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Title: Oxygen therapy improves cerebral oxygen delivery and neurovascular function in hypoxemic chronic obstructive pulmonary disease patients

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Running Title: Cerebral oxygen delivery in COPD

Abstract: We investigated the role of hypoxemia on cerebral blood flow (CBF), oxygen delivery (CDO2), and neurovascular coupling (coupling of CBF to neural activity, NVC) in hypoxemic chronic obstructive pulmonary disease (COPD) patients (n=14). Resting CBF (duplex ultrasound), peripheral oxyhemoglobin saturation (SpO2; pulse-oximetry), and NVC (transcranial Doppler) were assessed prior to and following a 20-minute wash-in of supplemental oxygen (~3L/min). While SpO2 increased from 91.0{plus minus}3.3 to 97.4{plus minus}3.0% (P<0.01), CBF was unaltered (593.0{plus minus}162.8 vs. 590.1{plus minus}138.5 mL·min-1; P=0.91) with supplemental O2. In contrast, both

CDO2 (98.1{plus minus}25.7 vs. 108.7{plus minus}28.4 mL·dL-1; P=0.02) and NVC were improved. Specifically, the increase in PCA cerebrovascular conductance was increased to a greater extent following O2 normalization (+40%, from a 20.4{plus minus}9.9 to 28.0{plus minus}10.4% increase in conductance; P=0.04) while the PCA cerebrovascular resistance decreased to a greater extent during O2 normalization (+22% from a -16.7{plus minus}7.3 to -21.4{plus minus}6.6% decrease in resistance; P=0.04). The cerebral vasculature of COPD patients appears insensitive to oxygen as CBF was unaltered in response to O2 supplementation leading to improved CDO2. In patients, the improvements in CDO2 and neurovascular function with supplemental O2 may underscore the cognitive benefits associated with O2 therapy.

New Findings: What is the central question of this study? • How does oxygen therapy influence cerebral blood flow, cerebral oxygen delivery, and neurovascular function in chronic obstructive pulmonary disease patients? What is the main finding and its importance? • Oxygen therapy improves cerebral oxygen delivery and neurovascular function in chronic obstructive pulmonary disease patients. • This improvement in cerebral oxygen delivery and neurovascular function may provide a physiological link between oxygen therapy and a reduced risk of cerebrovascular disease (e.g., stroke, mild cognitive impairment & dementia) in chronic obstructive pulmonary disease.

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Oxygen therapy improves cerebral oxygen delivery and neurovascular function in hypoxemic chronic obstructive pulmonary disease patients

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ABSTRACT

We investigated the role of hypoxemia on cerebral blood flow (CBF), oxygen delivery (CDO_2), and neurovascular coupling (coupling of CBF to neural activity, NVC) in hypoxemic chronic obstructive pulmonary disease (COPD) patients (n=14). Resting CBF (duplex ultrasound), peripheral oxyhemoglobin saturation (SpO_2; pulse-oximetry), and NVC (transcranial Doppler) were assessed prior to and following a 20-minute wash-in of supplemental oxygen (~3L/min). While SpO_2 increased from 91.0±3.3 to 97.4±3.0% (P<0.01), CBF was unaltered (593.0±162.8 vs. 590.1±138.5 $mL \cdot min^{-1}$; P=0.91) with supplemental O_2. In contrast, both CDO_2 (98.1±25.7 vs. 108.7±28.4 $mL \cdot dL^{-1}$; P=0.02) and NVC were improved. Specifically, the increase in PCA cerebrovascular conductance was increased to a greater extent following O_2 normalization (+40%, from a 20.4±9.9 to 28.0±10.4% increase in conductance; P=0.04) while the PCA cerebrovascular resistance decreased to a greater extent during O_2 normalization (+22% from a -16.7±7.3 to -21.4±6.6% decrease in resistance; P=0.04). The cerebral vasculature of COPD patients appears insensitive to oxygen as CBF was unaltered in response to O_2 supplementation leading to improved CDO_2. In patients, the improvements in CDO_2 and neurovascular function with supplemental O_2 may underscore the cognitive benefits associated with O_2 therapy.

NEW FINDINGS

What is the central question of this study?

- How does oxygen therapy influence cerebral blood flow, cerebral oxygen delivery, and neurovascular function in chronic obstructive pulmonary disease patients?

What is the main finding and its importance?

- Oxygen therapy improves cerebral oxygen delivery and neurovascular function in chronic obstructive pulmonary disease patients.
- This improvement in cerebral oxygen delivery and neurovascular function may provide a physiological link between oxygen therapy and a reduced risk of cerebrovascular disease (e.g., stroke, mild cognitive impairment & dementia) in chronic obstructive pulmonary disease.

ABBREVIATIONS: CaO_2, arterial oxygen content; CBF, cerebral blood flow; CDO_2, cerebral oxygen delivery; CO, cardiac output; CO_2, carbon dioxide; COPD, chronic obstructive pulmonary disease; CVC, cerebrovascular conductance; CVR, cerebrovascular resistance; *e*CaO_2, estimated arterial oxygen content; *e*CDO_2, estimated cerebral oxygen delivery; FEV, forced expiratory volume; FVC, forced vital capacity; gCBF, global cerebral blood flow; Hb, hemoglobin; HR, heart rate; ICA, internal carotid artery; ICAv, internal carotid artery blood velocity; MAP, mean arterial pressure; MCA; middle cerebral artery; MCAv, middle cerebral artery blood velocity; NVC, neurovascular coupling; O_2, oxygen; PaO_2, partial pressure of arterial oxygen; PCA, posterior cerebral artery; PCAv, posterior cerebral artery blood velocity; Q_{ICA}, internal carotid artery blood flow; Q_{VA}, vertebral artery blood flow; SpO_2; peripheral oxyhemoglobin saturation; SV, stroke volume; VA, vertebral artery; VAv, vertebral artery blood velocity

KEY WORDS: Chronic obstructive pulmonary disease; cerebral blood flow; neurovascular coupling; hypoxia

INTRODUCTION

Patients with moderate-to-very severe chronic obstructive pulmonary disease (COPD) endure a state of chronic hypoxemia - a consequence of sub optimal gas exchange. Literature on cerebral vascular regulation in COPD is sparse (Beaudin *et al.*, 2017), despite an elevated risk of cognitive impairment (Thakur *et al.*, 2010), dementia (Liao *et al.*, 2015) and ischemic stroke (Feary *et al.*, 2010); this risk increases in proportion to disease severity (Portegies *et al.*, 2016). Physiological links between COPD, cerebrovascular dysfunction and risk of the aforementioned diseases have yet to be established.

In healthy individuals, a reduction in arterial oxygen content (CaO_2) leads to an increase in cerebral blood flow (CBF) due to cerebral vasodilator mechanisms (Kety & Schmidt, 1948; Hoiland *et al.*, 2016), which may be continuously active in hypoxemic COPD patients. Indeed, CBF is elevated in COPD commensurate to the level of hypoxemia (Albayrak *et al.*, 2006); however, whether this elevated CBF is great enough in magnitude to maintain cerebral oxygen delivery (CDO_2) is unknown. If patients are hypoxemic, low flow oxygen (~3L $\cdot$ min^{-1}) is typically prescribed (NOTTG, 1980; MRCWP, 1981) with the goal of increasing the partial pressure of arterial oxygen (PaO_2) to >60mmHg while avoiding hyperoxia (Qaseem *et al.*, 2011). This therapy reduces mortality (NOTTG, 1980; MRCWP, 1981) and the risk of cognitive impairment (Thakur *et al.*, 2010). Given the potential link between chronic cerebral hypo-perfusion (i.e. vascular insufficiency – reduced CDO_2) and the pathogenesis of neurovascular injury and dementia (Iadecola, 2010), understanding the influence of oxygen therapy on CBF, CDO_2 and neurovascular function in COPD is of immediate importance.

We examined two primary hypotheses: 1) that CBF would be reduced in COPD patients following O_2 normalization leading to unchanged CDO_2 despite elevated CaO_2, and 2) in the face of unchanged CDO_2 no change in neurovascular function would be observed.

MATERIALS AND METHODS

Ethical Approval

The study was approved by the institutional Ethics Committee (University of Split, Croatia; Reg. no. 2181-198-03-03-13-0017) and the University of British Columbia Clinical Research Ethics Board (H16-01028). Written informed consent was obtained from all participants and all experimental procedures conformed to the standards set by the *Declaration of Helsinki,* except for registration in a database.

Participants (COPD)

At the Split Clinical Hospital Centre Pulmonary Diseases Clinic (Split, Croatia), 342 COPD patients were screened for eligibility during hospital stays or ambulatory visits. Diagnosis of COPD was classified according to the criteria of the Global Initiative for Obstructive Lung Disease (GOLD) (Vestbo *et al.*, 2013). The primary inclusion criterion was chronic hypoxemia defined as arterial oxygen saturation of ≤93% objectively confirmed on at least two different occasions during the six previous months (n=84). The related arterial blood gas values from these measurements are reported in Table 1. Patients who had suffered from an acute exacerbation, active respiratory infection or infection of other localisation within six weeks prior to the visit were excluded (n=32). Likewise, patients who had a relevant coexisting condition such as interstitial lung disease, cancer, renal failure, thromboembolic disease or major cardiovascular event during the previous year were also excluded (n=25). Those patients who could not provide informed consent or comply with the study protocol due to a mental or physical condition were also excluded (n=10). One patient did not participate due to scheduling conflicts. Details on the remaining 16 patients included in the present study are presented in Table 1.

Experimental overview (COPD)

Patients arrived at the laboratory having abstained from exercise, alcohol and caffeine for a minimum of 12 hours. Additionally, the patients had fasted for four hours, and current smokers had their last cigarette a minimum of eight hours prior to testing.

All cardiorespiratory variables were sampled continuously at 1KHz via an analogue-to-digital converter (Powerlab, 16/30; ADInstruments, Colorado Springs, CO). Heart rate (HR) was

measured by an electrocardiogram (Lead II; ADI bioamp ML132), while beat-to-beat blood pressure was measured by finger photoplethysmography (Finapres NOVA, Finapres Medical Systems, Amsterdam, Netherlands). The Finapres reconstructed brachial waveform was used for the calculation of mean arterial pressure (MAP) after values were back calibrated to an automated brachial blood pressure measurement made at rest. Pulse oximetry (Finapres NOVA) was utilized to determine peripheral oxyhemoglobin saturation (SpO_2). Patients were instrumented with transcranial Doppler ultrasound (Spencer Technologies, Seattle, WA) according to previously described methods for location and standardization techniques (Willie *et al.*, 2011). Raw velocity traces of the MCA (right side) and PCA (left side) were recorded. All data were interfaced with LabChart (Version 7).

Following at least 20 minutes of supine rest, resting volumetric CBF measurements were made using duplex ultrasound (Terason T3200, Teratech, Burlington, MA) according to previously described methods (Thomas *et al.*, 2015). Measurements of the internal carotid (ICA) and vertebral (VA) were made ipsilateral to the MCA and PCA, respectively. Images were recorded and stored as video files for offline analysis using automated edge detection software (Woodman *et al.*, 2001). No less than a one-minute video was used for the assessment of ICA and VA flow. Global CBF (gCBF) was estimated as the twice the sum of the unilateral ICA and VA flow measurements. Reliable images of the ICA were collected in all patients; however, due to excessive neck movement from respiration (e.g. sternocleidomastoid contraction), reliable VA images were only captured in seven patients. Therefore, the resulting sample size for VA and gCBF is based on n=7.

After the resting measures, the neurovascular coupling (NVC) response was assessed. For this test, participants performed five cycles of 30-seconds eyes open followed by 30-seconds eyes closed while PCA and MCA blood velocities were recorded. During the 30-seconds of eyes open patients read standardized material. This test was conducted in accordance to published guidelines (Phillips *et al.*, 2016). The hemodynamic response to the five cycles was averaged and used for analysis. Reductions in NVC are an indicator of impaired cerebrovascular function and have been reported in a number of pathologies (e.g. stroke & dementia) (Phillips *et al.*, 2016).

Following initial resting measurements and NVC, low flow O_2 was administered via nasal cannula to normalize SpO_2 to ≥96% for 20 minutes, following which time resting measurements and NVC were repeated while O_2 supplementation was continued. Therefore, measurements of NVC and gCBF occurring 26.5±3 and 30.0±5.5 minutes following onset of O_2 normalization, respectively. Two subjects withdrew for reasons unstated, rendering the final maximum sample size as n=14 for pre- and post- O_2 normalization data.

Calculations

To provide further insight into the role of oxygen therapy on cerebral vascular function we have estimated CDO_2 by combining our pulse-oximetry data and gCBF measures as follows:

$$eCDO_2\ (mL \cdot min^{-1}) = gCBF\ (mL \cdot min^{-1}) \times eCaO_2\ (mL \cdot dL^{-1})/100$$

Where $eCDO_2$ represents *estimated* cerebral oxygen delivery and CaO_2 represents arterial oxygen content. Given the negligible contribution of dissolved O_2 to total CaO_2 (i.e. PaO_2 x 0.003) under physiological ranges of PaO_2, we estimated CaO_2 from SpO_2 and [Hb] as follows:

$$eCaO_2\ (mL \cdot dL^{-1}) = 1.35 \times [Hb]\ (g \cdot dL^{-1}) \times SpO_2\ (\%) \div 100$$

Where $eCaO_2$ represents *estimated* arterial oxygen content and [Hb] represents hemoglobin concentration. In the COPD patients [Hb] was taken from two separate arterial blood gases over 6-months prior to testing (i.e. same values as in Table 1).

Statistical Analyses

Sample size was determined *a priori* based upon similar studies (Patterson *et al.*, 1952; Albayrak *et al.*, 2006) and sample size calculations (G*Power, V3.1). It was determined that with a power of 0.8, 15 subjects would be required to detect a 100 mL · min^{-1} change in gCBF (e.g., 13% change from typical value of 750mL mL · min^{-1}) – or 25 mL · min^{-1} change in unilateral ICA flow. Resting variables pre- and post- O_2 normalization, as well as NVC parameters were

compared using two-tailed paired t-tests. When significant main effects were determined Bonferroni post hoc tests were ran, and corrected for multiple comparisons. Effect size was calculated as the mean difference divided by the standard deviation of the difference. Statistical analyses were performed in the Statistical Package for the Social Sciences (V24) with significance determined *a prior* as $P<0.05$.

RESULTS

O_2 normalization in COPD patients

In total, 14 participants completed both pre and post O_2 normalization testing. Resting variables are presented in Table 2. As expected, SpO_2 increased following O_2 normalization from 91.0±3.3 to 97.4±3.0 % ($P<0.01$). There was no change in internal carotid artery flow (Q_{ICA}), vertebral artery flow (Q_{VA}), gCBF (Figure 1), MCAv, PCAv, or MAP following O_2 normalization; however, there was a reduction in HR ($P=0.03$). Maintained gCBF in combination with elevated SpO_2 resulted in improved $eCDO_2$ in the COPD patients (98.1±25.7 vs. 108.7±28.4 mL · dL^{-1}; $P=0.02$). The sample sizes for each comparison are noted in Table 2.

Results from the neurovascular coupling trials (n=11) pre and post O_2 normalization are presented in Table 3 and Figure 2. Notably, the peak relative and absolute increases in PCAv were unaltered following O_2 normalization (Table 3 & Figure 2). Despite this the peak percent increase in PCA cerebrovascular conductance (CVC) upon transition from eyes closed to eyes open increased by ~40% (from 20.4±9.9 to 28.0±10.4%) following O_2 normalization ($P=0.04$). Accordingly, the peak drop in PCA cerebrovascular resistance (CVR) was also increased from -16.7±7.3 to -21.4±6.6% ($P=0.04$) following O_2 normalization. We also observed a significant improvement in the magnitude of the peak absolute reduction in CVR (-0.46±0.25 vs. -0.64±0.27; $P<0.01$). The lack of change in PCAv despite the apparent influence on changes in vasomotor tone (i.e. CVC & CVR) following can be attributed to a differing MAP response during NVC prior to and during O_2 normalization (Figure 3). It can be seen by the mean trace (Figure 3A) and the peak (Figure 3B) and average (Figure 3C) change in MAP during NVC that the greater average and peak increase in MAP during room air breathing facilitated the increase

in PCAv during NVC. Therefore, the same magnitude of PCAv response (Figure 2A, B & C) despite a lower driving force (i.e. MAP) resulted in the larger changes in vasomotor tone during O_2 normalization (Figure 2, panels D-I).

DISCUSSION

The primary novel findings of the current study are that, contrary to our hypothesis, acute normalization of SpO_2 with low flow supplemental O_2 does not alter resting CBF in COPD patients; however, O_2 normalization improves both CDO_2 and NVC (a functional marker of cerebrovascular health). Collectively our results indicate that O_2 therapy is related to an improvement in neurovascular function in COPD, potentially related to improved CDO_2. Further, our results indicate a cerebrovascular insensitivity to normalization of SpO_2 in patients with COPD; however, this insensitivity of CBF to acute increases in SpO_2 appears to possess a positive effect, as increased CaO_2 without a reduction in gCBF is responsible for the improved CDO_2 in COPD.

There is a paucity of experimental studies examining how altered resting arterial blood gases effect CBF in COPD patients (Beaudin *et al.*, 2017). Herein we have provided support for the notion that O_2 normalization does not affect CBF in moderate-to-very severe COPD patients. While we are aware our gCBF measures are limited in sample size (n=7), we did collect ICA flow and intracranial velocity data in a larger percentage of our subjects (n=14 for ICA flow) and these data reinforce our gCBF findings of no change with O_2 normalization. In comparison, the first study to investigate the influence of oxygen on CBF in COPD patients was in 1952, where investigators administered 85-100% oxygen to hypoxemic emphysema patients for 20-minutes increasing SaO_2 from 68 to 93% (Patterson *et al.*, 1952). While one would expect removal of a hypoxic stimulus to reduce CBF secondary to disengaging hypoxic cerebral vasodilation, the opposite effect was observed - CBF was elevated by ~14% (Patterson *et al.*, 1952). However, this elevation in CBF was likely due to the 12 mmHg increase in the partial pressure of carbon dioxide that occurred during O_2 breathing (presumably as a result of hypoventilation). More

recently, a transcranial Doppler study by Cannizzaro and colleagues observed no influence of O_2 normalization on intra-cranial cerebral blood velocity in hypercapnic COPD patients (Cannizzaro *et al.*, 1997). These latter findings may be due to: 1) transcranial Doppler ultrasound is limited in its capacity to assess changes in volumetric CBF due to exclusively quantifying blood velocity (Ainslie & Hoiland, 2014; Hoiland & Ainslie, 2016); 2) the hypercapnic vasodilation typically associated with the high $PaCO_2$ observed in the patients (mean: 64.7mmHg) may have overridden any influence of disengaging hypoxic cerebral vasodilation to hypoxia; or 3) there is no influence of O_2 normalization on CBF in COPD patients (i.e. a lack of O_2 sensitivity). Our study supports the notion that O_2 normalization does not affect CBF in moderate to very severe CODP patients.

Our data in COPD patients are at odds with those previously collected in healthy individuals whereby a reduction in gCBF is observed following O_2 normalization 1 week after arrival to 5050 m (Willie *et al.*, 2015). Indeed, the prototypical response to withdrawal of a hypoxic stimulus is a reduction in CBF. This indicates that the lack of responsiveness to O_2 normalization in COPD is not representative of normal cerebrovascular function. To judiciously interpret this notion, it is important to consider that differences between healthy individuals and COPD patients to O_2 normalization may be the result of differences in systemic inflammation, oxidative stress, age, or medications and their potential influences in vascular control (Hoffman *et al.*, 1984; Barnes, 2014; Austin *et al.*, 2016). Importantly, this abnormal response (i.e. lack of response) in COPD patients to O_2 normalization underlies the primary finding of unchanged CBF with concurrently improved CDO_2 and NVC following O_2 normalization in COPD. Of relevance to the experimental stimulus, previous data providing similar O_2 supplementation have shown an increase in PaO_2 without a concurrent change in $PaCO_2$ (van Helvoort *et al.*, 2006) in COPD patients indicating the lack of change of gCBF in our COPD patients is unlikely due to altered $PaCO_2$ but related to vascular changes that may be a result of their disease and/or medications. However, while it cannot be ignored that the physiological consequences of O_2 normalization depend to an extent on whether the stimulus is poikilocapnic or isocapnic, our current experimental design reflects the stimulus associated with home O_2 therapy.

A recently conducted clinical trial (LTOTTR, 2017) has called into question the efficacy of long-term oxygen therapy on reducing mortality in COPD patients although previous landmark trials have displayed a reduction in mortality with long-term oxygen therapy (NOTTG, 1980; MRCWP, 1981). Differences in study patients notwithstanding, this important question arises: Are there other potential benefits of long-term oxygen therapy worth considering? For example, there is an increased risk of stroke, dementia, and mild cognitive impairment in patients with COPD (reviewed in: (Lahousse *et al.*, 2015)). However, the physiological pathways linking COPD to deteriorated cerebral vascular function and increased risk have yet to be disentangled. While cerebrovascular insufficiency is a contributory factor to coinciding cerebral vascular dysfunction and neurodegeneration (Iadecola, 2010), O_2 therapy reduces the risk of cognitive impairment in COPD patients (Thakur *et al.*, 2010). Thus, it stands to reason that a mechanism for this is an improvement in CDO_2. Indeed, the observed improvement in NVC coincided with improved CDO_2 and may represent a physiological link between long-term O_2 therapy and the reduced risk for dementia. As CDO_2 is the product of CaO_2 and CBF, an increase in SaO_2 will improve CDO_2 if the consequent increase in CaO_2 is not outweighed by disengagement of hypoxic cerebral vasodilation and a reduction in CBF. The lack of sensitivity to O_2 normalization observed in our COPD patients contributed to the increase in CDO_2 with low flow supplementation O_2 and may be fortuitously beneficial in the context of low O_2 therapy and cerebrovascular function.

CONCLUSIONS

Although low flow supplemental O_2 does not alter volumetric gCBF in COPD patients, the increased SpO_2 results in improved CDO_2 and neurovascular function. This improvement in CDO_2 and neurovascular function with supplemental O_2 may underscore the cognitive benefits, and reduced risk of cognitive impairment associated with O_2 therapy in COPD.

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AUTHOR CONTRIBUTIONS

PNA and ZD, conception and design of research; RLH, SM, OFB, CKW, TM, MS, ZD, and PNA performed experiments; RLH analyzed the data; RLH, SM, OFB, CKW, TM, MS, ZD, and PNA interpreted the results of the experiment; RLH drafted the manuscript; RLH, SM, OFB, CKW, TM, MS, ZD, and PNA edited / revised the manuscript and approved the final version.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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TABLES

Table 1. Participant characteristics.

	COPD (n=16)
Age (years), mean (SD)	69.4 (8.7)
Sex (male), No. (%)	11 (68.8)
Height (cm), mean (SD)	171.8 (6.5)
Weight (kg), mean (SD)	75.6 (14.2)
Body mass index (kg/m^2), mean (SD)	25.6 (4.6)
Cigarette smoking status	
Current, No. (%)	6 (37.5)
Former, No. (%)	8 (50.0)
Non-smoker, No. (%)	2 (12.5)
Smoking pack-years, mean (SD)	50.1 (44.6)
Co-morbidities	
Hypertension, No. (%)	9 (56.3)
Diabetes mellitus, No. (%)	3 (18.8)
Coronary artery disease, No. (%)	1 (6.3)
Peripheral artery disease, No. (%)	2 (12.5)
Medication use	
β-blockers, No. (%)	4 (25.0)
Calcium channel blockers, No. (%)	3 (18.8)
ACE inhibitors or angiotensin antagonists, No. (%)	8 (50.0)
Diuretics, No. (%)	12 (75.0)
Statins, No. (%)	1 (6.3)
Acetylsalicylic acid, No. (%)	2 (12.5)
Inhaled corticosteroids, No. (%)	14 (87.5)
Systemic corticosteroids, No. (%)	1 (6.3)
Short-acting β-agonists, No. (%)	4 (25.0)
Long-acting β-agonists, No. (%)	16 (100.0)
Short-acting anticholinergics, No. (%)	4 (25.0)
Long-acting anticholinergics, No. (%)	11 (68.8)
Theophylline, No. (%)	8 (50.0)
Roflumilast, No. (%)	1 (6.3)
Methyldigoxine, No. (%)	1 (6.3)
Cardiorespiratory Variables	
Systolic blood pressure (mm Hg), mean (SD)	132.2 (24.6)
Diastolic blood pressure (mm Hg), mean (SD)	76.9 (13.0)
FEV1 (% of predicted), mean (SD)	32.9 (12.7)
FVC (% of predicted), mean (SD)	55.1 (15.2)
FEV1/FVC ratio (%), mean (SD)	44.9 (9.6)
FEF25-75 (% of predicted), mean (SD)	11.3 (4.9)
SaO_2 (%), mean (SD)	88.8 (4.0)
PaO_2 (kPa), mean (SD)	7.5 (1.1)
$PaCO_2$ (kPa), mean (SD)	6.2 (0.9)
pH, mean (SD)	7.43 (0.03)
[Hb] (g/dL) mean (SD)	13.9 (1.4)
Home oxygen therapy, No. (%)	12 (75.0)
O_2 washout period (h), mean (SD)	6.5(5.8)
Severity of airflow limitation (GOLD)	
Stage 1, No. (%)	0 (0.0)
Stage 2, No. (%)	2 (12.5)
Stage 3, No. (%)	5 (31.3)
Stage 4, No. (%)	9 (56.3)
Dyspnea grade (mMRC), mean (SD)	3.2 (0.5)
Acute exacerbations ≥2 per year, No. (%)	13 (81.3)
Combined COPD assessment	
Group A, No. (%)	0 (0.0)
Group B, No. (%)	1 (6.3)
Group C, No. (%)	0 (0.0)
Group D, No. (%)	15 (93.8)

Table 2. Cerebral and cardiovascular variables pre- and post-oxygen normalization in COPD patients.

	Room air	O_2 normalization	n	P-Value	Effect size
Q_{ICA} (mL · min^{-1})	231.2±59.0	231.6±68.0	14	0.97	0.01
ICAv (cm · sec^{-1})	29.72±7.25	30.62±8.06	14	0.27	0.31
ICA diameter (mm)	5.81±0.98	5.73±1.05	14	0.13	0.43
Q_{VA} (mL · min^{-1})	61.4±35.1	70.2±49.3	7	0.32	0.41
VAv (cm · sec^{-1})	18.32±5.81	18.72±5.66	7	0.55	0.24
VA diameter (mm)	3.82±0.85	3.73±0.92	7	0.49	0.28
gCBF (mL · min^{-1})	593.0±162.8	590.1±138.5	7	0.91	0.05
MCAv (cm · sec^{-1})	51.4±10.4	51.5±5.6	9	0.96	0.24
PCAv (cm · sec^{-1})	36.4±11.1	36.5±12.8	12	0.93	0.03
MAP (mmHg)	90.2±17.3	96.3±18.4	14	0.14	0.42
HR (beats · min^{-1})	81.5±16.0	77.7±13.0*	14	**0.03**	0.65
SV (mL)	81.5±39.1	85.5±50.8	14	0.63	0.13
CO (L · min^{-1})	6.4±2.6	6.4±3.3	14	0.99	0.00
SaO_2 (%)	91.0±3.3	97.4±3.0*	14	**<0.01**	1.41
eCaO_2 (mL · dL^{-1})	17.2±2.0	18.4±1.9*	14	**<0.01**	1.39
eCDO_2 (mL · min^{-1})	98.1±25.7	108.7±28.4	7	**0.02**	1.17

Data are presented as mean ± standard deviation. * denotes a significant change from room air, $P<0.05$.

Table 3. Peak changes in neurovascular coupling tests.

	Absolute data				Relative data			
	Room air	O_2 normalization	P-Value	Effect size	Room air	O_2 normalization	P-Value	Effect Size
ΔPCAv ($cm \cdot s^{-1}$)	7.81±4.57	7.87±4.31	0.93	0.03	24.2±12.3	23.1±12.0	0.41	0.26
Time to peak (s)	13.29±4.73	16.09±4.60	0.10	0.54				
ΔMAP (mmHg)	8.2±3.5	5.5±2.7	**0.01**	0.91	10.1±4.8	6.0±3.2	**<0.01**	1.20
Time to peak (s)	12.8±6.5	9.4±8.0	0.23	0.39				
ΔPCAv CVC ($cm \cdot s^{-1} \cdot mmHg^{-1}$)	0.08±0.05	0.11±0.06	0.27	0.35	20.4±9.9	28.0±10.4	**0.04**	0.71
Time to peak (s)	9.25±6.28	12.93±5.05	0.09	0.56				
ΔPCAv CVR ($mmHg \cdot cm^{-1} \cdot s^{-1}$)	-0.46±0.25	-0.64±0.27	**<0.01**	1.38	-16.7±7.3	-21.4±6.6	**0.04**	0.69
Time to peak (s)	9.8±6.2	12.91±5.02	0.17	0.44				

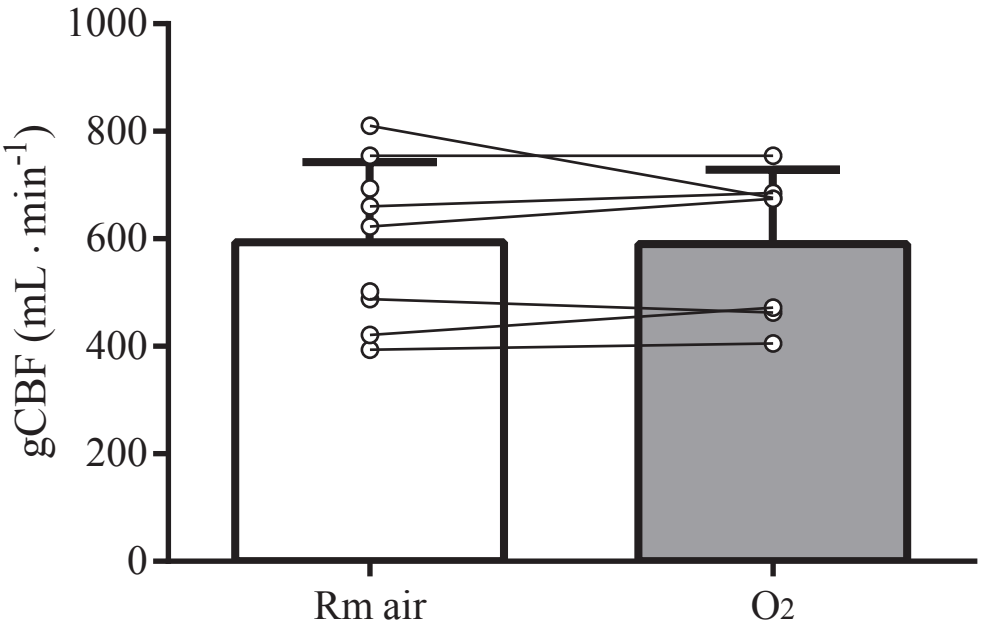
N=11. PCAv, posterior cerebral artery blood velocity; CVC, cerebrovascular conductance; CVR, cerebrovascular resistance.

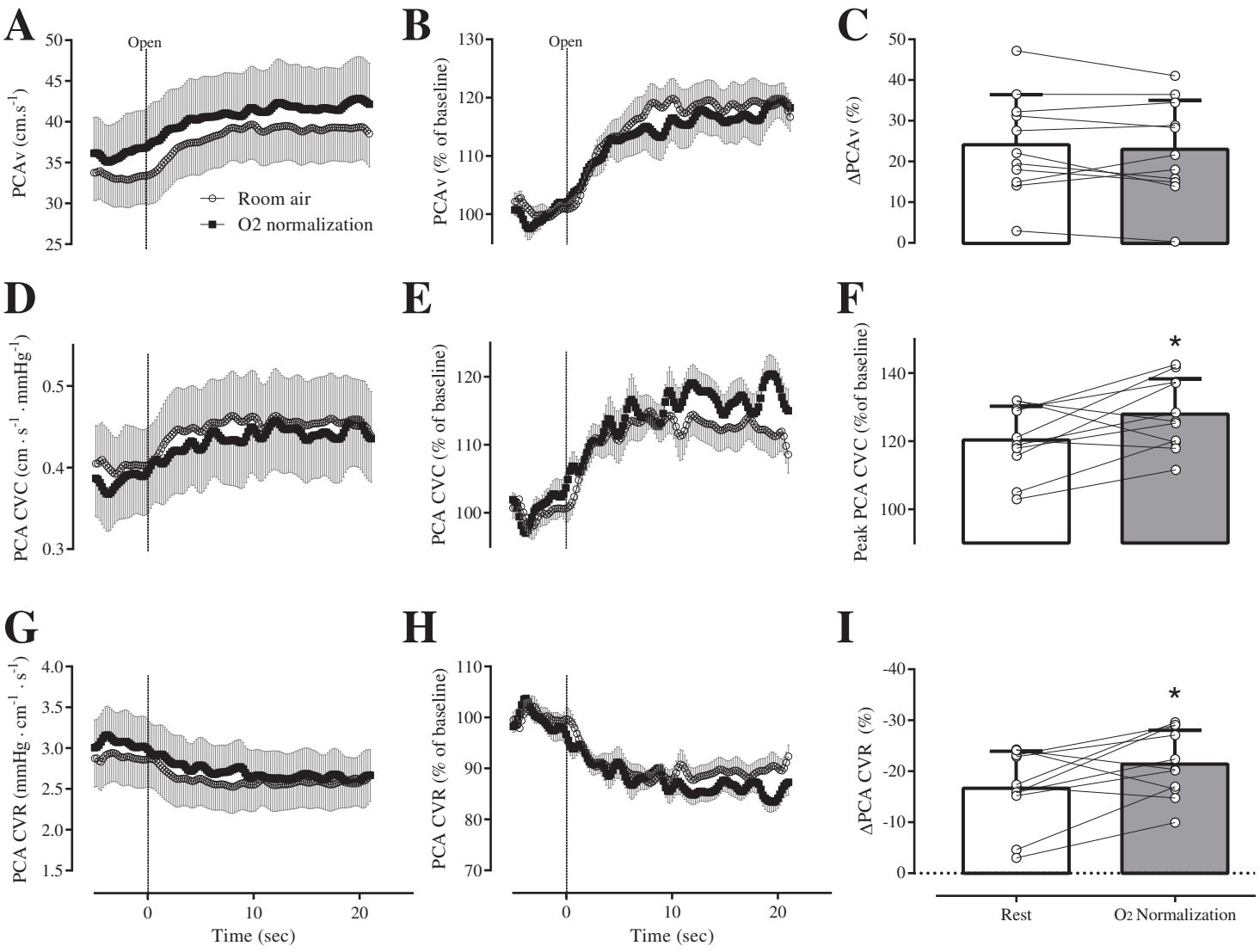
FIGURES

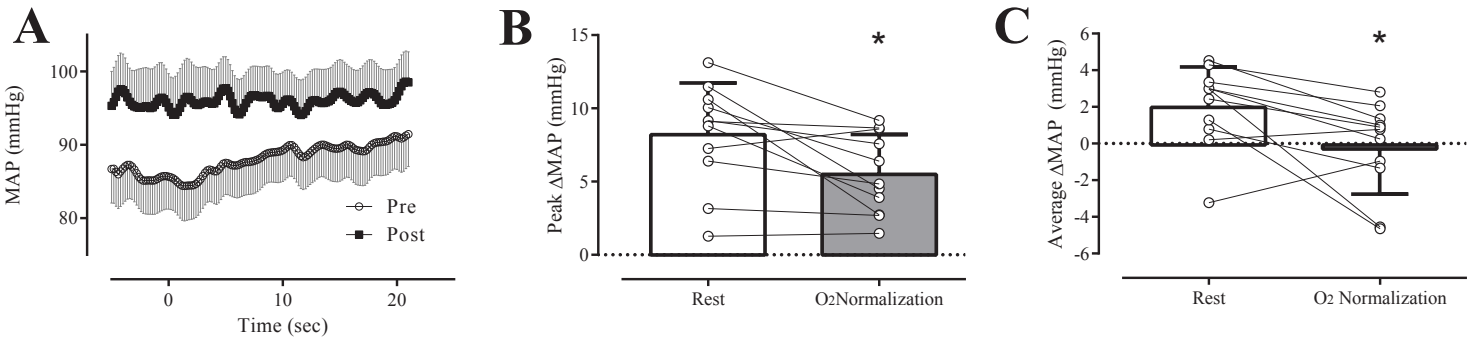
Figure 1. Cerebral blood flow prior to and following oxygen normalization in COPD patients. Individual data for the COPD patients are depicted with the open circle symbol (○) with the mean and standard deviation superimposed as bar graphs (pre: white bar, post: grey bar). The resulting sample sizes were n=7 for the COPD. There was no change in global cerebral blood flow (gCBF) following O_2 normalization.

Figure 2. Neurovascular coupling responses prior to and following O_2 normalization. For panels A, B, D, E, G & H pre oxygen normalization data are represented by the open circles (○), while the post O_2 normalization data are represented by the closed square symbol (■) with error bars representing the standard error. Panel A depicts the absolute PCAv response to NVC, while Panel B depicts the relative (%) change in PCAv during NVC. Panel C highlights the individual %peak changes in PCAv during NVC prior to and following O_2 normalization – there was no significant difference (P=0.41; Effect size=0.26). Panel D depicts the absolute PCA cerebrovascular conductance (CVC) response during NVC, while Panel E depicts the relative (%) change in PCA CVC during NVC. Panel F highlights the individual %peak changes in PCA CVC during NVC prior to and following O_2 normalization – the CVC response was improved during O_2 normalization (P=0.04; Effect size=0.71). Panel G depicts the absolute PCA cerebrovascular resistance (CVR) response during NVC, while Panel H depicts the relative (%) change in PCA CVR during NVC. Panel I highlights the %peak changes in PCA CVR during NVC prior to and following O_2 normalization - the CVR response was improved during O_2 normalization (P=0.04; Effect size=0.69). * denotes P<0.05. N=11 for NVC comparisons.

Figure 3. Mean arterial pressure during neurovascular coupling. In Panel A pre oxygen normalization data are represented by the open circles (○), while the post O_2 normalization data are represented by the closed square symbol (■) with error bars representing the standard error. Panel B highlights the individual data for the peak absolute (mmHg) change in mean arterial pressure (MAP) during NVC – the MAP response was significantly lower during O_2 normalization (P=0.01; Effect size=0.91). Panel C highlights the individual data for the average absolute (mmHg) change in mean arterial pressure (MAP) during NVC (analogous to area under the curve as time is matched between trials) – the MAP response was significantly lower during O_2 normalization (P=0.02; Effect size=0.84).


1000
800
600
400
200
0
gCBF (mL · min-1)
Rm air
O2


A
B
C
D
E
F
G
H
I
Open
Room air
O2 normalization
PCAv (cm.s-1)
PCAv (% of baseline)
ΔPCAv (%)
PCA CVC (cm · s-1 · mmHg-1)
PCA CVC (% of baseline)
Peak PCA CVC (%of baseline)
PCA CVR (mmHg · cm-1 · s-1)
PCA CVR (% of baseline)
ΔPCA CVR (%)
Time (sec)
Rest
O2 Normalization
*


A
MAP (mmHg)
100
90
80
Pre
Post
0
10
20
Time (sec)
B
Peak ΔMAP (mmHg)
15
10
5
0
*
Rest
O2Normalization
C
Average ΔMAP (mmHg)
6
4
2
0
-2
-4
-6
*
Rest
O2 Normalization