Respiratory Physiology & Neurobiology 221 (2016) 41–48

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

Effects of heart failure on cerebral blood flow in COPD: Rest and exercise

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ARTICLE INFO

Article history:
Received 5 August 2015
Received in revised form 7 October 2015
Accepted 10 October 2015
Available online 31 October 2015

Keywords:
Cerebral oxygenation
Chronic obstructive pulmonary disease
Comorbidity
Near-infrared spectroscopy

ABSTRACT

Cerebral blood flow (CBF) and oxygenation (COx) are generally well-preserved in COPD. It is unknown whether prevalent cardiovascular co-morbidities, such as heart failure, may impair CBF and COx responses to exertion. Eighteen males with moderate-to-severe COPD (8 with and 10 without overlapping heart failure) underwent a progressive exercise test with pre-frontal CBF and COx measurements (indocyanine green and near-infrared spectroscopy). Mean arterial pressure and cardiac output were lower from rest to exercise in overlap. Only COPD patients demonstrated an increase in arterialized PCO_2 towards the end of progressive exercise. CBF index was consistently higher and increased further by ~40% during exercise in COPD whereas a ~10% reduction was observed in overlap. COx was lower in overlap despite preserved arterial oxygenation. In conclusion, heart failure introduces pronounced negative effects on CBF and COx in COPD which may be associated with clinically relevant outcomes, including dyspnea, exercise intolerance, cerebrovascular disease and cognitive impairment.

1. Introduction

Cerebral blood flow (CBF) is regulated via the integration of multiple physiological adjustments, including those in blood pressure, cardiac output, neurovascular coupling, arterial blood gas tensions and autonomic nervous system activation (Ogoh and Ainslie, 2009; Willie et al., 2014; Brassard et al., 2014). Physical exercise influences all of these processes making CBF regulation a formidable challenge for patients with cardiopulmonary and metabolic diseases (Kim et al., 2012, 2015).

In this context, it is rather surprising that patients with stable chronic obstructive pulmonary disease (COPD) usually present with preserved (or increased) CBF at rest (Yildiz et al., 2012; Cornwell and Levine, 2015; Alosco and Hayes, 2015) and during exercise (Oliveira et al., 2012; Vogiatzis et al., 2013; Hartmann et al., 2014). This finding might be explained by their tendency to upregulate $PaCO_2$, a potent cerebral vasodilator (Ogoh and Ainslie, 2009). This might become more evident during exercise as patients are frequently unable to increase ventilation to properly wash-out CO_2 released from lactate buffering or, in more severe COPD, CO_2 derived from cellular metabolism (O'Donnell et al., 2014). At least in those who are not overtly hypoxemic at rest, effective cerebral vasodilation may offset mild-to-moderate decrements in PaO_2 thereby preserving cerebral oxygenation (COx) (Jensen et al., 2002; Van de Ven et al., 2001). In fact, we (Oliveira et al., 2012) and others (Higashimoto et al., 2011) have found similar increases in COx (measured by near-infrared spectroscopy) during exercise in non- to mildly-hypoxemic COPD patients and healthy controls.

A different scenario, however, may emerge in the presence of a common and disabling co-morbidity of COPD: heart failure (Rutten et al., 2006; Güder and Rutten, 2014). In fact, impaired resting CBF, (Choi et al., 2006; Kim et al., 2012) which is further worsened under the stress of exercise, (Koike et al., 2004, 2006; Fu et al., 2011) has been reported in heart failure with reduced left ventricular ejection fraction. These abnormalities have been ascribed to the combined effects of impaired cerebral auto-regulation, decreased mean arterial pressure and cardiac output, alveolar hyperventilation (i.e., low $PaCO_2$) and sympathetic over-excitation. (Alosco and Hayes, 2015) Of note, patients with coexistent COPD-heart failure ("overlap") have higher prevalence of cerebrovascular disease (Rutten et al., 2006; Güder and Rutten, 2014) and cognition disorders (Alosco et al., 2014) than COPD patients without heart failure. Interestingly, we found previously lower COx during rapidly-incremental

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http://dx.doi.org/10.1016/j.resp.2015.10.005
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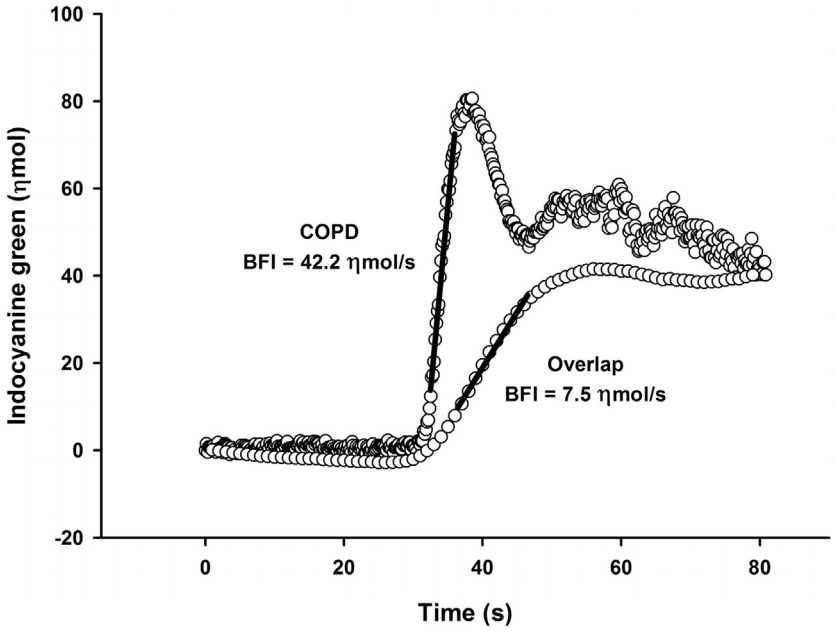

Fig. 1. Cerebral blood flow index (BFI) calculation based on indocyanine green kinetics measured by near-infrared spectroscopy in representative COPD and overlap patients.

exercise in overlap compared to COPD (Oliveira et al., 2013). Collectively, these findings prompted the hypothesis that the reported "protective" effects of COPD on exercise CBF could be overridden by the ominous pathophysiological consequences of heart failure on cerebral hemodynamics (Koike et al., 2004; Choi et al., 2006; Koike et al., 2006; Fu et al., 2011; Kim et al., 2012).

The aim of this study was thus to investigate the influence of heart failure on CBF and COx in COPD patients from rest to exercise. We specifically postulated that, compared with age- and gender-matched COPD, overlap patients would present with reduced CBF thereby leading to lower COx.

2. Methods

2.1. Subjects

Eighteen sedentary males with well-established moderate-to-severe COPD (Global Initiative for Obstructive Lung Disease stages 2 and 3) (Vestbo et al., 2013) comprised the study group. Eight patients had echocardiographic evidences of heart failure with reduced left ventricular ejection fraction (<50%). Patients were seen prospectively by the same respirologists and cardiologists. Disease treatment for both diseases was decided by consensus and optimized carefully before study entry. Main exclusion criteria included: long-term O_2 therapy, recent (within a year) rehabilitation, previous stroke or transitory ischemic attack, osteomuscular limitation to cycling, type I or non-controlled type II diabetes mellitus and clinical history of peripheral (including carotidal) arterial disease. All subjects gave written informed consent and the study was approved by the Medical Ethics committee of the Sao Paulo Hospital, Sao Paulo, Brazil.

2.2. Measurements

2.2.1. Lung function

Spirometry, lung diffusing capacity, and static lung volumes were evaluated (1085 ELITE D^{TM}, Medical Graphics). Resting blood gases were obtained from samples from the radial artery.

2.2.2. Cardiopulmonary exercise testing

Patients performed a four-stage (4 min each with 4 min rest in-between) cycle ergometer test at 20%, 40%, 60% and 80% of the peak workload (WR_{peak}) achieved on a previous incremental test. Oxygen uptake ($\dot{V}O_2$, mL/min), carbon dioxide output ($\dot{V}CO_2$, mL/min), respiratory exchange ratio (R), minute ventilation ($\dot{V}E$, L/min) and end-tidal partial pressure for CO_2 ($PETCO_2$, mmHg) were obtained breath-by-breath and averaged into 20s bins. Cardiac output (L/min) was assessed continuously by a calibrated signal-morphology impedance cardiography system (Physioflow PF-5^{TM}, Manatec) (Charloux et al., 2000). Arterial oxygen saturation was measured non-invasively by pulse oximetry (SpO_2, %). Breathlessness and leg effort were rated according to the 10-point Borg category-ratio scale every minute. Blood gases were measured from arterialized (art) earlobe capillary samples concomitantly to CBF, i.e., at the 3rd min of each stage as described below.

2.2.3. Cerebral blood flow & oxygenation

Continuous-wave, spatially-resolved near-infrared spectroscopy (NIRS) was used to measure COx (changes in oxyhemoglobin concentration ($\Delta[O_2Hb]$, μmol/L) and tissue oxygenation index (TOI, %)) and, by injecting the light-absorbing tracer indocyanine green (ICG) dye, (pre-frontal cortical) CBF (Kuebler et al., 1998; Habazettl et al., 2010) (NIRO 200, Hamamatsu Photonics KK, Hamamatsu, Japan). One set of NIRS optodes was placed on the skin over the left pre-frontal cortex region of the forehead, secured using double-sided adhesive tape and hold with a custom-built net headset. The optode separation distance was 4 cm, corresponding to a penetration depth of ~2 cm. The spectrophotometer measured ICG concentration following a 5 mg/mL bolus injection of ICG in the right forearm vein. ICG injections were performed during the third minute of exercise. Given that light attenuation is influenced by ICG, O_2Hb and deoxyhaemoglobin, the independent contribution of ICG was assessed using a matrix operation that incorporates pathlength-specific extinction coefficients for each of the light absorbing chromophores (Hamamatsu Photonics KK). As proposed by Kuebler et al. (1998), a CBF index was calculated as the maximal change in ICG divided by its rise time (10–90% amplitude) (ηmol/s) (Fig. 1).

Table 1
Resting and peak exercise variables in COPD and overlap patients.

	COPD ($n=10$)	Overlap ($n=8$)
General characteristics		
Age (yrs)	65 ± 8	65 ± 6
Weight (kg)	60 ± 8	72 ± 5*
Height (cm)	164 ± 78	166 ± 28
Body mass index (kg/m^2)	22 ± 3	25 ± 2*
Packs/year	38 ± 7	33 ± 5
Left ventricular ejection fraction (%)	64 ± 13	30 ± 5*
Main co-morbidities		
Hypertension	6	5
Type II diabetes	5	6
Hypercolesterolemia	1	3
Lung function		
FVC (% pred)	84 ± 12	72 ± 9
FEV_1 (% pred)	44 ± 15	54 ± 8
FEV_1/FVC	41 ± 11	55 ± 7*
TLC (% pred)	111 ± 13	87 ± 21*
RV (% pred)	165 ± 30	128 ± 35*
D_{LCO} (% pred)	68 ± 21	63 ± 4
PaO_2 (mmHg)	57 ± 9	64 ± 3
$PaCO_2$ (mmHg)	39 ± 6	34 ± 1
Peak exercise		
Work rate (W)	57 ± 18	52 ± 16
Work rate (% pred)	57 ± 16	46 ± 15
$\dot{V}O_2$ (mL/min)	1018 ± 180	1080 ± 275
$\dot{V}O_2$ (% pred)	69 ± 11	60 ± 13
$\dot{V}CO_2$ (mL/min)	1060 ± 259	1082 ± 351
RER	1.06 ± 0.25	1.08 ± 0.35
$\dot{V}E$ (L/min)	37.7 ± 11.3	40.6 ± 14.0
Heart rate (% pred)	85 ± 13	68 ± 18*
SpO_2 (%)	87 ± 5	93 ± 3*
Dyspnea score	7 ± 2	9 ± 1
Leg effort score	7 ± 2	10 ± 1*

Values are mean ± SD or frequencies. Abbreviations: FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s; TLC = total lung capacity; RV = residual volume; D_{LCO} = lung diffusing capacity for carbon monoxide; PaO_2 = arterial partial pressure for oxygen; $PaCO_2$ = arterial partial pressure for carbon dioxide; $\dot{V}O_2$ = oxygen uptake; $\dot{V}CO_2$ = carbon dioxide production; RER = respiratory exchange ratio; $\dot{V}E$; minute ventilation; SpO_2 = oxygen saturation by pulse oximetry.
* $p < 0.05$.

2.3. Statistical analysis

Results are reported as means ± SD, unless stated otherwise. COPD and overlap patients were contrasted by non-paired *t* or Mann–Whitney's test or a χ^2 test for differences in proportions. Two-way analysis of variance was used to assess between-group differences at a given time point and intra-group differences (exercise vs. rest). Statistical significance was set at $p < 0.05$.

3. Results

3.1. Patients' characteristics at rest and peak exercise

All patients were under triple therapy for COPD (long-acting anti-muscarinics and β_2-adrenoceptor agonists/inhaled corticosteroids). In addition, overlap patients were receiving selective β-blockers, ACE inhibitors and diuretics. As shown in Table 1, COPD and overlap groups were well-matched by age and main co-morbidities. Overlap patients, however, were heavier than their counterparts with COPD. As expected, while COPD patients showed an obstructive pattern with hyperinflation and air trapping, overlap patients had mixed obstructive and restrictive abnormalities. Lung diffusing capacity (D_{LCO}) did not differ between groups. There were also no between-group differences in WR_{peak} and peak $\dot{V}O_2$. However, peak SpO_2 was lower in overlap compared to COPD ($p < 0.05$). As expected from β-blocker usage, overlap had greater heart rate reserves at exercise termination. Of note, they showed greater symptom burden, particularly regarding to leg effort scores (Table 1).

3.2. Metabolic, ventilatory and sensory responses

As anticipated from similar WR_{peak}, COPD and overlap exercised at similar work rate and metabolic demands (and thus $\dot{V}O_2$ and $\dot{V}CO_2$) at each submaximal exercise intensity (Table 2). Absolute and relative (to $\dot{V}CO_2$) ventilatory responses, however, were greater in overlap patients. For instance, while $\dot{V}E$ increased ~13 L/min from 20% to 80% WR_{peak} in COPD, it increased ~20 L/min in overlap. Consequently, $\dot{V}E/\dot{V}CO_2$ was significantly higher (and $PETCO_2$ lower) at 60% and 80% WR_{peak} in overlap ($p < 0.05$). Similar to maximal exercise, leg effort scores were higher at 80% WR_{peak} in overlap compared to COPD (Table 2).

3.3. Pulmonary gas exchange responses

There were marked between-group differences in arterial blood gases during exercise. For instance, while SpO_2 (%) progressively decreased in COPD (~10 unities less from rest to 80% WR_{peak}), it remained remarkably stable in overlap (Fig. 2A). As shown in Fig. 2B, Part CO_2 increased by 2–3 mmHg from rest to 20% WR_{peak} in both groups. Thereafter, Part CO_2 remained stable at around 40 mmHg in COPD and decreased by ~3 mmHg from 20% to 80% WR_{peak} in overlap. As a consequence, Part CO_2 at 80% WR_{peak} was significantly lower in overlap compared to COPD ($p < 0.05$).

3.4. Cardiovascular and hemodynamic responses

Stroke volume and, particularly, heart rate were lower from rest to exercise (i.e., rest, 20 and 80% WR_{peak}) in overlap (Fig. 3, upper panels). Thus, cardiac output was downwardly shifted during exercise in that group (i.e., rest, 20 and 80% WR_{peak}; Fig. 3C). In fact, while cardiac output increased more than 5 L/min from rest to 80% WR_{peak} in COPD, it increased only ~2 L/min in overlap (Fig. 3C). Mean arterial pressure was also consistently lower across exercise intensities in overlap (~20 mmHg less; Fig. 3D).

3.5. Cerebral blood flow and oxygenation

Resting CBF in overlap was markedly lower compared to COPD ($p < 0.01$). In addition, whereas CBF increased 41.1 ± 8.9 % from rest to 80% WR_{peak} in COPD it decreased 10.2 ± 8.2 % in overlap. CBF thus remained consistently lower throughout exercise in overlap (Fig. 2C). As shown in Fig. 4, this was related both to lower ICG amplitude and slower rising time ($p < 0.01$). COx analyses showed that the area under the curve of exercising ΔO_2Hb and TOI responses were also significantly lower in overlap compared to COPD (427 ± 110 a.u. vs. 1101 ± 323 a.u. and 5395 ± 230 a.u. vs. 7406 ± 476 a.u., respectively; $p < 0.01$). Furthermore, while discrete ΔHbO_2 values increased on average ~10 μmol from rest to 80% WR_{peak} in COPD ($p < 0.05$), they failed to increase during exercise in overlap (Fig. 2D).

4. Discussion

This is the first study to demonstrate that marked impairments in resting cerebral (pre-frontal) blood flow (CBF) are further amplified under the stress of exercise in COPD patients presenting heart failure as co-morbidity ("overlap"). Cerebral oxygenation (COx) was

Table 2
Physiological and sensory responses at standardized sub-maximal exercise intensities in COPD and overlap patients.

	20% Peak		40% Peak		60% Peak		80% Peak	
	COPD	Overlap	COPD	Overlap	COPD	Overlap	COPD	Overlap
Work rate (W)	11 ± 3	9 ± 5	25 ± 7	23 ± 2	35 ± 11	35 ± 2	47 ± 15	43 ± 12
$\dot{V}O_2$ (mL/min)	611 ± 106	613 ± 181	711 ± 107	709 ± 204	820 ± 122	978 ± 230	1032 ± 270	982 ± 109
$\dot{V}CO_2$ (mL/min)	564 ± 110	552 ± 200	673 ± 132	739 ± 250	808 ± 181	942 ± 330	1045 ± 336	1082 ± 219
RER	0.92 ± 0.05	0.88 ± 0.06	0.94 ± 0.07	0.90 ± 0.09	0.97 ± 0.08	0.83 ± 0.12	1.00 ± 0.78	1.08 ± 0.09
$\dot{V}_E$ (L/min)	21.9 ± 4.8	22.7 ± 6.5	25.2 ± 5.5	29.4 ± 7.5	28.4 ± 7.0	36.5 ± 8.8*	34.9 ± 14.5	42.1 ± 10.1*
$\dot{V}_E/\dot{V}CO_2$	39 ± 5	42 ± 5	38 ± 4	41 ± 4	35 ± 5	39 ± 2*	33 ± 6	40 ± 5*
$P_{ET}CO_2$ (mmHg)	38 ± 5	33 ± 5	38 ± 5	32 ± 4	40 ± 6	36 ± 3*	42 ± 7	32 ± 6*
Dyspnea score	2 ± 1	0.5 ± 1	3 ± 2	3 ± 1	7 ± 4	5 ± 3	8 ± 3	5 ± 2*
Leg effort score	1 ± 0.5	2 ± 1	2 ± 1	4 ± 2	4 ± 2	6 ± 2	5 ± 3	9 ± 4*

COPD vs. overlap. $\dot{V}O_2$ = oxygen consumption; $\dot{V}CO_2$ = carbon dioxide production; RER = respiratory exchange ratio; $\dot{V}E$; minute ventilation; $P_{ET}CO_2$ = end tidal partial for carbon dioxide.
* $p < 0.05$.

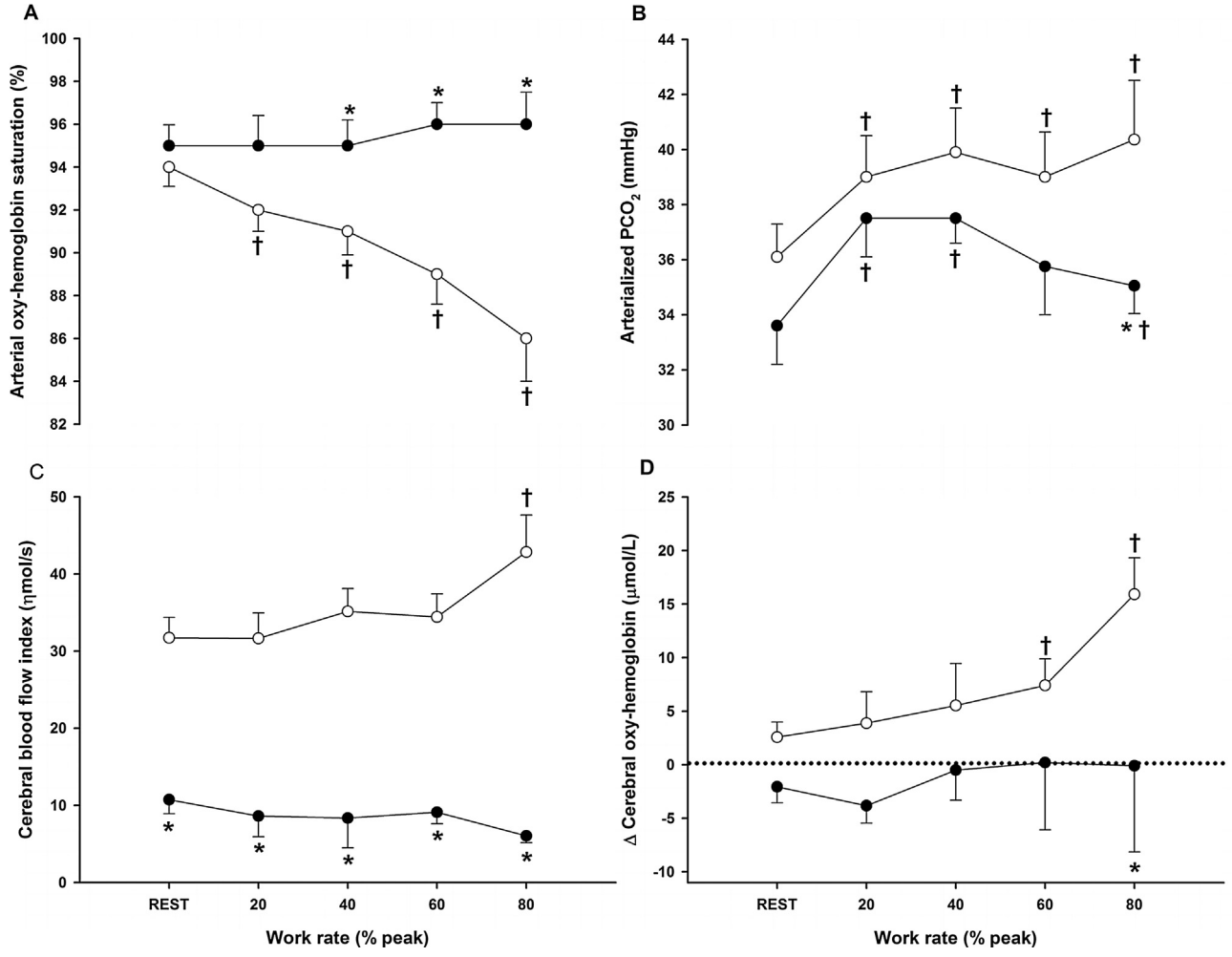

Fig. 2. Arterial oxygen saturation, arterialized partial pressure of carbon dioxide and cerebral blood flow and oxygenation in COPD (open symbols) and overlap (closed symbols).
*Between-group differences at a given time point; † intra-group differences versus rest.

also significantly reduced in overlap despite better preserved arterial oxygenation compared to COPD without heart failure. These abnormalities were associated with lower systemic perfusion pressure (↓mean arterial pressure) and flow (↓cardiac output) together with lower tensions of a potent cerebral vasodilator (↓$PaCO_2$). This study sets the scene for future investigations aimed at relating CBF and COx with clinically-relevant outcomes in overlap, including dyspnea, (Higashimoto et al., 2011) exercise intolerance, (Mentz et al., 2013; Oliveira et al., 2014) cerebrovascular disease (Nagayama et al., 2007) and cognitive impairment (Leto and Feola, 2014).

There is growing recognition that heart failure has devastating consequences for patients with COPD (Rutten et al., 2006; Güder and Rutten, 2014). Unfortunately, little is known on how these

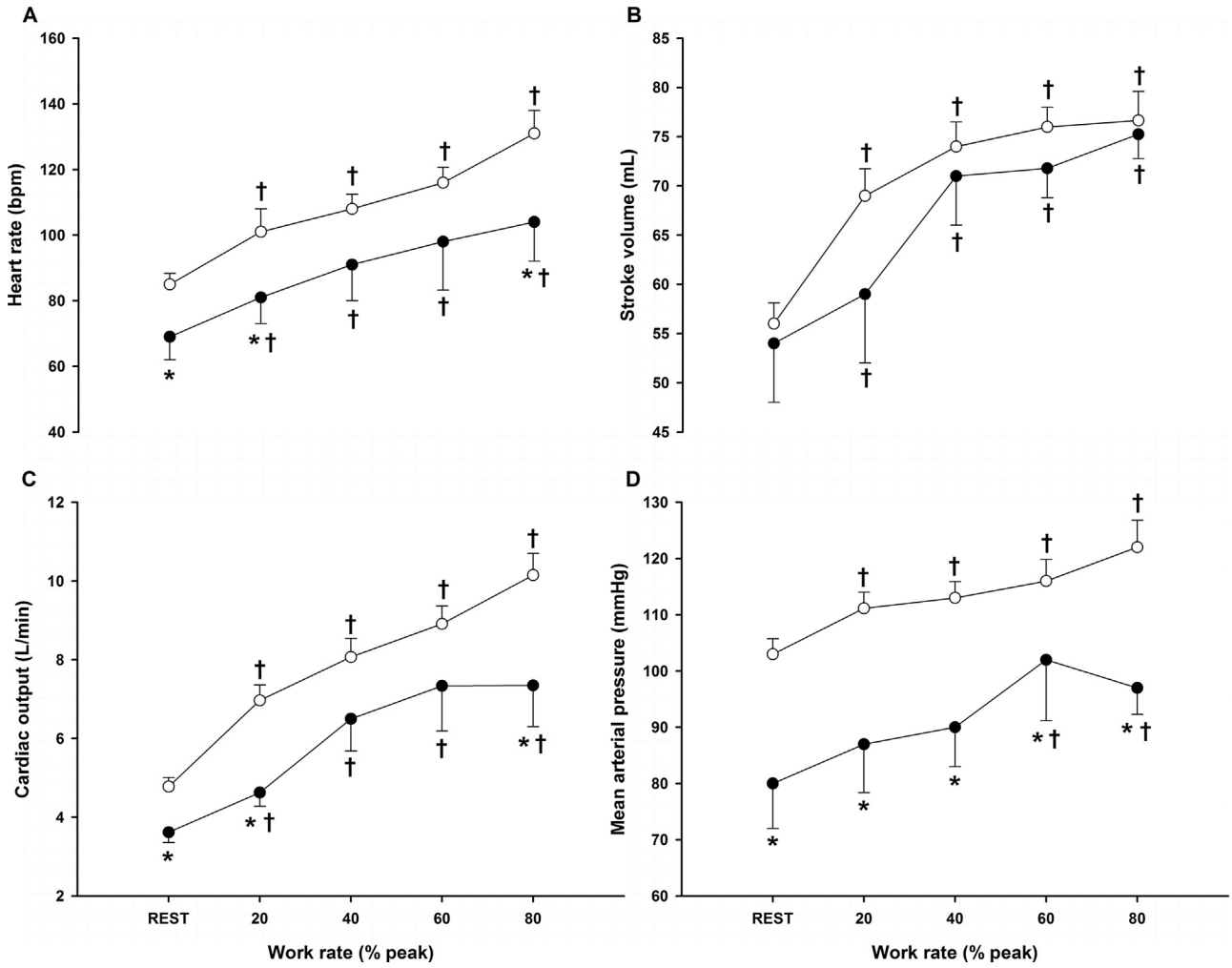

Fig. 3. Cardiovascular and hemodynamic responses to discontinuous, incremental exercise test in COPD (open symbols) and overlap (closed symbols). *Between-group differences at a given time point; † intra-group differences versus rest.

complex diseases interact to increase morbidity and mortality. The present study sheds light on a hitherto unexplored pathophysiological consequence of COPD-heart failure coexistence: impaired CBF and COx. The present data show that, while already present at rest, these abnormalities were magnified upon exertion (Fig. 2). This indicates that required adjustments to maintain, or increase, CBF and COx were particularly dysfunctional under challenging physiological conditions in overlap compared to COPD.

In this context, it should be recognized that CBF regulation during exercise is influenced by several physiological factors in addition to cerebral metabolic and neuronal activity (Ogoh and Ainslie, 2009). For instance, previous studies showed that a 1 mmHg increase and decrease in $PaCO_2$ led to an approximate 3–6% increase and 1–3% decrease in CBF, respectively (as reviewed by Willie et al., 2014). Even considering that potential impairments in cerebrovascular reactivity to CO_2 may have lessened these variations in CBF, (Xie et al., 2005) Part CO_2 (and $PETCO_2$) in the present study were typically lower during exercise in overlap compared to COPD. It is also noteworthy that between-group differences in Part CO_2 and CBF concomitantly widened from 60% to 80% peak exercise (Fig. 2B and C). Lower Part CO_2 can be explained by greater ventilatory responses to metabolic demand (i.e., higher $\dot{V}E/\dot{V}CO_2$) found in overlap (Table 2), a well-known physiological correlate of heart failure (Piepoli et al., 2010). Although hyperventilation likely attenuated exertional hypoxemia (Fig. 2A), this was outweighed by lower CBF as COx was significantly impaired in overlap (Fig. 2D), i.e., O_2 delivery was possibly insufficient to meet cerebral O_2 demands. In contrast, COPD patients maintained stable Part CO_2 values throughout exercise, likely secondary to worsening mechanical-ventilatory constraints (O'Donnell et al., 2014) induced by higher operating lung volumes (Table 1). In this sense, the "protective" effects of exertional hypercapnia on CBF in COPD (Yildiz et al., 2012; Oliveira et al., 2012; Vogiatzis et al., 2013; Hartmann et al., 2014; Cornwell and Levine, 2015; Alosco and Hayes, 2015) may have been offset by alveolar hyperventilation due to higher ventilatory drive in heart failure (Piepoli et al., 2010) combined with COPD.

Another major putative mechanism for impaired CBF in overlap patients was the consistently low mean arterial pressure (Fig. 3D). Although cerebral auto-regulation has long been thought to maintain CBF over a large range of mean arterial pressures, (Lassen, 1959) this has been more recently disputed (Ogoh and Ainslie, 2009). In fact, this seems to be particularly relevant during exercise where relatively mild decrements in mean arterial pressure may impair CBF (Willie et al., 2014). Moreover, there is recent evidence that impairments in cardiac output can negatively influence CBF during exercise, independently of $PaCO_2$ and cerebral auto-regulation (Ogoh et al., 2005). It could also be argued that negative cardiopulmonary interactions in overlap (in addition to

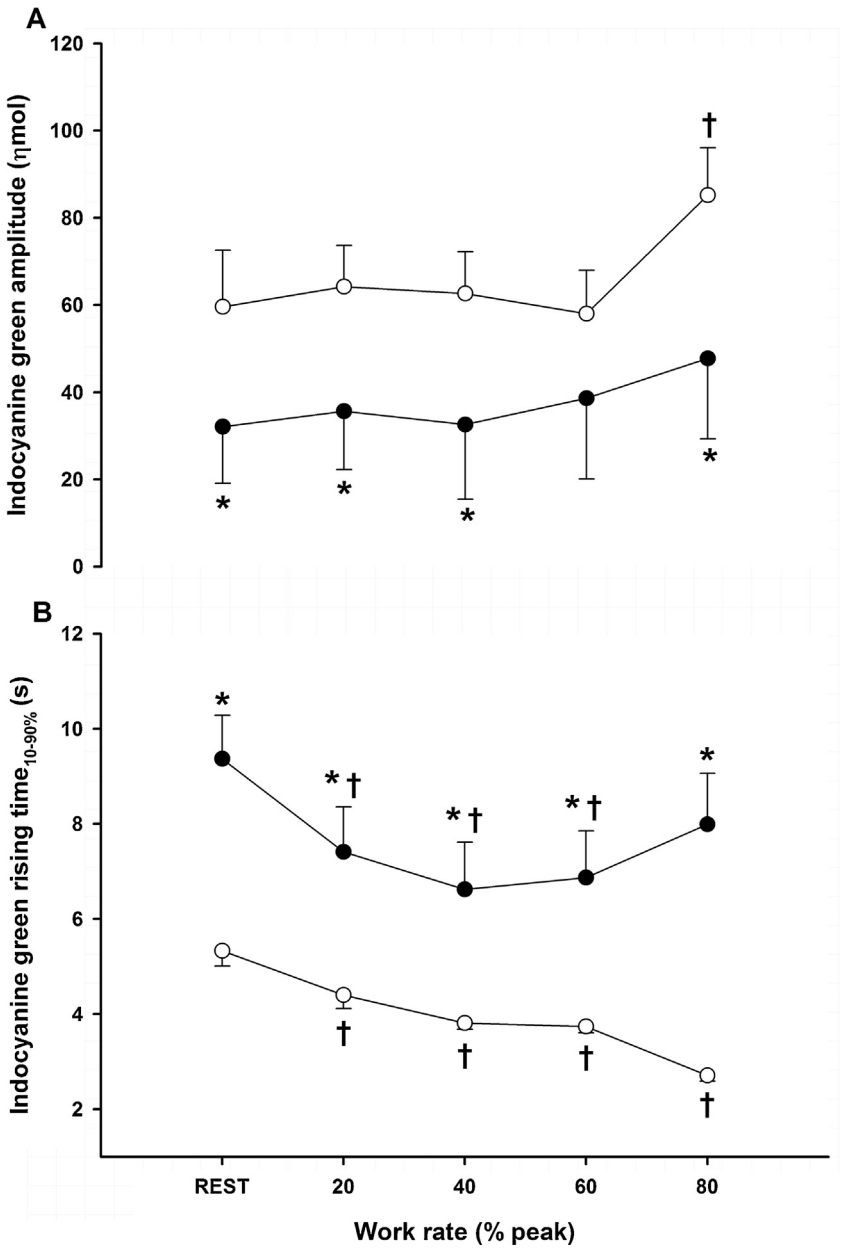

Fig. 4. Changes in indocyanine green amplitude and rising time as measured by near-infrared spectroscopy in COPD (open symbols) and overlap (closed symbols). *Between-group differences at a given time point; † intra-group differences versus rest.

the negative chronotropic effects of β-blockers) might lead to greater decrements in cardiac output thereby further impairing CBF (Oliveira et al., 2014). In fact, even in COPD patients without heart failure, improvements in cardiac output with non-invasive ventilation (under the same arterial oxygen content) (Rodrigues et al., 2013) had positive effects on COx. Thus, lower cerebral perfusion pressure (↓mean arterial pressure) and/or flow (↓cardiac output) may have compounded with higher intra-cerebral vessel resistance (↓$PaCO_2$) to impair CBF and COx in overlap. Collectively, these results illustrate the notion that CBF regulation in disease is a complex integrative process that involves pulmonary gas exchange and cardiovascular/hemodynamic function in addition to intracranial mediators of cerebral vessel resistance (Willie et al., 2014).

There are other physiological derangements associated with heart failure that might bear a negative influence on CBF in overlap. Neurohumoral and/or metabolic factors such as the renin-angiotensin system, endothelin, adiponectin and other metabolites have been related to chronic changes in vascular function (Choi et al., 2006). Although controversial, (van Lieshout and Secher, 2008) it is also conceivable that elevated sympathetic nerve activity may induce cerebral vasoconstriction. In addition, abnormal arterial baroreflex control of sympathetic nerve activity may negatively influence CBF during exercise (Ogoh et al., 2006).

The observed abnormalities on CBF and COx likely have relevant implications for the clinical care of overlap patients. Firstly, low CBF and COx might negatively influence patients' cognition, (Alosco et al., 2014; Leto and Feola, 2014) an important outcome related to disability and quality of life in COPD and heart failure. Secondly, these derangements might lead to reductions in central motor drive to the working muscles ("central fatigue")(Oliveira et al., 2014) and/or increased perception of negative respiratory (Higashimoto et al., 2011) and muscular sensations (Table 1) thereby contributing to early exercise termination. However, COPD and overlap had similar WR_{peak} (Table 1), suggesting

that those impairments did not contribute decisively to reduce peak exercise capacity in the present study. Whether this also holds true for endurance exercise tolerance remains to be investigated. Thirdly, they provide plausible mechanistic bases for the reported greater risk of overlap patients to develop cerebrovascular disease and ischemic stroke (Mentz et al., 2013, 2014). Finally, CBF regulation might also be impaired in other conditions such as COPD exacerbation, (Yildiz et al., 2012) heart failure decompensation (Choi et al., 2006) and mechanical ventilation (Cannizzaro et al., 1997). In those challenging situations, our results suggest that extra care should be taken to avoid iatrogenic reductions in cerebral perfusion induced by volume depletion (excessive diuresis), low cardiac output (high intrathoracic pressures) (Oliveira et al., 2014) or sudden decrease in the prevailing $PaCO_2$ tensions (alveolar hyperventilation) (Cannizzaro et al., 1997).

The present investigation has, naturally, some limitations. CBF index by NIRS is only a relative measure of blood flow, i.e., it is proportional to flow with an unknown factor of proportionality. Thus, BFI is better suited to intra- rather than inter-subject comparisons. (Habazettl et al., 2010) Nevertheless, Fig. 4 shows that both ICG kinetic parameters were consistently different, i.e. lower amplitude and faster rate of increase in overlap compared to controls. Thus, although our results showed a marked decrease in CBF in overlap patients (Fig. 2C), we were unable to precise the extent of those impairments. We used ΔO_2Hb and TOI (which depends on both O_2Hb and deoxy-Hb) to assess changes in COx during incremental exercise. Owing to the fact that fractional O_2 extraction is substantially lower in the cerebral tissue compared to skeletal muscle (Ogoh and Ainslie, 2009) and the influence of venous blood volume on cerebral deoxy-Hb (Hoshi et al., 2001), the former likely reflects better changes in CBF under dynamic conditions. Thus, if HbO_2 and HHb increase proportionally with CBF, cerebral TOI might become relatively stable. In fact, Hoshi et al. (2001) found that HbO_2 was the most sensitive NIRS-based indicator of changes in CBF in a perfused rat brain model. Our patients had no previous history/diagnosis of carotidal disease but we cannot rule out the hypothesis that worse extra-cranial atherosclerotic disease contributed to lower CBF in overlap herein (Nagayama et al., 2007). We acknowledge that our sample is relatively small and certainly not representative of the whole spectrum of COPD and heart failure severity. Nevertheless, it is unlikely that systematic type II error was present as most of the between-group differences were sufficiently large to reach statistical significance at the 5% level. The impact of heart failure on patients with end-stage COPD showing overt respiratory insufficiency at rest (i.e., hypoxemia and/or hypercapnia) (Jensen et al., 2002) remains to be investigated.

In conclusion, this is the first demonstration that marked impairments in resting CBF are worsened by the stress of exercise in COPD patients presenting heart failure as co-morbidity. These abnormalities precluded COx to increase throughout exercise, a likely consequence of the combined deleterious effects of systemic hemodynamic impairment and lower $PaCO_2$ in overlap. If CBF and COx prove to be associated with clinically-relevant outcomes (e.g., dyspnea, exercise intolerance, cerebrovascular disease and cognitive impairment), cerebral hemodynamics and oxygenation may become useful therapeutic targets for overlap patients.

Conflict of interest

All authors declare that they have no conflict of interest related to the present study.

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