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Letter to the Editor

Heart Failure Impairs Cerebral Oxygenation During Exercise in Patients with COPD

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Summarizing sentence

Exercise capacity and cerebral oxygenation are reduced in COPD-heart failure overlap compared to COPD in isolation.

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To the Editor

Impaired systemic O_2 delivery – particularly during exertion - is the key pathophysiological feature shared by chronic obstructive pulmonary disease (COPD) and heart failure with reduced left ventricular ejection fraction (HF_{rEF}). Unfortunately, COPD and HF_{rEF} frequently coexist not only because their high individual prevalence but also due to common risk factors, including cigarette smoking, advanced age, oxidative stress, and systemic inflammation.[1]

It is expected that any reduction in the rate of O_2 transfer due to COPD and/or HF_{rEF} would be particularly deleterious to tissues heavily dependent upon constant O_2 flow, e.g., the central nervous system (as reviewed in ref. [2]). Exercise cerebral oxygenation (COx as non-invasively determined by near-infrared spectroscopy) depends upon the dynamic balance between the instantaneous rate of O_2 delivery and O_2 utilization.[3] Koike et al., for instance, reported that CHF HF_{rEF} was associated with appreciable decreases in COx during exertion [4]. Our laboratory found that exercise COx might be impaired in some patients with more advanced COPD – even if not overtly hypoxemics.[5] Moreover, improvement in cardiac output with non-invasive ventilation (under same arterial O_2 content) had positive effects on COx in COPD.[6] These data suggest that reduced cerebral blood flow might be mechanistically linked to impaired exercise COx in some patients with moderate-to-severe COPD. It is conceivable that the presence of HF_{rEF} would further deteriorate this scenario by adding components of dysfunctional cerebral auto-regulation, lower cardiac output and hypocapnea-induced vasoconstriction.[4] The compound effects of HF_{rEF} *plus* COPD on COx and its relationship with exercise tolerance, however, remain unknown. In order to address these issues, we simultaneously assessed COx, systemic haemodynamics and gas exchange during progressive exercise in COPD patients presenting or not with HF_{rEF} as co-morbidity.

Thirty-three men with stable, non-hypercapnic ($PaCO_2$ < 45 mmHg at rest) COPD with a long history of smoking (> 20 pack-years), breathlessness in daily life (modified Medical Research Council Scale scores > 2), and moderate-to-severe airflow obstruction comprised the study group. Patients from the COPD+HF_{rEF} group (N= 18) presented with left ventricular EF by Doppler echocardiography < 40 % and well-established diagnosis of CHF (dyspnea on exertion, elevated jugular venous pressure, cardiomegaly, peripheral oedema and pulmonary crepitations) due to underlying ischaemic heart disease. All patients were under standard contemporary therapy for HF_{rEF}. Fifteen patients from the COPD clinic without clinical, echocardiographic and laboratorial evidences of CHF (N= 15) were matched by age and MRC grade (**Table**). Main exclusion criteria included long-term ambulatory O_2 therapy, severe pulmonary hypertension (mean pulmonary artery pressure ≥ 40 mm Hg), anaemia ([haemoglobin] < 13 g%), and recent exacerbation (within 1 month). After signing an informed consent (as approved by the local Medical Ethics Committee), patients underwent a ramp-incremental cardiopulmonary exercise test with assessment of arterialized PCO_2. Changes from rest (Δ) in pre-frontal COx (oxy-hemoglobin, [HbO_2]) by near infrared spectroscopy (NIRO 200™; Hamamatsu Photonics KK, Japan) and cardiac output by trans-thoracic cardioimpedance (PhysioFlow PF-5™, Manatec Biomedical, France).[7] Based on a pooled analysis of our previous data in normal older subjects and patients with COPD,[5,6] Δ COx increases < 1.10 fold and/or any reduction were assumed to indicate a physiologically-inadequate response. One-way ANOVA with repeated measures was used to identify statistically significant between group differences across different time-points. Pearson's correlation analysis was used to assess association between variables. For all tests, a statistical significance of 0.05 was used.

We found that COPD+HF_{rEF} patients had lower maximal exercise capacity than their counterparts with COPD. In addition, the former group showed

increased ventilatory response to metabolic demand which was associated with greater O_2 saturation (**Figure 1b**) but lower arterialized and end-tidal PCO_2 than their counterparts with COPD (**Table**). COPD+HF_{rEF} patients showed blunted hemodynamic responses (cardiac output and mean arterial pressure) during sub-maximal (**Figures 1c** and **1d**) and maximal exercise (**Table**). Changes in ΔCOx with exercise progression were also reduced in the COPD+HF_{rEF} group (**Figure 1a**). In fact, whereas ΔCOx increased in 11/15 (73.3%) patients with COPD it remained stable or even decreased in 14/18 (77.7%) patients with COPD+HF_{rEF}. ΔCOx was particularly impaired in patients in whom mean systemic arterial pressure remained stable or decreased ($p<0.05$). Interestingly, peak work rate was related to sub-maximal ΔCOx (area under the curve to an iso-work rate of 40 W) only in the COPD+HF_{rEF} group ($r= 0.67$, $p<0.01$).

Lower arterial O_2 content could be a potential explanation for reduced COx in COPD+ HF_{rEF} as CHF *per se* can reduce lung diffusing capacity, worsen ventilation/perfusion mismatch and decrease mixed O_2 venous pressure. However, we found rather the opposite as these patients showed better-preserved arterial oxygenation than their counterparts with COPD alone. Lower PCO_2 and impaired cerebral perfusion pressure (either due to low mean arterial pressure and/or cardiac output) emerge as the obvious culprits. Indeed, mean arterial pressure – a major determinant of cerebral blood flow – [8] was reduced throughout the exercise tests and related to COx in COPD+HF_{rEF}. Slight impairments in mean arterial pressure might reduce cerebral blood flow, particularly in the presence of impaired auto-regulation and excessive sympathetic drive.[3,8] There is also some evidence that decreased cardiac output may impair exercise COx, independent of mean arterial pressure.[8] All patients were under cardio-selective β–blocker therapy and diminished heart rate response was the main mechanism for a reduced exercise cardiac output. This suggests a link between pharmacologically-induced decrements in exercise chronotropic response and low exercise COx.

What are the practical relevance of these findings ? Our data suggest that pharmacological treatment of HF_{rEF} should take into consideration that the pre-frontal cortex is particularly sensitive to pressure perfusion impairments in patients with COPD. Impaired exercise ΔCOx is an independent prognostic factor in patients with cardiovascular disease and a predictor of cerebral ischaemic events.[3] It is noteworthy that stroke is more frequent in COPD patients when HF_{rEF} coexists.[9] It is also conceivable that COx deficits reported herein would be observed in other clinical scenarios, such as acute exacerbations or diuretic-induced hypovolemia. Derangements in ΔCOx may also reduce motor output ("central fatigue") and contribute to early exercise cessation.[2] In fact, ΔCOx was related to peak exercise capacity only in the COPD+HF_{rEF} group. If future studies establish a cause-effect relationship, interventions aimed at improving cerebral blood flow during exertion might prove useful ergogenic aids for these patients.

Limitations of this study include its small sample size, heterogeneity of COPD severity, non-invasive determination of cardiac output, lack of cognition and cerebral blood flow measurements. It should be recognized, however, that $\Delta[HbO_2]$ is not only a useful indicator of changes in intra-cerebral perfusion but also relates closely with cognition (reviewed in ref. [10]). The COPD+HF_{rEF} group showed less airflow obstruction than their counterparts with COPD. Thus, we might have underestimated the deleterious effects of HF_{rEF} on cerebral haemodynamics in COPD. It also remains to be demonstrated whether impairment in COx in COPD+HF_{rEF} is out of proportion relative to HF_{rEF} alone.

In conclusion, this study provides novel evidence that the coexistence of HF_{rEF} impairs cerebral oxygenation (and conceivably cerebral blood flow) during exercise in moderate-to-severe COPD. Additional studies are warranted to address whether this might be contributory to exercise intolerance and its clinical implications for prognosis, treatment and rehabilitation of the fast-growing population of patients with the COPD+HF_{rEF} overlap.

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Table. Resting and exercise characteristics in COPD patients presenting or not heart failure with reduced ejection fraction (HF_{rEF}) as co-morbidity.

	COPD+HF_{rEF} (N= 18)	**COPD (N= 15)**
General characteristics		
Age (yrs)	67 ± 7	65 ± 8
Body mass index (kg/m²)	25.0 ± 4.1	24.2 ± 3.9
Smoking (pack-yrs)	51.3 ± 30.1	45.5 ± 26.5
Left ventricular ejection fraction (%)	35.3 ± 7.6*	64.9 ± 3.8
Lung Function		
FEV_1		
(L)	1.70 ± 0.52	1.31 ± 0.64
(% pred)	64.1 ± 18.3*	46.3 ± 15.6
FEV_1/FVC	63.1 ± 9.3*	41.7 ± 9.4
TLC (% pred)	83.5 ± 22.5*	109.3 ± 12.6
T_{LCO} (% pred)	51.4 ± 14.2	56.9 ± 16.1
PaO_2 (mmHg)	65.3 ± 7.0	61.9 ± 9.2
$PaCO_2$ (mmHg)	34.1 ± 3.3	37.6 ± 6.6
Exercise		
Peak work rate (W)	53 ± 24	65 ± 24
Peak oxygen uptake		
L/min	1.03 ± 0.32*	1.21 ± 0.30
% predicted	52 ± 12*	64 ± 14
Cardiac output (L/min)		
Absolute	8.9 ± 2.6*	10.9 ± 3.0
Δ from rest	3.1 1.8*	4.3 ± 1.5
Mean arterial pressure (mmHg)		
Absolute	99 ± 20*	120 ± 14
Δ from rest	8 ± 5*	22 ± 7
$\Delta\dot{V}E/\Delta\dot{V}CO_2$	38.7 ± 9.3*	28.8 ± 7.2
$P_{ET}CO_2$ (mmHg)	31.8 ± 5.8*	37.6 ± 6.1
PCO_2art (mmHg)		
Absolute	32.4 ± 5.2*	38.1 ± 6.7
Δ from rest	0.6 ± 2.3*	4.7 ± 2.1
SpO_2 (%)		
Absolute	93 ± 3*	90 ± 6
Δ from rest	0 ± 3*	-4 ± 3

Definition of abbreviations: FEV_1= forced expiratory volume in one second; FVC= forced vital capacity; TLC= total lung capacity; T_{LCO}= transfer factor; Pa= arterial partial pressure; $\dot{V}E$= ventilation; $\dot{V}CO_2$= carbon dioxide output; P_{ET}= end-tidal pressure; art= arterialized blood; SpO_2= oxyhemoglobin saturation by pulse oximetry.

FIGURE LEGEND

Figure. Changes in (a) pre-frontal cerebral oxygenation (ΔCOx), (b) oxyhaemoglobin saturation by pulse oximetry (SpO_2), (c) cardiac output (Q_T), and (d) mean arterial pressure (MAP) as a function of exercise intensity in COPD patients presenting (*closed circles*) or not (*open circles*) heart failure with reduced ejection fraction (HF_{rEF}) as co-morbidity.

Footnotes: Data are mean (SE); * $p<0.05$ for between group comparisons; † for intra-group comparisons against unloaded cycling.