Inspiratory resistance decreases limb blood flow in COPD patients with heart failure

To the Editor:

Chronic heart failure (CHF) with reduced left ventricular ejection fraction is a common and disabling comorbidity of chronic obstructive pulmonary disease (COPD) [1]. Understanding the mechanisms underlying exercise intolerance is paramount to providing a rationale to effectively rehabilitate the fast-growing population of patients with COPD plus CHF.

The inspiratory muscles, in particular, are characteristically overloaded in COPD plus CHF, with greater elastic and resistive work of breathing. Moreover, these muscles might be functionally weakened as ventilation increases during exercise in patients with COPD [2]. It has been postulated that fatiguing contractions would stimulate diaphragmatic thinly myelinated group III and unmyelinated group IV fibres, thereby increasing limb sympathetic outflow and vascular resistance. The so-called respiratory muscle metaboreflex would then redirect blood flow from locomotor to respiratory muscles to avoid, or at least postpone, the impending failure of the "vital pump" [3, 4]. In this context, we previously found marked blood flow reduction to nonactive and active limbs during inspiratory resistive loading in CHF [5]. Work from our laboratory also showed improved peripheral muscle oxygen delivery after respiratory muscle unloading (under stable cardiac output and arterial oxygen content) in CHF-free COPD [6] and COPD-free CHF [7]. It is therefore conceivable that the coexistence of CHF would potentiate the respiratory muscle metaboreflex in patients with a primary diagnosis of COPD.

After giving informed consent, 22 optimally treated patients with moderate-to-severe (Global Initiative for Chronic Obstructive Lung Disease stage II–III) COPD (10 with coexistent CHF, *i.e.* left ventricular ejection fraction <45% by echocardiography) and 10 age- and sex-matched controls underwent a ramp-incremental exercise test for peak oxygen uptake determination. On a different visit, subjects were randomly assigned to breathe through an inspiratory resistance set at 60% maximal inspiratory pressure (MIP) to task failure (*i.e.* mouth pressure <80% of the individual target during three consecutive breaths) or 2% MIP for 3 min. While being continuously encouraged by the same investigator, participants maintained a mean±SD breathing frequency of 15±1 breaths·min^{-1} and duty cycle (inspiratory to total respiratory time ratio) of 0.7±0.1 by following visual feedback. Arterial oxygen saturation measured by pulse oximetry (S_{PO_2}), end-tidal carbon dioxide tension (P_{ETCO_2}) and mean arterial blood pressure (MAP) were measured during the trials. Calf blood flow was obtained by venous occlusion plethysmography (TL-400; Hokanson, Bellevue, WA, USA) and vascular resistance was calculated as MAP/calf blood flow. Between-group comparisons across time points were performed by two-way repeated-measures ANOVA with Bonferroni adjustment. The overall probability of a type I error was set at 5%.

COPD plus CHF patients showed greater forced expiratory volume in 1 s (FEV_1) but lower forced vital capacity than their counterparts without CHF. They had the lowest MIP and peak oxygen uptake amongst the three groups ($p<0.05$; data not shown). Resting calf blood flow was lower (and resistance higher) in this group compared to controls. The 2% MIP trial had no significant effect on the responses of interest (fig. 1a, c and e). Owing to the differences in MIP, COPD plus CHF patients performed the 60% MIP trials at lower absolute loads than COPD and controls (36±5, 50±10 and 68±7 cmH_2O, respectively; $p<0.01$). Time to task failure in these trials was ~35% and ~50% lower in the COPD plus CHF group compared with the other groups (185±35, 284±82 and 365±88 s, respectively; $p<0.01$). Despite shorter trials, calf blood flow was reduced (and vascular resistance increased) to a greater extent in COPD plus CHF than COPD alone ($p<0.05$) (fig. 1b, d and f). End-test heart rate and S_{PO_2}, however, were higher in the former group (96±9 *versus* 92±13 beats·min^{-1} and 92±2% *versus* 84±3%, respectively; $p<0.05$). Decrements in calf blood flow were inversely related to MIP and peak oxygen uptake across the groups ($r= -0.66$ and -0.69, respectively; $p<0.01$).

The present study showed supporting evidence of exacerbated respiratory muscle metaboreflex in patients with COPD plus CHF compared with those with COPD in isolation and healthy controls. Notably, this was observed despite the respiratory muscles having been challenged at lower absolute intensities in this group.

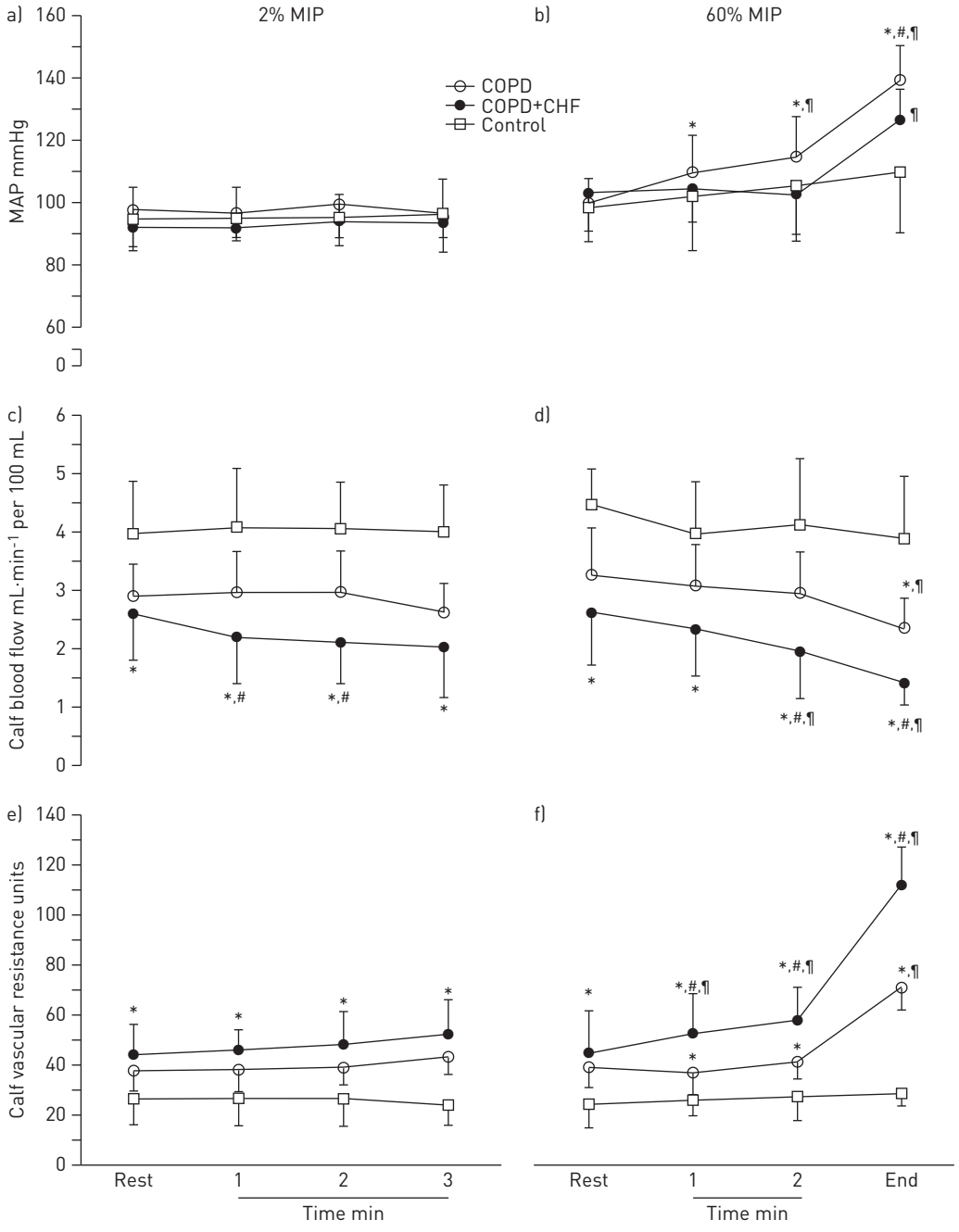

FIGURE 1 Physiological responses to inspiratory resistive loading set at 2% (sham) and 60% maximal inspiratory pressure (MIP) in patients with chronic obstructive pulmonary disease (COPD) or COPD plus chronic heart failure (CHF) and healthy controls. The 2% MIP trials lasted 3 min in all participants. Compared with controls, however, the 60% trials were significantly shorter in the COPD plus CHF group compared with COPD alone and controls, respectively (see main text for actual values). Data are presented as mean±SD. MAP: mean arterial blood pressure. *: $p<0.05$, COPD plus CHF or COPD *versus* controls; #: $p<0.05$, COPD plus CHF *versus* COPD; ¶: $p<0.05$, within-group difference from rest.

CHF *per se* is associated with sympathetic overstimulation and it could be argued that the disease would exacerbate the metaboreflex regardless of any coexisting condition. In fact, calf vascular resistance was higher in COPD plus CHF even before the inspiratory resistance challenges, which suggests increased resting sympathetic tone in these patients. Considering that patients with CHF alone were not evaluated, it remains uncertain whether impairment in calf blood flow would be greater in COPD plus CHF than CHF matched by haemodynamic impairment. Albeit to a lesser extent (and after longer trials), patients with COPD alone also showed increased vascular resistance. The respiratory muscle metaboreflex is expected to be particularly active when cardiac output is taxed by negative cardiopulmonary interactions such as those elicited by

dynamic hyperinflation [8–11]. Our experimental conditions (large inspiratory resistance and duty cycle) probably reduced diaphragmatic blood flow through forceful inspiration and increased the operating lung volumes as the expiratory time became shorter. It should be noted, however, that impaired cardiac output alone is unlikely to fully justify lower calf blood flow in COPD plus CHF than COPD, as vascular resistance was higher in the former group. FEV1 and S_{PO_2} were both greater in COPD plus CHF, which argues against a role of worsening airflow obstruction and hypoxaemia in explaining these findings.

We found significant correlations between lower calf blood flow during the 60% MIP trials and reduced MIP and peak oxygen uptake. This is in line with the notion that the respiratory muscle metaboreflex is likely to be exacerbated in patients with inspiratory muscle weakness [5]. Moreover, the reflex might have contributed to exercise limitation in patients with COPD plus CHF. Previous findings showing concomitant increases in exercise tolerance and leg oxygen delivery after heliox [8, 9] and bronchodilators [10, 11] in COPD also lend support to this notion. The present results, however, cannot be unrestrictedly extrapolated for exercise conditions, as the modulating effects of functional sympatholysis on the peripheral effects of inspiratory resistive loading were not tested.

We acknowledge that neither increased limb muscle sympathetic nerve activity nor respiratory muscle fatigue were experimentally demonstrated in COPD plus CHF. Nevertheless, it is difficult to envisage an alternative explanation for the observed increase in calf vascular resistance with respiratory muscle overloading. Subjects were actively encouraged to sustain the 60% MIP trials and the continuous recording of mouth pressure indicated a pattern of slow and progressive decline towards the threshold for test interruption, which suggests fatigue development rather than lack of motivation. P_{ETCO_2} remained stable in all groups, which is reassuring that hyperventilation did not contribute to peripheral vasoconstriction in COPD plus CHF. A relatively young group of patients (typically 45–60 years old) volunteered for study participation and larger effects of inspiratory resistive loading on peripheral blood flow might have been found had we evaluated older patients with larger perfusion deficits.

We conclude that volitional efforts against an inspiratory resistance to task failure were associated with increased vascular resistance and lower blood flow in the resting calf of patients with COPD who had comorbid CHF. This is the first study to suggest augmented respiratory muscle metaboreflex activity in these patients, a deleterious adjustment that might contribute to poor tolerance to exertion. Whether inspiratory muscle training could mitigate this phenomenon, as previously shown in healthy subjects [12], and contribute to enhance patients' exercise capacity remains open to investigation.

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Inspiratory resistance lowers limb blood flow and relates to impaired exercise capacity in patients with COPD plus CHF http://ow.ly/qMRYK

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Exercise oxygen uptake efficiency slope independently predicts poor outcome in pulmonary arterial hypertension

To the Editor:

Pulmonary arterial hypertension (PAH) remains a disabling and frequently lethal disease despite remarkable advances in treatment. Cardiopulmonary exercise testing (CPET) has proved a valuable tool to objectively quantify disease severity and estimate prognosis in these patients [1–3].

Exercise intolerance is characteristically multifactorial in PAH. Among its potential contributing mechanisms, increased ventilatory response, deranged pulmonary mechanics, peripheral muscle impairment and reduced oxygen delivery have been more widely investigated [1–5]. In this context, a CPET-derived variable that conflates the effects of increased ventilation and poor O_2 transfer and/or peripheral O_2 utilisation is the O_2 uptake efficiency slope (OUES) [6]. OUES is the slope of the linear relationship between O_2 uptake ($V'O_2$) and the logarithmic transformation of minute ventilation ($V'E$) during rapidly incremental exercise, *i.e.* it aims to reflect how effectively O_2 is extracted from the atmosphere and taken into the body as exercise progresses. We recently found that a combination of increased sub-maximal exercise $V'E$ as a function of carbon dioxide output ($V'CO_2$) and reduced O_2 delivery/utilisation (as suggested by shallow $V'O_2$–work rate relationship) were independent predictors of negative outcome in PAH of mixed aetiology [7]. These findings prompted the hypothesis that OUES would combine the prognostic information provided separately by those variables, thereby being the single predictor of poor outcome in our cohort.

In order to address this question, we revisited our dataset and contrasted OUES prognostic relevance with that of a range of resting and cardiopulmonary exercise responses to ramp-incremental cycle ergometry. In the previous report [7], we described results from a group of 84 patients in whom 16 PAH-related deaths and two atrial septostomies were observed in a 5-year follow-up. In this present article, we extend these observations to 98 patients (70 females, 48 with idiopathic PAH and 50 with associated PAH) followed for up to 6.5 years, in whom 17 PAH-related deaths and four atrial septostomies were recorded. Receiver operating characteristic (ROC) curves were used to obtain the best cut-offs for prognostication. Cox proportional hazards and Kaplan–Meier cumulative survival analyses were performed following standard procedures. The statistical significance for all tests was $p<0.05$.

We found that event-positive patients showed lower OUES than their counterparts (mean$\pm$SD 0.72 ± 0.27 L·min^{-1} per log$V'E$ *versus* 0.91 ± 0.31 L·min^{-1} per log$V'E$, $p<0.05$). OUES was significantly related to prognosis in the univariate analysis (hazard ratio (HR) (95% CI) 9.5 (3.8–23.8), $p<0.01$). The ROC curve analysis (area under the curve 0.688, 95% CI 0.542–0.833; $p<0.01$) indicated a best OUES cut-off for prognostication of 0.56 L·min^{-1} per log$V'E$. Among a range of resting and exercise variables, only peak O_2 uptake ($V'O_2$peak), $V'E/V'O_2$peak, change in $(\Delta)V'E/\Delta V'CO_2$ and $\Delta V'O_2/\Delta$work rate were also predictors of poor outcome in the univariate analysis (HR (95% CI) 2.4 (1.1–5.7), 8.4 (1.2–55), 4.2 (1.5–11.6) and 6.8 (2.6–17.3), respectively; $p<0.05$). Considering the close similarity between OUES and $V'E/V'O_2$peak, multivariate regression analyses were performed using either of these variables. The