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Contrasting the physiological effects of heliox and oxygen during exercise in a patient with advanced COPD

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Case history

A 64-year-old man with a history of long-term cigarette smoking (>36 pack-years) and diagnosis of chronic obstructive pulmonary disease (COPD) (forced expiratory volume in 1s (FEV₁): 47% predicted; FEV₁/forced vital capacity: 61% predicted) was referred to an outpatient pulmonary rehabilitation programme [1]. The patient exhibited gas trapping at rest (residual volume/total lung capacity (TLC): 167% predicted; inspiratory capacity (IC)/TLC: 29%) and reported exertional dyspnoea at grade 3 on the 1-5 Medical Research Council scale [2]. The patient's medication included bronchodilators and inhaled steroids. The patient poorly tolerated the cardiopulmonary exercise test (sustained at 75% of his peak exercise capacity, WR_{peak}). This was demonstrated by substantially reduced endurance time (6 min 30 s), profound dynamic hyperinflation (reduction in IC from rest by 232 mL), moderate exertional hypoxaemia (arterial oxygen saturation measured by pulse oximetry (SpO₂) 87%) and reported severe breathlessness as the predominant reason for terminating exercise (*i.e.* score of 8 on the 1-10 Borg scale [3]) (table 1).

Question

How can we enhance patient's poor exercise tolerance during rehabilitation?

Answer

Testing procedures

The patient underwent two constant-load cycling exercise tests on two different days, each sustained at 75% WR_{peak} while breathing normoxic helium (helium 79% and oxygen 21%, heliox) or pure (100%) oxygen [4].

Ventilatory responses and symptoms

Table 1 presents the results of the exercise tests regarding ventilatory responses and symptoms scores. As expected, endurance time was prolonged during heliox and oxygen administration as compared to normoxia (by 64% and 72%, respectively). At isotime (*i.e.* data that were obtained on heliox or oxygen trials at the same time point as at the limit of tolerance in room air), V_E was greater compared to normoxia with heliox breathing secondary to greater V_T; during oxygen breathing V_E was lower compared to room air breathing due to a reduction in breathing frequency and V_T (table 1). Furthermore, IC, inspiratory time and duty cycle of inspiration were higher and V_T/IC ratio (an index of ventilatory reserves and V_T constraint) was lower during heliox or oxygen breathing compared with breathing room air. Dyspnoea and leg fatigue scores at isotime were lower on both heliox and oxygen breathing trials compared with normoxia.



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In COPD patients the ergogenic effect of heliox or oxygen breathing might be related both to improvements in ventilatory parameters (that lessen dyspnoea) and to enhanced oxygen delivery to respiratory and locomotor muscles <http://bit.ly/2JJBTc>

Central haemodynamic responses

Figure 1 presents the central haemodynamic responses during heliox and oxygen breathing. At isotime, while breathing heliox, cardiac output and systemic vascular conductance were greater compared with room air breathing (figures 1a and 1b). At rest and during exercise breathing oxygen, arterial oxygen content (CaO_2) was greater compared with normoxia (figure 1c). Accordingly, systemic oxygen delivery during both heliox and oxygen breathing was greater compared with room air breathing (figure 1d).

Respiratory and locomotor muscle haemodynamic and oxygenation responses

Figures 2 and 3 present the results of respiratory and locomotor muscle haemodynamic and oxygenation responses. At isotime, during heliox breathing, respiratory and locomotor muscle blood flow was greater compared with room air breathing (figure 2a-c). Furthermore, respiratory and locomotor muscle oxygen delivery during both heliox and oxygen breathing were greater (figure 2d-f) and the respiratory and locomotor muscle oxygen desaturation was lower compared

Table 1 Constant load exercise data at 75% WRpeak

Variables	Normoxia	Normoxic helium	100% oxygen
Endurance time s	390	640	670
	t_{lim}	Isotime	Isotime
V'E L·min⁻¹	43.7	48.6	37.4
V_T L	1.68	1.87	1.56
Breathing frequency breaths·min⁻¹	26	26	24
t_i s	0.69	0.99	0.98
t_i/t_{tot} %	34	43	46
ΔIC L	-0.232	0.080	-0.090
V_T/IC ratio	0.76	0.74	0.66
SaO₂ %	87	91	99
Borg dyspnoea score	8	5	5
Borg leg fatigue score	6	5	4

Isotime data are those obtained on normoxic heliox and 100% oxygen at the same time as at the limit of tolerance (t_{lim}) on room air. WRpeak: peak work rate at the preliminary incremental test in room air; V'E: minute ventilation; V_T: tidal volume; t_i: inspiratory time; t_i/t_{tot}: duty cycle of inspiration; ΔIC: change in IC from baseline; SaO₂: arterial oxygen saturation.

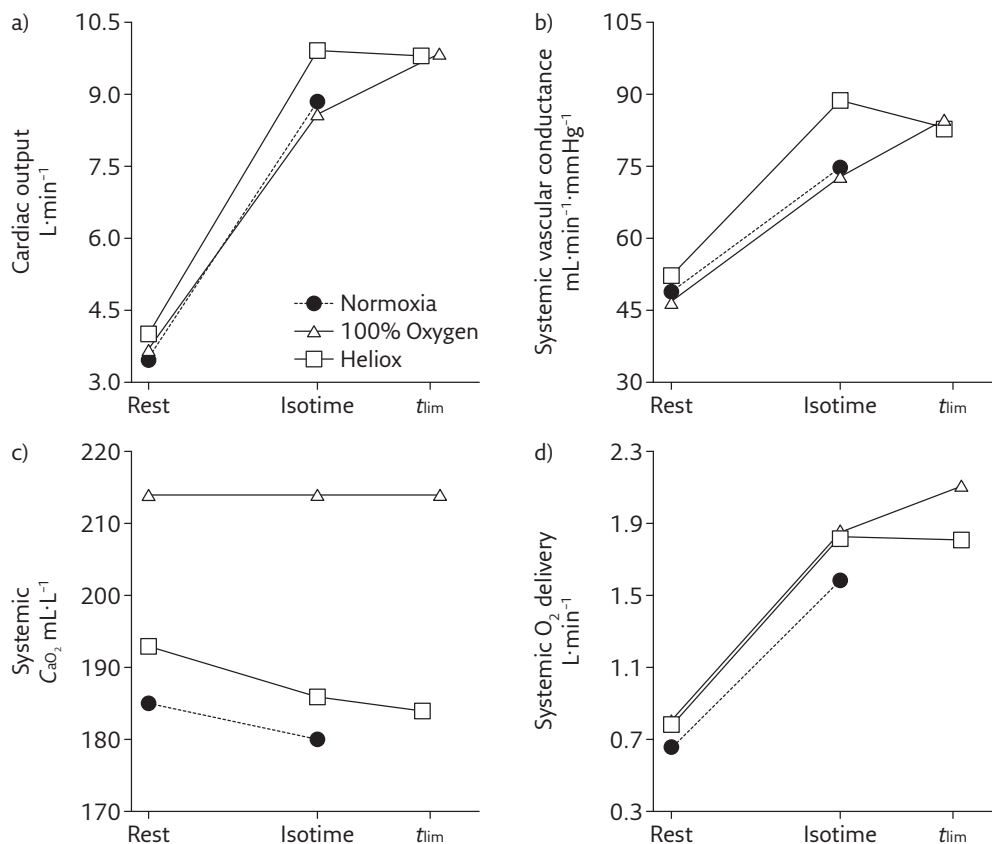


Figure 1 Central haemodynamic responses. a) Cardiac output; b) systemic vascular conductance; c) systemic CaO_2 ; and d) systemic oxygen delivery recorded at rest, at the time of exhaustion in room air (isotime), and at the limit of exercise tolerance (t_{lim}) while breathing normoxic heliox, pure (100%) oxygen or room air. Isotime data are those obtained on normoxic heliox or 100% oxygen at the same time as at the limit of exercise tolerance on room air.

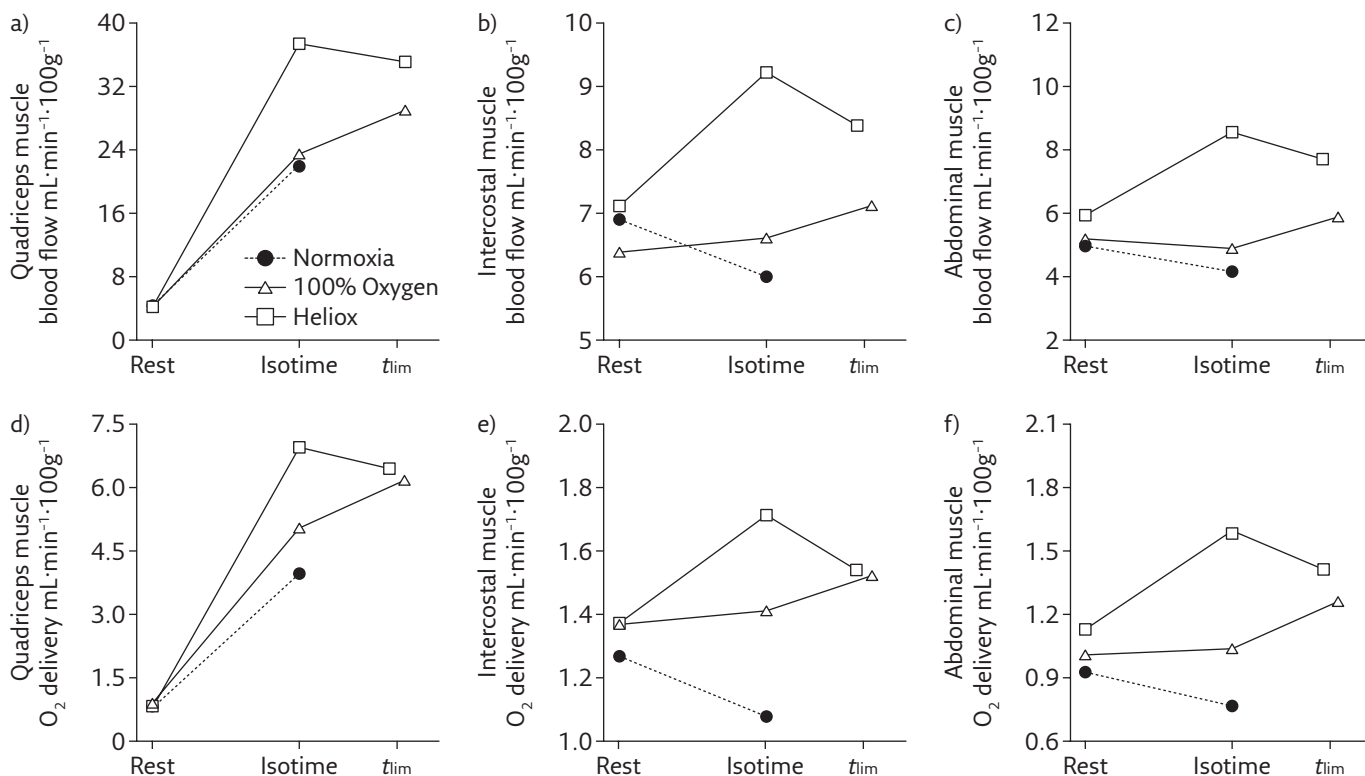


Figure 2 Quadriceps, intercostal, and abdominal muscle haemodynamic responses. a) Quadriceps muscle blood flow; b) intercostal muscle blood flow; c) abdominal muscle blood flow; d) quadriceps muscle oxygen delivery; e) intercostal muscle oxygen delivery; and f) abdominal muscle oxygen delivery recorded at rest, at the time of exhaustion in room air (isotime), and t_{lim} breathing normoxic heliox, pure (100%) oxygen or room air. Isotime data are those obtained on normoxic heliox or 100% oxygen at the same time as at the limit of exercise tolerance on room air.

with room air breathing (figure 3a–c). In addition, arterial lactate concentration during both heliox and oxygen breathing was lower than room air breathing (figure 3d).

Discussion

Summary of the physiological effects of heliox and oxygen breathing during exercise

Collectively the findings indicate that the increase in endurance time during heliox or oxygen breathing can be attributed to a number of physiological adjustments associated with improvements in respiratory, cardiovascular and muscle cellular metabolic responses. The improvement in ventilatory response was accompanied by lower dyspnoea and leg fatigue perceptions during both supplementations (table 1) and by a lower degree of reduction in respiratory (both inspiratory and expiratory) and locomotor muscle oxygen saturation compared with room air (figure 3). Increases in respiratory and locomotor muscle oxygen availability by heliox and oxygen administration were due to higher systemic oxygen delivery (figure 1) albeit for different reasons; namely, greater cardiac output and local muscle perfusion with heliox administration (figures 1 and 2) and higher

arterial oxygen concentration with oxygen breathing (figure 1). In conclusion, along with the alleviation of ventilatory constraints by heliox and oxygen breathing compared with room air (table 1) [5], a common basis for enhanced endurance time by heliox or oxygen administration is the improved respiratory and locomotor muscle oxygen delivery and reduced metabolic acidosis and sensations of breathlessness and leg discomfort afforded by both interventions (figure 4) [4].

Heliox and oxygen breathing on reducing dyspnoea during exercise

As far as dyspnoea is concerned, an interesting observation in this case is the fact that heliox and oxygen acted differently on the reduction of exertional dyspnoea. Specifically, during exercise, heliox increased \dot{V}_E (by shifting the operating lung volumes downward) but oxygen decreased \dot{V}_E compared with room air breathing (table 1) [4–9]. Nevertheless, during both interventions the patient reported less shortness of breath (table 1), either through making him breathe less (with oxygen) or making him breathe more but with less constraints (heliox). Indeed, heliox supplementation as an ergogenic strategy is based on the idea that a lighter gas mixture could be moved to and from the lung airways more easily than atmospheric air [6, 7].

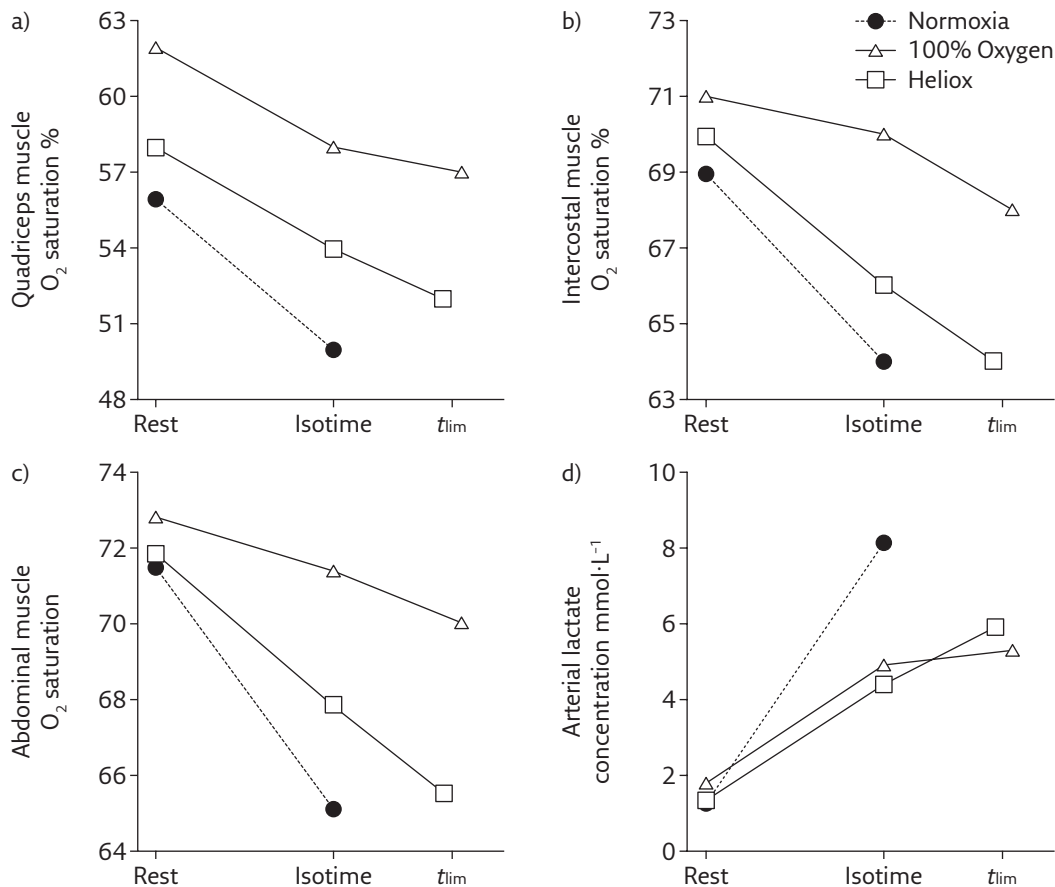


Figure 3 Quadriceps, intercostal, and abdominal muscle oxygenation responses and metabolic responses. a) Quadriceps muscle oxygen saturation; b) intercostal muscle oxygen saturation; c) abdominal muscle oxygen saturation; and d) arterial lactate concentration recorded at rest, at the time of exhaustion in room air (isotime), and t_{lim} while patient breathed normoxic heliox, pure (100%) oxygen or room air. Isotime data are those obtained on normoxic heliox or 100% oxygen at the same time as at the limit of exercise tolerance on room air.

Heliox reduces turbulent airway resistance and both inspiratory and expiratory pressures during exercise as compared with room air breathing [8, 9]. Due to these effects, the patient demonstrated higher \dot{V}_E , less dynamic hyperinflation (expressed as change in IC from rest) and improved cardiac function during exercise when compared to room air breathing (table 1 and figure 1) [4, 9–11].

However, it is known that oxygen administration primarily increases arterial oxygen concentration but also lessens \dot{V}_E (table 1) and ventilatory drive, potentially *via* inhibition of carotid bodies and/or improved metabolic conditions of the skeletal muscles (manifested by increases in intracellular pressure of oxygen and concentrations of phosphocreatine and a reduction in intracellular concentrations of inorganic phosphate) [5, 10, 12]. The effects of oxygen supplementation on operating lung volumes (end-inspiratory and end-expiratory lung volumes), \dot{V}_I , breathing pattern and exercise induced-dynamic hyperinflation might be more pronounced in hypoxaemic patients as compared to normoxic or to patients with mild arterial oxygen desaturation [13–15]. Furthermore, it has been postulated that patients who exhibit a reduction in dynamic hyperinflation in response

to oxygen breathing appear to have greater airway obstruction, greater ventilatory constraints during exercise and poorer exercise performance with steeper dyspnoea/ventilation slopes as compared to their counterparts [12, 16]. Therefore, it can be argued that during exercise hypoxaemic patients might experience greater reduction in dyspnoea sensations in response to reductions in \dot{V}_E following oxygen administration [12, 15].

Heliox and oxygen breathing: central and local haemodynamic responses during exercise

The mechanisms orchestrating the ergogenic effect of heliox and oxygen breathing on exercise capacity were not limited to the alleviation of ventilatory constraints during exercise. The results from this case and other studies suggest that extrapulmonary improvements could potentially alleviate exercise induced-dyspnoea in patients with COPD [17, 18]. Furthermore, during heliox and oxygen breathing the patient exhibited improved respiratory and locomotor muscle metabolic condition as indicated by the smaller

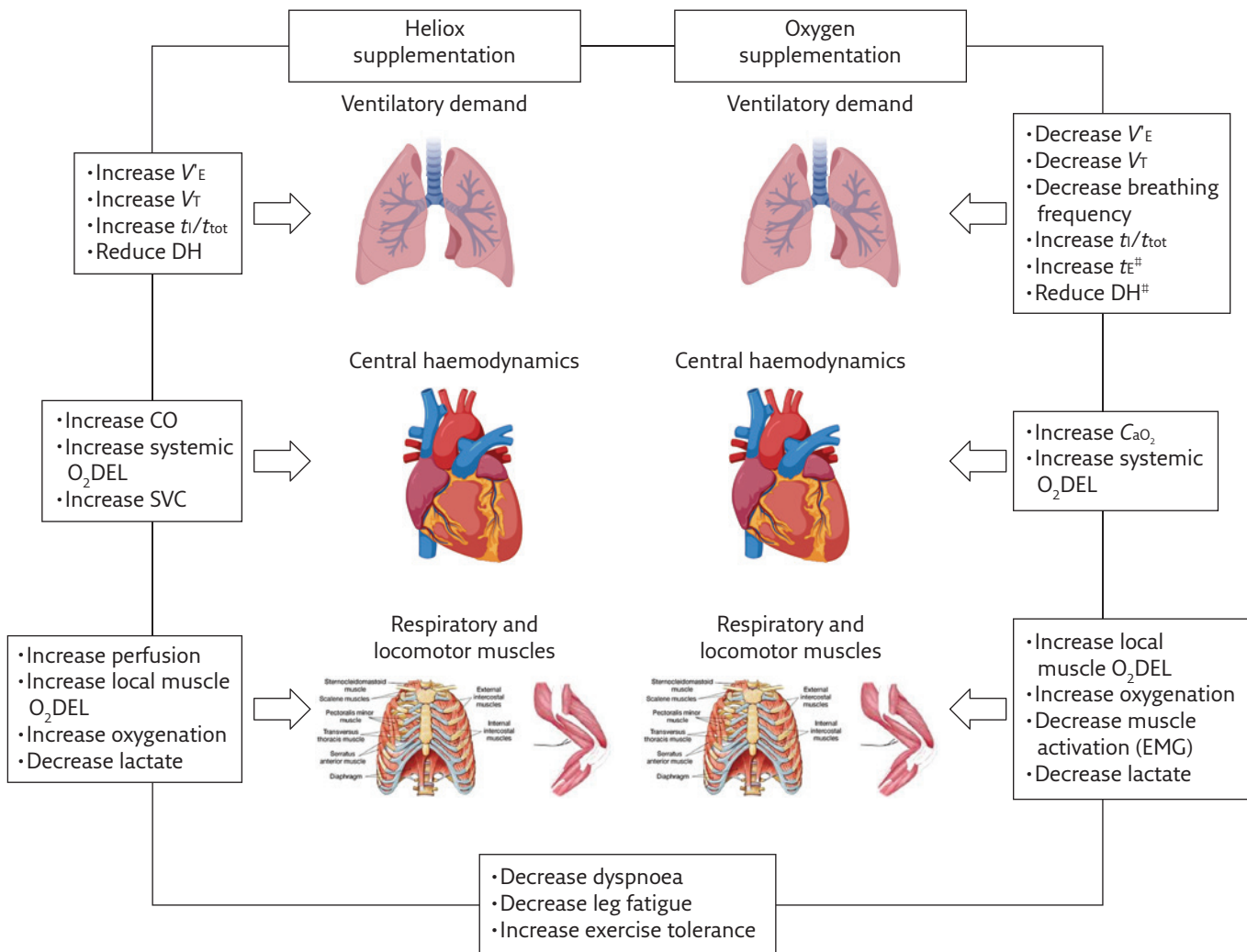


Figure 4 A schematic representation conceptualising the acute physiological responses a patient with COPD exhibits during exercise breathing heliox or oxygen compared with exercise in room air. t_E : expiratory time; DH: dynamic hyperinflation; CO: cardiac output; O_2DEL : oxygen delivery; SVC: systemic vascular conductance; EMG: electromyography. \ddagger : profoundly in hypoxaemic patients. Figure partially created using BioRender.

decrease in local muscle oxygenation that was accompanied by less lactic acidosis as compared with room air (figure 3). These beneficial effects are of critical importance when considering that exercise-induced respiratory and leg muscle fatigue can contribute to the increase in dyspnoea perceptions [19, 20]. Indeed, in the neurobiological model of dyspnoea proposed by DEMPSEY *et al.* [19] neural inputs that reach the somatosensory cortex and contribute to dyspnoea sensations originate from the locomotor and respiratory muscles *via* the group III-IV muscle afferents. During exercise in room air, a restriction in oxygen delivery to the respiratory and locomotor muscles occurs due to the inability of the circulatory system to fully satisfy their energy demands [21]. This, in turn, could exaggerate both respiratory and locomotor muscle fatigue and thus further increase dyspnoea perceptions during exercise. Furthermore, during heliox and oxygen breathing the greater increase in respiratory and locomotor muscle oxygen delivery compared with room air may have postponed

exercise-induced skeletal muscle fatigue and thus alleviated muscle sensory afferent traffic in type III-IV nerves innervating the respiratory and locomotor muscle, also contributing to the reduction in dyspnoea sensations (table 1). In addition, reductions in ventilatory drive with oxygen breathing in patients with COPD during exercise have been associated with reduced peripheral chemoreceptor afferent activity [22]. Importantly, GOSSELIN *et al.* [23] demonstrated that oxygen supplementation can reduce quadriceps muscle electromyogram activity at any given work rate compared with exercise in room air.

In summary, the beneficial effects of supplemental heliox and oxygen on respiratory and locomotor muscle metabolic and muscle contractile function would be expected to delay the onset of lactic acidosis accompanied by improvements in dyspnoea, leg discomfort and exercise tolerance in patients with COPD. In support of this notion, significant associations between the improvement

in respiratory muscle oxygen delivery and the lower lactic acidosis and dyspnoea perceptions reported during exercise while breathing heliox or oxygen compared with room air were recently demonstrated [24]. A conceptual representation of the effect of heliox and oxygen breathing during exercise is presented in figure 4.

Clinical perspectives and future directions

Over the past two decades a number of research studies have documented that acute administration of heliox and oxygen prolongs endurance cycling time or walking distance during the 6-min walk test (6MWT) and shuttle walking tests [25–27]. Heliox and oxygen supplementation have been shown to increase peak exercise capacity during cycling compared with breathing air [28]. Evidence does also support the ergogenic effect of heliox and oxygen breathing on exercise capacity during small mass exercise (*i.e.* leg knee extension) [29]. Nevertheless, it has been shown that not all patients with COPD can benefit from heliox supplementation. The noticeable effects of heliox breathing on exercise capacity may be more pronounced in those patients exhibiting more severe airflow obstruction and a greater degree of ventilatory limitation during exercise [25, 30].

The increase in the concentration of oxygen (helium-hyperoxia) in the inhaled gas (*i.e.* 72%He–28%O₂, 70%He–30%O₂ or 60%He–40%O₂) has shown to have an additive effect, leading to more advantageous improvement in exercise capacity (*i.e.* shuttle walking, 6MWT or constant-load cycling) than those observed with oxygen or heliox alone in patients with mild-to-moderate arterial hypoxaemia during exercise [25–27]. Specifically, an optimal combination of helium and oxygen, such as 60%He–40%O₂, has been demonstrated to greater reduce the resistive work of breathing and the work to overcome intrinsic positive end-expiratory pressure compared with hyperoxia (*i.e.* nitrogen 60% and oxygen 40%) or heliox (helium 79% and oxygen 21%) alone [26]. In addition, by inspiring helium-hyperoxia gas mixture, patients' S_aO₂ was significantly higher than on heliox and comparable to that during hyperoxia, thus further justifying the advantages of using helium-hyperoxia gas mixture in the clinical setting in patients with COPD [26]. By contrast, supplemental oxygen can improve exercise capacity and dyspnoea sensations in patients with or without exercise-induced hypoxaemia. Furthermore, it has been documented that the plateauing effect of oxygen on improving exercise tolerance, operational lung volumes and inspiratory flows and dyspnoea ratings in non-hypoxaemic COPD patients is optimal at inspiratory oxygen fractions of 0.5 [31].

Evidence from randomised controlled trials [25, 32–34], that investigated whether breathing heliox and oxygen administration during rehabilitative

Self-evaluation questions

- 1) Compared with room air, heliox and oxygen breathing increase exercise endurance time in patients with COPD by which of the following mechanism(s)?
 - a) Lessening the ventilatory constraints
 - b) Improving cardiac output
 - c) Improving respiratory and locomotor muscle oxygen delivery
 - d) a and b
 - e) a and c
- 2) Which of the following statements best reflects the acute physiological responses during exercise while breathing heliox or oxygen in COPD?
 - a) Both heliox and oxygen improve cardiac output and arterial oxygen content
 - b) Heliox improves cardiac output, local muscle perfusion and oxygen arterial oxygen content
 - c) Both heliox and oxygen improve cardiac output and muscle oxygen delivery
 - d) Both heliox and oxygen improve muscle perfusion and arterial oxygen content
- 3) Concerning dyspnoea perceptions in patients with COPD during exercise, which of the following statement(s) is/are correct?
 - a) Heliox reduces turbulent airway resistances and oxygen reduces \dot{V}_E during exercise as compared to room air
 - b) Heliox and oxygen improve local muscle oxygenation during exercise and reduce arterial lactate concentration compared with room air
 - c) Improving respiratory and locomotor muscle oxygen delivery by heliox and oxygen supplementation might postpone exercise-induced muscle fatigue

exercise could enhance physiological training effects in patients with COPD, suggested that the improvement may be apparent only when heliox and oxygen allow a higher training load to be applied than the standard practice of rehabilitation with medical air [35]. In this context, a recent study by ALISON *et al.* [36], investigated whether supplemental oxygen during an 8-week supervised exercise training programme (intervention group) was more effective than room air training (sham group) in improving exercise, functional capacity and quality of life in patients with COPD. Despite the significant increase in exercise capacity and quality of life that was observed following the exercise training period in both groups, the study did not reveal greater benefits during training with supplemental oxygen compared with room air. The oxygen breathing group did not achieve a greater training dose per session than the room air group despite significantly lower dyspnoea and perceived exertion scores that were reported during training sessions. Nevertheless, if the progression of training intensity was standardised to elicit the same level of dyspnoea and/or rate of perceived exertion as in the room air group, this potentially might have

resulted in greater functional and clinical benefits in the oxygen training group.

Conclusion

In patients with COPD the ergogenic effect of heliox or oxygen breathing might be related not

only to improvement in ventilatory parameters that contribute to lessen dyspnoea but also to enhanced oxygen delivery to respiratory and locomotor muscles. Rehabilitative exercise training interventions using heliox or oxygen supplementation should focus on increasing training intensity for achieving greater physiological training benefits.

Key points

- The prolonged exercise time that patients with COPD exhibit while breathing heliox or oxygen, compared with room air, are attributed to a number of physiological adjustments that include a decrease in dynamic hyperinflation, metabolic acidosis and thus sensations of breathlessness and leg discomfort.
- Increase in oxygen delivery to the respiratory and locomotor muscles by heliox and oxygen administration compared with room air are attributed to different mechanisms; namely, greater cardiac output and skeletal muscle perfusion with heliox breathing and higher arterial oxygen concentration with oxygen breathing.
- Increase in respiratory and locomotor muscle oxygen delivery by heliox or oxygen supplementation is accompanied by improved skeletal muscle metabolic conditions, which are reflected by greater muscle oxygen saturation and lower arterial lactate concentration during exercise.
- Decrease in dyspnoea perceptions during exercise whilst breathing heliox or oxygen can be due to the decrease in respiratory and locomotor muscle fatigue and sensory afferent traffic in type III-IV nerves, secondary to the increase in respiratory and locomotor muscle oxygen delivery.

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Author contributions

Both authors contributed to the content, writing and final approval of the manuscript.

Conflict of interest

None declared.

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Suggested answers

- 1) e.
- 2) b.
- 3) a, b, c.