



Cerebral cortex oxygen delivery and exercise limitation in patients with COPD

Ioannis Vogiatzis^{*,#}, Zafeiris Louvaris^{*,#}, Helmut Habazettl^{†,‡},
Vasileios Andrianopoulos^{*}, Harrieth Wagner[§], Charis Roussos^{*},
Peter D. Wagner[§] and Spyros Zakynthinos^{*}

ABSTRACT: In healthy humans, cerebral oxygen desaturation during exercise affects motor unit recruitment, while oxygen supplementation enhances cerebral oxygenation and work capacity. It remains unknown whether in patients with chronic obstructive pulmonary disease (COPD), the well-documented improvement in exercise tolerance with oxygen supplementation may also be partly due to the increase in cerebral oxygenation.

Using near infrared spectroscopy, we measured both frontal cerebral cortex blood flow (CBF) using indocyanine green dye and cerebrovascular oxygen saturation (St_{O_2}) in 12 COPD patients during constant-load exercise to exhaustion at 75% of peak capacity. Subjects exercised while breathing air, 100% oxygen or normoxic heliox, the latter two in balanced order.

Time to exhaustion while breathing air was less than for either oxygen or heliox (mean \pm SEM 394 ± 35 versus 670 ± 43 and 637 ± 46 s, respectively). Under each condition, CBF increased from rest to exhaustion. At exhaustion, CBF was higher while breathing air and heliox than oxygen (30.9 ± 2.3 and 31.3 ± 3.5 versus 26.6 ± 3.2 mL·min⁻¹ per 100 g, respectively), compensating for the lower arterial oxygen content (Ca_{O_2}) in air and heliox, and leading to similar cerebral cortex oxygen delivery (CQO_2 for air was 5.3 ± 0.4 , for oxygen was 5.5 ± 0.6 and for heliox was 5.6 ± 1.0 mL O₂ per min per 100 g). In contrast, end-exercise St_{O_2} was greater while breathing oxygen compared with air or heliox (67 ± 4 versus 57 ± 3 and $53 \pm 3\%$, respectively), reflecting Ca_{O_2} rather than CQO_2 .

Prolonged time to exhaustion by breathing oxygen and heliox, despite these having a similar CQO_2 to air, a lower St_{O_2} with heliox than oxygen, and yet similar endurance time and similar St_{O_2} in air and heliox despite greater endurance with heliox, do not support the hypothesis that an improvement in cerebral cortex oxygen availability plays a contributing role in increasing exercise capacity with oxygen or heliox in patients with COPD.

KEYWORDS: Cerebral blood flow, chronic obstructive pulmonary disease, exercise, near-infrared spectroscopy

In patients with chronic obstructive pulmonary disease (COPD), exercise intolerance is multifactorial [1], involving respiratory-mechanical [2], pulmonary gas exchange [3], haemodynamic [4] and peripheral muscle abnormalities [5]. These abnormalities may ultimately prevent adequate oxygen transfer from the atmosphere to, and/or utilisation of oxygen by, the mitochondria [6]. The importance of reduced arterial oxygen transport as a factor limiting exercise tolerance in COPD patients has been illustrated by studies where supplemental oxygen prevented exercise-induced arterial hypoxaemia, reduced ventilatory requirement and dyspnoea sensations, and improved leg

muscle oxygen delivery and utilisation, thereby enhancing exercise tolerance [7–9].

Studies in healthy subjects have shown that reduction in cerebral oxygenation, secondary to arterial hypoxaemia, may play a role in the subject's decision to terminate exercise in hypoxia [10–13]. In this context, a recent study by our group in healthy subjects revealed that during maximal hypoxic exercise, frontal cerebral cortex blood flow (CBF) was insufficient to offset the lower arterial oxygen content and, as such, at exercise exhaustion frontal cerebral cortex oxygen delivery (CQO_2) was lower compared with normoxia [14]. These

AFFILIATIONS

^{*}Dept of Critical Care Medicine and Pulmonary Services, Evangelismos Hospital, M. Simou and G.P. Livanos Laboratories,

[#]Dept of Physical Education and Sport Sciences, National and Kapodistrian University of Athens, Athens, Greece.

[†]Institute of Physiology, Charité Campus Benjamin Franklin,

[‡]Institute of Anesthesiology, German Heart Institute, Berlin, Germany.

[§]Dept of Medicine, University of California San Diego, La Jolla, CA, USA.

CORRESPONDENCE

I. Vogiatzis
Dept of Critical Care Medicine and Pulmonary Services
Evangelismos Hospital
M. Simou and G.P. Livanos
Laboratories
3 Ploutarhou Str.
10675 Athens
Greece
E-mail: gianvog@phed.uoa.gr

Received:

Jan 26 2012

Accepted after revision:

April 09 2012

First published online:

May 03 2012

This article has supplementary material available from www.erj.ersjournals.com

findings were taken to indicate that a critical reduction in CQO_2 in hypoxia compared with normoxia could constitute the signal limiting exercise performance, because cerebral oxygen desaturation during exercise is known to affect motor unit recruitment, while oxygen supplementation enhances cerebral oxygenation and work capacity [15].

Oxygen supplementation is also known to enhance exercise capacity in patients with COPD [7, 16]. Enhanced exercise performance has been attributed to the alleviation of ventilatory constraints, improved oxygen delivery to locomotor muscles and reduced perceptions of breathlessness and leg discomfort [1–5]. Whether improvement in exercise tolerance with oxygen supplementation in patients with COPD may also be partly due to the increase in cerebral oxygenation [15] currently remains unknown.

Accordingly, the present study aimed to investigate whether oxygen supplementation substantially improves CQO_2 , thus potentially constituting a contributing factor to enhanced exercise capacity in COPD. We applied two methods known to increase exercise tolerance by increasing systemic oxygen delivery in COPD, *i.e.* pure oxygen supplementation [7–9] and normoxic heliox breathing [17–19]. The former increases oxygen delivery mainly by increasing arterial oxygen content [7], whereas the latter does so mainly by improving blood flow [18, 19]. It was reasoned that if, at exhaustion of exercise while breathing room air, CQO_2 was significantly lower compared with that while breathing pure oxygen or normoxic heliox, this would suggest that, as in healthy subjects [20], an improvement in cerebral cortex oxygen availability may play a contributing role in increasing exercise capacity in patients with COPD.

METHODS

Subjects

12 patients with clinically stable COPD participated in the study according to the following inclusion criteria: 1) a post-bronchodilator forced expiratory volume in 1 s (FEV_1) $<60\%$ predicted without significant reversibility ($<12\%$ change of the initial FEV_1 value or <200 mL); 2) optimal medical therapy according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) [21] and 3) moderate hypoxaemia (arterial blood oxygen saturation $<93\%$ but $>84\%$) in room air during preliminary exercise testing. Exclusion criteria included clinically manifest cor pulmonale, cardiovascular illness, musculoskeletal abnormalities or other diseases that could contribute to exercise limitation. The study was approved by the University Evangelismos Hospital Ethics Committee and was conducted in accordance with the guidelines of the Declaration of Helsinki. Prior to participation in the study, all patients gave written, signed, informed consent.

Experimental design

Experiments were conducted in two visits. During visit 1, patients performed a preliminary incremental exercise test to the limit of tolerance while breathing room air (peak work rate (WR_{peak})) to establish the work rate corresponding to 75% of peak. During visit 2, patients underwent three constant-load exercise tests at 75% WR_{peak} to the limit of tolerance (*i.e.* exhaustion), initially breathing room air and then breathing in a balanced sequence of either pure oxygen or normoxic heliox (replacement of inspired nitrogen by helium). The three exercise

tests during visit 2 were separated by 120 min of rest. During constant-load exercise, CBF (assessed by near-infrared spectroscopy (NIRS) using the light-absorbing tracer indocyanine green (ICG) dye), as well as cardiac output (also assessed by ICG dye dilution) [18], were measured at rest and at the limit of tolerance (online supplementary material). As endurance time was expected to be significantly prolonged while breathing either pure oxygen or normoxic heliox [7–9, 17–19], measurements during these trials were also performed at the time-point where exercise in room air was terminated (*i.e.* at isotime) in order to detect whether potential differences in CQO_2 at isotime could, in part, explain differences in endurance time while breathing oxygen or heliox. NIRS was also used to continuously record frontal cortex cerebrovascular oxygen saturation (St_tO_2) as an indication of cerebral cortical oxygen availability (online supplementary material) [12–14].

Subject preparation

During visit 2, subjects were prepared with catheters inserted using local anaesthesia and sterile technique into the right radial artery and forearm vein. The catheters were used to collect blood samples and to inject ICG and sample blood after each injection for cardiac output measurements (online supplementary material).

Cardiac output

Cardiac output was determined by the dye dilution method, using known volumes of ICG (1.0 mL at 5 mg·mL⁻¹) injected into the right forearm vein followed by a rapid 10-mL flush of isotonic saline. Blood was withdrawn from the right radial artery using an automated pump (Harvard Apparatus, Holliston, MA, USA) at 20 mL·min⁻¹ through a linear photodensitometer (Pulsion ICG; ViCare Medical, Birkerød, Denmark) connected to a cardiac output computer (Waters CO-10; Waters, Rochester, MN, USA) through a closed-loop, sterile tubing system, as described and referenced in detail in the online supplementary material.

CBF and St_tO_2 by NIRS

To measure CBF, one set of NIRS optodes was placed on the skin over the left frontal cortex region of the forehead, secured using double-sided adhesive tape. A special net headset was used to hold the NIRS probe firmly attached over the frontal cortex region. The optode separation distance was 4 cm, corresponding to a penetration depth of ~ 2 cm. Optodes were connected to a NIRO 200 spectrophotometer (Hamamatsu Photonics KK, Hamamatsu, Japan), which was used to measure ICG concentration following the same 5-mg bolus injection of ICG in the right forearm vein used for cardiac output assessment, as described in detail in the online supplementary material.

St_tO_2 was assessed continuously throughout the whole testing period by the same NIRO 200 spectrophotometer as used for the measurement of CBF and described in detail in the online supplementary material.

Blood analysis and calculations

Arterial oxygen tension ($P_{\text{a}}\text{O}_2$) and arterial carbon dioxide tension ($P_{\text{a}}\text{CO}_2$), pH, haemoglobin concentration and arterial oxygen saturation ($\text{S}_{\text{a}}\text{O}_2$) were measured from 2-mL blood samples using a blood gas analyser combined with a co-oximeter (ABL 625; Radiometer, Copenhagen, Denmark) within

a few seconds of collection. Arterial oxygen content (C_{a,O_2}) was computed using the formula ($C_{a,O_2}=(1.34 \times Hb \times S_{a,O_2})+(0.003 \times P_{a,O_2})$), where Hb is haemoglobin.

Statistical analysis

Data are presented as mean \pm SEM, unless otherwise stated. Sample size capable of detecting between-condition (*i.e.* room air, and pure oxygen) difference of 20% was estimated for the change in CQO_2 at exhaustion using the standard deviations from our previous study in healthy subjects [14]. The minimum sample size was calculated to be 10 patients based on 80% power, and a two-sided value of 0.05 was considered to be significant. One-way ANOVA with repeated measures was used to identify statistically significant differences across the three exercise tests at isotime or at exhaustion, and across different time-points (rest, isotime and exhaustion) within each constant-load exercise test. When ANOVA detected statistical significance, pair-wise differences were identified using Tukey's honestly significant difference *post hoc* procedure. The level of significance was set at $p < 0.05$.

RESULTS

Subjects characteristics and exercise capacity

Patients had moderate-to-severe airway obstruction with increased static lung volumes, substantial reductions in carbon monoxide diffusion capacity and moderately reduced resting P_{a,O_2} (table 1). Three patients were GOLD stage II, six were GOLD stage III, and the remaining three were GOLD stage IV. Subjects exhibited reduced maximal exercise capacity with moderate haemoglobin desaturation (table 2). During constant-

load exercise at 75% WR_{peak} , time to exhaustion while breathing air was less than for oxygen or heliox (mean \pm SEM 394 ± 35 versus 670 ± 43 and 637 ± 46 s, respectively; $p < 0.001$ for both) (table 3).

Central haemodynamic responses

Cardiac output was similar at rest during room air, oxygen or heliox breathing, and during exercise increased from rest in all three conditions ($p < 0.001$). Cardiac output was greater at exhaustion during exercise in air ($p = 0.04$) and at isotime breathing heliox ($p = 0.04$) compared with isotime while breathing pure oxygen. However, cardiac output at exhaustion did not differ between air, oxygen or heliox breathing (fig. 1a). At rest, C_{a,O_2} was lower in room air compared with oxygen ($p < 0.001$) and heliox breathing ($p = 0.01$), and it was lower during heliox compared with pure oxygen breathing ($p < 0.001$). During exercise, C_{a,O_2} did not change from rest while breathing pure oxygen, whereas it decreased compared with rest during room air and heliox breathing ($p < 0.05$). C_{a,O_2} was lower at exhaustion in air compared with isotime during both oxygen ($p < 0.001$) and heliox breathing ($p = 0.01$); at this isotime, C_{a,O_2} was lower during heliox compared with oxygen breathing ($p < 0.001$). Furthermore, at exhaustion, C_{a,O_2} was lower in air compared with oxygen ($p < 0.001$) and heliox ($p = 0.01$), and it remained lower while breathing heliox compared with oxygen breathing ($p < 0.001$) (fig. 1b). Systemic oxygen delivery was similar at rest during room air, oxygen or heliox breathing, and during exercise increased from rest in all three conditions ($p < 0.001$). Systemic oxygen delivery did not differ across the three conditions at isotime; however, at exhaustion, systemic oxygen delivery was greater ($p = 0.002$) in oxygen compared with both air and heliox breathing (fig. 1c).

Frontal cerebral cortex haemodynamic and oxygenation responses

CBF was similar at rest in room air, oxygen and heliox, and significantly increased from rest across all three conditions ($p < 0.001$). CBF was greater at exhaustion in air ($p = 0.03$) and at isotime while breathing heliox ($p = 0.02$) compared with isotime while breathing oxygen. Similarly, at exhaustion, CBF in oxygen was lower than in heliox ($p = 0.03$) and air ($p = 0.04$) breathing (fig. 2a). CQO_2 was similar at rest in air, oxygen and heliox, and

TABLE 1 Pulmonary function data

Age yrs	66 \pm 5
Height cm	169 \pm 9
Weight kg	73 \pm 14
BMI kg·m ⁻²	25.5 \pm 4.1
FFMI kg·m ⁻²	17.7 \pm 2.6
FEV ₁ L	1.2 \pm 0.4
FEV ₁ % pred	42.2 \pm 12.9
FVC L	2.7 \pm 0.7
FVC % pred	71.2 \pm 17.2
TLC L	8.1 \pm 1.8
TLC % pred	130 \pm 20
RV L	4.4 \pm 1.3
RV % pred	209 \pm 50
FRC L	5.5 \pm 1.3
FRC % pred	171 \pm 30
DL _{CO} % pred	37.4 \pm 11.1
P_{a,O_2} mmHg	72 \pm 10
P_{a,CO_2} mmHg	39 \pm 7
S_{a,O_2} %	93 \pm 4
pH	7.44 \pm 0.29

Data are presented as mean \pm SD for 12 subjects. BMI: body mass index; FFMI: fat-free mass index; FEV₁: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; FRC: functional residual capacity; DL_{CO}: diffusing capacity of the lung for carbon monoxide; P_{a,O_2} : arterial oxygen tension; P_{a,CO_2} : arterial carbon dioxide tension; S_{a,O_2} : arterial oxygen saturation.

TABLE 2 Peak exercise data in room air[#]

WR_{peak} W	62 \pm 19
$VO_{2,peak}$ L·min ⁻¹	1.12 \pm 0.18
$f_{C,peak}$ beats·min ⁻¹	115 \pm 14
$V'_{E,peak}$ L·min ⁻¹	39 \pm 10
$V'_{T,peak}$ L·min ⁻¹	1.3 \pm 0.4
$f_{R,peak}$ breaths·min ⁻¹	31 \pm 7
S_{p,O_2} %	88 \pm 4
Borg dyspnoea score	7.3 \pm 2.1
Borg leg effort score	5.5 \pm 2.6

Data are presented as mean \pm SD for 12 subjects. WR_{peak} : peak work rate; $VO_{2,peak}$: peak oxygen uptake; $f_{C,peak}$: peak cardiac frequency; $V'_{E,peak}$: peak minute ventilation; $V'_{T,peak}$: peak tidal volume; $f_{R,peak}$: peak respiratory frequency; S_{p,O_2} : arterial oxygen saturation measured by pulse oximetry. #: results of the preliminary incremental exercise test to the limit of tolerance.

TABLE 3 Constant load exercise data at 75% of the peak work rate in room air[#]

Variables	Air		Normoxic heliox		100% oxygen	
	Exhaustion	Isotime [¶]	Exhaustion	Isotime [¶]	Exhaustion	Isotime [¶]
Endurance time s	394 ± 35		637 ± 46		670 ± 43	
<i>P</i> _{a,O₂} mmHg	67 ± 4	69 ± 4	68 ± 3	540 ± 14 ^{*,+}	533 ± 23 ^{*,+}	
<i>P</i> _{a,CO₂} mmHg	48 ± 2	45 ± 2	44 ± 2 [*]	51 ± 3 ^{*,+}	52 ± 3.0 ^{*,+}	
<i>S</i> _{a,O₂} %	89 ± 2	91 ± 2 [*]	91 ± 2 [*]	99 ± 1 ^{*,+}	99 ± 1 ^{*,+}	
pH	7.32 ± 0.03	7.33 ± 0.02	7.33 ± 0.02	7.30 ± 0.05 ^{*,+}	7.30 ± 0.03 ^{*,+}	
Borg dyspnoea scores	7.4 ± 2.0	5.7 ± 1.8 [*]	6.7 ± 1.5	4.9 ± 1.0 [*]	6.3 ± 1.3	
Borg leg effort scores	5.8 ± 2.3	5.3 ± 2.1	5.9 ± 2.3	4.4 ± 1.5 [*]	5.8 ± 2.2	

Data are presented as mean ± SEM for 12 subjects. *P*_{a,O₂}: arterial oxygen tension; *P*_{a,CO₂}: arterial carbon dioxide tension; *S*_{a,O₂}: arterial oxygen saturation. [#]: peak work rate relates to the preliminary incremental test; [¶]: obtained on heliox and 100% oxygen at the same time as at exhaustion on room air. *: *p* < 0.05 versus exhaustion in room air; +: *p* < 0.05 versus normoxic heliox at the same time-point of exercise.

increased during exercise in all three conditions (*p* < 0.001). CQO₂ values, compared at either at isotime or at exhaustion, were not different for air, oxygen or heliox (fig. 2b).

At rest, frontal cortex cerebrovascular oxygenation, as expressed by *St*_{t,O₂}, was lower in air (*p* = 0.02) and heliox (*p* = 0.003) than in oxygen. During exercise, *St*_{t,O₂} did not change from rest while breathing air or heliox, but increased with oxygen (*p* = 0.004). *St*_{t,O₂} was lower at exhaustion in air and at isotime during heliox breathing than at isotime breathing oxygen (*p* < 0.001 for both). Furthermore, at exhaustion, *St*_{t,O₂} in air was lower compared with oxygen (*p* < 0.001) and higher compared with heliox (*p* = 0.04); *St*_{t,O₂} during heliox was also lower compared with pure oxygen breathing (*p* < 0.001) (fig. 2c).

Arterial blood gas analysis and symptoms

*P*_{a,O₂}, *P*_{a,CO₂} and *S*_{a,O₂} were higher while pH were all lower (*p* < 0.05) in pure oxygen compared with air and heliox breathing at both isotime and exhaustion (table 3). Dyspnoea at exhaustion on air was greater compared with isotime during exercise on either heliox (*p* = 0.04) or oxygen (*p* = 0.007). Similarly, at exhaustion on air, leg discomfort was greater compared with isotime on oxygen (*p* = 0.03).

DISCUSSION

In healthy humans, cerebral desaturation during exercise is known to affect the recruitment of those motor neurones controlling the slow-twitch muscle fibre population that is responsible for performing submaximal work tasks [15]. In this regard, besides known pathophysiological factors that limit exercise tolerance in COPD, *i.e.* ventilatory restriction, reduced oxygen delivery to respiratory and peripheral muscles and locomotor muscle dysfunction [2–5], which ultimately lead to intense sensations of dyspnoea and leg discomfort, exercise limitation in COPD might be directly affected by the inability of the brain to maintain a given motor output consequent to a reduction in its mitochondrial oxygen tension [15]. Such a possibility appears plausible when considering that oxygen supplementation enhances both cerebral oxygenation and work capacity in healthy humans [20] and exercise capacity in patients with COPD [7, 16].

In order to test this possibility, we specifically designed and conducted the present study, which was independent of our previous endeavours, to explore peripheral and respiratory muscle blood flow [18] by applying two methods known to increase both exercise tolerance and systemic oxygen delivery in COPD: 1) oxygen administration [7–9], to increase arterial oxygen content; and 2) administration of normoxic heliox, which has recently been shown to increase peripheral blood flow during exercise in COPD [18, 19]. Along these lines, it was reasoned that if at exhaustion while breathing room air, CQO₂ was significantly lower compared with that while breathing pure oxygen or normoxic heliox, this would suggest that, as in healthy subjects [20], an improvement in cerebral cortex oxygen availability may play a contributing role in enhancing exercise capacity in patients with COPD.

Three major outcomes from the present study, however, suggest the opposite, *i.e.* that endurance time in COPD patients is not associated with limited cerebral oxygen transport or availability. First, CQO₂ at isotime or at exhaustion was not different among air, oxygen and heliox, although the latter inspirates supported much longer times to exhaustion. Secondly, *St*_{t,O₂} was higher on oxygen than heliox yet endurance times were similar. Thirdly, *St*_{t,O₂} was similar on breathing air and heliox, yet the latter supported a much longer endurance time. The most likely limitations for exercise tolerance in room air were the intense sensations of dyspnoea and leg discomfort consequent to exercise-induced dynamic hyperinflation [2, 8, 16] and limitation in peripheral muscle oxygen delivery and/or peripheral muscle dysfunction [5, 7, 19, 21], respectively. The expected reduction in the degree of exercise-induced dynamic hyperinflation and enhanced peripheral muscle oxygen delivery by oxygen and heliox most probably alleviated dyspnoea sensations and leg discomfort, respectively (table 3) [7, 18, 19].

Lack of significant differences in CQO₂ at exhaustion in air, oxygen and heliox could be attributed to CBF differences (fig. 2), compensating for the changes in *Ca*_{a,O₂} under each condition (fig. 1). Increased CBF in air was most probably due to cerebral vasodilatation previously documented to occur during graded reduction in *S*_{a,O₂} in hypoxic exercise in healthy individuals [22]. Indeed, at exhaustion in air, *P*_{a,O₂} and *S*_{a,O₂}

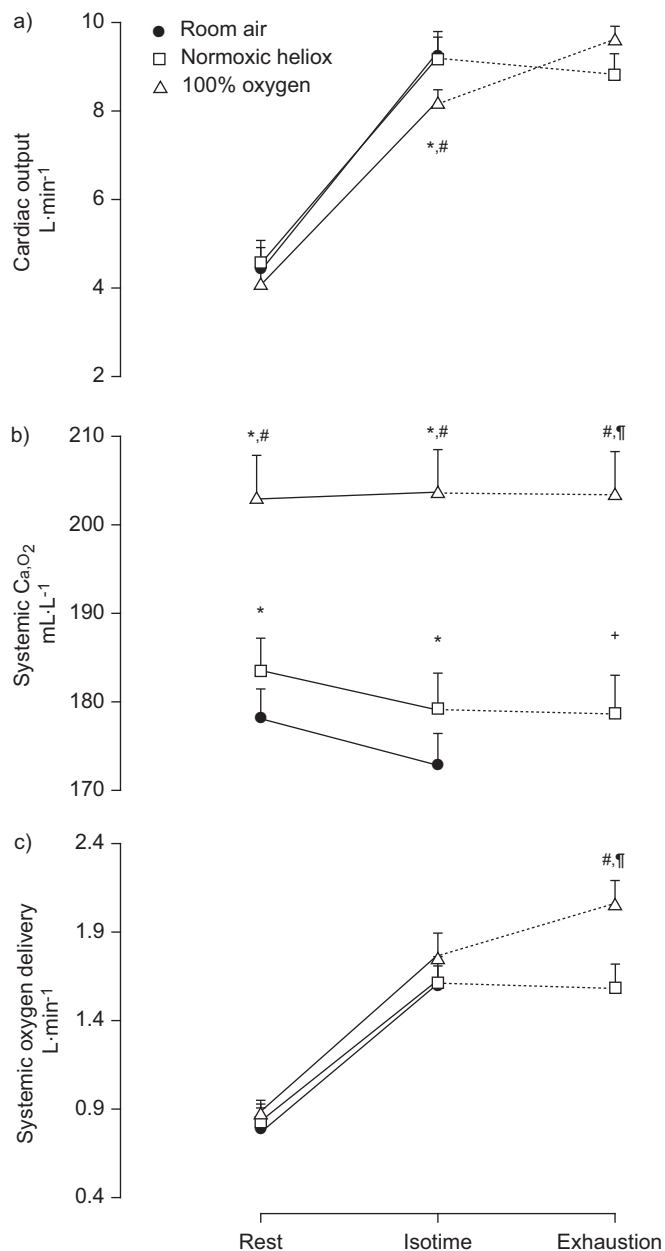


FIGURE 1. Central haemodynamic responses. a) Cardiac output, b) arterial oxygen content (Ca_aO_2) and c) systemic oxygen delivery recorded at rest, at the time of exhaustion in room air (isotime) and at the limit of exercise tolerance (exhaustion) while breathing room air, normoxic heliox or 100% oxygen. Values are mean \pm SEM for 12 subjects. Isotime data are those obtained on normoxic heliox and 100% oxygen at the same time as at exhaustion on room air. *: $p < 0.05$ compared with room air; #: $p < 0.05$ compared with normoxic heliox; †: $p < 0.05$ compared with exhaustion in room air, all at the same time point of exercise. Significant differences between data at isotime or exhaustion and rest are not indicated on the figure.

fell to 67 ± 4 mmHg and $89 \pm 2\%$, respectively (table 3). Therefore, our findings most probably concur with those in healthy subjects in that during high-intensity exercise, the vasodilator influence of hypoxia leads to hypoxia-induced changes in cerebral autoregulation and sympathetic nerve activity [23]. However, it is likely that the effect of hypoxia on measures of CQO_2 and St_tO_2 might have been greater had

subjects exhibiting greater and clinically significant desaturation been studied.

Another important factor that may have contributed to maintaining greater CBF in room air and heliox as compared with isotime during exercise with oxygen could be the greater increase in cardiac output with exercise in both room air and heliox (fig. 1). The greater increase in cardiac output in both conditions in which patients breathed normoxic gas mixtures was probably due to previously reported hypoxic sympathetic stimulation in an attempt to preserve systemic oxygen delivery [23–26].

Additional evidence that CQO_2 does not constitute the signal to curtail exercise in COPD patients is provided by the findings of heliox breathing, which, as in the case of oxygen, also prolonged exercise endurance time, while CQO_2 at both isotime and at the point of exhaustion was identical to that at exhaustion in room air. Heliox allowed exercise-induced arterial haemoglobin desaturation almost in the same way that air does (Sa_aO_2 $91 \pm 2\%$; table 3) but, at the same time enhanced systemic oxygen delivery through an increase in cardiac output. Although Ca_aO_2 decreased during heliox breathing exercise, CBF was highly comparable with that at exercise termination in room air, thereby compensating for decreased Ca_aO_2 and ensuring identical CQO_2 at isotime and at the point of exhaustion as with pure oxygen breathing.

Cerebral cortex haemodynamic responses during exercise in patients with COPD are different compared with those in healthy subjects recently reported by our group [14] in that CBF at the limit of tolerance in COPD patients was maintained at significantly greater levels compared with resting conditions, while in hypoxaemic healthy individuals at the limit of tolerance, CBF declined towards baseline. The latter was attributed to the significant reduction in $P_a\text{CO}_2$ secondary to hyperventilation, most probably causing cerebral vascular vasoconstriction. In contrast with healthy individuals, COPD patients in the present study demonstrated relative hypoventilation during exercise reflected by elevated $P_a\text{CO}_2$ levels compared with rest (tables 1 and 3), which if anything would have facilitated cerebral vascular vasodilation [10, 27].

A finding of the present study is dissociation between CQO_2 and cerebrovascular oxygen saturation, as expressed by St_tO_2 , which is often taken to reflect cerebral oxygen availability during exercise [10, 12, 13, 15, 20]. Accordingly, at exhaustion in air, St_tO_2 was significantly lower than at isotime during oxygen, whereas CQO_2 was nearly identical. The reason for this disparity between cerebrovascular oxygen saturation and CQO_2 is that measurements of St_tO_2 by NIRS yield oxygen saturation readings of all the blood in the brain within the optode field of view, *i.e.* arterial, capillary and venous. The value recorded depends on oxygen saturation of all vessels within the field of view in proportion to their relative volume, and as such it is highly dependent on Sa_aO_2 [28, 29]. Hence, cerebrovascular oxygen saturation assessed by NIRS [10, 12, 13] reflects not only the balance between CQO_2 and utilisation, but also the effects of hypoxia- and exercise-induced arterial haemoglobin oxygen desaturation [29]. Accordingly, interpreting St_tO_2 alone cannot accurately explain whether high values differ from low values because of arterial saturation differences or because of blood flow differences. In addition, St_tO_2 values cannot be compared

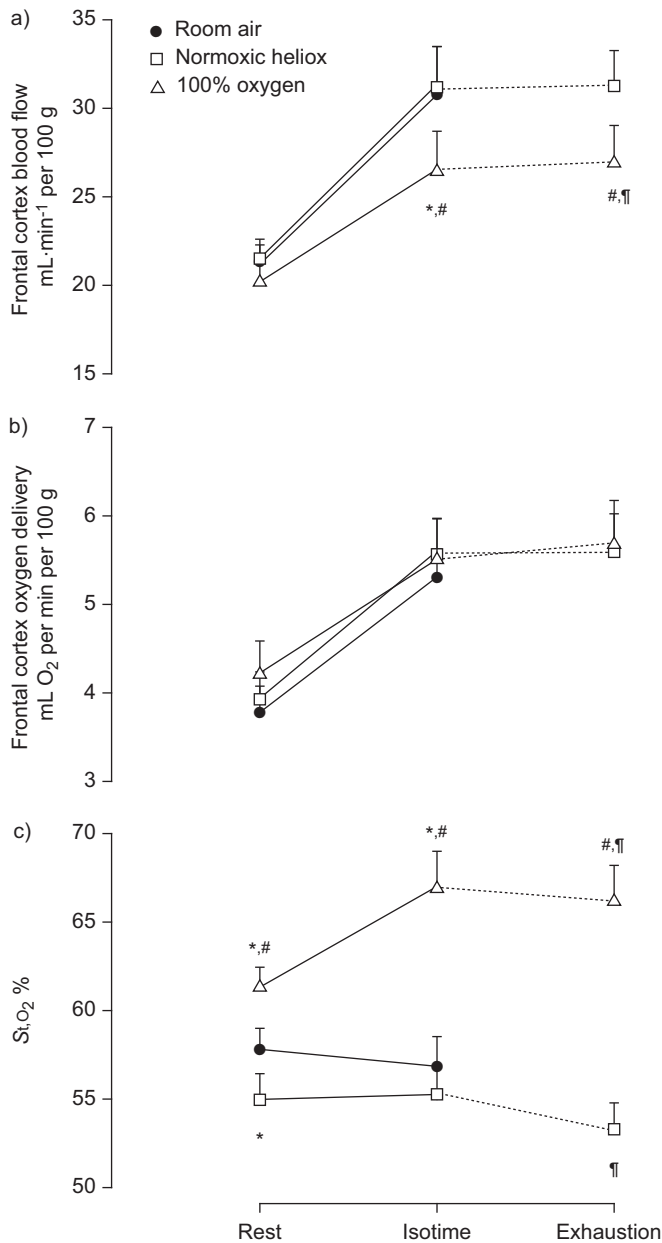


FIGURE 2. Frontal cortex cerebrovascular oxygenation and haemodynamic responses. a) Frontal cerebral cortex blood flow, b) frontal cerebral cortex oxygen delivery and c) frontal cerebral cortex cerebrovascular oxygen saturation (St,O_2) recorded at rest, at the time of exhaustion in room air (isotime) and at the limit of exercise tolerance (exhaustion) while breathing room air, normoxic heliox or 100% oxygen. Values are mean \pm SEM for 12 subjects. Isotime data are those obtained on normoxic heliox and 100% oxygen at the same time as at exhaustion on room air. *: $p < 0.05$ compared with room air; #: $p < 0.05$ compared with normoxic heliox; †: $p < 0.05$ compared with exhaustion in room air, all at the same time point of exercise. Significant differences between data at isotime or exhaustion and rest are not indicated on the figure.

between different groups of COPD patients as these values rather reflect different brain oxygenation states when arterial saturation is different between groups. Nevertheless, our findings are consistent with those of JENSEN *et al.* [30], who demonstrated that cerebrovascular oxygen saturation was

improved during hyperoxic compared with atmospheric exercise in patients with COPD. However, in the study by JENSEN *et al.* [30], the exercise-induced increase in cerebral total haemoglobin concentration (taken as an index of blood volume) was not affected by hyperoxia, whereas in the present study, the increase in CBF from rest to exercise was lower in hyperoxia compared with normoxia. The lack of greater improvement in CBF during exercise with administered oxygen might be due to the fact that an increase in P_{a,O_2} by inhalation of a hyperoxic gas has been demonstrated to induce direct vasoconstrictive effects in arterioles, thereby reducing cerebral blood flow [31].

CQO₂ measurements were performed using optodes affixed over the pre-frontal cortex region of the forehead because it has been shown, at least in healthy subjects [13], that in hypoxia, the magnitude of changes in cerebrovascular oxygenation indices is greater in pre-frontal than in pre-motor and motor cortex regions. In addition, the pattern of blood flow responses to intense exercise could be different among brain regions, as indicated by studies measuring blood flow in the internal carotid and vertebral arteries in humans [32]. Thus, the “true” global brain response might not necessarily mirror the local responses investigated here in the left frontal region of the forehead.

Furthermore, similar optode placement allows the results of the present study in COPD to be compared with those in healthy fit subjects [14]. The peak increase from rest in cerebral blood flow in healthy subjects who become hypoxaemic during exercise while breathing a hypoxic gas mixture (~30%) [14] is very similar to that reported in the present study (~28%) in patients with COPD becoming mildly hypoxaemic while breathing a normoxic gas mixture. This finding highlights once more the importance of cerebral autoregulation in maintaining cerebral blood flow and, thus, cerebral oxygen supply in tandem with the increased metabolism during hypoxaemic exercise, which becomes highly dependent on an enhanced gradient for oxygen diffusion [15].

In conclusion, the results of the present study show dissociation between cerebral oxygen delivery or cerebrovascular oxygen saturation and time to exhaustion uncovered by comparing endurance using three different inspired gases, air, normoxic heliox and 100% oxygen. Although future studies engaging larger sample size are certainly necessary, the present findings do not support the hypothesis that an improvement in cerebral cortex oxygen availability plays a contributing role in enhancing exercise capacity in patients with COPD.

SUPPORT STATEMENT

This work was supported by Thorax Foundation and by grants from the “A. Perotti” visiting Professorship fund of the Thorax Foundation.

STATEMENT OF INTEREST

None declared.

REFERENCES

- Gallagher C. Exercise limitation and clinical exercise testing in chronic obstructive pulmonary disease. *Clin Chest Med* 1994; 15: 305–326.
- O'Donnell DE, Webb KA. The major limitation to exercise performance in COPD is dynamic hyperinflation. *J Appl Physiol* 2008; 105: 753–755.

- 3 Barbera JA, Roca J, Ramirez J, *et al.* Gas exchange during exercise in mild chronic obstructive pulmonary disease. Correlation with lung structure. *Am Rev Respir Dis* 1991; 144: 520–525.
- 4 Mahler DA, Brent BN, Loke J, *et al.* Right ventricular performance and central circulatory hemodynamics during upright exercise in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1984; 130: 722–729.
- 5 Debigare R, Maltais F. The major limitation to exercise performance in COPD is lower limb muscle dysfunction. *J Appl Physiol* 2008; 105: 751–753.
- 6 Wagner PD. Determinants of maximal oxygen transport and utilization. *Annu Rev Physiol* 1996; 58: 21–50.
- 7 Maltais F, Simon M, Jobin J, *et al.* Effects of oxygen on lower limb blood flow and oxygen uptake during exercise in COPD. *Med Sci Sports Exerc* 2001; 33: 916–922.
- 8 O'Donnell DE, D'Arsigny C, Webb KA. Effects of hyperoxia on ventilatory limitation during exercise in advanced chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 892–898.
- 9 Richardson RS, Sheldon J, Poole DC, *et al.* Evidence of skeletal muscle metabolic reserve during whole body exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 159: 881–885.
- 10 Imray CH, Myers SD, Pattinson KT, *et al.* Effect of exercise on cerebral perfusion in humans at high altitude. *J Appl Physiol* 2005; 99: 699–706.
- 11 Rasmussen P, Stie H, Nielsen B, *et al.* Enhanced cerebral CO₂ reactivity during strenuous exercise in man. *Eur J Appl Physiol* 2006; 96: 299–304.
- 12 Subudhi AW, Dimmen AC, Roach RC. Effects of acute hypoxia on cerebral and muscle oxygenation during incremental exercise. *J Appl Physiol* 2007; 103: 177–183.
- 13 Subudhi AW, Miramon BR, Granger ME, *et al.* Frontal and motor cortex oxygenation during maximal exercise in normoxia and hypoxia. *J Appl Physiol* 2009; 106: 1153–1158.
- 14 Vogiatzis I, Louvaris Z, Habazettl H, *et al.* Frontal cerebral cortex blood flow, oxygen delivery and oxygenation during normoxic and hypoxic exercise in athletes. *J Physiol* 2011; 589: 4027–4039.
- 15 Secher NH, Seifert T, Van Lieshout JJ. Cerebral blood flow and metabolism during exercise: Implications for fatigue. *J Appl Physiol* 2008; 104: 306–314.
- 16 O'Donnell DE, Bain DJ, Webb KA. Factors contributing to relief of exertional breathlessness during hyperoxia in chronic airflow limitation. *Am J Respir Crit Care Med* 1997; 155: 530–535.
- 17 Palange P, Valli G, Onorati P, *et al.* Effect of Heliox on lung dynamic hyperinflation, dyspnea, and exercise endurance capacity in COPD patients. *J Appl Physiol* 2004; 85: 1637–1642.
- 18 Vogiatzis I, Habazettl H, Aliverti A, *et al.* Effect of helium breathing on intercostal and quadriceps muscle blood flow during exercise in COPD patients. *Am J Physiol Regul Integr Comp Physiol* 2011; 300: R1549–R1559.
- 19 Chiappa CR, Queiroga F Jr, Meda E, *et al.* Heliox improves oxygen delivery and utilization during dynamic exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009; 179: 1004–1010.
- 20 Nielsen HB, Boushel R, Madsen P, *et al.* Cerebral desaturation during exercise reversed by O₂ supplementation. *Am J Physiol* 1999; 277: H1045–H1052.
- 21 Global Initiative for Chronic Obstructive Lung Disease: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Executive summary, 2005. www.goldcopd.org/Guidelines/guideline-executive-summary%3a-global-strategy-for-the-diagnosis%2c-management%2c-and-prevention-of-copd.html Date last accessed: November 27, 2012.
- 22 Gupta AK, Menon DK, Czosnyka M, *et al.* Thresholds for hypoxic cerebral vasodilation in volunteers. *Anesth Analg* 1997; 85: 817–820.
- 23 Ogoh S, Dalsgaard MK, Yoshiga CC, *et al.* Dynamic cerebral autoregulation during exhaustive exercise in humans. *Am J Physiol Heart Circ Physiol* 2005; 288: H1461–H1467.
- 24 Knight DR, Schaffartzik W, Poole DC, *et al.* Effects of hyperoxia on maximal leg O₂ supply and utilization in men. *J Appl Physiol* 1993; 75: 2586–2594.
- 25 Calbet JA, Boushel R, Radegran G, *et al.* Determinants of maximal oxygen uptake in severe acute hypoxia. *Am J Physiol Regul Integr Comp Physiol* 2003; 284: R291–R303.
- 26 Calbet JA, Gonzalez-Alonso J, Helge JW, *et al.* Cardiac output and leg and arm blood flow during incremental exercise to exhaustion on the cycle ergometer. *J Appl Physiol* 2007; 103: 969–978.
- 27 Bhambhani Y, Malik R, Mookerjee S. Cerebral oxygenation declines at exercise intensities above the respiratory compensation threshold. *Respir Physiol Neurobiol* 2007; 156: 196–202.
- 28 Schindler E, Zickmann B, Muller M, *et al.* Zerebrale Oxymetrische durch Infrarot-Spektroskopie im Vergleich zur kontinuierlich gemessenen Sauerstoffsättigung im Bulbus Vena jugularis bei Eingriffen an der Arteria carotis interna. [Cerebral oximetry by infrared spectroscopy in comparison with continuous measurement of oxygen saturation of the jugular vein bulb in interventions of the internal carotid artery.] *Vasa* 1995; 24: 168–175.
- 29 Tobias JD. Cerebral oxygenation monitoring: near-infrared spectroscopy. *Expert Rev Med Devices* 2006; 3: 235–243.
- 30 Jensen G, Nielsen HB, Ide K, *et al.* Cerebral oxygenation during exercise in patients with terminal lung disease. *Chest* 2002; 122: 445–450.
- 31 Ogoh S, Aislie PN. Cerebral blood flow during exercise: mechanisms of regulation. *J Appl Physiol* 2009; 107: 1370–1380.
- 32 Sato K, Sadamoto T. Different blood flow responses to dynamic exercise between internal carotid and vertebral arteries in women. *J Appl Physiol* 2010; 109: 864–869.