Excess ventilation in COPD-heart failure overlap: implications for dyspnea and exercise intolerance

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Scientific Knowledge on the Subject
Heart failure is a common and disabling co-morbidity of COPD. Understanding the mechanisms of diminished exercise tolerance in those with combined diseases is paramount to mitigate symptom burden and improve health-related quality of life. In this context, there is growing evidence that heart failure increases the ventilatory requirements for exercise in COPD (ventilatory inefficiency). The mechanisms of this increased ventilatory inefficiency and its consequences for exercise intolerance remains poorly understood in this growing patient population.

What This Study Adds to the Field
Ventilatory inefficiency was inversely related to the regulated CO$_2$ tension in arterialized blood. Thus, particularly high ventilatory equivalents for CO$_2$ were found in a sub-group of patients presenting with resting and exercise hypocapnia (alveolar hyperventilation). Increased drive to breathe led to a ventilatory response beyond that required to wash-out metabolically produced CO$_2$ and overcome an enlarged physiological dead space. Although alveolar hyperventilation was beneficial to arterial oxygenation, increases in ventilation led to earlier critical mechanical constraints, greater dyspnea scores and poorer exercise tolerance. Decreasing neural drive without disturbing pulmonary gas exchange (e.g., exercise training) might prove useful to enhance exercise tolerance in COPD-heart failure patients in whom an incremental cardiopulmonary exercise test demonstrates poor ventilatory efficiency.
Abstract

Background: An increased ventilatory response to exertional metabolic demand (high ventilation (\(V_E\))/carbon dioxide output (\(VCO_2\)) relationship) is a common finding in patients with coexistent COPD-heart failure. We aimed to determine the mechanisms underlying high \(V_E/VCO_2\) and its impact on operating lung volumes, dyspnea and exercise tolerance in these patients.

Methods: Twenty-two ex-smokers with combined COPD and heart failure with reduced left ventricular ejection fraction (LVEF) undertook, after careful treatment optimization, a progressive cycle exercise test with capillary (c) blood gas collection.

Results: Regardless the chosen metric (increased \(V_E \cdot VCO_2\) slope, \(V_E/VCO_2\) nadir or end-exercise \(V_E/VCO_2\)), ventilatory inefficiency was closely related to PcCO\(_2\) (r values from -0.80 to -0.84; p<0.001) but not dead space /tidal volume ratio. Ten patients consistently maintained exercise PcCO\(_2\) ≤ 35 mmHg (hypocapnia). These patients had particularly poor ventilatory efficiency than non-hypocapnic patients. (p<0.05) Despite the lack of between-group differences in spirometry, lung volumes and LVEF, hypocapnic patients had lower resting PaCO\(_2\) and lung diffusing capacity (p<0.01). Excessive ventilatory response in this group was associated with higher exertional PaO\(_2\). The hypocapnic group, however, had worse mechanical inspiratory constraints and higher dyspnea scores for a given work rate leading to poorer exercise tolerance compared to their counterparts (p<0.05).

Conclusion: Heightened neural drive promoting a ventilatory response beyond that required to overcome an increased “wasted” ventilation led to hypocapnia and poor exercise ventilatory efficiency in COPD-heart failure overlap. Excessive ventilation led to better arterial oxygenation but at the expense of earlier critical mechanical constraints and intolerable dyspnea.

Word count= 247
INTRODUCTION

Heart failure with reduced left ventricular ejection fraction is a common and devastating co-morbidity of COPD.(1)(2) Patients with overlapping COPD-heart failure characteristically present with impaired exercise capacity due to breathlessness and/or increased muscle fatigability.(3)(4)(5) Understanding the mechanisms underlying patients’ diminished tolerance to exertion is paramount to mitigate symptom burden and improve health-related quality of life in this patient population.

There is growing recognition that exercise intolerance in COPD-heart failure overlap is associated with an increased ventilatory response to metabolic demand, i.e., high minute ventilation (\(\dot{V}E\))/carbon dioxide output (\(\dot{V}CO_2\)) relationship (ventilatory inefficiency).(6)(7) We (8)(9)(10), and others (11)(12), found that ventilatory inefficiency varies greatly in COPD-heart failure patients with similar resting pulmonary (FEV\(_1\)) and cardiac (left ventricular ejection fraction) impairment. The structural and physiological determinants underpinning such large variability, however, remains poorly understood.

In COPD alone, greater emphysema burden (13) (14) has been associated with increased \(\dot{V}E/\dot{V}CO_2\) in patients whose mechanical-ventilatory reserves are still sufficient to overcome the effects of enlarged dead space (\(V_D\)).(15)(16)(17) Higher ventilatory demand worsened gas trapping leading to dynamic hyperinflation and greater inspiratory constraints, i.e. lower tidal volume (\(V_T\)). Thus, exercise physiological \(V_D/V_T\) (“wasted” ventilation) did not decrease as expected due to the compressive effects of localized hyperinflation on lung vessels (high \(V_D\)) and/or lower \(V_T\) in patients with
worse ventilatory inefficiency. As a consequence of increased ventilatory drive and
greater neuromechanical dissociation, these patients with increased $\dot{V}e/\dot{V}CO_2$ reported
higher dyspnea and poorer exercise tolerance.(15)(16)(17) As the disease progresses,
however, worsening ventilatory constraints - and an upward displacement of the $CO_2$
set-point (hypercapnia) – act to decrease $\dot{V}e/\dot{V}CO_2$.(18)(19) (20) In heart failure alone,
disease progression is associated with higher $\dot{V}e/\dot{V}CO_2$ due to a high $VD/Vt$ and an
increased ventilatory drive leading to hypocapnia in highly-variable combinations.(21)
(22)(23) Based on these assertions, it is reasonable to hypothesize that COPD-heart
failure patients with greater ventilatory inefficiency would present with a deleterious
combination of higher $V_D/V_T$ and lower $PaCO_2$ than their counterparts with lower
$\dot{V}e/\dot{V}CO_2$.

To date, however, no study has examined the mechanisms of high $\dot{V}e/\dot{V}CO_2$
during exercise in COPD-heart failure overlap. Accordingly, our main objective was to
examine the determinants of ventilation-gas exchange abnormalities during progressive
exercise in these patients. We were also specifically interested in exploring a putative
link between ventilatory inefficiency and higher exercise operating lung volumes.
(15)(16)(17) As a corollary, we aimed to investigate whether those mechanical
consequences of ventilatory inefficiency, if present, would have negative clinical
consequences in terms of increased dyspnea and poor tolerance to physical effort.
MATERIALS AND METHODS

A detailed Material and Methods section is available in the Online Supplement.

Subjects

Twenty-two stable patients with an established clinical and functional diagnosis of COPD (post-bronchodilator FEV$_1$/forced vital capacity (FVC) ratio < lower limit of normal and GOLD spirometric stages 2-3)(24) and documented heart failure with reduced left ventricular ejection fraction (LVEF) (≤ 40%) were prospectively enrolled in academic centers from Brazil and Canada. Other key inclusion criteria were: age 50 years or older and a smoking history of at least 10 pack-years. Exclusion criteria and additional information on study design is available in the Online Supplement. After written informed consent, subjects underwent, on different days, a ramp-incremental cycle cardiopulmonary exercise test (CPET) for familiarization purposes and a stepwise progressive test with detailed measurements of ventilatory, sensory-perceptual and arterialized blood gas responses. This cross-sectional study received ethical approval from the Federal University of Sao Paulo Hospital ’s Research Ethics Board (REB) (# 1151/2015) and Queen’s University Affiliated Teaching Hospitals REB (DMED-1588-13).

Procedures

Transthoracic echocardiogram and chest HRCT with quantification of emphysema burden (25) were performed according to current recommendations (as detailed in the online supplement). Pulmonary function tests (spirometry, static lung volumes and lung
diffusing capacity) were performed using automated equipment (1085 ELITE D™, Medical Graphics Corp, St. Paul, MN in Brazil and Vmax229d; SensorMedics, Yorba Linda, CA in Canada). The same reference values were used in both laboratories. (26)(27)(28)(29) CPET was conducted on an electronically-braked cycle ergometer (Ergoline 800s; SensorMedics, Yorba Linda, CA) using a SensorMedics Vmax229d system in both laboratories. Key measurements included: standard breath-by-breath cardiorespiratory and breathing pattern parameters, dynamic operating lung volumes calculated from inspiratory capacity (IC) maneuvers (30) and dyspnea intensity assessed with the modified 10-point Borg scale.

The stepwise progressive CPET consisted of steady state rest, unloaded exercise (“0 W”) followed by 10-W increases in work rate every 3 minutes to symptom limitation. Patients performed a 3-min stepwise test to allow (near) steady-state arterial blood gas tensions. ΔVe-ΔVCO₂ slope and intercept by linear regression, Ve/VCO₂ nadir and end-exercise Ve/VCO₂ were obtained. Capillary (c) blood samples from the ear lobe were obtained at rest and during the last 30 s of each stage after application of a vasodilation-inducing emulsion (Finalgon®TM, GBm, Germany). Blood samples were analyzed immediately after each test (ABL800 FLEX; Radiometer, Copenhagen, Denmark). Concomitant arterial blood gases were obtained in 5 patients: in keeping with previous data (31), there was a close agreement between capillary and arterial values at rest and during exercise (e-Figure 1). VD/VT was calculated using the modified Bohr equation (Enghoff’s modification) and A-aPO₂ was estimated using the ideal alveolar gas equation.
Statistical Analysis

The statistical software package used was IBM™ SPSS™ Statistics version 24. Unpaired t test (or Mann-Whitney test when appropriated) were used to compare between-subject differences. $\chi^2$ test was used to compare frequencies. Association between selected continuous variables was investigated by Pearson’s product-moment correlation test. Two-way ANOVA with repeated measures were used to compare dyspnea intensity and cardiorespiratory, metabolic, gas exchange, and operating lung volumes at rest and during iso-work rates. A P<0.05 level of significance was used for all analyses.

RESULTS

Clinical and resting functional characteristics

Twenty-two patients were enrolled. Most patients were men in the late 60s or early 70s, mildly overweight, ex-smokers with heart failure secondary to ischemic heart disease with other systemic co-morbidities (Table 1). As anticipated by inclusion criteria, patients typically had moderate to severe airflow limitation. In line with the expected restrictive effects of heart failure on static lung volumes,(32) patients presented with generally preserved total lung capacity (TLC) but higher than expected residual volume and RV/TLC ratio, i.e., pulmonary gas trapping. Moreover, patients had decreased inspiratory capacity (IC)/TLC ratios (Table 2).
Physiological determinants of ventilatory inefficiency

In line with our previous studies, we found a large variability on ventilatory inefficiency regardless the chosen metric ($\Delta \dot{V}E - \Delta \dot{V}CO_2$ slope from 20 to 50, $\Delta \dot{V}E - \Delta \dot{V}CO_2$ intercept from -3.2 L/min to 10.1 L/min, $\dot{V}E/\dot{V}CO_2$ nadir from 27 to 48 and end-exercise $\dot{V}E/\dot{V}CO_2$ from 29 to 48). Higher $\dot{V}E/\dot{V}CO_2$ nadir values were associated with greater $\Delta \dot{V}E - \Delta \dot{V}CO_2$ (typically > 34) and lower $\Delta \dot{V}E - \Delta \dot{V}CO_2$ intercept (typically < 4 l/min).

Moreover, both $V_D/V_T$ and $PcCO_2$ at the nadir varied markedly (from 0.26 to 0.49 and 30 mmHg to 52 mmHg, respectively) (Figure 1).

As depicted in Figure 1A, $\dot{V}E/\dot{V}CO_2$ nadir was largely independent of simultaneously-measured $V_D/V_T$ (p>0.05) but increased in close association with decrements in $PcCO_2$ (p<0.001; Figure 1B). Similar results were found when the chosen metric of ventilatory inefficiency was $\Delta \dot{V}E - \Delta \dot{V}CO_2$ slope and end-exercise $\dot{V}E/\dot{V}CO_2$ (r= -0.80 and -0.82, respectively; p<0.001). In fact, there was a hyperbolic decrease in $PcCO_2$ as a function of alveolar hyperventilation, i.e., progressively higher alveolar ventilation ($\dot{V}_A$)/$\dot{V}CO_2$ ratio (Figure 1C). Measured $\dot{V}_E$ expressed as a function of predicted $\dot{V}_E$ (from measured $\dot{V}CO_2$, $PcCO_2$ and $V_D/V_T$; equation [4] in the online supplement) was remarkable close to the line of identity (Figure 1D).

Clinical and resting variables: hypocapnic versus non-hypocapnic patients

Considering that $PcCO_2$ showed a key role in defining the prevailing exertional ventilatory response (Figure 1), patients were separated into two groups according to the presence or not of consistently-low exercise $PcCO_2$ ($\leq$ 35 mmHg): hypocapnic (N=
10) and non-hypocapnic group (N= 12). There were no between-group differences in key demographic, anthropometric and clinical variables (Table 1). The hypocapnic group, however, had significantly lower lung diffusing capacity (DlCO) either in absolute values or expressed relative to alveolar volume (p<0.05). Arterial blood gases and parameters of acid-base balance showed normal pH but lower PaCO₂ and bicarbonate in this group, i.e., metabolically-compensated chronic respiratory alkalosis (p<0.05) Moreover, these patients had better resting arterial oxygenation than their counterparts (Table 2). Although patients from both groups did not present with extensive emphysema burden in the chest CT (typically < 20% low attenuation areas), there was a trend to the hypocapnic group of presenting with larger emphysematous areas (p=0.10; Table 1). Most echocardiographic variables did not significantly differ between the groups; however, the TAPSE/PASP ratio was lower in the hypocapnic group (p<0.05).

**Exercise responses: hypocapnic versus non-hypocapnic patients**

Compared with the non-hypocapnic group, hypocapnic patients presented with lower peak work rate and oxygen uptake (VO₂) (Table 3). The hypocapnic group showed higher VCO₂ and respiratory exchange ratio; thus, there was no between-group difference in these variables despite a lower peak work rate in this group (p>0.05; Table 3).

Sub-maximal VE and VE/VCO₂ at a given work rate were systematically higher in the hypocapnic group (Figures 2A and 2B). Moreover, VE/VCO₂ relationship was
consistently higher in this group regardless the chosen metric of ventilatory inefficiency (e-Figure 2). As shown in Figure 2C, V̇D/V̇T values at a given work rate did not differ between groups. Consequently, V̇A was higher and end-tidal PCO₂ lower in this group across exercise intensities (Figures 2D and 2E, respectively). Conversely, arterialized (and end-tidal PO₂; data not shown) were consistently higher at a given work rate in the hypocapnic group (p<0.05; Figure 2F).

Higher V̇E at a given work rate in the hypocapnic group was associated with similar V̇T (Figure 3A) but greater respiratory frequency (Figure 3B), i.e., the respiratory frequency/ V̇T ratio was systematically higher compared to the non-hypercapnic group (Figure 4A). Thus, expiratory time was significantly shorter in the former group (Figure 3C). As a likely result of greater dynamic hyperinflation,(30) IC decreased across exercise at a faster rate (Figure 3D). Consequently, V̇T/IC ratio was greater at higher exercise intensities (Figure 4B). Higher end-expiratory lung volume but similar V̇T led the hypocapnic patients to reach earlier critical inspiratory constraints (Figure 3E and Figure 3F). Of note, mean inspiratory flow (V̇T/inspiratory time ratio) and the duty cycle (inspiratory/total time ratio) were both higher in this group (Figure 4C and Figure 4D).

Patients in the hypocapnic group reported higher dyspnea ratings at all submaximal work rates and at peak exercise compared with their counterparts (Figure 5A). There was no significant between group differences in ratings of exertional leg discomfort at submaximal exercise (data not shown) or end-exercise (Table 3); thus,
systematically higher dyspnea-leg effort differences were found in the non-hypocapnic group across exercise intensities (Figure 5B) (p<0.01).

**DISCUSSION**

The main original findings of this study involving stable patients with COPD-heart failure overlap are: 1) heightened ventilatory stimulation was instrumental to explain exercise ventilatory inefficiency as patients with lower PaCO₂ had to overcome an enlarged physiological dead space in order to (alveolar) hyperventilate and 2) excessive ventilation helped to preserve arterial oxygenation but at the expense of dynamic hyperinflation, earlier mechanical constraints on ventilation, greater dyspnea and reduced exercise capacity. The results indicate that breathlessness and poor exercise tolerance in overlapping COPD-heart failure are strongly influenced by inter-patient variability on respiratory centers’ chemostimulation as excessive exertional ventilation hastens dynamic abnormalities in pulmonary mechanics.

*Ventilation-gas exchange coupling*

There is growing recognition that poor ventilatory efficiency (high \( \frac{\dot{V}_E}{\dot{V}CO_2} \) relationship) is a key exercise pathophysiological feature across the spectrum of COPD severity. (19)(20) In the present study, we uncover the mechanisms behind the remarkable heterogeneity in \( \dot{V}_E-\dot{V}CO_2 \) previously described by us (8)(9)(10) and others (11)(12) in COPD patients presenting with heart failure as co-morbidity. Thus, an increased ventilatory drive led to a ventilatory response beyond that required to wash-
out metabolically produced CO$_2$ and overcome an enlarged dead space fraction of the breath (physiological VD/VT). Although patients with worse ventilatory inefficiency (i.e., the hypocapnic group) did not present with increased physiological VD/VT compared to their counterparts, the effect of a given decrement in PcCO$_2$ in increasing VE/VCO$_2$ was amplified by the presence of larger “wasted” ventilation. The resulting alveolar hyperventilation downwardly-displaced the level at which PcCO$_2$ was chronically regulated, a self-perpetuating consequence of a high ventilatory drive. Consequently, a hyperbolic decrease in PcCO$_2$ as a function of VA/VCO$_2$ ratio (Figure 1C) is highly consistent with a tight control of arterial CO$_2$ tension in patients showing ample differences in VD/VT (Figure 1A).(7)(8)

In this context, it is noteworthy that non-hypocapnic patients maintained exercise PcCO$_2$ close to the resting eucapnic level or allowed it to raise despite starting exercise with seemingly similar mechanical-ventilatory reserves than the hypocapnic patients (Table 2; Figure 2). Although overt hypercapnia did not develop in all patients from the former group, this behavior seems in line with the concept of a “preventive” submissive hypercapnia (34), i.e., avoiding decrements or raising PcCO$_2$ reduced the ventilatory needs and, potentially, the work performed by the respiratory muscles. In other words, the respiratory controller of non-hypocapnic patients opted “not to fight” in order to delay critical inspiratory constraints. Conversely, the hypocapnic group responded to the high ventilatory drive even at expense of excessive ventilation to the available reserves. From the gas exchange perspective, this strategy was beneficial as
patients maintained better arterial oxygenation than their counterparts (Figure 2F) despite similar efficiency in intra-pulmonary oxygenation, i.e., same P(A-c)O₂ (Table 3).

The dichotomous behavior regarding exercise PcCO₂ trajectory showed in Figure 2 resembles that long described in pink puffers (type A) versus blue bloaters (type B) COPD patients.(35)(36) Although there was a trend for hypocapnic patients to present with larger emphysematous areas, it is noteworthy that emphysema burden was typically mild to moderate in our sample. Moreover, overt hypocapnia is not commonly seen in type A patients.(35)(36) Thus, it is conceivable that the well-established consequences of heart failure on ventilatory drive (21)(37)(23) had a dominant role in inducing a low PcCO₂ in the hypocapnic group.

The heightened ventilatory drive leading to alveolar hyperventilation and better arterial oxygenation is likely part of a concerted systemic response to improve tissue O₂ delivery in face of a failing heart.(38) It should be acknowledged, however, that SpO₂ was typically above 90% in the non-hypocapnic group; thus, oxygen delivery was well-maintained in both groups. Owing to similar Vd/Vt (Figure 2C) and higher PaO₂ (Figure 2F) compared to the non-hypocapnic, higher wasted ventilation (39) and increased stimulation of carotid bodies by hypoxemia (37) seems unlikely. Sympathetic over-stimulation, lactacidosis, and increased stimulation or a heightened sensitivity of central chemoreceptors and peripheral muscle ergoreceptors might be involved (as reviewed in ref. (38)). Of note, resting TAPSE/PASP ratio was significantly lower in patients with worse ventilatory inefficiency (Table 2) suggesting right ventricle-pulmonary circulation uncoupling. Lower DLCO in this group also suggests more
extensive pulmonary microvascular abnormalities. In fact, Guazzi and co-workers found a close relationship between low TAPSE/PASP and increased $\dot{V}e/\dot{V}CO_2$ in patients with heart failure.\(^{(40)}\) Although the underlying mechanisms are unclear, they might involve higher afferent stimulation from cardio-pulmonary receptors in patients with higher exertional pulmonary arterial pressures.\(^{(38)}\)(\(^{41}\)) Greater emphysema burden in this group may have also contributed to higher pulmonary vascular resistance and worse right ventricular exercise contractile reserve.\(^{(40)}\) Under this unfavorable combination of circumstances, overstimulation of stretch receptors in the right heart chambers (Bainbridge reflex) may have played an important role in patient’s hyperventilation.\(^{(42)}\)(\(^{43}\)) Whether further improving pulmonary hemodynamics in this particular group of COPD-heart failure patients with higher $\dot{V}e/\dot{V}CO_2$ lessens exercise ventilation merits further investigation.

Lung mechanical and sensory responses to exercise in COPD-heart failure

Owing to larger inspiratory volume reserves compared to COPD,\(^{(44)}\) higher exertional ventilation is associated with relatively minor negative mechanical consequences in heart failure alone.\(^{(41)}\) Conversely, we found important negative mechanical consequences of increased exercise ventilation in the hypocapnic group, i.e. higher operating lung volumes leading to earlier inspiratory constraints (Figure 3D-3F). For instance, IRV at 30 W in this group was, on average, almost half of that observed in the non-hypocapnic group (Figure 3F). Thus, a shorter expiratory time (Figure 3C) secondary to a high respiratory rate (Figure 3B) led to dynamic increases in gas
trapping and higher end-expiratory lung volume (Figure 3E) in the hypocapnic group. As the operating lung volumes increased and the patients approached critical inspiratory constraints (VT/IC ratio ~ 0.7 and peak IRV ~0.5 L), (30) VT tended to stabilize (Figure 3B) and VE increased mainly due to higher respiratory frequency. It is noteworthy, however, that higher respiratory frequency was found in this group even at exercise intensities not associated with substantial inspiratory constraints (Figure 4A). Of note, chemostimulation is characteristically associated with a tachypneic breathing pattern (37)(45) which also suggests that excessive ventilation in this group was mainly driven by an increased ventilatory drive. This is corroborated by consistently higher mean inspiratory flow in this group (Figure 4C), an index of increased ventilatory drive.(30)

The hypocapnic patients payed a too-high sensory “price” to preserve exertional PCO₂. For instance, this group presented with consistently higher dyspnea scores throughout exercise (Figure 5B) and at exercise cessation (Table 3) compared to their counterparts. It is noteworthy that dyspnea ratings were higher at a given work rate in the former group even at exercise intensities that preceded those associated with critical inspiratory constraints. Thus, increased VE per se played an adjunct role in the symptom genesis, likely secondary to an increased respiratory neural drive to the overloaded respiratory muscles.(46) Of note, hypocapnic patients did present with larger duty cycles (Figure 4D) which might have contributed to higher inspiratory neural drive. Further increases in dyspnea at near maximum exercise likely resulted from the interaction of such a high drive with the mounting mechanical constraints.(30)
contrast, the relative contribution of leg effort to exercise limitation was significantly higher in non-hypocapnic group. Thus, symptoms related to intrinsic muscle dysfunction and poor muscle O$_2$ delivery (impaired muscle blood flow) (4) were not overshadowed by breathlessness in patients with lower exertional ventilation.

**Practical implications**

The present study has some important implications for the functional assessment of patients with COPD-heart failure. Based on our results, it became apparent that resting cardio-pulmonary assessment is poorly predictive of patient’s ventilatory response to exertion. Nevertheless, a low DL$_{CO}$ coupled with resting hypocapnia in patients with low TAPSE/PASP ratio on echocardiography should raise concerns about excessive ventilation during activity. Direct CPET measurements of ventilatory inefficiency and operating lung volumes are important in exposing abnormalities in ventilatory control and pulmonary gas exchange which are ultimately relevant to symptoms and exercise tolerance in individual patients. Of note, although ventilatory inefficiency is an important marker of heart failure severity,(9)(23-26) there is no unequivocal evidence of a causative role in impairing exercise tolerance. Our results provide novel evidence that excessive exertional ventilation mechanistically contribute to poor exercise tolerance when COPD and heart failure coexists. Thus, ventilatory inefficiency carries an even greater relevance to patient’s functioning on overlapping COPD-heart failure than heart failure alone. By identifying the sub-group of COPD-heart failure patients in whom lessening the ventilatory response to exertion is more likely to positively impact on
exertional dyspnea, a rationale can be developed to guide further therapeutic and rehabilitative interventions. For instance, it is conceivable that these patients would benefit from further increases in mechanical-ventilatory reserves (i.e., COPD treatment optimization) and/or decreases in the ventilatory drive (e.g., reducing afferent stimuli from ergo- and cardiopulmonary receptors)(21)(37)(23)(40). Moreover, patients with poorer ventilatory efficiency are likely to benefit mostly from rehabilitative strategies associated with low-to-minimal ventilatory stress e.g., small muscle mass training, (47) neuromuscular electrical stimulation (48) and one-legged training (49).

**Study limitations**

As a clinical physiology, observational study involving invasive measurements in a high-risk population our study sample was necessary small. However, the study was sufficiently powered to uncover the origins of increased $\dot{V}E/\dot{V}CO_2$ in overlapping COPD-heart failure. Before study entry, patients’ treatment was carefully optimized by respirologists and cardiologists in conjunction; thus, we minimized the confounding effects of undertreatment of COPD or heart failure, a major hindrance of studies involving these patients (1)(2). Considering the large heterogeneity in both diseases, our results should not be unrestrictedly extrapolated to more severe patients, e.g., those with more extensive emphysema, advanced cachexia or resting hypoxemia. Nevertheless, our sample is likely representative to the ambulatory population commonly referred to functional assessment in pulmonary function and exercise testing laboratories. Additional studies with invasive hemodynamic might prove particularly
informative to better assess the relationship between right ventricle-pulmonary circulation uncoupling and ventilatory inefficiency in individual patients.\(^{(38)(40)(41)}\)

**Conclusions**

This study is the first to uncover the key mechanism explaining the highly-variable consequences of heart failure on exertional ventilation in COPD: alveolar hyperventilation (hypocapnia). Excessive ventilation in these patients enhanced arterial oxygenation but at the expense of forcing earlier mechanical-inspiratory constraints and greater exertional dyspnea which ultimately impairs exercise tolerance. In association with emerging evidence that a high \(\dot{V}E/\dot{V}CO_2\) relationship is mechanistically linked to exertional dyspnea in patients with largely preserved FEV\(_1\),\(^{(15)(16)(17)}\) a marker of disease progression \(^{(19)}\) and a predictor of poor survival in patients with \(^{(9)}\) and without \(^{(50)}\) coexistent heart failure, our results indicate that CPET-based measurements of ventilatory inefficiency provide unique physiological information which is clinically-relevant to contemporary COPD management.
References


Table 1. General characteristics.

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</tr>
<tr>
<td>Diabetes</td>
<td>11</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>CKD (CrCl &lt; 60 ml/min)</td>
<td>9</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td><strong>Heart failure treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin, N</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Furosemide, N</td>
<td>20</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>ACE-I or ARBs, N</td>
<td>21</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Nitrates, N</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Hydralazine, N</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>β-blockers, N</td>
<td>22</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Others</td>
<td>22</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td><strong>COPD treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAMA</td>
<td>16</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>LABA</td>
<td>22</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>ICS (+LABA)</td>
<td>16</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Others</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>HRCT % emphysema</td>
<td>13.6 ± 10.0</td>
<td>14.1 ± 10.6</td>
<td>12.4 ± 9.8</td>
</tr>
</tbody>
</table>

*P*<0.05. Values are mean ± SD, frequency (N) or median [range]. **Abbreviations:** NYHA= New York Heart Association; mMRC=modified Medical Research Council scales; CKD= chronic kidney disease; CrCl= creatinine clearance; ACE-I= angiotensin-converting-enzyme inhibitor; ARB= angiotensin receptor blockers; LAMA= long-acting anti-muscarinic, LABA= long-acting β₂ adrenoceptor agonist, ICS= inhaled corticosteroids, HRCT: high-resolution computed tomography.
Table 2. Resting functional and echocardiographic findings.

<table>
<thead>
<tr>
<th></th>
<th>All patients (N= 22)</th>
<th>Hypocapnic Group (N = 10)</th>
<th>Non-Hypocapnic Group (N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.56 ± 0.34</td>
<td>1.58 ± 0.30</td>
<td>1.54 ± 0.39</td>
</tr>
<tr>
<td>% predicted</td>
<td>60 ± 11</td>
<td>63 ± 12</td>
<td>58 ± 10</td>
</tr>
<tr>
<td>FVC, L</td>
<td>3.03 ± 0.70</td>
<td>2.94 ± 0.61</td>
<td>3.06 ± 0.78</td>
</tr>
<tr>
<td>% predicted</td>
<td>82 ± 12</td>
<td>83 ± 11</td>
<td>81 ± 14</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>0.56 ± 0.10</td>
<td>0.57 ± 0.08</td>
<td>0.55 ± 0.12</td>
</tr>
<tr>
<td>MVV, L/min</td>
<td>59 ± 14</td>
<td>60 ± 13</td>
<td>58 ± 16</td>
</tr>
<tr>
<td>IC, L</td>
<td>2.33 ± 0.37</td>
<td>2.30 ± 0.39</td>
<td>2.36 ± 0.36</td>
</tr>
<tr>
<td>% predicted</td>
<td>80 ± 10</td>
<td>82 ± 11</td>
<td>79 ± 10</td>
</tr>
<tr>
<td>TLC, L</td>
<td>6.15 ± 1.01</td>
<td>6.12 ± 0.79</td>
<td>6.18 ± 1.10</td>
</tr>
<tr>
<td>% predicted</td>
<td>98 ± 11</td>
<td>102 ± 6</td>
<td>96 ± 14</td>
</tr>
<tr>
<td>RV, L</td>
<td>3.01 ± 0.65</td>
<td>3.10 ± 0.70</td>
<td>2.95 ± 0.59</td>
</tr>
<tr>
<td>% predicted</td>
<td>148 ± 30</td>
<td>154 ± 32</td>
<td>142 ± 29</td>
</tr>
<tr>
<td>IC/TLC</td>
<td>37 ± 7</td>
<td>36 ± 6</td>
<td>38 ± 7</td>
</tr>
<tr>
<td>RV/TLC, %</td>
<td>48 ± 7</td>
<td>52 ± 8</td>
<td>47 ± 6</td>
</tr>
<tr>
<td>% predicted</td>
<td>139 ± 17</td>
<td>140 ± 19</td>
<td>137 ± 16</td>
</tr>
<tr>
<td>DLCO, ml/min/mmHg</td>
<td>16.4 ± 2.9</td>
<td>11.6 ± 1.7 *</td>
<td>20.4 ± 3.9</td>
</tr>
<tr>
<td>% predicted</td>
<td>58 ± 12</td>
<td>43 ± 10 *</td>
<td>62 ± 14</td>
</tr>
<tr>
<td>DLCO/VA, ml/min/mmHg/L</td>
<td>3.8 ± 0.7</td>
<td>2.6 ± 0.5 *</td>
<td>4.3 ± 0.9</td>
</tr>
<tr>
<td>% predicted</td>
<td>62 ± 15</td>
<td>58 ± 14 *</td>
<td>87 ± 17</td>
</tr>
<tr>
<td>VA/TLC</td>
<td>0.78 ± 0.08</td>
<td>0.77 ± 0.08</td>
<td>0.79 ± 0.08</td>
</tr>
<tr>
<td>MIP, cmH₂O</td>
<td>-68 ± 30</td>
<td>-66 ± 28</td>
<td>-74 ± 32</td>
</tr>
<tr>
<td>% predicted</td>
<td>71 ± 24</td>
<td>72 ± 23</td>
<td>70 ±20</td>
</tr>
<tr>
<td><strong>Arterial blood</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>pH</td>
<td>7.40 ± 0.03</td>
<td>7.41 ± 0.02</td>
<td>7.39 ± 0.03</td>
</tr>
<tr>
<td>HCO₃⁻, mmol/L</td>
<td>24 ± 2</td>
<td>21 ± 3 *</td>
<td>26 ± 2</td>
</tr>
<tr>
<td>PaCO₂, mmHg</td>
<td>36 ± 3</td>
<td>32 ± 2 *</td>
<td>39 ± 3</td>
</tr>
<tr>
<td>PaO₂, mmHg</td>
<td>75 ± 8</td>
<td>79 ± 4 *</td>
<td>72 ± 8</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>94 ± 2</td>
<td>96 ± 2 *</td>
<td>93 ± 1</td>
</tr>
<tr>
<td><strong>Echocardiogram</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>38 ± 6</td>
<td>39 ± 6</td>
<td>38 ± 7</td>
</tr>
<tr>
<td>LVEDV, mm</td>
<td>60 ± 8</td>
<td>60 ± 6</td>
<td>61 ± 8</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>147 ± 50</td>
<td>153 ± 42</td>
<td>141 ± 59</td>
</tr>
<tr>
<td>LA, mm</td>
<td>42 ± 7</td>
<td>43 ± 8</td>
<td>42 ± 6</td>
</tr>
<tr>
<td>RV, mm</td>
<td>25 ± 4</td>
<td>27 ± 3</td>
<td>23 ± 5</td>
</tr>
<tr>
<td>PASP, mmHg †</td>
<td>37 ± 6</td>
<td>42 ± 7</td>
<td>32 ± 6</td>
</tr>
<tr>
<td>TAPSE, mm ‡</td>
<td>19 ± 3</td>
<td>17 ± 2</td>
<td>21 ± 3</td>
</tr>
</tbody>
</table>
TAPSE/PASP, mm/mmHg § 0.55± 0.13 0.45 ± 0.14 * 0.67± 0.12

* P<0.05 Values are mean ± SD. † N= 9 vs. 7 and ‡ N= 8 vs. 10, respectively. FEV₁ = forced expiratory volume in one second; FVC= forced vital capacity; MVV= maximal voluntary ventilation; IC= inspiratory capacity; TLC= total lung capacity; RV= residual volume; D_LCO= lung diffusing capacity for carbon monoxide; V̅A= alveolar volume; MIP= maximal inspiratory pressure; pH=hydrogen-ionic potential; HCO₃⁻ = bicarbonate; Pa= arterial partial pressure; Sa= arterial saturation; LVEF= left ventricular ejection fraction; LVEDV= left ventricular end-diastolic volume; LVMI= left ventricular mass index; LA= left atrium; RV= right ventricle; PASP= pulmonary artery systolic pressure; TAPSE= tricuspid annular plane systolic excursion.
Table 3. Physiological and sensory responses to step-wise, progressive incremental cardiopulmonary exercise testing.

<table>
<thead>
<tr>
<th></th>
<th>Hypocapnic Group (N = 10)</th>
<th>Non-Hypocapnic Group (N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak WR, W</td>
<td>43 ± 12 *</td>
<td>58 ± 14</td>
</tr>
<tr>
<td><strong>Metabolic/cardiovascular responses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak $\dot{V}O_2$, L/min</td>
<td>0.94 ± 0.18 *</td>
<td>1.18 ± 0.15</td>
</tr>
<tr>
<td>Peak $\dot{V}O_2$, mL/min/kg</td>
<td>12.1 ± 3.1*</td>
<td>16.0 ± 2.9</td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.08 ± 0.08</td>
<td>1.10 ± 0.07</td>
</tr>
<tr>
<td>$\Delta\dot{V}O_2$-∆WR slope, mL/min/W</td>
<td>9.7 ± 2.6</td>
<td>9.9 ± 2.8</td>
</tr>
<tr>
<td>Peak HR, bpm</td>
<td>114 ± 18</td>
<td>111 ± 25</td>
</tr>
<tr>
<td><strong>Ventilatory responses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak $\dot{V}E$/MVV, %</td>
<td>75.5 ± 11.9</td>
<td>73.4 ± 9.9</td>
</tr>
<tr>
<td>Peak $V_t$, L</td>
<td>1.12 ± 0.64</td>
<td>1.23 ± 0.80</td>
</tr>
<tr>
<td>Peak $f$, rpm</td>
<td>34 ± 12</td>
<td>31 ± 10</td>
</tr>
<tr>
<td>Peak $\dot{V}E$/V$CO_2$</td>
<td>43 ± 4 *</td>
<td>32 ± 6</td>
</tr>
<tr>
<td>$\dot{V}E$/V$CO_2$ nadir</td>
<td>42 ± 5 *</td>
<td>33 ± 6</td>
</tr>
<tr>
<td>% predicted</td>
<td>152 ± 28 *</td>
<td>118 ± 37 *</td>
</tr>
<tr>
<td>$\Delta\dot{V}E$-$\Delta$V$CO_2$ slope</td>
<td>43 ± 6 *</td>
<td>27 ± 7</td>
</tr>
<tr>
<td>% predicted</td>
<td>147 ± 24 *</td>
<td>110 ± 31 *</td>
</tr>
<tr>
<td>$\Delta\dot{V}E$-$\Delta$V$CO_2$ intercept, L/min</td>
<td>1.1 ± 2.1 *</td>
<td>5.1 ± 2.9</td>
</tr>
<tr>
<td>Peak-rest IC, L</td>
<td>-0.48 ± 0.37*</td>
<td>-0.28 ± 0.30</td>
</tr>
<tr>
<td>Peak EILV/TLC, %</td>
<td>0.83 ± 0.06 *</td>
<td>0.78 ± 0.08</td>
</tr>
<tr>
<td>Peak EELV/TLC, %</td>
<td>0.70 ± 0.08 *</td>
<td>0.66 ± 0.07</td>
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<tr>
<td><strong>Pulmonary gas exchange responses</strong></td>
<td></td>
<td></td>
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<tr>
<td>Peak Pet$CO_2$, mmHg</td>
<td>28 ± 4 *</td>
<td>41 ± 5</td>
</tr>
<tr>
<td>Peak Pc$CO_2$, mmHg</td>
<td>32 ± 3 *</td>
<td>43 ± 4</td>
</tr>
<tr>
<td>Peak P(c-ET)CO$_2$, mmHg</td>
<td>-4 ± 4</td>
<td>-2 ± 4</td>
</tr>
<tr>
<td>Peak VD/$V_t$</td>
<td>0.37 ± 0.07</td>
<td>0.38 ± 0.06</td>
</tr>
<tr>
<td>Peak P(A–c)O$_2$, mmHg</td>
<td>38.5 ± 7.7</td>
<td>39.3 ± 6.7</td>
</tr>
<tr>
<td>Peak SpO$_2$, %</td>
<td>96 ± 3 *</td>
<td>92 ± 3</td>
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<tr>
<td><strong>Sensory responses</strong></td>
<td></td>
<td></td>
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<tr>
<td>Peak dyspnea score</td>
<td>8.5 [3-10] *</td>
<td>5 [2-8]</td>
</tr>
<tr>
<td>Peak leg effort score</td>
<td>5.5 [2-8]</td>
<td>6 [1-8]</td>
</tr>
<tr>
<td>Peak dyspnea – leg effort scores</td>
<td>3 [5 to –1]</td>
<td>-1 [2 to –4]</td>
</tr>
<tr>
<td>Peak dyspnea &gt; leg effort scores, N</td>
<td>8 *</td>
<td>3</td>
</tr>
</tbody>
</table>

* P<0.05 Values are mean ± SD, frequency (N) or median (range). Abbreviations: WR= work rate; \( \dot{V}O_2 \)= oxygen uptake; RER= respiratory exchange ratio; HR= heart rate; \( \dot{V}E \)= ventilation; MVV= maximal voluntary ventilation; \( \dot{V}T \)= tidal volume; f= respiratory rate; \( \dot{V}CO_2 \)= carbon dioxide output; IC= inspiratory capacity; EILV= end-inspiratory lung volume; EELV= end-expiratory lung volume; TLC= total lung capacity; PET= end-tidal partial pressure; Pc= capillary pressure; VD/VT= dead space / tidal volume ratio; SpO2=oxygen saturation by pulse oximetry.
**Figure Legends**

**Figure 1.** Relationship between physiological dead space (V\textsubscript{D}) / tidal volume (V\textsubscript{T}) ratio (panel A) and capillary (c) PCO\textsubscript{2} (panel B) with ventilation (\tilde{V}\textsubscript{E}) / CO\textsubscript{2} output (\tilde{V}\textsubscript{CO}\textsubscript{2}) ratio in COPD-heart failure patients. Hypocapnic (closed symbols, N= 10) and non-hypocapnic patients (open symbols, N= 12) are identified. Panel C shows the hyperbolic decrease in PcCO\textsubscript{2} as a function of alveolar ventilation (\tilde{V}\textsubscript{A}) / \tilde{V}\textsubscript{CO}\textsubscript{2} ratio. *Panel D* depicts the close relationship between predicted \tilde{V}\textsubscript{E} (from \tilde{V}\textsubscript{CO}\textsubscript{2}, physiological V\textsubscript{D} / V\textsubscript{T} and PcCO\textsubscript{2}) with measured \tilde{V}\textsubscript{E} in both groups. Values at the \tilde{V}\textsubscript{E}/\tilde{V}\textsubscript{CO}\textsubscript{2} nadir (minimum).

**Figure 2.** Ventilatory (panels A-D) and pulmonary gas exchange (panels E-F) responses to incremental cardiopulmonary exercise testing in COPD-heart failure patients separated by presence (N= 10) or not (N= 12) of exercise hypocapnia (closed symbols and open symbols, respectively). *P*<0.05 for between-group comparisons at rest, standardized work rates and the highest work rate attained by all subjects in a given group. Values are means ± SEM. *Abbreviations:* V\textsubscript{D}/V\textsubscript{T}= dead space / tidal volume ratio; \tilde{V}\textsubscript{A}= alveolar ventilation; Pc= capillary (arterialized) partial pressure; PET= end-tidal partial pressure.

**Figure 3.** Pattern and timing of breathing (panels A-C) and operating lung volume (panels D-F) during incremental exercise in cardiopulmonary exercise testing in COPD-heart failure patients separated by presence (N= 10) or not (N= 12) of exercise hypocapnia (closed symbols and open symbols, respectively). Shadowed areas in panels E and F represent the volumes typically associated with critical inspiratory constraints in COPD (30,45). *P*<0.05 for between-group comparisons at rest, standardized work rates and the highest work rate attained by all subjects in a given group. Values are means ± SEM. *Abbreviations:* VT= tidal volume; \textit{f}= respiratory rate; IC= inspiratory capacity; EILV= end-inspiratory lung volume; EELV= end-expiratory lung volume; TLC= total lung capacity; IRV= inspiratory reserve volume.

**Figure 4.** Breathing pattern (panels A and B), mean inspiratory flow (panel C) and timing of breathing (panel D) in COPD-heart failure patients separated by presence (N= 10) or not (N= 12) of exercise hypocapnia (closed symbols and open symbols, respectively). *P*<0.05 for between-group comparisons at rest, standardized work rates and the highest work rate attained by all subjects in a given group. Values are means ± SEM. *Abbreviations:* VT= tidal volume; \textit{f}= respiratory rate; IC= inspiratory capacity; TI= inspiratory time; T\textsubscript{TOT}= total respiratory cycle time.

**Figure 5.** Exertional symptoms (Borg scale ratings) during incremental cardiopulmonary exercise testing in COPD-heart failure patients separated by presence (N= 10) or not (N= 12) of exercise hypocapnia (closed symbols and open symbols, respectively).
* $P<0.05$ for between-group comparisons at rest, standardized work rates, the highest work rate attained by all subjects in a given group. Values are means ± SEM.
Figure 1. Relationship between physiological dead space (VD) / tidal volume (VT) ratio (panel A) and capillary (c) PCO2 (panel B) with ventilation (VE) / CO2 output (VCO2) ratio in COPD-heart failure patients. Hypocapnic (closed symbols, N= 10) and non-hypocapnic patients (open symbols, N= 12) are identified. Panel C shows the hyperbolic decrease in PcCO2 as a function of alveolar ventilation (VA) /VCO2 ratio. Panel D depicts the close relationship between predicted VE (from VCO2, physiological VD / VT and PcCO2) with measured VE in both groups. Values at the VE/VCO2 nadir (minimum).
Figure 2. Ventilatory (panels A-D) and pulmonary gas exchange (panels E-F) responses to incremental cardiopulmonary exercise testing in COPD-heart failure patients separated by presence (N= 10) or not (N= 12) of exercise hypocapnia (closed symbols and open symbols, respectively).

254x190mm (96 x 96 DPI)
Figure 3. Pattern and timing of breathing (panels A-C) and operating lung volume (panels D-F) during incremental exercise in cardiopulmonary exercise testing in COPD-heart failure patients separated by presence (N= 10) or not (N= 12) of exercise hypocapnia (closed symbols and open symbols, respectively). Shadowed areas in panels E and F represent the volumes typically associated with critical inspiratory constraints in COPD (30,45).

254x190mm (96 x 96 DPI)
Figure 4. Breathing pattern (panels A and B), mean inspiratory flow (panel C) and timing of breathing (panel D) in COPD-heart failure patients separated by presence (N= 10) or not (N= 12) of exercise hypcapnia (closed symbols and open symbols, respectively).

254x190mm (96 x 96 DPI)
Figure 5. Exertional symptoms (Borg scale ratings) during incremental cardiopulmonary exercise testing in COPD-heart failure patients separated by presence (N= 10) or not (N= 12) of exercise hypocapnia (closed symbols and open symbols, respectively).

254x190mm (96 x 96 DPI)
ON-LINE DATA SUPPLEMENT

MATERIALS AND METHODS

Subjects

Twenty-two stable patients with an established clinical and functional diagnosis of COPD according to the Global Initiative for COPD (GOLD) guidelines (post-bronchodilator FEV₁/forced vital capacity (FVC) ratio < lower limit of normal and GOLD spirometric stages 2-3) (1) and documented heart failure with reduced left ventricular ejection fraction (LVEF) (≤ 40%) (2) were prospectively enrolled in academic centers from Brazil and Canada. Other key inclusion criteria were: age 50 years or older and a smoking history of at least 10 pack-years. Study’s respirologists (FFA, LEN, DOD, JAN) and cardiologists (AR, FM, MCA) carefully optimized patient’s treatment before study. Patients underwent measurements described below only after an agreement had been reached between respirologists and cardiologists regarding disease stability for at least 2 months. Main exclusion criteria: COPD and/or heart failure exacerbation in the preceding 2 months; presence of asthma or other respiratory condition that could contribute to dyspnea or exercise limitation; contraindications to exercise testing; use of daytime oxygen; and body mass index (BMI) less than 18.5 kg/m² or greater than 35 kg/m².
Study Design

This cross-sectional study received ethical approval from the Federal University of Sao Paulo Hospital’s Research Ethics Board (REB), Brazil (# 1151/2015) and Queen’s University and Affiliated Teaching Hospitals REB, Canada (DMED-1588-13). After written informed consent, subjects completed two visits. Visit 1 included pre- and post-bronchodilator (400µg salbutamol) spirometry, body plethysmography and lung diffusing capacity measurements and a ramp-incremental cycle cardiopulmonary exercise test (CPET). Visit 2 included post-bronchodilator spirometry followed by a step-wise incremental cycle CPET with detailed measurements of ventilatory, sensory-perceptual and arterialized blood gas responses.

Procedures

Transthoracic echocardiogram

All individuals underwent a comprehensive two-dimensional (2D) echocardiography with a GE Vivid 7 (GE Healthcare, USA) echocardiography system with a 1.5 to 4.3 Mhz phase array transducer under continuous electrocardiographic monitoring. The quantification of the cardiac chambers was performed according to American Society of Echocardiography guidelines.(3) The left ventricular ejection fraction was calculated according to a modified Simpson’s rule and the right ventricular systolic function was assessed by the tricuspid annular plane systolic excursion (TAPSE). (3) The pulmonary artery
systolic pressure (PASP) was estimated by continuous wave Doppler assessment of maximal tricuspid velocity and the estimated right atrial pressure by inferior vena cava diameter and its respiratory changes.(4)

Chest high-resolution computed tomography (HRCT)

HRCT with quantification of emphysema burden were performed according to current recommendations.(5) All measurements were performed by an expert in quantitative CT image analysis. Emphysema was estimated by using the relative area of the CT attenuation histogram with attenuation of -950 HU or less (Pulmonary Workstation 2.0, VIDA Diagnostics, Coralville, Iowa).

Pulmonary function tests

Spirometry, static lung volumes, lung diffusing capacity and maximal static respiratory pressures were performed using automated equipment (1085 ELITE D™, Medical Graphics Corp, St. Paul, MN in Brazil and Vmax229d; SensorMedics, Yorba Linda, CA in Canada) according to current guidelines. Reported values were expressed in absolute and % predicted values. The same reference values were used in both centers (6)(7)(8)(9).

Cardiopulmonary exercise tests (CPET)

Exercise tests were conducted on an electronically-braked cycle ergometer (Ergoline 800s; SensorMedics, Yorba Linda, CA) using a SensorMedics
Vmax system in both laboratories. Measurements included: standard breath-by-breath cardiorespiratory and breathing pattern parameters; oxygen saturation by pulse oximetry (SpO2); heart rate (HR) by 12-lead ECG; arterial blood pressure by auscultation; dynamic operating lung volumes calculated from inspiratory capacity (IC) maneuvers (11) and dyspnea intensity assessed with the modified 10-point Borg scale.

The rate of work rate increment in the ramp test (12) was individually selected according to reported exercise tolerance (typically 5–10 W). Slope of the Δ oxygen uptake (ΔVO₂)/Δwork rate was obtained by linear regression (14).

The stepwise progressive CPET consisted of steady state rest, unloaded exercise (“0 W”) followed by 10-W increases in work rate every 3 minutes to symptom limitation. We averaged the last 30-second data point of each stage (i.e., for steady state or near steady state). ΔVE-ΔVCO₂ slope and intercept by linear regression, VE/VCO₂ nadir and end-exercise VE/VCO₂ were obtained and compared with predicted values according to Neder and co-workers.(14)(15)

**Arterialized (capillary) blood**

We collected capillary (c) blood samples from the ear lobe after application of a vasodilation-inducing emulsion (Finalgon™, GBm, Germany) at rest and during the last 30 s of each stage. Blood samples were analyzed immediately after each test for PCO₂, PO₂, oxygen saturation (SO₂) and pH (ABL800 FLEX; Radiometer, Copenhagen, Denmark). Concomitant arterial blood
gases were obtained in 5 patients: as shown in e-Figure 1, there was a close agreement between capillary and arterial values at rest and during exercise (within ~ 2 mmHg for PCO₂ and within ~ 4 mmHg for PO₂ with mean bias near zero for both variables). V₃/VT was calculated using the modified Bohr equation (Enghoff’s modification; equation [1]) and (A-c)PO₂ was estimated using the ideal alveolar gas equation (equation [2]):

\[
\frac{V_D}{VT} = \left[ \frac{(PcCO_2 - P_ECO_2)}{(PcCO_2)} \right] - \left( \frac{V_{DM}}{V_T} \right) \quad [\text{Eq. 1}]
\]

\[(A-c)PO_2 = \{FiO_2 \times (P_B - P_{H_2O}) - [PcCO_2 \times (1-FiO_2 \times (1-RER))]/RER\} \times PcO_2 \quad [\text{Eq. 2}]
\]

where \(V_{DM}\) is the mouthpiece and pneumotachograph dead space. FiO₂ is the inspired fraction of oxygen, \(P_B\) is the barometric pressure, \(P_{H_2O}\) is the partial pressure of water vapor and RER is the measure respiratory exchange ratio.

Arterialized blood gas tensions and derive data were also used to calculate alveolar ventilation and “estimated” \(\dot{V}E\) according to its physiological determinants (16)(17):

\[
\dot{V}_A = 863 \times \dot{V}CO_2 / PcCO_2 \quad \text{[Eq. 3]}
\]

\[
\dot{V}_E = \left(863 \times \dot{V}CO_2\right) / \left[PcCO_2 \times (1 - V_D/VT)\right] \quad \text{[Eq. 4]}
\]

**Statistical Analysis**

The statistical software package used was IBM SPSS Statistics version 24. Unpaired t test (or Mann-Whitney test when appropriated) were used to compare group differences in general characteristics, lung function tests, emphysema burden by HRCT and echocardiographic measurements. The \(\chi^2\) test
was used to compare frequencies. Association between selected continuous variables was investigated by Pearson’s product-moment correlation test. Two-way ANOVA with repeated measures were used to compare dyspnea intensity and cardiorespiratory, metabolic, gas exchange, and operating lung volumes at rest and during iso-work rates. A \( P<0.05 \) level of significance was used for all analyses.

References


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On-Line Supplement: Figures

e-Figure 1. Bland-Altman plots showing mean bias and 95% confidence intervals for arterial-capillary PCO$_2$ and PO$_2$ differences in 5 COPD-heart failure patients (different symbols) at rest and during progressive exercise (10-30 W). Closed symbols indicate hypocapnic patients and open symbols indicated non-hypocapnic patients.
e-Figure 2. Individual values for different metrics of exercise ventilatory inefficiency (ventilation (VE)-CO₂ output (VCO₂) relationship) in patients with COPD-heart failure. Closed symbols indicate hypocapnic patients (N= 10) and open symbols indicate non-hypocapnic patients (N= 12).
e-Figure 3. Metabolic responses to incremental cardiopulmonary exercise testing in COPD-heart failure patients separated by presence (N=10) or not (N=12) of exercise hypocapnia (closed symbols and open symbols, respectively).

* P<0.05 for between-group comparisons at rest, standardized work rates and the highest work rate attained by all subjects in a given group. Values are means ± SEM. Abbreviations: VO₂ = oxygen uptake; VCO₂ = carbon dioxide output; RER = respiratory exchange ratio.
e-Figure 4. Leg effort scores as a function of exercise intensity in COPD-heart failure patients separated by presence (N= 10) or not (N= 12) of exercise hypocapnia (closed symbols and open symbols, respectively).