ERJ Express. Published on December 1, 2008 as doi: 10.1183/09031936.00014708

RELATIONSHIP BETWEEN VENTILATORY CONSTRAINT AND MUSCLE FATIGUE DURING EXERCISE IN COPD

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Dr. Butcher was supported by a Canadian Lung Association Fellowship.

Short Title : Hyperinflation and leg fatigue in COPD

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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.

Eleven patients with COPD (FEV_1 52%) 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 (r = - 0.77). Heliox increased exercise time (346s to 530s) and leg fatigue (15%). At isotime, there was no change in leg fatigue despite a reduction in EELV compared to end-exercise in both room air and heliox. The change in exercise time with heliox was best correlated with room air leg fatigue (r = - 0.79) and end-inspiratory lung volume (r = 0.68). Patients with COPD 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.

Key words: dynamic hyperinflation, exercise capacity, heliox, interpolated twitch, magnetic stimulation.

INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD) exhibit severe dyspnea 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 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 COPD patients [9].

Despite the well-established findings that many patients with COPD are primarily ventilatory limited, not all patients describe symptoms of dyspnea 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 recognized 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 to healthy age-matched adults [16] and this may be an important exercise-limiting factor [4]. Saey and colleagues studied the effects of a bronchodilator on exercise tolerance and quadriceps contractile fatigue [4]. They found

that patients who fatigued their leg muscles to a greater degree increased exercise tolerance less after breathing the bronchodilator despite significant improvements in pulmonary function [4]. Although Saey and colleagues [4] showed muscle fatigue to be an important limiting factor during exercise in COPD, they did not report measures of ventilatory limitation. Therefore, it is unknown if their patients with greater muscle fatigue were also ventilatory limited during exercise, and if 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 our knowledge, the relationship between measures of ventilatory limitation and leg muscle fatigue has not been reported. Therefore, the purpose of this study was to test the hypotheses that, in patients with COPD, a) higher levels of ventilatory limitation during exercise would be associated with less leg muscle fatigue and b) delaying ventilatory limitation with heliox would increase exercise tolerance and leg muscle fatigue. Some of the results of this study have been previously reported in the form of an abstract [17].

METHODS

Subjects

Eleven patients with COPD (Table 1) were recruited from the pulmonary rehabilitation program at the Centre for Lung Health, Edmonton, Alberta. All subjects had previously completed at least 8 weeks of exercise rehabilitation and had stable COPD at the time of the study. Post-rehabilitation patients were selected to minimize the fear/anxiety

associated with exercise-induced dyspnea that is common in exercise-inexperienced patients in order to increase the potential for a maximal physiologic 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 this study, which was approved by the University of Alberta Health Research Ethics Board.

Study design

We conducted a single-blinded, randomized, crossover trial. Subjects underwent pulmonary function testing and a graded exercise test (GXT) to symptom limitation on a cycle ergometer prior to the experiments (results in Table 1). Each subject then performed two randomized constant work rate cycling trials, breathing either room air (RA) or heliox (HE) and, finally, another heliox trial, but stopping at isotime on the RA test (ISO). Each test was separated by at least 48 hours.

Baseline pulmonary function

To confirm diagnosis and determine disease severity, each patient had a pulmonary function test (Vmax22, SensorMedics, Yorba Linda, CA) to American Thoracic Society standards [18] within three months of the study. Lung volumes were determined using a constant-volume body plethysmograph (6200 Autobox; SensorMedics). Spirometry and single breath diffusing capacity (D_LCO) were compared to the reported norms of Crapo et al. [19] and lung volumes were compared to those from Goldman and Becklake [20].

Maximal voluntary ventilation (MVV) was estimated by forced expiratory volume in one second (FEV_1) x 35 [21].

Graded exercise test (GXT)

The GXT to symptom limitation was performed on an electronically-braked cycle ergometer (Ergometrics 800S, SensorMedics). The work rate increment (mean 10.9 ± 3.0 $W \cdot min^{-1}$) was determined individually by the supervising Respirologist (DDM), 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). Oxygen saturation (SpO_2) was measured using pulse oximetry (Sat-Trak, SensorMedics). Expired gas was ducted into a calibrated metabolic cart (TrueOne, Parvomedics, Salt Lake City, UT) and metabolic measurements were averaged every thirty seconds. The highest 30 second oxygen consumption (VO_2) obtained on this test was accepted as VO_{2peak}.

Constant work rate exercise tests and measurements

A five minute 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, Yorba Linda, CA) similar to that used previously [8]. The constant work rate cycle ergometry test during RA and HE was performed at 80% (mean 79.9 ± 3.9%) of the peak work rate obtained on the GXT and was stopped at symptom limitation. Either RA or HE was inspired from a ~60L reservoir bag. Expired gas was ducted to the metabolic cart, which was calibrated for the gas mixture used. Inspiratory

capacity (IC), tidal volume (V_T), ventilation (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., CT). Symptoms of dyspnea 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 minutes into recovery, right knee extension maximal voluntary contraction (MVC), interpolated twitch (ITT) [24,25], and potentiated twitch (TwVL) were obtained. Each subject was seated on an isokinetic dynamometer (System 3, Biodex Medical Systems Inc. Shirley, NY) with the right thigh horizontal (approximately 80° of hip flexion) and the knee flexed to approximately 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 approximately one second at peak torque and recorded during the MVC maneuvers. After sufficient practice (to achieve reproducibility within 5%), each subject performed 5 MVC maneuvers (30 seconds 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.) 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) 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) and stored on a computer for analysis. At the beginning of each subject's testing protocol, M-wave and TwQL recruitment curves (Figure 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 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 maneuvers at each measurement point. As well, a resting potentiated twitch (TwVL) was obtained 1-2 seconds after each of the above MVC maneuvers to determine the contractile properties of the vastus lateralis. Voluntary activation was calculated as 100 – (superimposed ITT/TwVL) x 100% [25]. Through pilot data of scores for MVC and TwVL, we demonstrated excellent test-retest reliability using our technique (ICC = 0.97 and 0.95, respectively).

The degree of contractile fatigue was measured as the percent 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 equal to or less than 85% of baseline [4]. Subjects were divided into fatiguers (TwVL equal to or less than 85% of baseline on the room air test) and non-fatiguers (TwVL greater than 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 RA and HE. 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 RA, HE, and ISO trials were analysed using one-way ANOVAs. Where significance was found in the ANOVAs, Tukey's HSD post hoc analysis was used to determine the individual group differences. As a sub-analysis, fatiguers and non-fatiguers were compared using non-parametric 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 alpha value of <0.05 was considered significant for all analyses and post hoc tests. Data are presented as mean ± SD unless

specified. All analyses were completed using Statistica version 6.1 (StatSoft Inc, Tulsa, OK).

RESULTS

Resting pulmonary function, ventilation, and lung volumes

Table 2 shows the pulmonary function and ventilation data for both the RA and HE tests. Heliox had a significant effect on FEV_1 and peak expiratory flow rate ($p<0.05$) with no change in FVC, EELV, EILV, or resting minute ventilation.

Exercise, ventilation, and fatigue data

Individual exercise tolerance times and 5 minute 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 minute 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 dyspnea and leg exertion at symptom limitation. At isotime, compared to the RA test, heliox increased oxygen saturation, and V_T/IC, and decreased symptoms of dyspnea and leg exertion, but maintained MVC and 5 minute TwVL to similar levels as the RA 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 (Figure 4).

Correlates

Change in exercise time between the RA and HE tests was correlated with the 5 minute TwVL during room air breathing ($r = 0.79$, $p<0.05$), change in FEV_1 ($r = 0.70$, $p<0.05$) and room air EILV ($r = 0.68$, $p<0.05$). Stepwise linear regression ($R^2 = 0.74$, $p<0.05$) revealed that only the 5 minute TwVL was retained as an independent predictor of change in exercise time. As well, 5 minute TwVL was correlated with EELV ($r = 0.77$, $p<0.05$) and change in EELV from rest to peak exercise ($r = 0.66$, $p<0.05$). Stepwise linear regression ($R^2 = 0.78$, $p<0.05$) revealed that only EELV was retained as an independent predictor of 5 minute TwVL. These results indicate that patients with the least muscle fatigue were more ventilatory limited and increased exercise tolerance with heliox to a greater degree. There were no significant correlations between exercise time, pulmonary function, muscle fatigue, ventilatory constraint, or perceptions of dyspnea and leg exertion.

Differences between fatiguers and non-fatiguers

Using similar criteria for defining fatigue as Saey et al. [4], it was noted that 4 out of our 11 patients could be defined as fatiguers. There were no significant differences between fatiguers and non-fatiguers for age, height, weight, FVC, TLC, D_LCO, resting EELV, resting EILV, baseline MVC, VO_{2peak}, V_{Epeak}, or peak work rate on the GXT. The non-fatiguers had significantly lower resting FEV_1 (44 ± 15 vs 66 ± 9%), higher EELV after room air constant workrate exercise (79 ± 5 vs. 67 ± 2% of TLC), and greater change in constant workrate exercise time with heliox (77 ± 26% vs. 11 ± 21%) compared with the fatiguers. Also, after room air exercise, inspiratory reserve volume was significantly less in the non-fatiguers (3.1 ± 1.5 vs. 13.6 ± 0.6% of TLC) indicating the non-fatiguers

exhibited greater ventilatory constraint than the fatiguers on room air.

DISCUSSION

The effect of changes in ventilatory constraint on leg muscle fatigue

Our 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 leg fatigue. These results support our 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.

Our results support the findings of Saey and colleagues [4] who examined the effect of ipratropium bromide on exercise tolerance and quadriceps muscle fatigue using a similar measure of contractile quadriceps fatigue. These authors demonstrated that patients who did not fatigue their leg muscles after 80% constant work rate cycling increased exercise tolerance (92%) and exhibited greater muscle fatigue (15%) with ipratropium. 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 our

subjects only increased exercise tolerance by 53% and had less severe COPD (FEV_1 52% vs 38%, respectively). We also demonstrated a significant correlation between change in exercise time and 5 minute TwVL in our patients. As expected, this correlation supports our 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, our 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 our patients increased exercise tolerance and leg fatigue with heliox. Compared to the 7 patients that did not meet the Saey et al. criteria for fatigue, the 4 who did had a tendency toward 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 ventilatory constraint. In addition, the 7 non-fatiguers each had an inspiratory reserve volume of less than 6% of total lung capacity, which has been shown to be indicative of impending ventilatory limitation [3], whereas the fatiguers each had an inspiratory reserve volume of greater than 13%, suggesting the non-fatiguers were more ventilatory limited. Further investigation is required to confirm this preliminary data.

Mechanisms of increased exercise tolerance with heliox

Similar to Palange et al [9], we showed that heliox reduces dynamic hyperinflation and increases exercise tolerance during cycling exercise in patients with COPD. Palange et

al. [9] found that that increased exercise tolerance with heliox was associated with both reduced dynamic hyperinflation and increased V_E at peak exercise. In contrast, we did not observe a significant increase in the peak exercise V_E rate with heliox. Our finding may be due to the fact that our subjects had a reduced response to heliox than those studied by Palange and colleagues [9]. Despite a similar change in FEV_1 with heliox, our subjects increased exercise time by a mean of 53% compared to the 114% observed by Palange et al. [9] using a similar exercise protocol. Patients studied by Palange's group were more severely obstructed than those in the present study (FEV_1 38% vs 52% predicted, respectively), and may have been more limited by ventilatory constraints. Nevertheless, it is apparent that in our subjects, the increase in exercise tolerance with heliox was associated more with reduced dynamic hyperinflation than to increased V_E.

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

Limitations

There are a few methodologic considerations that may limit the generalization of these results. First, we recruited patients who were enrolled in a post-rehabilitation exercise program. Exercise-experienced patients were selected in order to minimize the effects of

fear and anxiety associated with dyspnea 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 this study would have been different if patients who were not exercise-experienced were studied.

Second, subjects were blinded to the gas mixture being breathed; however, 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, standardized instructions were emphasized.

Third, we used cycling as a mode of exercise in this 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 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.

Fourth, we used magnetic stimulation at the vastus lateralis motor point, rather than at the femoral triangle as has been previously reported [4,16]. Based on pilot work in our laboratory, we found that we 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]. We were able to demonstrate an M-wave plateau in all of our subjects during magnetic stimulation and our TwVL measurements demonstrated excellent reliability, therefore, we believe our technique to be appropriate.

Lastly, we recruited patients with a relatively wide range of disease severity. As such, we found that the subjects with the lowest FEV_1 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 a gradual shift from being leg muscle fatigue limited after exercise to being progressively more ventilatory limited. We are unsure if our findings would be similar if our study population were more homogeneous.

CONCLUSIONS

We demonstrated that, in patients with COPD, 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.

Acknowledgements

The authors would like to acknowledge the technical assistance of Ashley Ryniak and Megan Hudson, as well as the support of the patients and staff of the Centre For Lung Health, Edmonton, Alberta.

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Table 1. Subject demographics, baseline pulmonary function, and GXT results.

Males/Females	6/5
Age (years)	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_LCO (% pred)	80.1 ± 13.9
Room air MVC (Nm)	397.1 ± 193.8
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	14.2 ± 4.6
WR_{peak} (W)	80.9 ± 28.1
V_{Epeak} ($L \cdot min^{-1}$)	45.5 ±16.8
V_E/MVV (%)	91.2 ± 17.9
SpO_2 (%)	89.4 ± 5.1
Reason for stopping	
Dyspnea (n)	4
Leg exertion (n)	5
Both equally (n)	2

Data presented as mean ± SD. GXT = graded exercise test, FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, TLC = total lung capacity, D_LCO = diffusion capacity of the lung for carbon monoxide, MVC = maximal voluntary contraction, VO_{2peak} = peak oxygen consumption, WR_{peak} = peak work rate, V_{Epeak} = peak minute ventilation, SpO_2 = oxygen saturation

Table 2. Resting pulmonary function data breathing air (RA) or heliox (HE).

	RA	HE
FEV_1 (L)	1.41 ± 0.58	1.58 ± 0.68*
FVC (L)	2.87 ± 0.87	2.96 ± 0.95
FEV_1/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
RR (bpm)	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 presented as mean ± SD. *$p<0.05$. FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, PEFR = peak expiratory flow rate, V_E = minute ventilation, V_T = tidal volume, RR = respiratory rate, EELV = end-expiratory lung volume, EILV = end-inspiratory lung volume, TLC = total lung capacity.

Table 3. Selected end-exercise results from the constant load exercise trials during room air (RA), heliox at symptom limitation (HE), or heliox at isotime (ISO) trials.

	RA	ISO	HE
Tolerance time (s)	355 ± 158	N/A	530 ± 270*
SpO_2 (%)	88.7 ± 5.0	92.1 ± 3.0*	90.9 ± 3.9
HR (bpm)	128.0 ± 14.7	125.5 ± 17.3	131.2 ± 18.5
RR (bpm)	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 ($L \cdot min^{-1}$)	45.6 ± 15.1	45.9 ± 16.2	50.3 ± 19.8
VT/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
5min MVC (% baseline)	99.0 ± 18.5	99.6 ± 12.0	90.8 ± 10.3*†
5min TwVL (% baseline)	85.7 ± 11.0	84.1 ± 11.0	72.4 ± 7.0*†
5min VA (% baseline)	103.8 ± 11.2	101.7 ± 5.6	99.9 ± 6.9
Dyspnea (/10)	5.5 ± 2.6	3.3 ± 2.0*	5.8 ± 2.9†
Leg Exertion (/10)	5.2 ± 2.7	3.6 ± 1.7*	5.9 ± 2.7†
Reason for stopping Dyspnea (n)	6	N/A	4
Leg Exertion (n)	5	N/A	5
Both equally (n)	0	N/A	2

Data presented as mean ± SD. *$p<0.05$ vs RA, †$p<0.05$ vs ISO. SpO_2 = oxygen saturation, HR = heart rate, RR = respiratory rate, 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

FIGURE LEGENDS

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

FIGURE 2. Individual data for exercise time (A) and 5 minute vastus lateralis twitch torque (B) for the room air (RA) and heliox (HE) tests. *$p<0.05$ vs RA.

FIGURE 3. Voluntary quadriceps muscle torque (left) and vastus lateralis twitch torque (right) after the room air and heliox tests. *$p<0.05$ vs room air test, †$p<0.05$ vs pre-test resting value. Data presented as mean (SD).

FIGURE 4. Exercise lung volumes during the room air (RA), heliox (HE) trials at peak exercise and isotime. *$p<0.05$ vs HE at isotime. Data presented as mean (SD).

FIGURE 5. Correlation plots for change in exercise time (A) and room air end-expiratory lung volume at end of exercise (B) vs. 5 minute vastus lateralis twitch torque.

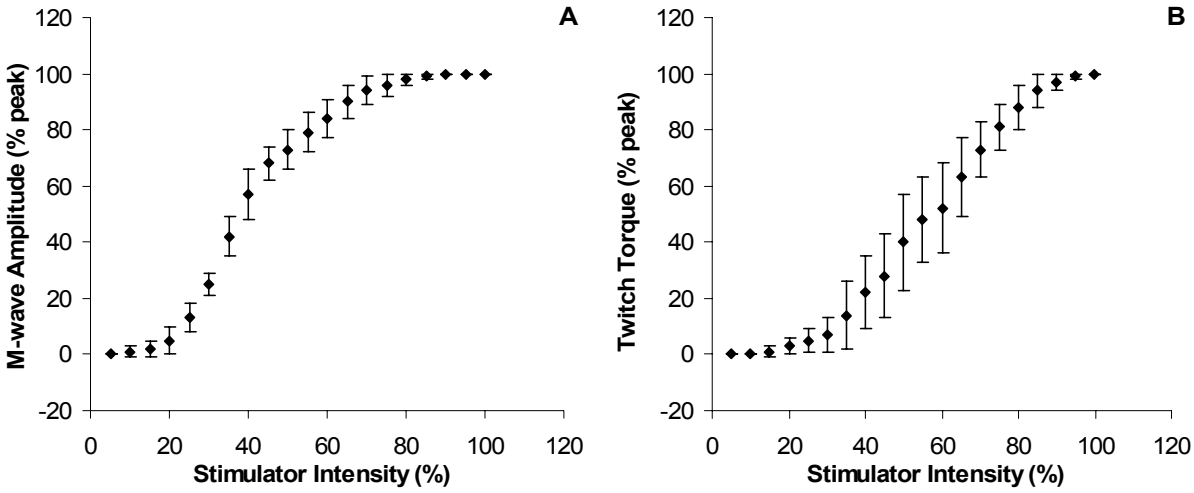
A
M-wave Amplitude (% peak)
120
100
80
60
40
20
0
-20
0
20
40
60
80
100
120
Stimulator Intensity (%)
B
Twitch Torque (% peak)
120
100
80
60
40
20
0
-20
0
20
40
60
80
100
120
Stimulator Intensity (%)

FIGURE 1.

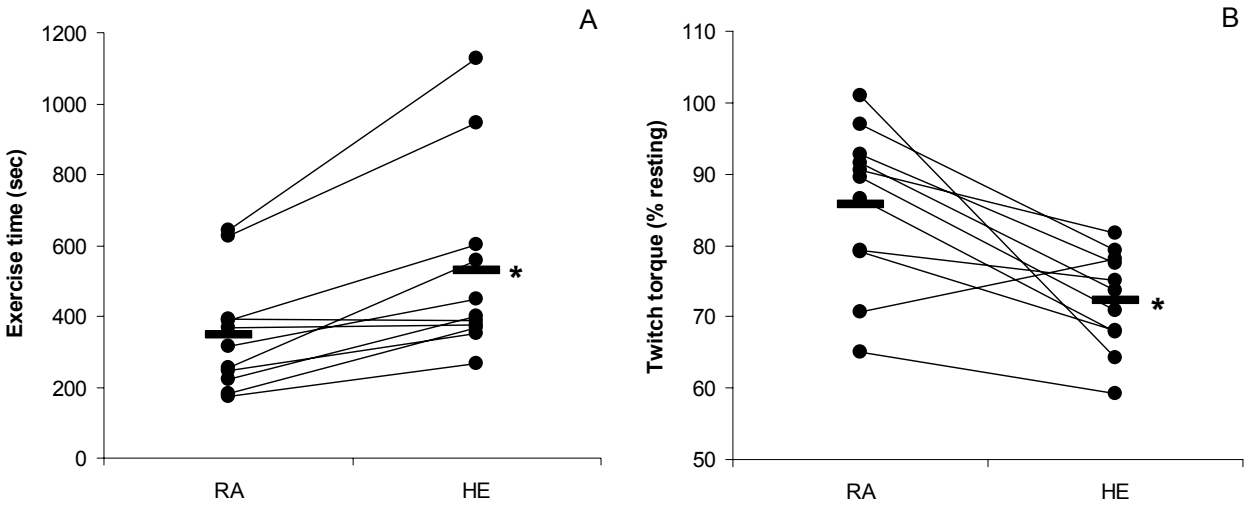
A
Exercise time (sec)
1200
1000
800
600
400
200
0
RA
HE
*
B
Twitch torque (% resting)
110
100
90
80
70
60
50
RA
HE
*

FIGURE 2.

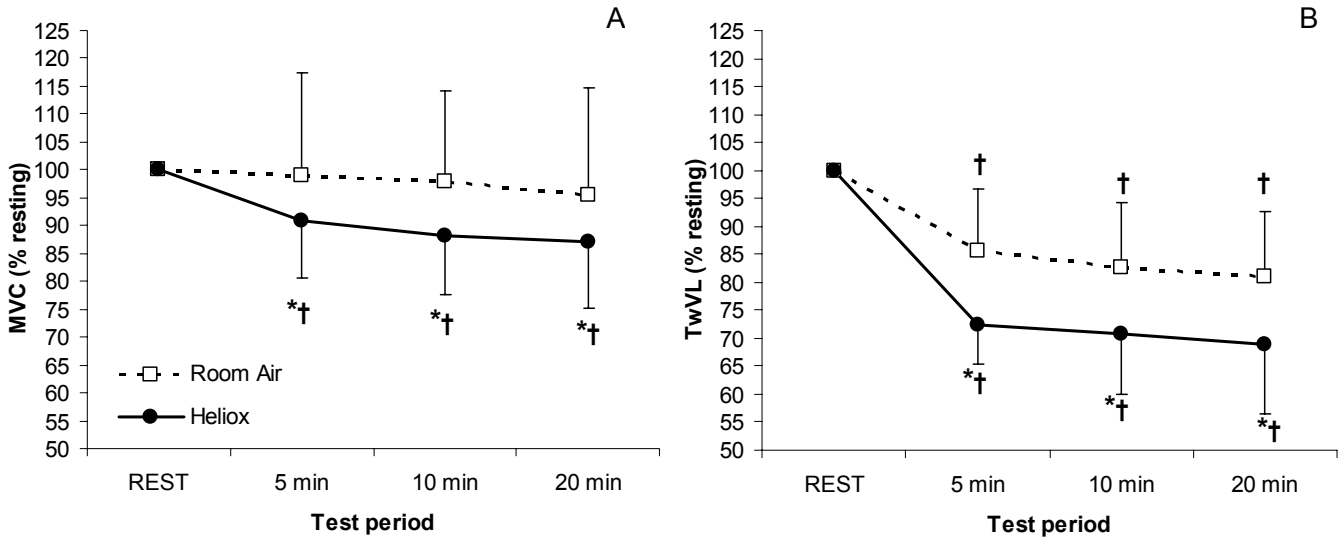
A
MVC (% resting)
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
*†
*†
*†
Room Air
Heliox
REST
5 min
10 min
20 min
Test period
B
TwVL (% resting)
†
†
†
*†
*†
*†
REST
5 min
10 min
20 min
Test period

FIGURE 3.

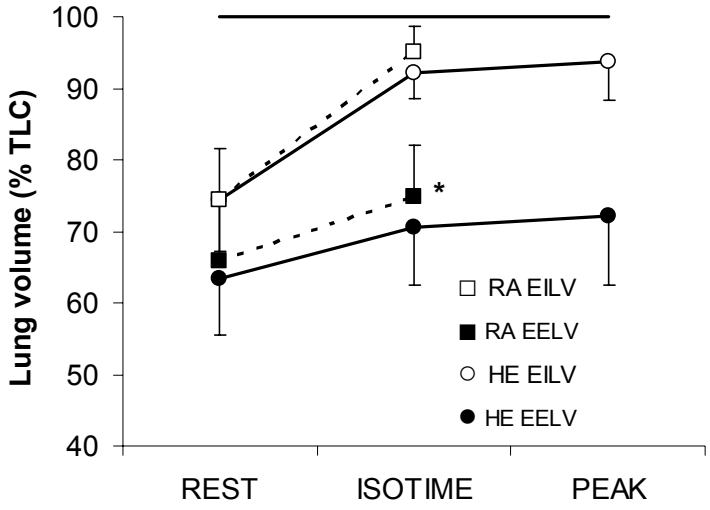
100
90
80
70
60
50
40
Lung volume (% TLC)
*
RA EILV
RA EELV
HE EILV
HE EELV
REST
ISOTIME
PEAK

FIGURE 4.

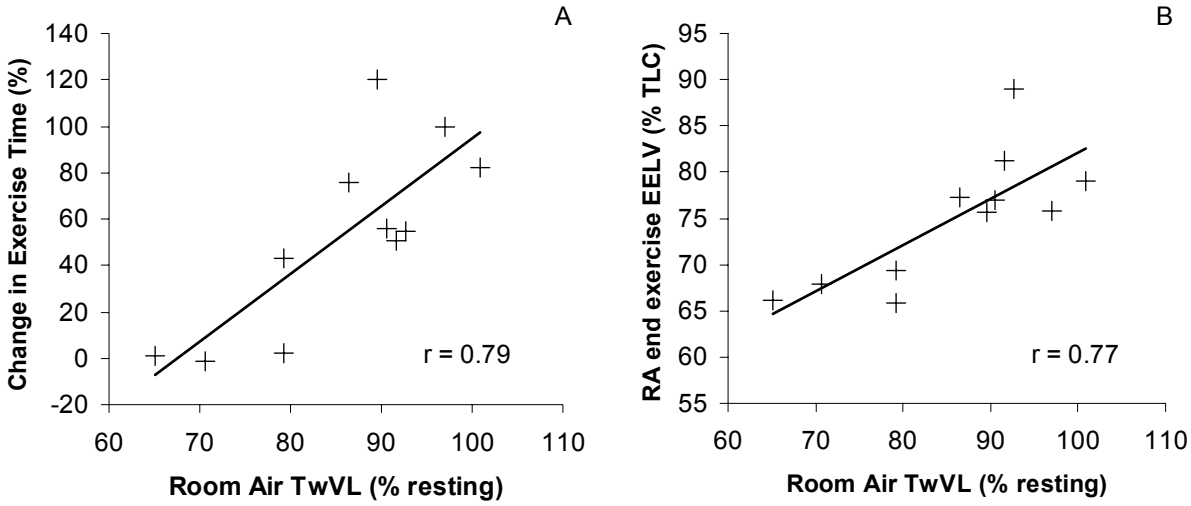
A
Change in Exercise Time (%)
140
120
100
80
60
40
20
0
-20
60
70
80
90
100
110
Room Air TwVL (% resting)
r = 0.79
B
RA end exercise EELV (% TLC)
95
90
85
80
75
70
65
60
55
60
70
80
90
100
110
Room Air TwVL (% resting)
r = 0.77

FIGURE 5.