Improvement in respiratory muscle O_2 delivery is associated with less dyspnoea during exercise in COPD

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To the Editor,

We previously demonstrated that compared to room air, both heliox and pure oxygen breathing increased inspiratory and expiratory muscle oxygen delivery (O_2DEL) and reduced dyspnoea sensations during constant-load exercise [1]. Taking into consideration that in COPD activity-related dyspnoea is exaggerated by exercise-induced respiratory muscle fatigue [2], we investigated the extent to which an improvement in respiratory muscle O_2DEL contributes to the mitigation of dyspnoea sensations during exercise.

We retrospectively analyzed data from our recently published work [1]. In [1], ten patients with COPD (FEV_1, 46±12% predicted), we simultaneously measured inspiratory (intercostals), expiratory (abdominal) and locomotor (vastus lateralis) muscle blood flow and O_2DEL during three constant-work rate exercise tests on a cycle ergometer (corresponding to 75% of peak work-rate) to the limit of tolerance whilst breathing: i) room air, ii) heliox (He: 0.79 and F_IO_2: O_2: 0.21) and iii) oxygen (F_IO_2: 1.0) -the latter two conditions were performed in balanced order- [1]. Dyspnoea sensations during exercise were assessed by the 0-10 Borg category-ratio scale. Exercise time was reported in [1] as significantly prolonged (by ~60%) during both heliox and oxygen breathing compared to room air. Data on heliox and oxygen breathing were analyzed at the same time-point (isotime) as at exhaustion in room air breathing. This ensured that the work of the locomotor muscles during cycling was identical between the three conditions. Shapiro-Wilk tests revealed that all data were normally distributed. Based on an expected effect size [p] of 0.76 that was calculated from the mean difference and the corresponding Standard Deviation of both intercostal and abdominal muscle O_2DEL between air and oxygen breathing at isotime, a sample size of 9 patients (using a correlation analysis, power of 0.80 and an alpha significance level of 0.05, 2-sided, calculated using GPower software, version 3.1) was deemed sufficient to address the objective of the study. Pearson

correlation coefficient analysis was performed to determine the associations between independent variables.

Exercise data expressed as absolute differences from room air during heliox and oxygen breathing are presented in Table 1. Interestingly, reductions in dyspnoea scores at isotime were each negatively correlated with increases in intercostals and abdominal muscle O_2DEL during both heliox and oxygen compared to room air (Figure 1), whilst weaker associations were found between increase in locomotor muscle oxygen O_2DEL and reductions in dyspnoea scores during both heliox and oxygen ($r= -0.53$, $p= 0.08$ and $r= -0.52$, $p= 0.09$ respectively). In addition, we found strong negative associations at isotime between the reductions in arterial lactate concentration and the improvement in intercostal and abdominal muscle O_2DEL whilst breathing heliox ($r= -0.84$ and $r= -0.78$, respectively, $p<0.001$) or oxygen ($r= -0.82$ and $r= -0.81$, respectively, $p<0.001$).

The present study expands what is known [3-5] by demonstrating that besides ventilatory constraints, limitation in both inspiratory and expiratory muscle O_2DEL during exercise may be associated with greater dyspnoea in COPD, whilst highlighting the sensitivity of the Borg scale to detect changes in physiological variables across different interventions. Importantly, our data shows that at a relatively similar minute ventilation (i.e., between room air and oxygen, Table 1), intensity of dyspnoea was lower for greater levels of respiratory muscle O_2DEL, thus providing convincing evidence for the role of respiratory muscle O_2DEL on dyspnoea relief during exercise in COPD. A neurobiologic model of dyspnoea in COPD reported by O'Donnell et al. [6] illustrated that neural inputs that reach the somatosensory cortex and contribute to dyspnoea, originate from the locomotor and respiratory muscles via the type III-IV afferents. Indeed, the study by Gagnon et al. [7], that investigated the potential mechanisms of dyspnoea in patients with COPD, demonstrated greater exercise tolerance and lower dyspnoea sensations when the signals from the lower limb muscle sensory afferents (type III-IV) were experimentally inhibited. The

underlying mechanism for our findings may be that an increase in respiratory muscle O_2DEL (by heliox and oxygen breathing) may have mitigated exercise-induced respiratory muscle fatigue [3] and thus muscle sensory afferent traffic in type III-IV nerves innervating the respiratory muscles [6]. In addition, the strong negative correlation that we found between the improvement in intercostal and abdominal muscle O_2DEL and the decrease in arterial blood lactate concentration further supports the notion of lower respiratory muscle fatigue both during heliox and oxygen breathing compared to room air. However, since arterial lactate increases are likely dominated by leg muscle lactate output, we cannot exclude the possibility that part of the relationship between dyspnoea and lactate is unrelated to respiratory muscle O_2DEL or part of reduction in dyspnoea is partially linked with reduction in respiratory muscle fatigue secondary to reduced respiratory muscle work [8] and improvement in lung mechanics following heliox and oxygen breathing (Table 1).

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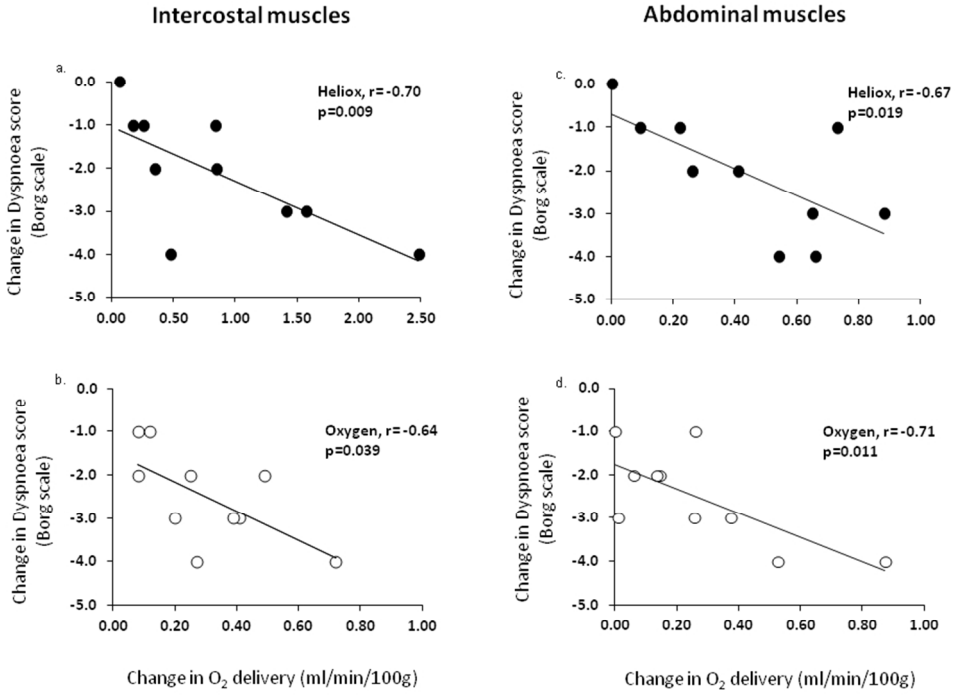
Table 1. Exercise data expressed as differences from air breathing.

Variables	Air	Heliox	100% Oxygen
Endurance time, s	406 ± 36	-	
	Exhaustion	Isotime†	Isotime†
V_E, l/min		+4.7 ± 0.6‡	-1.4 ± 0.4§
SaO_2, %		+4 ± 1‡	+11 ± 1‡§
IC, l		+0.227± 0.08‡	+0.080±0.01§
Ti, seconds		+0.27 ± 0.09‡	+0.28 ± 0.12‡
Ti/Ttot, %		+8 ± 2‡	+10 ± 3‡
Intercostal muscle blood flow, ml/min/100g		+4.3 ± 0.5‡	-0.3 ± 0.2§
Abdominal muscle blood flow, ml/min/100g		+2.3 ± 0.7‡	-0.2 ± 0.2§
Vastus Lateralis muscle blood flow, ml/min/100g		+6.9 ± 2.8‡	-0.1 ± 1.1§
Systemic arterial oxygen content, mlO_2/l		+8 ± 3‡	+42 ± 8‡§
Intercostal muscle O_2DEL, mlO_2/min/100g		+0.85 ± 0.24‡	+0.31± 0.10‡§
Abdominal muscle O_2DEL, mlO_2/min/100g		+0.45 ± 0.10‡	+0.28 ± 0.09‡
Vastus Lateralis O_2DEL, mlO_2/min/100g		+1.31 ± 0.34‡	+1.12 ± 0.41‡
Arterial lactate concentration, mmol/l		-1.21 ± 0.34‡	-1.58 ± 0.39‡
Borg dyspnoea scores		-2.0 ± 0.4‡	-2.5 ± 0.3‡

Exercise data during constant load exercise expressed as differences from air during heliox and 100% oxygen breathing. Values are expressed as means ± SEM for 10 subjects. V_E, minute ventilation; SaO_2, arterial oxygen saturation; IC, inspiratory capacity; Ti, time of inspiration; Ti/Ttot, duty cycle of inspiration; O_2DEL, oxygen delivery. † Isotime data are those obtained on normoxic heliox and 100% oxygen at the same time-point as at exhaustion on room air (i.e., 406 ± 36 sec). ‡ Denotes significant differences versus exhaustion in room air. § Denotes significant differences versus heliox.

Figure legend

Figure 1. Associations at isotime between the reductions (compared to room air breathing) in dyspnoea sensations and the improvement (compared to room air breathing) in respiratory (intercostal or abdominal) oxygen delivery whilst breathing heliox (a and c) and 100% oxygen (b and d). Data concern individual values of 10 patients. Regression coefficients and significance levels are given in each figure.



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