condition – the relative decline in P_{iso} was similar.
349 However, as COPD patients reached a far lower peak power output in the ramp-
350 incremental task, performance fatigue as a fraction of ramp power was greater in COPD

than in controls. In other words, COPD patients had a greater fatigability than controls. This is consistent with substantial locomotor fatigue reported previously in COPD (2, 27, 28, 44). The important distinction in our data is that maximal evocable power remained well in excess of the power output required by the task at intolerance.

Skeletal muscle weakness, atrophy, loss of oxidative capacity, and increased fatigability are serious problems in COPD (12, 29). We found that baseline P_{iso} was ~29% lower in COPD, likely reflecting the loss of muscle mass and fibrotic and fat muscle infiltration in patients (29). However, the limit of tolerance is more likely defined by dyspnea arising from ventilatory limitation, hyperinflation or increased respiratory muscle work rather than an inability of the atrophied locomotor muscles to produce the power required by the task (18, 22, 43). Therefore, while performance fatigue during cycling appears to elicit a large contribution from central mechanisms limiting power production in both COPD and controls (48), task failure in controls appears to be associated with a greater contribution from a muscle fatigue-induced reduction in locomotor power (10, 17), cf. (34).

Performance fatigue in COPD was strongly related to pulmonary function and an index of ventilatory limitation; the patients with the lowest FEV_1/FVC and greatest $\dot{V}_E/MVV$ showed the greatest fatigue (Figure 2). Feedback to the motor cortex from hyperinflation, increased accessory muscle work, or some other mechanism related to ventilatory limitation or dyspnea, may reduce motor cortex excitability and therefore limit evocable muscle activity and power production. This may be a mechanism by which the

common symptom of “leg fatigue” occurs in COPD patients. That is, not as a direct consequence of muscle fatigue from disruption of cross-bridge cycling, but via inhibition of central motor drive that requires, and is perceived as, an increased effort to drive locomotor muscles to maintain the task. Interestingly, pulmonary C-fiber receptors were originally hypothesized to contribute to the termination of high-intensity exercise in a similar CNS feedback-dependent manner (38). However, this mechanism remains highly controversial (51). In humans, for example, stimulation of the pulmonary C-fibers with intravenous lobeline increased the size of the H-reflex, magnified the EMG responses to transcranial magnetic stimulation, and did not inhibit voluntary force production (19). Thus, while the structures and mechanisms are not well-understood, it is very likely that flow limitation, high work of breathing, abnormal lung mechanics, and dyspnea conspire to reduce voluntary motor activity via negative feedback to the CNS (see (36)).

We want to emphasize that while locomotor power did not constrain the completion of the task *per se*, skeletal muscle deconditioning and/or dysfunction in COPD is a major contributor to poor quality of life, morbidity, and mortality. Firstly, absolute muscle power is lower in COPD vs healthy controls. Second, greater reliance on non-oxidative metabolism results in elevated ventilatory demands (6). Therefore, skeletal muscle contributes to bringing about task failure through taxing an already-challenged ventilatory system (29, 49), even though maximal evocable power does not fall to meet the task requirement in the way it does for healthy individuals. Thus, we wish to make it clear that our findings are not evidence to weaken the rationale and need for physical

rehabilitation in COPD. On the contrary, we feel that our data strengthen the rationale for rehabilitation. There is little doubt that rehabilitation reduces fatigability, contributes to improved quality of life, and reduces exacerbations and hospitalizations (3). Even with a large power reserve at the limit of tolerance, the absolute power eliciting intolerance in COPD was still far lower than controls, and a heightened fatigue appears to contribute to limiting performance (1). The consequences of a low maximal evocable power (whether fresh or fatigued) are devastatingly clear for a patient who cannot rise from a chair or climb a flight of stairs.

Skeletal Muscle Fatigue in COPD Patients and Controls

Due to the large differences in power between COPD and controls, more absolute muscle fatigue was present in controls. Consistent with this, unlike controls, there was no decline in MDF of maximal voluntary isokinetic power production at intolerance in COPD patients; a reduction in MDF is associated with muscle acidosis, muscle lactate accumulation (48) and fatigue (31). However, when normalized to a fraction of baseline P_{iso}, muscle fatigue was not different between patients and controls. While there is a small numerical difference between the normalized muscle fatigue of COPD and controls (Figure 4C), it is the heterogeneity of the responses that is most interesting, particularly the patients with no muscle fatigue. The wide variance in muscle fatigue for COPD patients is consistent with other reports in the literature, as is the presence of what might be a small subset of patients who fail to develop muscle fatigue during heavy cycle ergometry (2, 4). None of our measures for pulmonary function or disease severity explained the heterogeneity in muscle fatigue. This reinforces the common

finding that muscle dysfunction and exercise intolerance are only weakly or moderately correlated to standard measures of spirometric impairment in COPD (23, 37), despite being independent risk factors for poor outcome in population studies.

Where development of muscle fatigue is prevented due to a ceiling imposed by disease symptoms, the patients may possess a reserve of muscle power that they are unable to access. For example, after improvement in time to limitation with spinal anesthesia, COPD patients exhibited greater peripheral muscle fatigue 10 minutes after the limit of tolerance, measured by potentiated quadriceps twitch force (18). In this case, it appears as though a lower ventilatory demand with spinal anesthesia revealed an ability to access the metabolic and locomotor muscle power reserve (18, 22, 43). The hyperbolic-to-isokinetic switch, at limit of tolerance, is a non-invasive alternative to quantify this reserve in metabolism and power instantaneously at the point of limitation.

Activation Fatigue and Ventilatory Limitation

High $\dot{V}_E$/MVV was not related to activation fatigue at the limit of tolerance, and tended to relate to maximal evocable isokinetic muscle activity (r^2=0.26; p=0.07). However, the perceptions of effort and dyspnea are non-linear as a function of the task's demands and operating lung volumes (24, 36). Steep increases in symptoms above $\dot{V}_E$/MVV 0.8-0.9 and wide variance in $\dot{V}_E$/MVV at peak exercise in our cohort may have confounded the relationship between $\dot{V}_E$/MVV and activation fatigue (Figure 5B). In light of this we examined 4 patients with $\dot{V}_E$/MVV >0.9, and found worse pulmonary function, exacerbated performance fatigue, and a tendency (p=0.08) for activation fatigue to be

443 greater compared to patients with $\dot{V}_E$/MVV <0.9. Further work is clearly required to
444 determine whether central limitation to muscle activation is sensitive to the
445 encroachment of ventilatory limits, hyperinflation, accessory muscle work of breathing,
446 or other factors related to dyspnea that may reduce cortical motor excitability and limit
447 locomotor power.
448
449 *Future Directions and Limitations*
450 Our next step is to examine how effective interventions (7, 9, 30, 41, 47) for dyspnea
451 and exercise tolerance affect the rate and magnitude of performance fatigue and its
452 components. Whether effective interventions such as rehabilitation, HeO_2 breathing, or
453 supplemental O_2 allow access to a reserve in skeletal muscle power by alleviating
454 dyspnea, or by retarding the dynamics of skeletal muscle fatigue (or a combination of
455 the two) is unknown.
456
457 A limitation in our study is that we did not incorporate a method to separate activation
458 and muscle fatigue using a defined external stimulus (e.g. by muscle or nerve
459 stimulation). The experimental approach used simply quantifies the combination of
460 activation fatigue and muscle fatigue that sums to determine peak power output at the
461 point of limitation, under whatever level of motor activity that can be achieved by a
462 maximum voluntary effort. Therefore, it assesses the maximal voluntary performance,
463 and not the instantaneous capacity of the central nervous and muscular systems. The
464 relative contributions of baseline muscle weakness, capillary rarefaction, fiber type shift,
465 reduced muscle oxidative capacity, and other muscle abnormalities that contribute to

influence both central and peripheral components and fatigability in COPD are not determined. Similarly, our secondary indices of fatigue are reliant on surface EMG – an indirect assessment of muscle activity, by its nature. We do not know how the patterns of activity change during the exercise bout (as this was not velocity constrained), and whether this history of muscle activation changes the interpretation of our maximal-effort isokinetic measurements. However, it is unlikely that the differences in EMG amplitude between patients and controls are due to amplitude cancellation (13) or motor unit synchronization (15). It is less clear whether differences in the common input to the motor unit pool can explain the reduced maximal evocable EMG activity at intolerance in COPD (8).

Summary

We applied a new experimental approach with instantaneous switching between hyperbolic and isokinetic cycle ergometry to identify whether locomotor fatigue limits whole-body exercise and aerobic capacity in COPD patients. We found, both at baseline and immediately following intolerance of ramp-incremental cycling, isokinetic power was lower in COPD patients compared with age-matched healthy controls. In COPD, performance fatigue was negatively correlated with resting pulmonary function (FEV_1/FVC) and positively correlated with exercise ventilatory limitation ($\dot{V}_E/MVV$). In addition, the relative loss of locomotor power was ~2.4 times greater in COPD patients compared with controls. Despite this heightened fatigue, COPD patients, unlike controls, possessed a large reserve in maximal evocable isokinetic power at the tolerable limit (~2.6 times peak ramp power). As such, substantial fatigue is present in

COPD and associated with a significantly lesser ability to activate locomotor muscles compared to age-matched controls. However, this fatigue is not sufficient to constrain locomotor power and define the tolerable limit of whole-body exercise.

Competing Interests

Authors have no competing interests.

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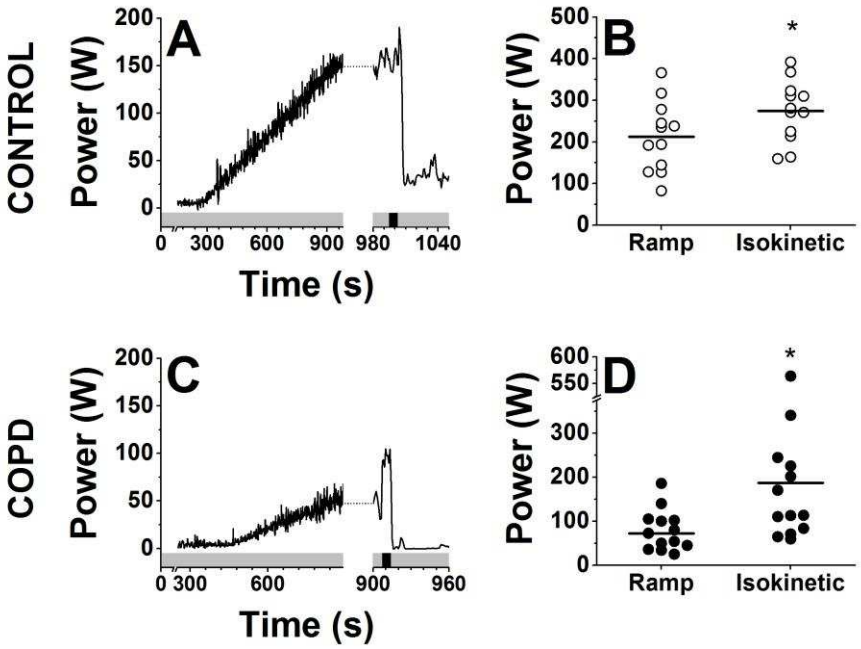


Figure 1. Representative participant data and group data for power production during ramp-incremental and maximal isokinetic cycling. The dotted lines indicate that data are continuous: the x-axis is expanded at the end of the ramp-incremental to better show the power output during the brief (<5 s) maximal isokinetic effort (black shading on x-axis). Grey shading along the x-axis represents hyperbolic ergometry (cadence independent power). Black shading along the x-axis represents maximal isokinetic cycling at 70 rpm. **Panel A:** Mean right crankarm power from a representative healthy control. **Panel B:** Group data from healthy controls comparing peak power achieved during ramp-incremental and isokinetic phases. Isokinetic refers to the brief (<5 s) maximal effort immediately following the limit of tolerance. **Panel C:** Mean right crankarm power from a representative COPD patient. **Panel D:** Group data from COPD patients comparing peak power achieved during ramp-incremental and isokinetic phases. *Different (p<0.05) from ramp-incremental peak power.

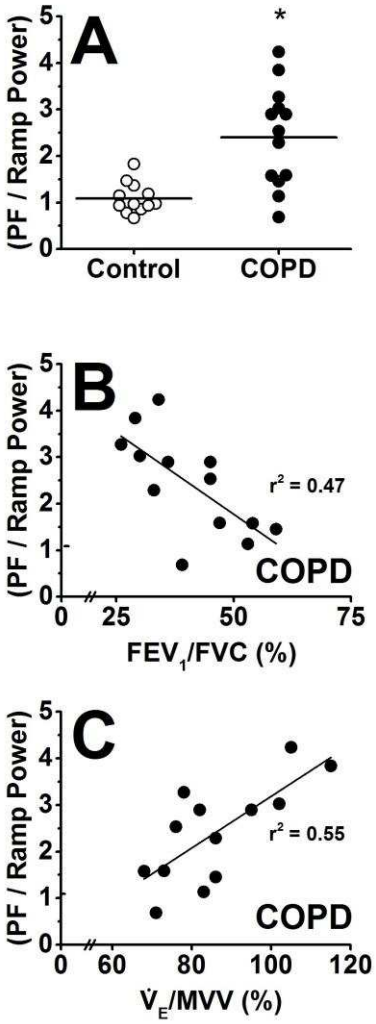
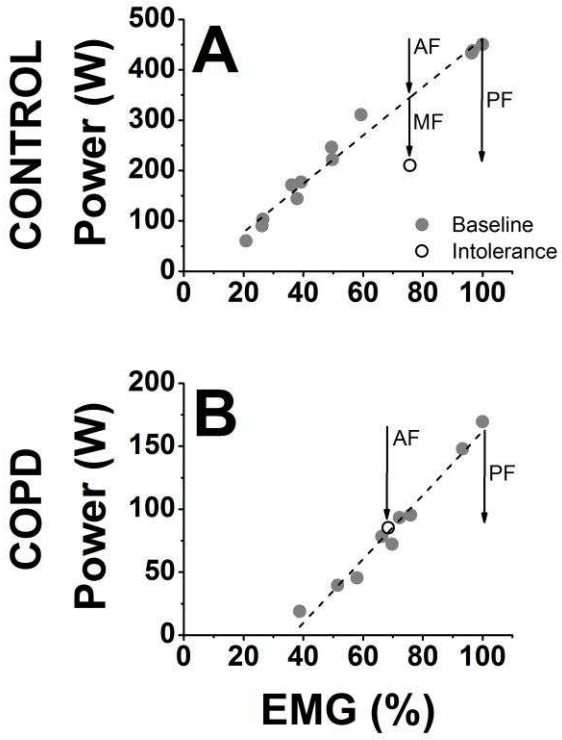


Figure 2. Performance fatigue during ramp-incremental exercise in COPD and controls. **Panel A:** Performance fatigue as a fraction of peak ramp power was significantly greater in COPD. *Different from CON (p<0.05) **Panel B:** Performance fatigue was strongly related to FEV_1/FVC in COPD (p<0.05), but there was no significant relationship in CON (data not shown). **Panel C:** Performance fatigue was strongly related to $\dot{V}_E$/MVV in COPD (p<0.05) but there was no significant relationship in CON (data not shown).



528

529 **Figure 3.** The relationship between EMG activity and isokinetic power (P_{iso}) in
530 representative COPD and control participants. The data includes the baseline (fatigue-
531 free) measurements (●) and the maximal effort measurement at the limit of tolerance
532 (○). All measurements were taken at 70 rpm. Performance fatigue (PF) arrow
533 represents the total reduction in power generation immediately at the limit of ramp-
534 incremental exercise. Activation fatigue (AF) represents the proportion of performance
535 fatigue resulting from a reduced maximal evocable muscle activity. Muscle fatigue (MF)
536 arrow represents the proportion of performance fatigue that can be attributed to muscle
537 fatigue i.e. a lower power than expected for the measured EMG. **Panel A:**
538 Representative control participant showing large muscle fatigue component (as a
539 fraction of the performance fatigue). **Panel B:** Representative COPD participant
540 showing no muscle fatigue component.

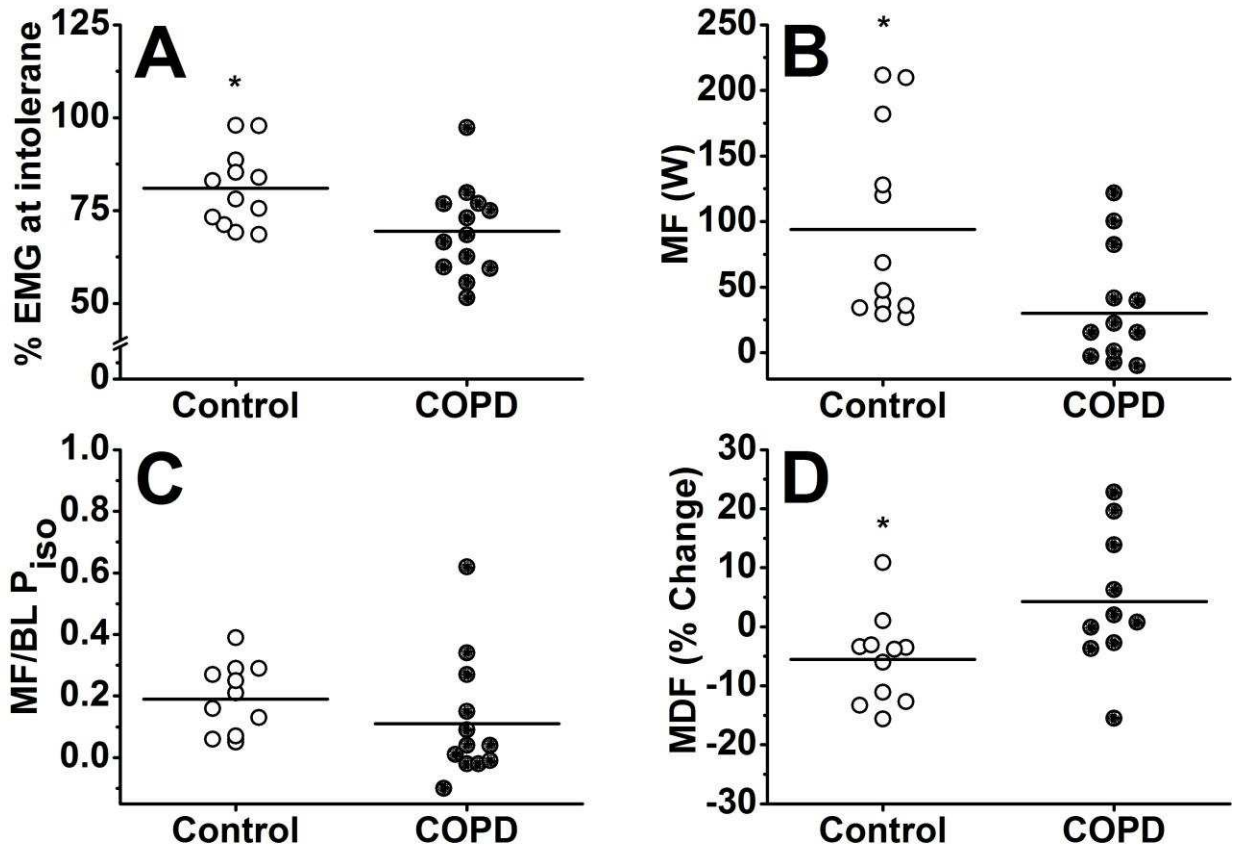
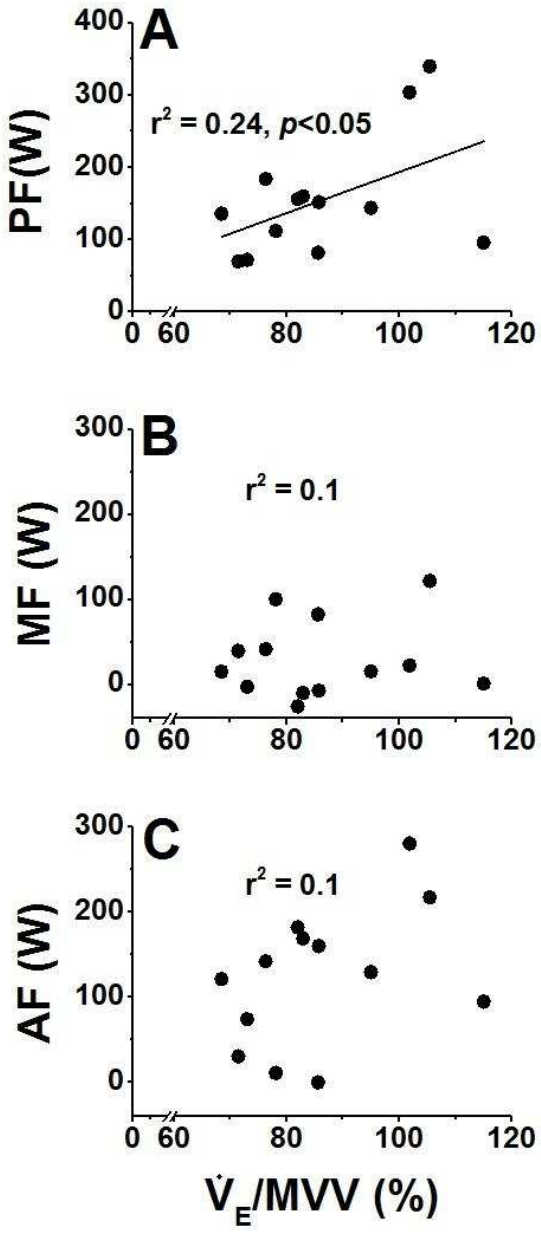


Figure 4. Maximal isokinetic muscle activity and fatigue at the limit of tolerance in COPD and controls. **Panel A:** Maximal evocable isokinetic muscle activity (RMS EMG) as a percentage of baseline (ΔEMG). *Difference between groups ($CI_{Difference}$ 2, 21 %, $p<0.05$). **Panel B:** Muscle fatigue (MF). *Difference between groups ($CI_{Difference}$ 12, 116 W, $p<0.05$). **Panel C:** Muscle fatigue (MF) expressed as a fraction of the baseline maximal isokinetic power (BL P_{iso}). Two groups not significantly different ($CI_{Difference}$ -10, 40%, $p>0.05$). **Panel D**: The relative change in in median frequency of isokinetic EMG activity between baseline and peak (ΔMDF). *Difference between groups ($CI_{Difference}$ 1, 19 %, $p<0.05$).



551

552 **Figure 5.** Relationship between $\dot{V}_E$/MVV and fatigue components in COPD patients.
553 **Panel A:** Performance fatigue (PF) plotted as a function of $\dot{V}_E$/MVV (r^2=0.24, p<0.05).
554 **Panel B:** Muscle fatigue (MF) plotted as a function of $\dot{V}_E$/MVV (r^2=0.1, p>0.05). **Panel**
555 **C:** Activation fatigue (AF) plotted as a function of $\dot{V}_E$/MVV (r^2=0.1, p>0.05).

Table 1. Patient characteristics at rest and peak exercise

	Control	COPD	*p*-value
N (m/f)	12 (10/2)	13 (11/2)	--
Characteristics			
Age, yr	65 ± 9	65 ± 11	0.96
Height, cm	172 ± 8	169 ± 7	0.28
Weight, kg	79 ± 13	70 ± 13	0.09
BMI, kg/m^2	26.8 ± 3.4	24.5 ± 4.1	0.15
Resting S_pO_2, %	97 ± 1	99 ± 1	0.04
Pulmonary Function			
FEV_1, L	3.1 ± 0.7	1.4 ± 0.6	<0.01
FEV_1, % predicted†	107 ± 16	49 ± 17	<0.01
FEV_1/FVC, %	75 ± 10	40 ± 11	<0.01
GOLD spirometric class, 2/3/4	--	4/8/1	--
RV, L	--	2.78 ± 0.65	--
RV, % predicted†	--	120 ± 13	--
FRC, L	--	4.11 ± 0.74	--
FRC, %predicted†	--	124 ± 26	--
TLC, L	--	5.96 ± 0.98	--
TLC, % predicted†	--	97 ± 17	--
RV/TLC	--	0.47 ± 0.09	--
D_LCO, $ml.min^{-1}.mm\ Hg^{-1}$	--	10.5 ± 4.1	--
D_LCO, % predicted†	--	42 ± 12	--
IC, L	--	2.2 ± 0.7	--
Ramp-Incremental Exercise			
Peak power, W	212 ± 84	72 ± 34	<0.01
$\dot{V}O_{2peak}$, $L.min^{-1}$	2.6 ± 0.9	1.2 ± 0.4	<0.01
$\dot{V}O_{2peak}$, $mL.min^{-1}.kg^{-1}$	32.2 ± 8.3	17.1 ± 5.7	<0.01
Peak HR, min^{-1}	147 ± 39	117 ± 17	0.13
Peak $\dot{V}_E$, $L.min^{-1}$	112 ± 34	47 ± 16	<0.01
Peak $\dot{V}_E/MVV$, %	81 ± 19	86 ± 14	<0.01
Peak S_pO_2, %	96 ± 3	95 ± 4	0.70
Peak IC, L	--	1.9 ± 0.6	--
Peak IRV, L	--	0.4 ± 0.3	--

Definition of abbreviations: BMI, body mass index; D_LCO, lung diffusion capacity; FEV_1, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, heart rate; IC, inspiratory capacity, IRV, inspiratory reserve volume; MVV, maximal voluntary ventilation; RV, residual volume; S_pO_2, oxygen saturation by pulse oximetry; TLC, total lung capacity; $\dot{V}_E$, ventilation; $\dot{V}O_2$, oxygen uptake. Data are mean ± SD. †Prediction equations used: (21, 42)

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