Letter to the Editor

Inspiratory Resistance Decreases Limb Blood Flow in COPD Patients with Heart Failure

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Summarizing sentence

Inspiratory resistive loading to task failure decreases limb blood flow and it is related to impaired exercise capacity in patients with COPD plus CHF.

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To the Editor:

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

The inspiratory muscles, in particular, are characteristically overloaded in both COPD and CHF in tandem 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 fibers 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 non-active and active limbs during inspiratory resistive loading in CHF [5]. Work from our laboratory also showed improved peripheral muscle O2 delivery after respiratory muscle unloading (under stable cardiac output and arterial O2 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 signing an informed consent, 22 optimally-treated patients with moderate-to-severe, GOLD 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 O2 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 3 consecutive breaths) or 2% MIP for 3 min. While being
continuously encouraged by the same investigator, participants maintained breathing frequency of 15 ± 1 breaths/min and duty cycle (inspiratory to total respiratory time) of 0.7± 0.1 by following visual feedback. Arterial O2 saturation by pulse oximetry (SpO2), end-tidal partial pressure for CO2 (PETCO2) and mean arterial blood pressure (MAP) were measured during the trials. Calf blood flow was obtained by venous occlusion plethysmography (TL-400™, Hokanson, Bellevue, 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+CHF patients showed greater FEV1 but lower FVC than their counterparts without CHF. They had the lowest MIP and peak O2 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 (Figure, left). Owing to the differences in MIP, COPD+CHF patients performed the 60% MIP trials at lower absolute loads than COPD and controls (36 ± 5 cmH2O, 50 ± 10 cmH2O, and 68 ± 7 cmH2O, respectively; p<0.01). Time to task failure in these trials were ~ 35 % and ~ 50% lower in the COPD+CHF group compared to the other groups (185 ± 35 s vs. 284 ± 82 s vs. 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+CHF than COPD (p<0.05; Figure, right). End-test heart rate and SpO2, however, were higher in the former group (96 ± 9 bpm vs. 92 ± 13 bpm and 92 ± 2 % vs. 84 ± 3 %; p<0.05). Decrements in calf blood flow were inversely related to MIP and peak O2 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 to those with COPD on isolation and healthy controls. Of note, this was observed despite the respiratory muscles have been challenged at lower absolute
intensities in this group. CHF *per se* is associated with sympathetic overstimulation and it could be argued that the disease would exacerbate the metaboreflex regardless any coexisting condition. In fact, calf vascular resistance was higher in COPD+CHF even before the inspiratory resistance challenges which suggest 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+CHF than CHF matched by hemodynamic impairment. Albeit at 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 the 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+CHF than COPD as vascular resistance was higher in the former group. FEV₁ and SpO₂ were both greater in COPD+CHF which pose against a role of worsening airflow obstruction and hypoxemia in explaining these findings.

We found significant correlations between lower calf blood flow during the 60% MIP trials and reduced MIP and peak O₂ 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+CHF. Previous findings showing concomitant increases in exercise tolerance and leg O₂ 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+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. PETCO₂ remained stable in all groups which is reassuring that hyperventilation did not contribute to peripheral vasoconstriction in COPD+CHF. A relatively young group of patients (typically 45 to 60 yrs 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 CHF as co-morbidity. 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.
REFERENCES

FIGURE LEGEND

FIGURE. Physiological responses to inspiratory resistive loading set at 2% (sham) and 60% maximal inspiratory pressure (MIP) in patients with chronic obstructive pulmonary disease (COPD), COPD plus chronic heart failure (CHF) and healthy controls. The 2% trials lasted 3 min in all participants. Compared to controls, however, the 60% trials were significantly shorter in the COPD+CHF group compared to COPD and controls, respectively (see text for actual values).
Footnotes: Values are mean ± SD. *= COPD + CHF or COPD vs controls; † = COPD + CHF vs. COPD; ‡ within-group difference from rest (p<0.05).