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Relationship between ventilatory constraint and muscle fatigue during exercise in COPD

S.J. Butcher*,#, O. Lagerquist#,¶, D.D. Marciniuk*,+, S.R. Petersen#, D.F. Collins#,¶ and R.L. Jones*

ABSTRACT: Dynamic hyperinflation and leg muscle fatigue are independently associated with exercise limitation in patients with chronic obstructive pulmonary disease (COPD). The aims of the present study were to examine 1) the relationship between these limitations and 2) the effect of delaying ventilatory limitation on exercise tolerance and leg muscle fatigue.

In total, 11 patients with COPD (with a forced expiratory volume in one second of 52% predicted) completed two cycling bouts breathing either room air or heliox, and one bout breathing heliox but stopping at room air isotime. End-expiratory lung volume (EELV), leg muscle fatigue and exercise time were measured.

On room air, end-exercise EELV was negatively correlated with leg fatigue. Heliox increased exercise time (from 346 to 530 s) and leg fatigue (by 15%). At isotime, there was no change in leg fatigue, despite a reduction in EELV compared with end-exercise, in both room air and heliox. The change in exercise time with heliox was best correlated with room air leg fatigue and end-inspiratory lung volume.

Patients with chronic obstructive pulmonary disease who had greater levels of dynamic hyperinflation on room air had less muscle fatigue. These patients were more likely to increase exercise tolerance with heliox, which resulted in greater leg muscle fatigue.

KEYWORDS: **Dynamic hyperinflation, exercise capacity, heliox, interpolated twitch, magnetic stimulation**

AFFILIATIONS
*Dept of Medicine and
#Faculty of Physical Education and Recreation and
¶Centre for Neuroscience, University of Alberta
Edmonton, AB, and
+Division of Respiratory Medicine, University of Saskatchewan
Saskatoon, SK, Canada.

CORRESPONDENCE
S.J. Butcher
School of Physical Therapy
University of Saskatchewan
1121 College Dr.
Saskatoon
SK
S7N 0W3
Canada
Fax: 1 3069666575
E-mail: scott.butcher@usask.ca

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STATEMENT OF INTEREST
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Patients with chronic obstructive pulmonary disease (COPD) exhibit severe dyspnoea and exercise intolerance [1]. Determining the source of exercise limitation in patients with COPD has been a topic of great interest recently [2–5]. Traditionally, an inability to increase minute ventilation (V'_E) due to expiratory flow limitation and dynamic hyperinflation was thought to be the primary exercise-limiting factor in most COPD patients [5]. Indeed, dynamic hyperinflation correlates very closely with reduced exercise tolerance [3] and therapies that decrease dynamic hyperinflation, such as bronchodilators [6] and supplemental oxygen [2], significantly improve exercise tolerance in many patients. Heliox (79% helium, 21% oxygen), through its effect of increasing expiratory flow rate [7], has also been shown to increase exercise tolerance time [8–10] by delaying dynamic hyperinflation in COPD patients [9].

Despite the well-established findings that many patients with COPD primarily have ventilatory limitation, not all patients describe symptoms of dyspnoea as the primary reason for stopping exercise. Many patients describe symptoms of leg fatigue as the primary limiting factor [11]. The systemic consequences of COPD on skeletal muscle strength [12, 13], morphology [14], oxygen delivery [15] and leg muscle fatigue [16] have now also been recognised as playing a significant role in decreased exercise tolerance, at least in some COPD patients. Quadriceps muscle fatigue is greater in COPD patients after cycling exercise compared with healthy age-matched adults [16], and this may be an important exercise-limiting factor [4]. SAEY *et al.* [4] studied the effects of a bronchodilator on exercise tolerance and quadriceps contractile fatigue. They found that patients who fatigued their leg muscles to a greater degree increased exercise tolerance less after inhaling the bronchodilator, despite significant improvements in pulmonary function. Although they showed muscle fatigue to be an important limiting factor during exercise in COPD, they did not report measures of ventilatory

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limitation. Therefore, it is unknown whether their patients with greater muscle fatigue were also ventilation limited during exercise and whether there was a relationship between the degree of ventilatory and muscular limitations. If ventilatory constraint is more prevalent in COPD patients who have less leg muscle fatigue, then improving ventilatory capacity should increase exercise tolerance, but increasing exercise could eventually lead to greater muscle fatigue. To the present authors' knowledge, the relationship between measures of ventilatory limitation and leg muscle fatigue has not been reported. Therefore, the purpose of the current study was to test the hypotheses that, in patients with COPD, 1) higher levels of ventilatory limitation during exercise would be associated with less leg muscle fatigue and 2) delaying ventilatory limitation with heliox would increase exercise tolerance and leg muscle fatigue. Some of the results of the present study have been previously reported in the form of an abstract [17].

METHODS

Subjects

In total, 11 patients with COPD (table 1) were recruited from the pulmonary rehabilitation programme at the Centre for Lung Health (Edmonton, AB, Canada). All subjects had previously completed ⩾8 weeks of exercise rehabilitation and had stable COPD at the time of the study. Post-rehabilitation patients were selected, in order to minimise the fear/anxiety associated with exercise-induced dyspnoea (which is common in exercise-inexperienced patients) and, thus, to increase the potential for a maximal physiological exercise response. Patients who required the use of supplemental oxygen, or who had significant musculoskeletal or cardiovascular conditions (assessed through a subjective medical history by a respirologist) were excluded. All subjects provided their written consent for the study, which was approved by the University of Alberta Health Research Ethics Board (Edmonton).

TABLE 1 Subject demographics, baseline pulmonary function and graded exercise test results

Males/females	6/5
Age yrs	65.5±7.4
Height cm	168.4±11.0
Weight kg	78.6±15.2
FEV$_1$ L	1.5±0.6
FEV$_1$ % pred	52.3±16.8 (range 19–69)
FVC L	3.4±0.8
FVC % pred	87.7±20.6
FEV$_1$/FVC %	44.0±13.9
TLC % pred	129.9±14.2
$D_{\mathrm{L,CO}}$ % pred	80.1±13.9
Room air MVC N·m	397.1±193.8
$V'_{\mathrm{O_2,peak}}$ mL·kg^{-1}·min^{-1}	14.2±4.6
WR$_{\mathrm{peak}}$ W	80.9±28.1
$V'_{\mathrm{E,peak}}$ L·min^{-1}	45.5 ±16.8
V'_{E}/MVV %	91.2±17.9
$S_{\mathrm{p,O_2}}$ %	89.4±5.1
Reason for stopping	
Dyspnoea	4
Leg exertion	5
Both[#]	2

Data are presented as n or mean±SD, unless otherwise stated. FEV$_1$: forced expiratory volume in one second; % pred: % predicted; FVC: forced vital capacity; TLC: total lung capacity; $D_{\mathrm{L,CO}}$: diffusing capacity of the lung for carbon monoxide; MVC: maximal voluntary contraction; $V'_{\mathrm{O_2,peak}}$: peak oxygen consumption; WR$_{\mathrm{peak}}$: peak work rate; V'_{E}: minute ventilation; $V'_{\mathrm{E,peak}}$: peak V'_{E}; MVV: maximal voluntary ventilation; $S_{\mathrm{p,O_2}}$: arterial oxygen saturation measured by pulse oximetry. [#]: dyspnoea and leg exertion.

Study design

A single-blinded, randomised, crossover trial was conducted. Subjects underwent pulmonary function testing and a graded exercise test (GXT) to symptom limitation on a cycle ergometer prior to the experiments (table 1). Each subject then performed two randomised constant work rate cycling trials, breathing either room air or heliox and, finally, another heliox trial, but stopping at isotime on the room air test. Each test was separated by ⩾48 h.

Baseline pulmonary function

To confirm diagnosis and determine disease severity, each patient had a pulmonary function test (Vmax22; SensorMedics, Yorba Linda, CA, USA) according to American Thoracic Society standards [18] within 3 months of the study. Lung volumes were determined using a constant-volume body plethysmograph (6200 Autobox; SensorMedics). Spirometry and single-breath diffusing capacity of the lung for carbon monoxide ($D_{\mathrm{L,CO}}$) were compared with the reported norms of CRAPO *et al.* [19] and lung volumes were compared with those from GOLDMAN and BECKLAKE [20]. Maximal voluntary ventilation (MVV) was estimated by multiplying the forced expiratory volume in one second (FEV$_1$) by 35 [21].

Graded exercise test

The GXT to symptom limitation was performed on an electronically braked cycle ergometer (Ergometrics 800S; SensorMedics). The work rate increment (mean±SD 10.9±3.0 W·min^{-1}) was determined individually by the supervising respirologist (D.D. Marciniuk), who based this decision on clinical judgment using disease severity and exercise history. Heart rate and rhythm were recorded using a single-lead ECG monitor (43200A monitor; Hewlett Packard, Palo Alto, CA, USA). The arterial oxygen saturation ($S_{\mathrm{p,O_2}}$) was measured using pulse oximetry (Sat-Trak; SensorMedics). Expired gas was ducted into a calibrated metabolic cart (TrueOne; Parvomedics, Salt Lake City, UT, USA) and metabolic measurements were averaged every 30 s. The highest 30-s oxygen consumption ($V'_{\mathrm{O_2}}$) obtained on this test was accepted as $V'_{\mathrm{O_2,peak}}$.

Constant work rate exercise tests and measurements

A 5-min wash-in period was used for both room air and heliox mixtures. Spirometry was performed using a bag-in-box system connected to a dry-rolling spirometer (SensorMedics) similar to that used previously [8]. The constant work rate cycle ergometry test during room air and heliox breathing was performed at 80% (mean±SD 79.9±3.9%) of the peak work rate obtained on the GXT and was stopped at symptom limitation. Either room air or heliox was inspired from a ~60-L reservoir bag. Expired gas was ducted to the metabolic cart, which was

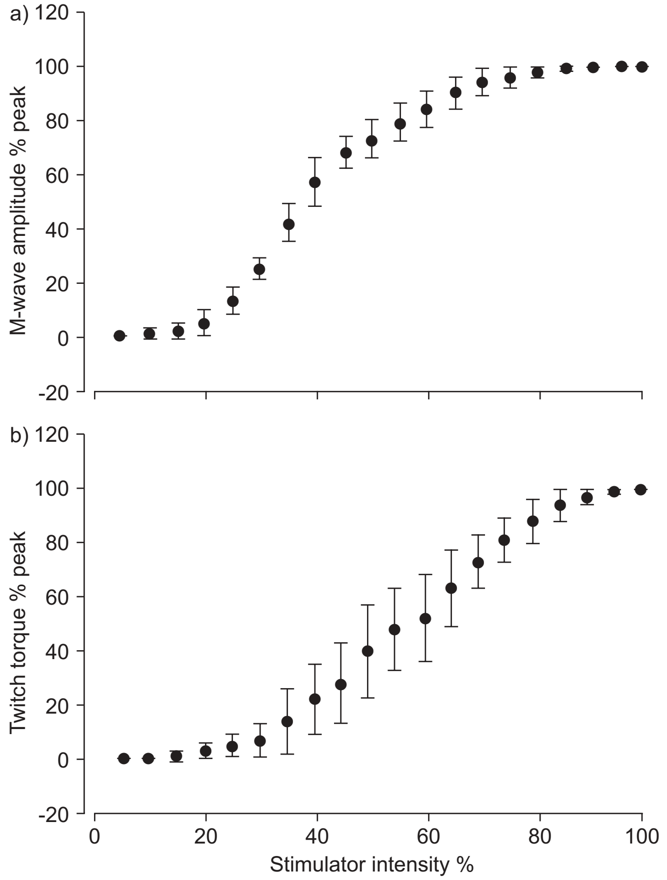

FIGURE 1. a) M-wave and b) resting twitch torque recruitment curves during progressive increases in magnetic stimulator intensity used to demonstrate supramaximality of the stimulator output. Data are presented as mean±SD.

calibrated for the gas mixture used. Inspiratory capacity (IC), tidal volume (V_{T}), V'_{E}, end-expiratory lung volume (EELV) and end-inspiratory lung volume (EILV) were measured using a bag-in-box system to estimate ventilatory constraint and dynamic hyperinflation [22]. Heart rate was recorded using telemetry (Polar USA Inc., Woodbury, NY, USA). Symptoms of dyspnoea and leg exertion were recorded using a Borg 10-point scale [23]. After each test, subjects were asked to identify the primary symptom limiting exercise.

Quadriceps measurements

Prior to each session and at 5, 10 and 20 min into recovery, right knee extension maximal voluntary contraction (MVC), interpolated twitch (ITT) [24, 25] and vastus lateralis twitch torque (TwVL) were obtained. Each subject was seated on an isokinetic dynamometer (System 3; Biodex Medical Systems Inc., Shirley, NY, USA) with the right thigh horizontal (~80° of hip flexion) and the knee flexed to ~90°. Straps were placed across the upper thigh to secure the legs to the dynamometer and ensure that torque generated was truly isometric. Using the dynamometer's isometric mode, maximal knee extension torque was averaged over ~1 s at peak torque and recorded during the MVC manoeuvres. After sufficient practice (to achieve reproducibility within 5%), each subject performed five MVC manoeuvres (30 s apart) and the highest value was recorded and used in the analysis. Subjects were provided with visual feedback of torque production and were encouraged to perform maximally.

Supramaximal muscle stimulation [26, 27] was applied over the right vastus lateralis motor point using a magnetic stimulator (Magpro R30; Medtronic Inc., Minneapolis, MN, USA) and parabolic coil (MMC 140; Medtronic Inc.) [28, 29]. The coil was placed over the approximate location of the vastus lateralis motor point then repeatedly stimulated the muscle at 50% of the stimulator output. Throughout these repeated stimuli, the position of the coil that produced the largest twitch torque was marked in permanent ink and replicated for all subsequent stimulations across each test day. Electromyographic (EMG) responses (M-waves) were recorded *via* bipolar surface Ag-AgCl electrodes (Vermed Medical Inc., Bellows Falls, VT, USA) placed over the belly of the right vastus lateralis muscle. Torque and EMG data were recorded at 2000 Hz using a custom program (LabView; National Instruments, Austin, TX, USA) and stored on a computer for analysis. At the beginning of each subject's testing protocol, M-wave and TwVL recruitment curves (fig. 1) were constructed from responses to 40 incremental stimuli. In all subjects, a maximal M-wave and twitch torque were obtained prior to reaching 100% of the stimulator's power output (mean±SD 83.4±9.6% and 92.1±7.2%, respectively). For the measurement of TwVL, the magnetic stimulator was set at 100% to evoke a supramaximal M-wave and twitch torque.

The ITT [24, 25] was performed on the last three MVC manoeuvres at each measurement point. Additionally, a resting TwVL was obtained 1–2 s after each of the above MVC manoeuvres in order to determine the contractile properties of the vastus lateralis. Voluntary activation was calculated as 100–(superimposed ITT/TwVL)×100% [25]. Through pilot data of scores for MVC and TwVL, excellent test–retest reliability was demonstrated using this technique (intra-class correlation coefficients 0.97 and 0.95, respectively).

The degree of contractile fatigue was measured as the per cent change from baseline in TwVL torque at each of the three testing times during recovery. Contractile fatigue was deemed to have occurred if post-exercise TwVL was $\leqslant$85% of baseline [4]. Subjects were divided into fatiguers (TwVL $\leqslant$85% of baseline on the room air test) and nonfatiguers (TwVL >85% of baseline on the room air test) for sub-analysis.

Analysis

One-way repeated-measures ANOVAs were used to determine differences between the three trials for end-exercise and muscle data. Pulmonary function data and exercise tolerance time were analysed using paired t-tests for room air and heliox. To examine the relationships between muscle, ventilatory, and exercise data, Pearson's correlation coefficients were used. Where significant correlations were found, stepwise multiple regression analysis was performed to identify independent predictors of important variables. Exercise responses, muscle strength and fatigue and ventilatory data for the room air, heliox, and isotime trials were analysed using one-way ANOVAs. Where significance was found in the ANOVAs, Tukey's honestly significant difference *post hoc* analysis was used to determine the individual group differences.

TABLE 2 Resting pulmonary function data breathing room air or heliox

	Room air	Heliox
FEV1 L	1.41±0.58	1.58±0.68*
FVC L	2.87±0.87	2.96±0.95
FEV1/FVC %	47.8±8.1	52.0±10.97*
PEFR $L \cdot s^{-1}$	6.40±2.64	7.94±3.38*
V'_E $L \cdot min^{-1}$	14.8±5.25	13.88±5.44
V_T L	0.90±0.38	0.79±0.36
f_R $breaths \cdot min^{-1}$	17.2±3.7	18.1±3.6
EELV % TLC	65.8±8.2	63.3±7.9
EILV %TLC	78.4±7.3	74.3±7.2

Data are presented as mean± SD. FEV1: forced expiratory volume in one second; FVC: forced vital capacity; PEFR: peak expiratory flow rate; V'_E: minute ventilation; V_T: tidal volume; f_R: respiratory frequency; EELV: end-expiratory lung volume; TLC: total lung capacity; EILV: end-inspiratory lung volume. *: $p<0.05$.

As a sub-analysis, fatiguers and nonfatiguers were compared using nonparametric statistics, due to the low sample size in each group. Mann–Whitney U-tests were used to compare the baseline subject characteristics, exercise responses and muscle strength and fatigue data. An α-value of <0.05 was considered significant for all analyses and *post hoc* tests. Data are presented as mean±SD unless specified.

RESULTS

Resting pulmonary function, ventilation and lung volumes

Table 2 shows the pulmonary function and ventilation data for both the room air and heliox tests. Heliox had a significant effect on FEV1 and peak expiratory flow rate ($p<0.05$) with no change in forced vital capacity (FVC), EELV, EILV or resting V'_E.

Exercise, ventilation and fatigue data

Individual exercise tolerance times and 5-min TwVL scores are presented in figure 2. Heliox increased exercise tolerance time by 53.1±40.5%, accompanied by a 14.5±11.8% decrease in 5-min TwVL ($p<0.05$). Selected exercise data are presented in table 3 and figure 3. Heliox also significantly decreased MVC, but did not change V'_E/MVV or V_T/IC at symptom limitation. There were no differences in perceptions of dyspnoea and leg exertion at symptom limitation. At isotime, compared with the room air test, heliox increased S_{p,O_2} and V_T/IC and decreased symptoms of dyspnoea and leg exertion, but maintained MVC and 5-min TwVL at levels similar to the room air test. There were no differences in voluntary activation across the three trials. EELV with heliox was reduced at isotime, but increased to a similar level at symptom limitation compared with the room air test (fig. 4).

Correlates

Change in exercise time between the room air and heliox tests was correlated with the 5-min TwVL during room air breathing ($r=0.79$, $p<0.05$; fig. 5a), change in FEV1 ($r=0.70$, $p<0.05$) and room air EILV ($r=0.68$, $p<0.05$). Stepwise linear regression revealed that only the 5-min TwVL was retained as an independent predictor of change in exercise time ($R^2=0.74$, $p<0.05$). Furthermore, 5-min TwVL was correlated with EELV ($r=0.77$, $p<0.05$; fig. 5b) and change in EELV from rest to peak exercise ($r=0.66$, $p<0.05$). Stepwise linear regression revealed that only EELV was retained as an independent predictor of 5-min TwVL ($R^2=0.78$, $p<0.05$). These results indicate that patients with the least muscle fatigue were more ventilation limited and increased their exercise tolerance to a greater degree with heliox. There were no significant correlations between exercise time, pulmonary function, muscle fatigue, ventilatory constraint or perceptions of dyspnoea and leg exertion.

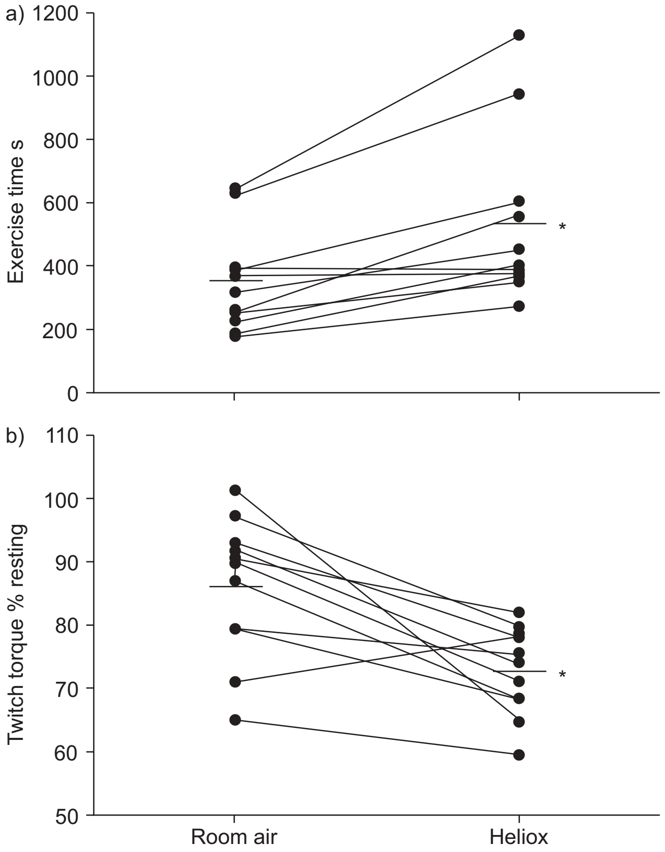

FIGURE 2. Individual data for a) exercise time and b) 5-min vastus lateralis twitch torque for the room air and heliox tests. *: $p<0.05$ *versus* room air.

Differences between fatiguers and nonfatiguers

Using criteria similar to SAEY *et al.* [4] for defining fatigue, it was noted that four out of the current 11 patients could be defined as fatiguers. There were no significant differences between fatiguers and nonfatiguers for age, height, weight, FVC, total lung capacity (TLC), $D_{L,CO}$, resting EELV, resting EILV, baseline MVC, $V'_{O_2,peak}$, $V'_{E,peak}$ or peak work rate on the GXT. The nonfatiguers had significantly lower resting FEV1 (44±15 *versus* 66±9%), higher EELV after room air constant work rate exercise (79±5 *versus* 67±2% of TLC) and greater change in constant work rate exercise time with heliox (77±26% *versus* 11±21%), compared with the fatiguers. Also, after room air exercise, inspiratory reserve volume was significantly less in the nonfatiguers (3.1±1.5 *versus* 13.6±0.6% of TLC), indicating that the nonfatiguers exhibited greater ventilatory constraint than the fatiguers on room air.

TABLE 3 Selected end-exercise results from the constant load exercise trials during room air, heliox at symptom limitation or heliox at isotime trials

	Room air	Isotime	Heliox
Tolerance time s	355±158	NA	530±270*
S_{p,O_2} %	88.7±5.0	92.1±3.0*	90.9±3.9
f_C beats·min^{-1}	128.0±14.7	125.5±17.3	131.2±18.5
f_R breaths·min^{-1}	33.9±6.7	31.7±7.1	35.4±9.8
V_T L	1.35±0.44	1.48±0.52	1.42±0.48
V'_E L·min^{-1}	45.6±15.1	45.9±16.2	50.3±19.8
V_T/IC %	80.9±10.7	73.5±10.2*	79.3±12.7
V'_E/MVV %	96.3±20.0	88.3±14.4	94.5±22.0
5-min MVC % baseline	99.0±18.5	99.6±12.0	90.8±10.3$^{*,+}$
5-min TwVL % baseline	85.7±11.0	84.1±11.0	72.4±7.0$^{*,+}$
5-min VA % baseline	103.8±11.2	101.7±5.6	99.9±6.9
Dyspnoea$^{\#}$	5.5±2.6	3.3±2.0*	5.8±2.9^{+}
Leg exertion$^{\#}$	5.2±2.7	3.6±1.7*	5.9±2.7^{+}
Reason for stopping			
Dyspnoea	6	NA	4
Leg exertion	5	NA	5
Both¶	0	NA	2

Data are presented as mean±SD or n. S_{p,O_2}: oxygen saturation; f_C: cardiac frequency; f_R: respiratory frequency; V_T: tidal volume; V'_E: minute ventilation; IC: inspiratory capacity; MVV: maximal voluntary ventilation; MVC: maximal voluntary contraction; TwVL: vastus lateralis twitch torque; VA: voluntary activation; NA: not available. $^{\#}$: divided by 10; ¶: dyspnoea and leg exertion. *: $p<0.05$ *versus* room air; $^{+}$: $p<0.05$ *versus* isotime.

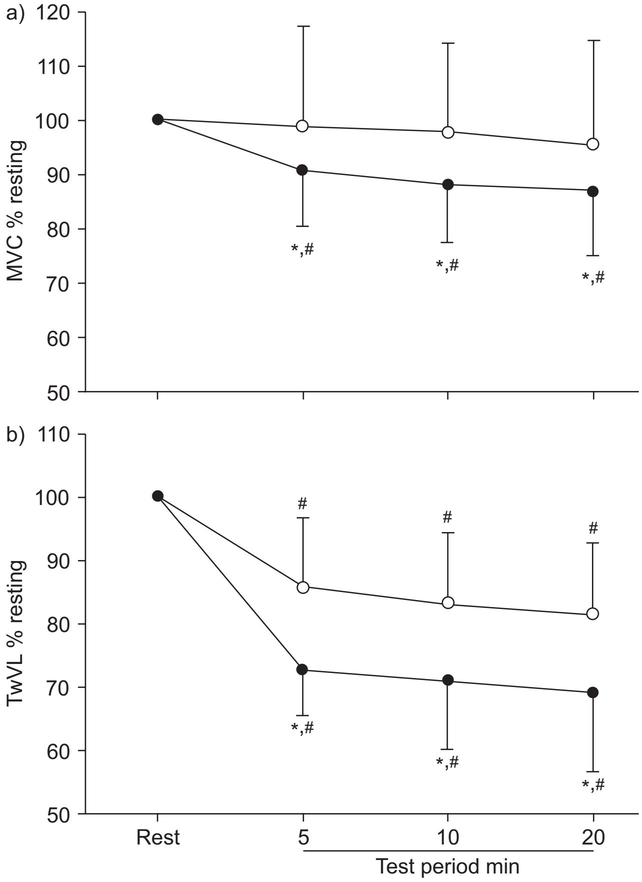

FIGURE 3. a) Maximal voluntary contraction (MVC) of quadriceps muscle and b) vastus lateralis twitch torque (TwVL) after the room air (○) and heliox (●) tests. Data are presented as mean±SD. *: $p<0.05$ *versus* room air; $^{\#}$: $p<0.05$ *versus* pre-test resting value.

DISCUSSION

The effect of changes in ventilatory constraint on leg muscle fatigue

The current findings indicate that, during room air breathing, increased ventilatory constraint was associated with lower levels of contractile muscle fatigue during high-intensity cycling exercise in patients with COPD. In addition, breathing heliox reduced ventilatory constraint, increased exercise time and increased vastus lateralis fatigue. This response was most pronounced in patients with greater ventilatory limitation and less initial leg fatigue, suggesting that those patients tended to be more limited by ventilatory constraint than by leg fatigue. The present results support the study hypotheses and suggest that the presence of a ventilatory limitation during cycling exercise impairs exercise prior to the attainment of a significant level of leg muscle fatigue. By delaying this ventilatory limitation with heliox, exercise capacity increases, which eventually leads to greater levels of leg muscle fatigue.

The present results support the findings of SAEY *et al.* [4], who examined the effect of ipratropium bromide on exercise tolerance and quadriceps muscle fatigue using a similar measure of contractile quadriceps fatigue. They demonstrated that patients who did not fatigue their leg muscles after 80% constant work rate cycling increased exercise tolerance and exhibited greater muscle fatigue with ipratropium (92% and 15% increases, respectively). These changes in muscle fatigue were similar in magnitude to the changes observed in the present study using heliox (15% increase in muscle fatigue), despite the fact that the current study subjects only increased exercise tolerance by 53% and had less severe COPD (FEV_1 52% *versus* 38% predicted, respectively). In the current study, a significant correlation between change in exercise time and 5-min TwVL was also demonstrated. As expected, this correlation supports the current authors' view and that of SAEY *et al.* [4], that lower levels of contractile muscle fatigue predict an increased change in exercise time with treatment of the ventilatory constraint. However, the current results are the first to demonstrate that this increase is also associated with significant changes in ventilatory constraint, and that there is a significant inverse relationship between the degree of ventilatory constraint and contractile muscle fatigue.

It is of interest that not all of the current study patients increased exercise tolerance and leg fatigue with heliox. Compared with the seven patients that did not meet the SAEY *et al.* [4] criteria for fatigue, the four who did had a tendency towards less severe disease, reduced EELV after room air exercise and increased exercise tolerance to a lesser degree, suggesting that they were more exercise limited by leg fatigue, rather than by ventilatory constraint. In addition, the seven nonfatiguers each had an inspiratory reserve volume of <6% of TLC, which has been shown to be indicative of impending ventilatory limitation [3], whereas the fatiguers each had an

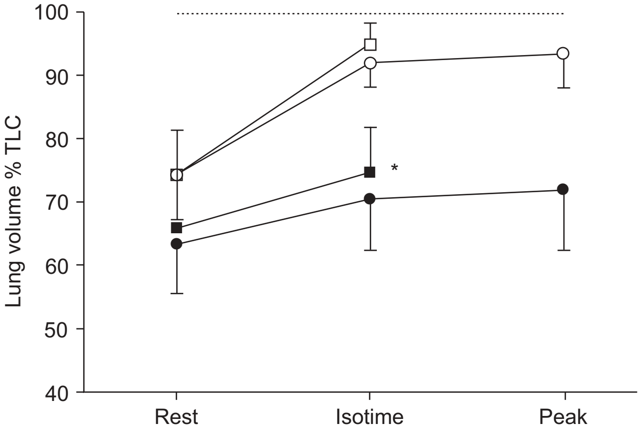

FIGURE 4. End-inspiratory lung volumes (☐ and ○) and end-expiratory lung volumes (■ and ●) as a percentage of total lung capacity (TLC; ·····) during the room air (☐ and ■) and heliox (○ and ●) trials at rest, at isotime and at peak exercise. Data are presented as mean ± SD. *: $p<0.05$ *versus* heliox at isotime.

inspiratory reserve volume of >13%, suggesting that the nonfatiguers were more ventilation limited. Further investigation is required to confirm this preliminary data.

Mechanisms of increased exercise tolerance with heliox

Similar to the study by PALANGE *et al.* [9], the current study showed that heliox reduced dynamic hyperinflation and increased exercise tolerance during cycling exercise in patients with COPD. PALANGE *et al.* [9] found that increased exercise tolerance with heliox was associated with both reduced dynamic hyperinflation and increased V'_E at peak exercise. In contrast, the current authors did not observe a significant increase in the peak exercise V'_E rate with heliox. The current finding may be due to the fact that the subjects had a response to heliox that was reduced in comparison with those studied by PALANGE *et al.* [9]. Despite a similar change in FEV_1 with heliox, the current study subjects increased exercise time by a mean of 53%, compared with the 114% observed by PALANGE *et al.* [9] using a similar exercise protocol. The patients studied by PALANGE *et al.* [9] were more severely obstructed than those in the present study (FEV_1 38% *versus* 52% predicted, respectively) and may have been more limited by ventilatory constraints. Nevertheless, it is apparent that, in the current study subjects, the increase in exercise tolerance with heliox was associated more with reduced dynamic hyperinflation than with increased V'_E.

Important observations in the present study were the decreased perceptions of both dyspnoea and leg fatigue at isotime with heliox. Although the primary outcome variables were physiological in nature, the associated perceptual changes could result in the patients ceasing exercise [1]. The reduction in both dyspnoea and leg exertion symptoms at isotime with heliox may be important reasons for subjects continuing to exercise beyond isotime.

Limitations

There are a few methodological considerations that may limit the generalisation of the current results. First, patients were recruited who were enrolled in a post-rehabilitation exercise programme. Exercise-experienced patients were selected in order to minimise the effects of fear and anxiety associated with dyspnoea that often limit exercise in patients who have not undergone exercise rehabilitation. It has been shown previously that rehabilitation decreases the degree of leg fatigue after exercise in patients with COPD [30]; therefore, it is possible that the results of the current study would have been different if patients who were not exercise-experienced had been studied.

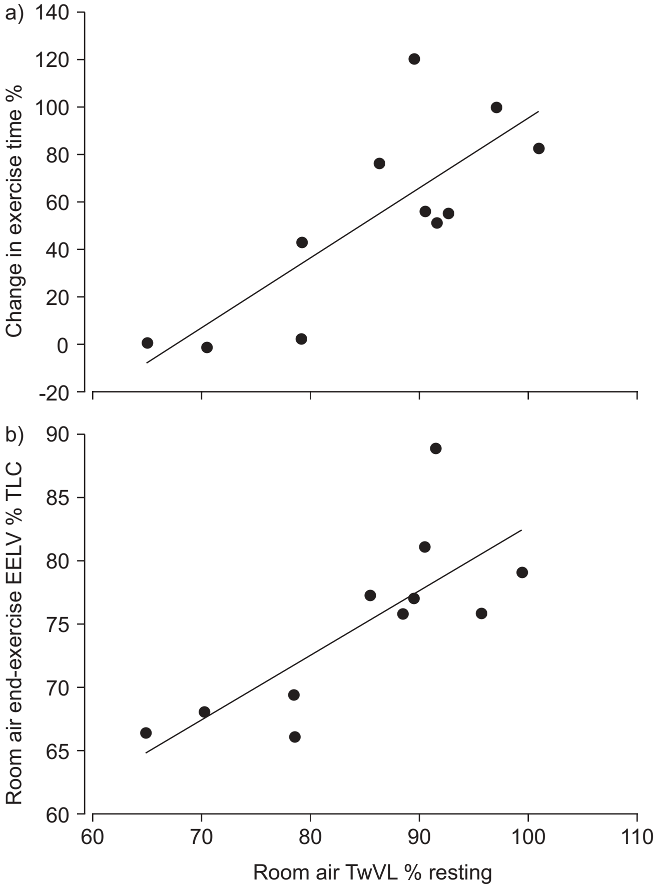

FIGURE 5. Correlation plots for a) change in exercise time and b) room air end-expiratory lung volume (EELV) at the end of exercise, *versus* 5-min vastus lateralis twitch torque (TwVL). TLC: total lung capacity. a) r=0.79; b) r=0.77.

Secondly, subjects were blinded to the gas mixture being breathed, but the study personnel were not. Due to the complexities of proper gas, pneumotach and spirometer calibration, and due to the nature of the exercise protocol, it was not possible to blind the study personnel. To compensate for this, standardised instructions were emphasised.

Thirdly, cycling was used as a mode of exercise in the current study. Walking may be a mode of exercise testing that better relates to functional activities in patients with COPD [31]; however, cycling is still used prominently as a testing and training modality. Heliox has also been shown to increase exercise tolerance during walking endurance tests [31, 32]; however, walking exercise results in lower levels of leg muscle fatigue than cycling exercise [33]. It is likely that the effects of heliox on walking performance would not result in significant levels of leg muscle fatigue. High-intensity cycling, however, may better reflect activities that recruit the leg muscles to a greater degree, such as stair climbing.

Fourthly, magnetic stimulation at the vastus lateralis motor point was used, rather than at the femoral triangle as has been previously reported [4, 16]. Based on pilot work, the current authors found that they were able to best demonstrate a plateau in isometric torque and M-wave amplitude at the motor point rather than the femoral triangle, and that this technique was more comfortable than femoral triangle stimulation [29]. A plateau in M-wave amplitude during progressive intensity motor stimulation is a critical criterion for fatigue studies, to ensure that stimulation is supramaximal [4, 25]. Supramaximal magnetic motor point stimulation has been used previously in other populations and has been shown to be valid and reliable [26–29]. The current authors were able to demonstrate an M-wave plateau in all of the study subjects during magnetic stimulation, and the TwVL measurements demonstrated excellent reliability; therefore, the technique appears to be appropriate.

Lastly, patients with a relatively wide range of disease severity were recruited. It was found that the subjects with the lowest FEV1 values also tended to be more limited by their ventilatory constraints than by leg fatigue. This finding suggests that, as disease severity increases throughout the course of a patient's disease, there is likely to be a gradual shift from being leg muscle fatigue limited after exercise to being progressively more ventilation limited. It is not clear whether findings would be similar if the study population were more homogeneous.

Conclusions

The present study demonstrated that, in patients with chronic obstructive pulmonary disease, there was an inverse relationship between the degree of contractile muscle fatigue and dynamic hyperinflation after high-intensity constant work rate exercise. Those patients who had greater levels of dynamic hyperinflation on room air also had less muscle fatigue. Patients with greater levels of dynamic hyperinflation were more likely to respond to the reduced ventilatory constraint due to heliox breathing by increasing exercise tolerance, which eventually caused greater contractile muscle fatigue. Researchers and clinicians should consider the relative balance between leg muscle and ventilatory limitation in each patient before prescribing therapies to reduce dynamic hyperinflation. In addition, future research should be directed toward understanding the importance of increasing leg muscle fatigue, through the use of heliox, in stimulating greater muscular adaptation to exercise training.

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