Impact of pulmonary system limitations on locomotor muscle fatigue in patients with COPD

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Amann M, Regan MS, Kobitary M, Eldridge MW, Boutellier U, Pegelow DF, Dempsey JA. Impact of pulmonary system limitations on locomotor muscle fatigue in patients with COPD. Am J Physiol Regul Integr Comp Physiol 299: R314–R324, 2010.—We examined the effects of respiratory muscle work [inspiratory (Wr-insp); expiratory (Wr-exp)] and arterial oxygenation (SpO2) on exercise-induced locomotor muscle fatigue in patients with chronic obstructive pulmonary disease (COPD). Eight patients (FEV1, 48 ± 4% of predicted) performed constant-load cycling to exhaustion (Crl; 9.8 ± 1.2 min). In subsequent trials, the identical exercise was repeated with 1) proportional assist ventilation + heliox (PAV); 2) heliox (He:21% O2); and 3) 60% O2 inspire (hyperoxia); or d) hyperoxic heliox mixture (He: 40% O2). Five age-matched healthy control subjects performed Ctrl exercise at the same relative workload but for 14.7 min (=best COPD performance). Exercise-induced quadriceps fatigue was assessed via changes in quadriceps twitch force (Qtw,pot) from before to 10 min after exercise in response to supramaximal femoral nerve stimulation. During Ctrl, absolute workload (124 ± 6 vs. 62 ± 7 W), Wr-insp (207 ± 18 vs. 301 ± 37 cmH2O·s·min−1), Wr-exp (172 ± 15 vs. 635 ± 58 cmH2O·s·min−1), and SpO2 (96 ± 1% vs. 87 ± 3%) differed between control subjects and patients. Various interventions altered Wr-insp, Wr-exp, and SpO2 from Ctrl (PAV; −55 ± 5%; −21 ± 7%; +6 ± 2%; He:21% O2; −16 ± 2%; −25 ± 5%; +4 ± 1%; hyperoxia: −11 ± 2%; −17 ± 4%; +16 ± 4%; He:40% O2; −22 ± 2%; −27 ± 6%; +15 ± 4%;). Ten minutes after Ctrl exercise, Qtw,pot was reduced by 25 ± 2% (P < 0.01) in all COPD and 2 ± 1% (P = 0.07) in healthy control subjects. In COPD, ΔQtw,pot was attenuated by one-third after each interventional trial; however, most of the exercise-induced reductions in Qtw,pot remained. Our findings suggest that the high susceptibility to locomotor muscle fatigue in patients with COPD is in part attributable to insufficient O2 transport as a consequence of exaggerated arterial hypoxemia and/or excessive respiratory muscle work but also support a critical role for the well-known altered intrinsic muscle characteristics in these patients.

In summary, to a faster accumulation of inorganic phosphates and hydrogen ions (44, 45, 63, 69)—metabolites that contribute to a faster rate of development of peripheral locomotor muscle fatigue (67).

A compromised O2 transport to limb locomotor muscles might also be expected in patients with COPD for two reasons. First, the impaired pulmonary gas exchange characterizing many of these patients often results in reduced hemoglobin saturation [arterial O2 saturation by pulse oximetry (SpO2)] compared with age-matched healthy control subjects at rest and especially during exercise (1, 17, 46, 53). Second, patients with COPD experience expiratory flow limitation, hyperinflation, and greater respiratory muscle work (Wt) at any given level of exercise (65), which may or may not lead to inspiratory and/or expiratory muscle fatigue (36, 38, 42, 56, 57). Accumulation of metabolites in the respiratory muscles activates unmyelinated group IV phrenic afferents, which, in turn, increases sympathetic vasconstrictor activity in the working limb via a supraspinal reflex (19). The result is a Wt–induced decrease in limb blood flow and a corresponding reduction in O2 delivery to the working muscles (27), which accelerate the development of locomotor muscle fatigue (4, 7). Furthermore, increased expiratory flow limitations and associated high expiratory pressure generation have been identified to cause a decrease in exercise in patients with COPD (2, 18, 54). The traditional view of perceived respiratory difficulty (dyspnea) as a critical factor restricting exercise is important and certainly plays a significant limiting role in many patients with COPD (34, 50). However, substantial exercise-induced locomotor muscle fatigue also occurs in many of these patients (34, 39–41), and their susceptibility to peripheral muscle fatigue is greater than in age-matched healthy control subjects exercising at the same work rate (39, 40). Peripheral muscle fatigue has been shown to play an important feedback role in limiting central motor output to the locomotor muscle (5, 6, 8, 9), and inducing preexercise limb fatigue reduces endurance exercise performance in healthy individuals (5) and in COPD (21).

One possible cause of the exacerbated susceptibility for peripheral fatigue in patients with COPD is attributable to the intrinsic properties of the locomotor muscles as caused by alterations presumably triggered by the disease (32). Key muscle abnormalities in many COPD patients include a shift from fatigue-resistant oxidative to nonoxidative fibers and reduced oxidative and increased glycolytic enzyme activities (16, 22–26, 44, 45, 59, 62). Together, these COPD-associated muscle abnormalities lead, at any given workload or O2 delivery, to a faster accumulation of inorganic phosphates and hydrogen ions (44, 45, 63, 69)—metabolites that contribute to a faster rate of development of peripheral locomotor muscle fatigue (67).
stroke volume and cardiac output during exercise in healthy humans (66) and canines (48).

Our study was designed to determine the extent to which the increased susceptibility to locomotor muscle fatigue in patients with COPD is determined by arterial hypoxemia and/or the work of the respiratory muscles. Our rationale for utilizing a variety of methods of improving limb O2 delivery, all of which are readily applicable during stationary exercise, was to identify an effective and useful way to reduce a patient’s susceptibility to exercise-induced locomotor muscle fatigue and thereby to improve his or her success in an exercise-based rehabilitation program. To these ends, we used mechanical ventilation and inhalation of low-density and/or hyperoxic gas mixtures during exercise to alleviate pulmonary system constraints on limb O2 delivery and employed the technique of supramaximal femoral nerve stimulation to quantify exercise-induced quadriceps fatigue.

METHODS

Participants

To ensure proper patient recruitment and to exclude other comorbidities, all subjects underwent a rigorous characterization process including medical history, physical examination, and ECG at rest and during incremental exercise. Standard pulmonary functions and high-resolution computed tomography scan evidence of emphysema were used to evaluate potential subjects. Written informed consent was obtained from each participant. All procedures were approved by the institution’s human subjects committee.

The characteristics of the eight participating patients and the five healthy age-matched control subjects are summarized in Tables 1–3. All subjects were nonsmoking (during and at least 10 mo before the study) and free of overt disease, other than COPD. All participants were sedentary, defined as no regular physical activity for at least the prior 6 mo. None of the subjects had orthopedic limitations that would prohibit them from performing cycling exercise. High-resolution computed tomography scan evidence of emphysema indicated mild to extensive upper lobe emphysema in six of the eight patients. All patients were receiving inhaled bronchodilators in the 6-mo period before and throughout the study. None of the patients received oral and/or inhaled corticosteroids during the 6 mo before the study. Six of the subjects received inhaled corticosteroids during the course of the study. One of the patients qualified for supplemental oxygen; however, he chose not to use it. All patients abstained from using their bronchodilator for at least 12 h before each experiment. Bronchodilators were used as needed after each experiment. None of the trials had to be terminated because of acute adverse effects. Four of the patients had body mass indexes (BMIs) between 37 and 39 kg/m2, forced expiratory volume in 1 s (FEV1) ranging between 1.26 and 1.51 liters, and SpO2 ranged from 92% to 94%. The remaining four patients had BMIs between 37 and 39 kg/m2, a FEV1 range of 1.24–2.0 liters, and SpO2 at peak workload, % 94.6 ± 0.3.

Table 2. Pulmonary function and gas exchange

<table>
<thead>
<tr>
<th>COPD</th>
<th>Healthy Control</th>
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</thead>
<tbody>
<tr>
<td>FVC, liters</td>
<td>2.9 ± 0.2</td>
</tr>
<tr>
<td>FEV1</td>
<td>1.6 ± 0.1</td>
</tr>
<tr>
<td>FEV1/FVC, %</td>
<td>55.0 ± 4.7</td>
</tr>
<tr>
<td>SVC, liters</td>
<td>3.5 ± 0.2</td>
</tr>
<tr>
<td>IC, liters</td>
<td>2.9 ± 0.2</td>
</tr>
<tr>
<td>ERV, liters</td>
<td>0.6 ± 0.1</td>
</tr>
<tr>
<td>RV, liters</td>
<td>2.9 ± 0.4</td>
</tr>
<tr>
<td>VTG, liters</td>
<td>4.0 ± 0.3</td>
</tr>
<tr>
<td>TLC, liters</td>
<td>6.9 ± 0.3</td>
</tr>
<tr>
<td>FEF25%, %</td>
<td>2.1 ± 0.4</td>
</tr>
<tr>
<td>FEF50%, %</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>FEF75%, %</td>
<td>0.4 ± 0.1</td>
</tr>
<tr>
<td>MVV, l/min</td>
<td>70.9 ± 9.4</td>
</tr>
<tr>
<td>DLCO, ml·min⁻¹·mmHg⁻¹</td>
<td>15.1 ± 1.4</td>
</tr>
<tr>
<td>DL/WA</td>
<td>2.4 ± 0.3</td>
</tr>
</tbody>
</table>

Values represent means ± SE. FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; FEV1/FVC, ratio of forced expiratory volume in 1 s to forced vital capacity; SVC, slow vital capacity; IC, inspiratory capacity; ERV, expiratory reserve volume; RV, residual volume; VTG, thoracic gas volume; TLC, total lung capacity; FEF25%, FEF50%, and FEF75%, forced expiratory flow at 25%, 50%, and 75% of FVC, respectively; MVV, maximal voluntary ventilation; DLCO, diffusing capacity of the lung for carbon monoxide; DL/WA, ratio of lung diffusional capacity to lung volume. *P < 0.05 vs. COPD.
Protocol

An incremental bicycle test was performed to determine each subject’s peak work capacity (Wpeak) and O2 consumption (VO2peak). After a 2-min warm-up at 20 W, the workload was increased by 25 W/min in the Healthy-Control group (11) and by 5–15 W/min in the COPD group until subjects could no longer continue. After these initial tests, we determined, in each of the subjects, the individual power output that caused voluntary exhaustion after 7–12 min of constant-load cycling. Each subject then performed three practice constant-workload trials at this workload (52 ± 2% of Wpeak) to exhaustion, to minimize learning effects. On later occasions, each subject performed three practice constant-workload trials. The first trial was performed to the limit of exhaustion while the subjects breathed unimpeded (Ctrl). The four subsequent trials were conducted in random order, and all subjects repeated the constant-load exercise at the same intensity (62 ± 7 W) and for the same duration (9.8 ± 1.2 min) as during Ctrl. In these four trials, exercise was performed under the following conditions: 1) with proportional assist ventilation and breathing heliox (79% He:21% O2) (PAV); 2) while breathing helium (79% He:21% O2) (Heliox); 3) while breathing a hyperoxic inspirate (60% O2:40% N) (Hyper); and 4) while breathing a hyperoxic heliox mixture (60% He:40% O2) (He:O2). The healthy subjects only performed the Ctrl trial, at the same relative intensity as the COPD patients (52 ± 2% of Wpeak). Each control subject exercised for 14.7 min, which was equal to the longest performance time among the COPD patients.

Exercise Responses

VO2, CO2 production (VCO2), and ventilatory parameters were measured with an open-circuit system (10). During all constant-workload trials, esophageal pressure (Pes) was measured via a balloon placed via the nares in the lower third of the esophagus (13). The inspiratory (Wir-in) and expiratory (Wir-exp) muscle pressure-time products were calculated (7). Voluntary inspiratory capacity measurements were performed at rest and during exercise in order to determine exercise-induced changes in end-expiratory lung volumes (7) (see Supplemental Material).1 Pulmonary function tests (PFTs) were conducted according to American Thoracic Society standards (12).

Neuromuscular Function

Electromyography. Surface electrodes were used to record M-wave properties of the right vastus lateralis, vastus medialis, and rectus femoris (see Supplemental Material) (5, 6).

Magnetic stimulation. A magnetic stimulator connected to a 70-mm figure-of-eight coil was used to stimulate the femoral nerve to evoke quadriceps twitch forces (Qtw). Supramaximality of magnetic stimulation was indicated by a near plateau in baseline Qtw and M-wave amplitudes with increasing stimulus intensities in every subject (see Supplemental Material). We measured potentiated Qtw (Qtw,pot) 5 s after a 5-s maximal voluntary contraction (MVC) of the quadriceps and repeated this procedure six times. Activation of the quadriceps during the MVCs was assessed with a superimposed twitch technique (47). The assessment procedure was performed before (~20 min) and 10 and 35 min after exercise; the pre- to postexercise difference in Qtw,pot was labeled as exercise-induced locomotor muscle fatigue. Further methodological details and reliability data are provided in the Supplemental Material.

Statistical Analysis

Repeated-measures ANOVA was used to test for within-group differences among the five experimental conditions. If ANOVA yielded a significant result, follow-up pairwise comparisons using the Holm's sequential Bonferroni procedure were conducted. Comparisons of exercise responses between patients with COPD and Healthy-Control subjects were made by unpaired t-test. Results are expressed as means ± SE. Statistical significance was set at P < 0.05.

RESULTS

Exercise Intensity and Symptom-Limited Exercise

Exercise intensity. Wpeak and VO2peak were lower in the COPD group than in the Healthy-Control group (Table 1). The workload necessary to achieve voluntary exhaustion within 7–12 min was 62 ± 7 W (range 45–90 W), equalling 52 ± 2% of Wpeak (range 47–59%). The age-matched Healthy-Control subjects exercised at the same relative exercise intensity, which was equivalent to 124 ± 6 W (range 110–145 W). The healthy subjects did not exercise to the limit of exhaustion, but the duration was fixed at 14.7 min, which equaled the longest time to exhaustion within the COPD group. The control subjects performed the constant-load exercise with relatively little upward drift over time in VO2, heart rate (HR), or minute ventilation (VE), as noted by the substantial differences in these variables at peak work rate (Table 1) versus the final minute of the constant work rate. However, COPD subjects did not reach a steady-state response as VO2 increased over time and VE, HR, and SpO2, at the end of exercise approached levels achieved at the peak of the increased exercise test.

Exercise-induced symptoms. Only Ctrl exercise in the COPD group was performed to the limit of exhaustion. The primary symptom of effort perception at exercise termination was not uniform. At the end of exercise, three of the eight patients complained primarily of breathlessness (9.5 ± 0.3 for dyspnea vs. 8.3 ± 0.3 for leg discomfort), two of the patients complained primarily of leg discomfort (8.0 ± 1.0 vs. 6.8 ± 0.8), and three patients reported identical Borg scale ratings for dyspnea and leg discomfort (9.3 ± 0.7 vs. 9.3 ± 0.7). The three subjects who complained primarily of dyspnea were characterized by greater hyperventilation (Ve/VCO2 = 33–36) during the final minute of exercise compared with those who complained primarily of leg discomfort (31–33). The subjects who complained primarily of leg discomfort were characterized by a greater level of end-exercise peripheral fatigue (range ΔQtw,pot −28% to −31%) compared with those who complained primarily of dyspnea (ΔQtw,pot −19% to −26%).

Operational Lung Volumes, Respiratory Muscle Pressure-Time Products, and SpO2

Operational lung volumes. End-expiratory (EELV) and end-inspiratory lung (EILV) volumes at rest and during exercise and at any given Ve were lower in Healthy-Control subjects versus COPD patients (Table 4 and Fig. 1). In Healthy-Control subjects, EELV was significantly reduced below resting values by 7 ± 2% at the sixth minute of exercise. With further increases in Ve from the sixth minute to the end of exercise, EELV rose again to reach preexercise resting values (P = 0.87) at the termination of the trial. EILV in all age-matched Healthy-Control subjects continuously rose with increasing Ve from rest to reach 81 ± 2% of total lung capacity (TLC) at the end of exercise. The average 1.6-liter increase in tidal volume (VT) from rest to the final minute of exercise in Healthy-Control subjects was accomplished by encroaching on the inspiratory reserve volume (IRV); reduced by ~51% from

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1 The online version of this article contains supplemental material.
compared with Ctrl exercise, Wr-insp was reduced by 11.0%

Perceived exertion; TI, inspiratory time; TE, expiratory time; Ttot, total time; VT, tidal volume; fR, respiratory frequency; V˙CO2, CO2 production; ICdyn, dynamic inspiratory capacity; IRV, inspiratory reserve volume; ERV, expiratory reserve volume; EILV, end-inspiratory lung volume; EELV, end-expiratory lung volume. *P < 0.05 vs. Healthy. aIC maneuvers are not feasible during exercise with PAV. See text for description of COPD interventional trials.

Values represent means ± SE. PAV, proportional assist ventilation; Wr-insp and Wr-exp inspiratory and expiratory muscle work, respectively; RPE, rating of perceived exertion; Ti, inspiratory time; Te, expiratory time; Ttot, total time; Vt, tidal volume; fR, respiratory frequency; V˙CO2, CO2 production; ICdyn, dynamic inspiratory capacity; IRV, inspiratory reserve volume; ERV, expiratory reserve volume; EILV, end-inspiratory lung volume; EELV, end-expiratory lung volume. *P < 0.05 vs. COPD-Ctrl; †P < 0.05 vs. Healthy. *n = 6; IC maneuvers are not feasible during exercise with PAV. See text for description of COPD interventional trials.

Preexercise resting values) in the face of an end-exercise EELV similar to that observed at rest. In COPD, EELV and EILV progressively increased from rest to the end of exercise (both P < 0.001). The 0.7-liter increase in Vt from rest to the final minute of exercise in COPD was achieved exclusively by encroaching on the IRV (reduced by 83% from preexercise baseline) in the face of a 67% increase in inspiratory reserve volume (ERV). Various interventional trials similarly increased the dynamic inspiratory capacity in all eight COPD patients and significantly decreased EILV and EELV to similar levels (Table 4).

Respiratory muscle work. Wf for both subject groups, as represented by [Peps × respiratory frequency (fR)], is shown in Figs. 2 and 3. Wr-insp and Wr-exp at any given ventilation were higher in the COPD group versus the Healthy-Control group. During Ctrl exercise, Wr-insp and Wr-exp were on average 42% and 246% higher in the COPD group versus the Healthy-Control group (both P < 0.05). Within the COPD group, compared with Ctrl exercise, Wr-insp was reduced by 11 ± 2%, 16 ± 2%, 22 ± 2%, and 55 ± 2% for Hyper, He:21% O2, He:40% O2, and PAV, respectively. Relative to Ctrl exercise, Wr-exp was reduced by 17 ± 4%, 25 ± 5%, 27 ± 6%, and 22 ± 7% for Hyper, He:21% O2, He:40% O2, and PAV, respectively (all P < 0.05). Wr-insp was more reduced during PAV versus He:21% O2 (P < 0.001), whereas Wr-exp was similar during these trials (P = 0.74). Wr-insp was more reduced during He:40% O2 versus Hyper (P < 0.001), whereas Wr-exp was similar during these trials (P = 0.22). Finally, Wr-insp was more reduced during PAV versus He:40% O2 (P < 0.001), whereas Wr-exp was similar during these trials (P = 0.51). The various attempts to reduce Wf during exercise in the COPD group resulted in closer Wr-insp values between COPD and Healthy-Control subjects (P > 0.4). Moreover, Wr-insp during the PAV trial was even lower compared with the healthy subjects (P < 0.05). Nonetheless, Wr-exp during various interventional trials was still between 150% and 181% higher (P < 0.01) in the patients compared with the healthy subjects.

Hemoglobin saturation. Hemoglobin saturation at rest, as estimated via pulse oximetry, was lower in COPD patients versus Healthy-Control subjects (P < 0.05). SpO2 fell from rest to the final minute of Ctrl exercise by 9 ± 2% (range 11–19%; P < 0.001) and 2 ± 0% (range 1–2%; P < 0.01) in COPD patients and Healthy-Control subjects, respectively. At the end of exercise, SpO2 was 10% lower in COPD patients versus Healthy-Control subjects (86.4% vs. 96.4%, respectively; P < 0.05). Compared with Ctrl exercise in COPD, end-exercise SpO2 was higher in each of the interventional trials (Table 4). SpO2 was similar during the 60% O2 trial and the He:40% O2 trial (P = 0.52) and, during both of these trials, higher compared with the Ctrl trial. SpO2 was also slightly higher during PAV versus He:21% O2 (P = 0.036).

Exercise-Induced Changes in Contractile Functions of Locomotor Muscle

M waves. Membrane excitability was maintained from before to after exercise in all trials and in both subject groups as indicated by unchanged M-wave characteristics (P > 0.2). This suggests that the observed changes in Qwexp are mainly due to changes within the quadriceps and that peripheral failure of
electrical transmission might be excluded as a determinant of peripheral fatigue.

**Contractile quadriceps fatigue.** Alterations in Q\textsubscript{tw,pot} measurements indicating peripheral locomotor muscle fatigue are shown in Table 5 and Fig. 4.

**COPD GROUP.** Ten minutes after exercise, group mean Q\textsubscript{tw,pot} was reduced from preexercise baseline in all subjects and all trials (P < 0.01) (range −19% to −31%) and, despite some recovery, remained reduced from baseline (P < 0.01) 35 min after exercise. Compared with the level of quadriceps fatigue following Ctrl, exercise-induced changes in Q\textsubscript{tw,pot} were substantially (P < 0.05) and similarly (P > 0.5) attenuated by about one-third 10 and 35 min after each of the four interventional trials, and these changes occurred in all eight COPD patients. MVC force and all within-twitch measurements [maximal rate of force development (MRFD), maximal rate of relaxation (MRR), contraction time (CT), one-half relaxation time (RT\textsubscript{0.5})] were altered from baseline at 10 min and, despite some recovery, 35 min after each trial (P < 0.01). Compared with Ctrl, exercise-induced changes in these variables were significantly and similarly reduced by 28–31% after each of the various interventional trials. However, the exercise-induced reductions in Q\textsubscript{tw,pot} were still significant with each of the interventions designed to reduce W\textsubscript{r} and/or improve arterial oxygenation. Percent voluntary muscle activation was reduced by 1.3 ± 0.5% 10 min after Ctrl (P < 0.05) and completely recovered 35 min after the trial (P = 0.79). Compared with preexercise baseline, there was a small but significant reduction in percent voluntary muscle activation after control exercise. The pre- to postexercise change in percent voluntary muscle activation was not significant in the interventional trials. However, there was no significant difference in postexercise voluntary muscle activation across various trials.

**HEALTHY-CONTROL GROUP.** After exercise in the Healthy-Control group, none of the variables measured to evaluate peripheral locomotor muscle fatigue was altered from baseline at 10 and 35 min after exercise (P > 0.1). Ten minutes after exercise, Q\textsubscript{tw,pot} in the five subjects was between 0.4% and 3.7% of preexercise values (P = 0.1), indicating that the exercise did not cause contractile quadriceps fatigue in any of the healthy subjects.

**DISCUSSION**

We determined the effects of preventing arterial hypoxemia and reducing W\textsubscript{r} on exercise-induced locomotor muscle fatigue
in obese COPD patients with moderately severe airway disease who experienced significant SpO2 desaturation during exercise. We confirmed the known enhanced susceptibility to limb muscle fatigue in patients with COPD relative to age-matched control subjects since all patients showed significant low-frequency quadriceps fatigue following exercise to exhaustion at 52% of their peak work rate, whereas no peripheral fatigue was detected in the Healthy-Control subjects exercising at the same relative intensity and for the same duration. Reducing the inspiratory muscle pressure-time product by 16–55% from control and/or preventing arterial O2 desaturation each had a significant but similar effect on alleviating limb fatigue by ~30%. There was then a clear limit to the effects of improving O2 transport on locomotor muscle fatigue, as the majority of exercise-induced limb fatigue was not influenced by these interventions. We interpret these findings to mean that exercise-induced limb fatigue in COPD is in part dependent upon O2 transport but is primarily attributable to the enhanced inherent fatigability of locomotor muscles in the COPD patient.

**Significance of Locomotor Muscle Fatigue**

Constant-load bicycle exercise (52% of Wpeak) to voluntary exhaustion resulted in substantial postexercise (10 min) locomotor muscle fatigue in all of the patients with COPD (ΔQtw,pot 19–31%), and, despite some recovery, peripheral fatigue was still significant 35 min after exercise (ΔQtw,pot 10–29%). These results confirm reports in which patients with COPD were exercised at ~60% of Wpeak, inducing a ΔQtw,pot of ~20–30% (39, 41). However, they contrast with other investigations that found that only a subset of patients with COPD, characterized by reduced muscle capillarization and an increased glycolytic enzyme activity, exhibit significant exercise-induced muscle fatigue (61, 62). Interestingly, exercise intensity was much higher (80% of Wpeak) in those investigations that found that only a subset of the patients with COPD developed exercise-induced locomotor muscle fatigue (61, 62).

The severity of the exercise-induced locomotor muscle fatigue as measured in the present patients might be put into perspective by comparing it to the level of end-exercise peripheral fatigue of well-trained young cyclists who exercised (82% of Wpeak, ~270 W, ~8 min) to exhaustion in acute moderate hypoxia [inspired O2 fraction (FIO2) 0.15] (7, 10). During hypoxic exercise, arterial desaturation in these athletes was slightly lower than that measured in the present patients with COPD (82% vs. 86%) and Wt was even greater (to support a Vt that was 2.5 times greater than in COPD) (7). However, at voluntary exhaustion, exercise-induced locomotor muscle fatigue in the athletes was only slightly greater compared with that observed in the patients with COPD (ΔQtw,pot of 30% vs. 25%).
Is Attenuation of Exercise-Induced Rate of Development of Locomotor Muscle Fatigue Meaningful in Terms of Endurance Exercise Performance?

First, although we did not measure this effect in the present study, several investigations utilized similar attempts to improve muscle O2 delivery, and thus attenuate the rate of peripheral fatigue development (4, 10), in patients with COPD and reported a 30–150% prolongation in time to exhaustion (e.g., Refs. 20, 30, 46, 52, 57). A similar improvement in time to exhaustion was also observed in healthy humans when the rate of peripheral fatigue development during exercise was attenuated via a 100% O2 inspirate (6). However, attributing these improvements in exercise performance of patients with COPD entirely to the attenuated rate of development of locomotor muscle fatigue was an oversimplification since the various interventions also relieved the perception of leg discomfort and dyspnea (Table 4), two recognized major contributors to exercise limitation in COPD (33, 43, 51, 54). Consistent with the idea of perception of leg discomfort as a key limitation to exercise performance in COPD are findings in healthy humans showing that sensory afferent feedback from the fatiguing locomotor muscles exerts inhibitory influences on central motor drive (i.e., reduced vastus lateralis EMG) during whole body exercise (5, 6, 8, 9).

Second, more direct evidence is available from studies in which peripheral locomotor muscle fatigue was experimentally induced in healthy individuals just before the start of a cycling performance test, and subsequent endurance performance was attenuated in a dose-dependent manner compared with the same test performed without preexercise-induced locomotor muscle fatigue (5). Most relevant to the present findings, peripheral locomotor muscle fatigue was induced in patients with COPD via electrical motor nerve stimulation just before the start of a constant-load bicycle performance test. This preexercise quadriceps fatigue significantly reduced the exercise time to voluntary exhaustion (21). Thus exercise-induced limb fatigue by itself appears to exert a significant effect on endurance exercise performance in healthy subjects and patients with COPD.

Limits on Convective O2 Transport as Determinant of Limb Fatigue

Each of the interventions designed to prevent arterial desaturation and/or facilitate limb blood flow (via reduced Wr) during exercise presumably improved leg muscle O2 delivery (see Improving Limb O2 Transport: Assumptions below) and attenuated end-exercise peripheral locomotor muscle fatigue by about one-third in all patients with COPD. However, we also observed that the degree to which improving deficits in O2 transport impacted limb muscle fatigue was clearly limited, with no evidence of a dose-response effect. Most striking in this regard was the comparison of PAV versus He:21% O2, in which PAV reduced the inspiratory muscle work to below levels in healthy subjects and over time as much as He:21% O2—but the effect on relieving limb fatigue was identical. We caution that our ability to distinguish significant differences between these interventions was limited by our statistical power, but also point out the <1–2% difference in group mean changes as well as the consistency across all subjects in the equivalence of effect between these interventions. We interpret the equivalent effects across all interventions to mean that there is a clear limit on the extent to which improving O2 transport in the COPD patient will impact limb fatigue.

It is especially important to note that about two-thirds of the original peripheral fatigue (induced via control exercise) still remained after various assisted trials. This residual amount of fatigue is substantial (see above), especially compared with the healthy age-matched control subjects who did not show any end-exercise quadriceps fatigue (or end-exercise symptoms of exhaustion) despite their twofold higher absolute workload. Combined, these observations indicate, in functional terms, that compromised limb O2 delivery in clinically stable patients with severe COPD might account for ~30% of their increased susceptibility to locomotor muscle fatigue, whereas the remainder (O2 delivery-independent portion of quadriceps fatigue) might be explained by the disease-associated morpho-
logical and bioenergetic alterations in the locomotor muscles (induced by sedentary lifestyle and/or inflammatory secondary effects) (16, 22–26, 44, 45, 59, 62).

We may have underestimated the degree of O2 delivery-dependent limb fatigue in COPD because our experiments did not include an intervention that would likely have truly maximized O2 delivery, for example, by combining inspiratory muscle unloading via PAV with a hyperoxic inspirate. However, the combined intervention would not have normalized the markedly high level of W_r-exp observed by us and others in many—but not all—patients with COPD during exercise (3, 37, 49, 58, 65). Although we significantly reduced W_r-exp via the heliox inspirate, the remaining W_r-exp was still elevated above normal (Fig. 2). The combination of high expiratory intrathoracic pressures and dynamic hyperinflation (Fig. 1, A and C), both of which are associated with expiratory flow limitations as seen in COPD, has previously been shown to mechanically constrain stroke volume and cardiac output and to decrease limb vascular conductance (48, 66)—which limits O2 delivery. Consequently, if we had been able to attenuate W_r-exp more, peripheral limb O2 transport would likely have been somewhat higher and end-exercise peripheral fatigue might have been alleviated to a greater extent (4) than the observed one-third reduction in ΔQtw_pot following the interventional trials (Table 5). On the other hand, given the consistencies in our observed effects of fairly wide variations in Spo2 and/or W_t-insp on exercise-induced limb fatigue, it may also be argued that this one-third effect represented the maximum influence of systemic O2 transport in these patients.

Generalizability of Findings

Our COPD subjects differed in two potentially important ways from many patients with COPD, which may influence the generalizability of our findings. First, most of our patients experienced significant arterial Spo2 desaturation during submaximal exercise. Arterial hypoaxemia has been reported in patients with COPD due to an inadequate ventilatory response and/or impaired alveolar to arterial O2 transport (17, 29, 46, 49). However, many COPD patients do not, even at moderately heavy exercise intensities, experience significant hypoaxemia. Accordingly, with hyperoxic inhalation, plasma and whole blood arterial O2 content and O2 delivery to working limbs (46) would increase in all patients with COPD, and this improvement in O2 delivery would certainly be greater in our hypoxemic group of patients, by roughly 20–25%. It would normally follow then that the increases in arterial O2 content with hyperoxia would also mean greater relief of the rate of development of limb fatigue in the more hypoxemic subjects as it appears to do in healthy individuals (60). However, since we found clear limits to the degree to which limb fatigue was relieved by our various attempts at improving O2 transport among patients with COPD, we would not necessarily expect greater increases in arterial O2 content to correspond to less fatigue relief.

Second, our patients had a higher BMI than most COPD patients and were similar to those recently studied by Ora et al. (55). These authors showed that obese patients with COPD are characterized by less lung hyperinflation at rest and at peak exercise but still show significant expiratory flow limitation and similar, abnormal increases in EELV with exercise compared with their nonobese counterparts. Accordingly, the increase in the elastic work (at any given increase in Vt) would be less in the obese patients with COPD and therefore there may be less respiratory muscle pressure development to relieve with our unloading interventions. At the same time, we emphasize that our patients’ generation of pleural pressures during mild-intensity exercise were 50% greater on inspiration and threefold greater on expiration than that observed in healthy control subjects (despite their lower Vt) and that the PAV plus heliox intervention removed all of the extra inspiratory load (above control) and a significant portion of the expiratory pressure development. Of further interest was the greater quadriceps strength in our obese patients with COPD (MVC was 41 ± 9% greater compared with Healthy-Control subjects), which is consistent with the higher peak power output on the cycle ergometer in obese patients with COPD compared
with nonobese patients with COPD (55). Despite this greater limb strength, all of our patients with COPD showed significant exercise-induced limb fatigue (at an exercise intensity requiring only 52% of their peak work rate), and all of the various interventions relieved a significant portion of this peripheral muscle fatigue. If anything, then COPD patients without comorbid obesity might experience greater absolute limb fatigue for a given exercise work rate. However, again, because of these clear limits to the degree of relief of this limb fatigue with improved O2 transport, we are doubtful that our attempts at increasing O2 transport would have substantially different effects on limb fatigue development in the different types of patients with COPD.

**Improving Limb O2 Transport: Assumptions**

In interpreting our findings concerning the effects of preventing arterial hypoxemia and unloading the respiratory muscles on limb fatigue, we have assumed—in the absence of direct measurements—that both types of these interventions elicited a significant improvement in O2 transport to the exercising limb. In the case of increased FIO2, the evidence is clear from studies in both healthy subjects (35) and patients with COPD (46) that O2 transport to the working limb is enhanced via increases in arterial O2 content. Unloading the respiratory muscles has been shown to increase limb vascular conductance and blood flow in near-maximum exercise—but not submaximal exercise—in healthy subjects (27, 28, 68), and this has been attributed to the relief of a respiratory muscle metaboreflex that activates sympathetically mediated limb vasoconstriction (19). Furthermore, increased expiratory intrathoracic pressure in healthy exercising subjects (66) or canines (48) reduces stroke volume and cardiac output. Thus respiratory muscle unloading would be expected to alleviate this mechanical effect on cardiac output with exercise-induced expiratory pressure development in patients with COPD. We cannot be certain that either of these mechanisms is operative during heliox breathing or PAV in our patients with COPD during submaximal exercise, but there are two types of findings that support our

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**Fig. 4.** Potentiated quadriceps twitch force expressed as a percentage of preexercise baseline before and 10 and 35 min after exercise. Preexercise baseline values were 167 ± 7 N and 149 ± 16 N for COPD group (n = 8) and Healthy-Control group (n = 5), respectively (P = 0.30). A: individual fatigue data for both subject groups under control conditions. B: group mean fatigue data under various conditions. +P < 0.05 from Healthy-Ctrl; *P < 0.05 from COPD-Ctrl and Healthy-Ctrl; #not significantly different from preexercise baseline.
assumption. First, Simon et al. (64) have shown that many—but not all—patients with COPD experience an elevated limb vascular resistance and a plateau of limb blood flow and limb VO₂ versus work rate even at very low submaximal work rates. Second, respiratory muscle unloading during submaximal exercise in patients with COPD (15) or congestive heart failure (14) increased limb muscle oxygenation. In summary, we attribute our observed effects of respiratory muscle unloading on exercise-induced limb fatigue in COPD to a concomitant increase in limb blood flow. These proposed unloading effects need to be tested with direct measures of stroke volume, limb blood flow, and vascular conductance across a wide range of workloads and intrathoracic pressures in patients with COPD.

Perspectives

Substantial peripheral quadriceps fatigue developed in patients with COPD during submaximal cycling exercise at a relative exercise intensity that did not induce peripheral fatigue in healthy age-matched control subjects exercising for the same duration. About one-third of the exercise-induced quadriceps fatigue was prevented when inspiratory muscle work was reduced and/or arterial O₂ content increased in the patients with COPD. Interventions that differed by as much as twofold in their ability to reduce inspiratory muscle work (i.e., PAV vs. He:21% O₂) produced no further relief of locomotor muscle fatigue, thereby revealing a distinct limit to the beneficial effects of improving O₂ transport on limb fatigue. These data suggest that ~30–40% of the exercise-induced limb fatigue in patients with COPD might be accounted for by airway disease-related pulmonary limitations affecting O₂ transport to working limb muscle. The majority of the exercise-induced limb muscle fatigue in patients with COPD was attributable to their inherent deficits in muscle morphology and bioenergetics.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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