

# Excess Ventilation in Chronic Obstructive Pulmonary Disease–Heart Failure Overlap

## Implications for Dyspnea and Exercise Intolerance

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### Abstract

**Rationale:** An increased ventilatory response to exertional metabolic demand (high  $\dot{V}_E/\dot{V}_{CO_2}$  relationship) is a common finding in patients with coexistent chronic obstructive pulmonary disease and heart failure.

**Objectives:** We aimed to determine the mechanisms underlying high  $\dot{V}_E/\dot{V}_{CO_2}$  and its impact on operating lung volumes, dyspnea, and exercise tolerance in these patients.

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

**Measurements and Main Results:** Regardless of the chosen metric (increased  $\dot{V}_E-\dot{V}_{CO_2}$  slope,  $\dot{V}_E/\dot{V}_{CO_2}$  nadir, or end-exercise  $\dot{V}_E/\dot{V}_{CO_2}$ ), ventilatory inefficiency was closely related to  $P_{CCO_2}$  ( $r$  values from  $-0.80$  to  $-0.84$ ;  $P < 0.001$ ) but not dead space/tidal volume ratio. Ten patients consistently maintained exercise  $P_{CCO_2}$  less than or equal

to 35 mm Hg (hypocapnia). These patients had particularly poor ventilatory efficiency compared with patients without hypocapnia ( $P < 0.05$ ). Despite the lack of between-group differences in spirometry, lung volumes, and left ventricular ejection fraction, patients with hypocapnia had lower resting  $P_{aCO_2}$  and lung diffusing capacity ( $P < 0.01$ ). Excessive ventilatory response in this group was associated with higher exertional  $P_{CO_2}$ . The group with hypocapnia, however, had worse mechanical inspiratory constraints and higher dyspnea scores for a given work rate leading to poorer exercise tolerance compared with their counterparts ( $P < 0.05$ ).

**Conclusions:** 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 chronic obstructive pulmonary disease–heart failure overlap. Excessive ventilation led to better arterial oxygenation but at the expense of earlier critical mechanical constraints and intolerable dyspnea.

**Keywords:** ventilation; exercise; chronic obstructive pulmonary disease; cardiopulmonary exercise test

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## At a Glance Commentary

### Scientific Knowledge on the

**Subject:** Heart failure is a common and disabling comorbidity of chronic obstructive pulmonary disease.

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 chronic obstructive pulmonary disease (ventilatory inefficiency). The mechanisms of this increased ventilatory inefficiency and its consequences for exercise intolerance remain poorly understood in this growing patient population.

### What This Study Adds to the

**Field:** Ventilatory inefficiency was inversely related to the regulated CO<sub>2</sub> tension in arterialized blood. Thus, particularly high ventilatory equivalents for CO<sub>2</sub> were found in a subgroup 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<sub>2</sub> and overcome an enlarged physiologic 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 patients with chronic obstructive pulmonary disease and heart failure.

Heart failure with reduced left ventricular ejection fraction is a common and devastating comorbidity of chronic obstructive pulmonary disease (COPD) (1, 2). Patients with overlapping COPD and heart failure characteristically present with impaired exercise capacity caused by breathlessness and/or increased muscle

fatigability (3–5). 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  $\dot{V}_E/V_{CO_2}$  relationship [ventilatory inefficiency]) (6, 7). We (8–10), and others (11, 12), found that ventilatory inefficiency varies greatly in COPD–heart failure patients with similar resting pulmonary (FEV<sub>1</sub>) and cardiac (left ventricular ejection fraction) impairment. The structural and physiologic determinants underpinning such large variability, however, remain poorly understood.

In COPD alone, greater emphysema burden (13, 14) has been associated with increased  $\dot{V}_E/V_{CO_2}$  in patients whose mechanical-ventilatory reserves are still sufficient to overcome the effects of high V<sub>D</sub> (15–17). Higher ventilatory demand worsened gas trapping leading to dynamic hyperinflation and greater inspiratory constraints (i.e., lower V<sub>T</sub>). Thus, exercise physiologic V<sub>D</sub>/V<sub>T</sub> (“wasted” ventilation) did not decrease as expected because of the compressive effects of localized hyperinflation on lung vessels (high V<sub>D</sub>) and/or lower V<sub>T</sub> in patients with worse ventilatory inefficiency. As a consequence of increased ventilatory drive and greater neuromechanical dissociation, these patients with increased  $\dot{V}_E/V_{CO_2}$  reported higher dyspnea and poorer exercise tolerance (15–17). As the disease

**Table 1.** General Characteristics

	All Patients (n = 22)	Hypocapnic Group (n = 10)	Nonhypocapnic Group (n = 12)
<b>Demographic</b>			
Male:female	16:6	7:3	9:3
Age, yr	67.4 ± 7.6	67.9 ± 8.9	67.1 ± 6.2
Height, cm	167 ± 6	167 ± 7	168 ± 5
Body mass, kg	73.8 ± 11.9	72.3 ± 13.4	74.1 ± 10.1
Body mass index, kg/m <sup>2</sup>	26.5 ± 4.2	26.3 ± 4.5	26.8 ± 3.9
<b>Clinical</b>			
Smoking status, current	7	3	4
NYHA class (I/II:III/IV)	12:10	4:6	8:4
Ischemic heart failure	15	7	8
mMRC dyspnea	2.3 (1–3)	2.5 (1–3)*	2 (0–3)
<b>Comorbidities</b>			
Diabetes	11	4	7
CKD (CrCl < 60 ml/min)	9	4	5
<b>Heart failure treatment</b>			
Digoxin	4	3	1
Furosemide	20	9	11
ACE-I or ARBs	21	9	12
Nitrates	5	3	2
Hydralazine	4	2	2
β-Blockers	22	10	12
Others	22	10	12
<b>COPD treatment</b>			
LAMA	16	6	10
LABA	22	10	12
ICS (+LABA)	16	7	9
Others	8	4	4
HRCT % emphysema	13.6 ± 10.0	14.1 ± 10.6	12.4 ± 9.8

*Definition of abbreviations:* ACE-I = angiotensin-converting enzyme inhibitor; ARBs = angiotensin receptor blockers; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CrCl = creatinine clearance; HRCT = high-resolution computed tomography; ICS = inhaled corticosteroids; LABA = long-acting β<sub>2</sub>-adrenoceptor agonist; LAMA = long-acting muscarinic receptor antagonists; mMRC = modified Medical Research Council scales; NYHA = New York Heart Association.

Values are mean ± SD, n, or median (range).

\*P < 0.05.

progresses, however, worsening ventilatory constraints, and an upward displacement of the CO<sub>2</sub> set-point (hypercapnia), act to decrease  $\dot{V}_E/\dot{V}_{CO_2}$  (18–20). In heart failure alone, disease progression is associated with higher  $\dot{V}_E/\dot{V}_{CO_2}$  because of a high  $V_D/V_T$  and an increased ventilatory drive leading to hypocapnia in highly variable combinations (21–23). 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<sub>2</sub> 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 (15–17). 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.

## Methods

A detailed 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<sub>1</sub>/FVC ratio less than lower limit of normal and Global Initiative for Chronic Obstructive Lung Disease spirometric stages 2–3) (24) and documented heart failure with reduced left ventricular ejection fraction ( $\leq 40\%$ ) 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 are 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 (#1151/2015) and Queen's University Affiliated Teaching Hospitals research ethics board (DMED-1588-13).

### Procedures

Transthoracic echocardiogram and chest high-resolution computed tomography with quantification of emphysema burden (25) were performed according to current recommendations (see 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

**Table 2.** Resting Functional and Echocardiographic Findings

	All Patients (n = 22)	Hypocapnic Group (n = 10)	Nonhypocapnic Group (n = 12)
<b>Lung function</b>			
FEV <sub>1</sub> , L	1.56 ± 0.34	1.58 ± 0.30	1.54 ± 0.39
% predicted	60 ± 11	63 ± 12	58 ± 10
FVC, L	3.03 ± 0.70	2.94 ± 0.61	3.06 ± 0.78
% predicted	82 ± 12	83 ± 11	81 ± 14
FEV <sub>1</sub> /FVC	0.56 ± 0.10	0.57 ± 0.08	0.55 ± 0.12
MVV, L/min	59 ± 14	60 ± 13	58 ± 16
IC, L	2.33 ± 0.37	2.30 ± 0.39	2.36 ± 0.36
% predicted	80 ± 10	82 ± 11	79 ± 10
TLC, L	6.15 ± 1.01	6.12 ± 0.79	6.18 ± 1.10
% predicted	98 ± 11	102 ± 6	96 ± 14
RV, L	3.01 ± 0.65	3.10 ± 0.70	2.95 ± 0.59
% predicted	148 ± 30	154 ± 32	142 ± 29
IC/TLC	0.37 ± 0.07	0.36 ± 0.06	0.38 ± 0.07
RV/TLC	0.48 ± 0.07	0.52 ± 0.08	0.47 ± 0.06
% predicted	139 ± 17	140 ± 19	137 ± 16
DL <sub>CO</sub> , ml/min/mm Hg	16.4 ± 2.9	11.6 ± 1.7*	20.4 ± 3.9
% predicted	58 ± 12	43 ± 10*	62 ± 14
DL <sub>CO</sub> /VA, ml/min/mm Hg/L	3.8 ± 0.7	2.6 ± 0.5*	4.3 ± 0.9
% predicted	62 ± 15	58 ± 14*	87 ± 17
VA/TLC	0.78 ± 0.08	0.77 ± 0.08	0.79 ± 0.08
MIP, cm H <sub>2</sub> O	−68 ± 30	−66 ± 28	−74 ± 32
% predicted	71 ± 24	72 ± 23	70 ± 20
<b>Arterial blood</b>			
pH	7.40 ± 0.03	7.41 ± 0.02	7.39 ± 0.03
HCO <sub>3</sub> <sup>−</sup> , mmol/L	24 ± 2	21 ± 3*	26 ± 2
PaCO <sub>2</sub> , mm Hg	36 ± 3	32 ± 2*	39 ± 3
PaO <sub>2</sub> , mm Hg	75 ± 8	79 ± 4*	72 ± 8
SaO <sub>2</sub> , %	94 ± 2	96 ± 2*	93 ± 1
<b>Echocardiogram</b>			
LVEF, %	38 ± 6	39 ± 6	38 ± 7
LVEDV, mm	60 ± 8	60 ± 6	61 ± 8
LVMI, g/m <sup>2</sup>	147 ± 50	153 ± 42	141 ± 59
LA, mm	42 ± 7	43 ± 8	42 ± 6
Right ventricle, mm	25 ± 4	27 ± 3	23 ± 5
PASP, mm Hg <sup>†</sup>	37 ± 6	42 ± 7	32 ± 6
TAPSE, mm <sup>‡</sup>	19 ± 3	17 ± 2	21 ± 3
TAPSE/PASP, mm/mm Hg	0.55 ± 0.13	0.45 ± 0.14*	0.67 ± 0.12

*Definition of abbreviations:* DL<sub>CO</sub> = diffusing capacity of the lung for carbon monoxide; HCO<sub>3</sub><sup>−</sup> = bicarbonate; IC = inspiratory capacity; LA = left atrium; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; MIP = maximal inspiratory pressure; MVV = maximal voluntary ventilation; PASP = pulmonary artery systolic pressure; RV = residual volume; TAPSE = tricuspid annular plane systolic excursion; TLC = total lung capacity. Values are mean ± SD.

\*P < 0.05

<sup>†</sup>N = Nine patients with hypocapnia and seven without hypocapnia.

<sup>‡</sup>N = Eight patients with hypocapnia and 10 without hypocapnia.

Vmax229d; SensorMedics, Yorba Linda, CA in Canada). The same reference values were used in both laboratories (26–29). CPET was conducted on an electronically braked cycle ergometer (Ergoline 800s; SensorMedics) 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-minute stepwise test to allow (near) steady-state arterial blood gas tensions.  $\Delta\dot{V}_E-\Delta\dot{V}_{CO_2}$  slope and intercept by linear regression,  $\dot{V}_E/\dot{V}_{CO_2}$  nadir, and end-exercise  $\dot{V}_E/\dot{V}_{CO_2}$  were obtained. Capillary (c) blood samples from the ear lobe were obtained at rest and during the last 30 seconds of each stage after application of a vasodilation-inducing emulsion (Finalgon, GBm, Germany). Blood samples were analyzed immediately after each test (ABL800 FLEX; Radiometer, Copenhagen, Denmark). Concomitant arterial blood gases were obtained in five patients: in keeping with previous data (31), there was a close agreement between capillary and arterial values at rest and during exercise (see Figure E1 in the online supplement).  $V_D/V_T$  was calculated using the modified Bohr equation (Enghoff modification) and  $P(A-a)O_2$  was estimated using the ideal alveolar gas equation.

### Statistical Analysis

The statistical software package used was IBM SPSS Statistics version 24.0 (IBM Corp, Armonk, NY). Unpaired Student’s *t* test (or Mann-Whitney test when appropriated) were used to compare between-subject differences. Chi-square test was used to compare frequencies. Association between selected continuous variables was investigated by Pearson product-moment correlation test. Two-way analysis of variance with repeated measures was used to compare dyspnea intensity and cardiorespiratory, metabolic, gas exchange, and operating lung volumes at rest and during isowork rates. A  $P < 0.05$  level of significance was used for all analyses.

## Results

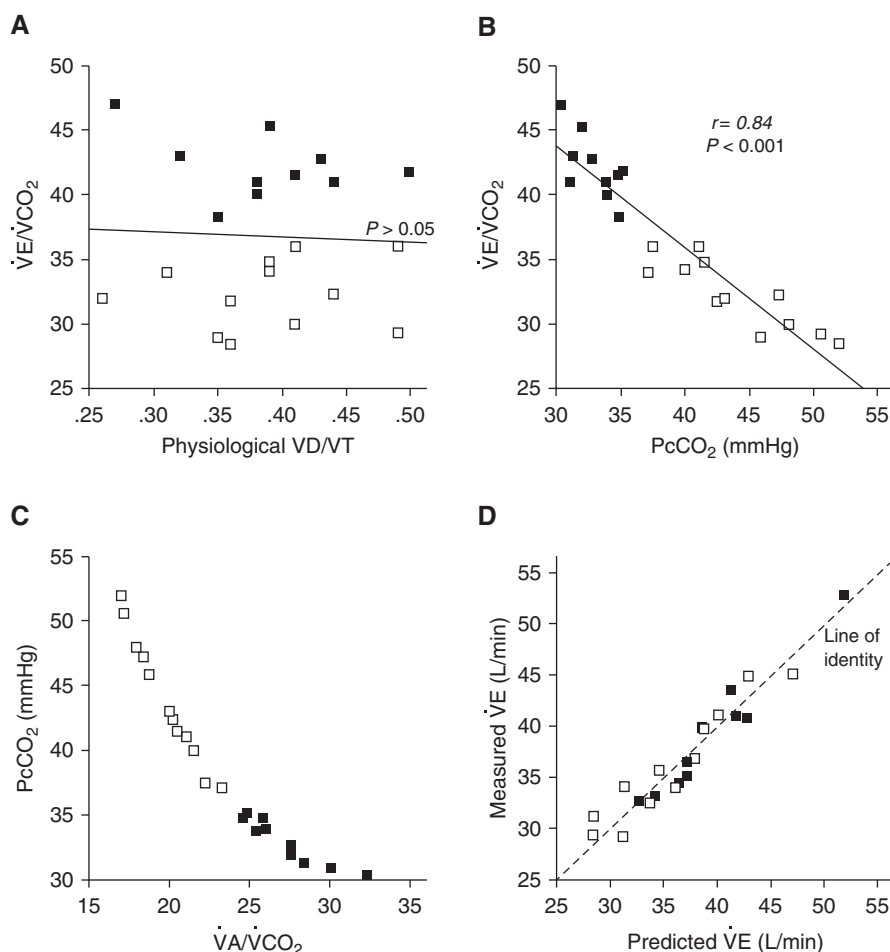
### Clinical and Resting Functional Characteristics

Twenty-two patients were enrolled. Most patients were men in their late 60s or early 70s, mildly overweight, ex-smokers with heart failure secondary to ischemic heart disease with other systemic comorbidities (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 residual volume/TLC ratio (i.e., pulmonary gas trapping). Moreover, patients had decreased IC/TLC ratios (Table 2).

### Physiologic 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  $\Delta\dot{V}_E-\Delta\dot{V}_{CO_2}$  slope (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  $P_{cCO_2}$  at the nadir varied markedly (from 0.26 to 0.49 and 30 mm Hg to 52 mm Hg, respectively) (Figure 1).

As depicted in Figure 1A,  $\dot{V}_E/\dot{V}_{CO_2}$  nadir was largely independent of



**Figure 1.** Relationship between  $V_D/V_T$  ratio (A) and capillary (c)  $P_{cCO_2}$  (B) with  $\dot{V}_E/\dot{V}_{CO_2}$  ratio in chronic obstructive pulmonary disease–heart failure patients. Patients with hypocapnia (solid symbols;  $n = 10$ ) and without hypocapnia patients (open symbols;  $n = 12$ ) are identified. (C) Hyperbolic decrease in  $P_{cCO_2}$  as a function of  $V_A/\dot{V}_{CO_2}$  ratio. (D) Close relationship between predicted  $\dot{V}_E$  (from  $\dot{V}_{CO_2}$ , physiologic  $V_D/V_T$ , and  $P_{cCO_2}$ ) with measured  $\dot{V}_E$  in both groups. Values are shown at the  $\dot{V}_E/\dot{V}_{CO_2}$  nadir (minimum).

simultaneously measured  $V_D/V_T$  ( $P > 0.05$ ) but increased in close association with decrements in  $P_{cCO_2}$  ( $P < 0.001$ ) (Figure 1B). Similar results were found when the chosen metric of ventilatory inefficiency was  $\Delta V_E - \Delta V_{CO_2}$  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  $P_{cCO_2}$  as a function of alveolar hyperventilation (i.e., progressively higher  $\dot{V}_A/\dot{V}_{CO_2}$  ratio) (Figure 1C). Measured  $\dot{V}_E$  expressed as a function of predicted  $\dot{V}_E$  (from measured  $\dot{V}_{CO_2}$ ,  $P_{cCO_2}$ , and  $V_D/V_T$ ) (Equation [4] in the online supplement) was remarkably close to the line of identity (Figure 1D).

### Clinical and Resting Variables: Patients with versus without Hypocapnia

Considering that  $P_{cCO_2}$  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  $P_{cCO_2}$  ( $\leq 35$  mm Hg): hypocapnic ( $n = 10$ ) and nonhypocapnic 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 diffusing capacity of the lung for carbon monoxide ( $DL_{CO}$ ) 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  $P_{aCO_2}$  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 computed tomography (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 tricuspid annular plane systolic excursion (TAPSE)/pulmonary artery systolic pressure (PASP) ratio was lower in the hypocapnic group ( $P < 0.05$ ).

### Exercise Responses: Patients with versus without Hypocapnia

Compared with the nonhypocapnic group, patients with hypocapnia presented with lower peak work rate and  $\dot{V}O_2$  (Table 3). The hypocapnic group showed higher  $\dot{V}CO_2$ , 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).

Submaximal  $\dot{V}_E$  and  $\dot{V}_E/\dot{V}_{CO_2}$  at a given work rate were systematically higher in the hypocapnic group (Figures 2A and 2B). Moreover,  $\dot{V}_E/\dot{V}_{CO_2}$  relationship was consistently higher in this group regardless the chosen metric of ventilatory inefficiency (see Figure E2). As shown in Figure 2C,  $V_D/V_T$  values at a given work rate did not

differ between groups. Consequently,  $\dot{V}_A$  was higher and end-tidal  $P_{CO_2}$  lower in this group across exercise intensities (Figures 2D and 2E, respectively). Conversely, arterialized (and end-tidal  $P_{O_2}$ ; data not shown) were consistently higher at a given work rate in the hypocapnic group ( $P < 0.05$ ) (Figure 2F).

Higher  $\dot{V}_E$  at a given work rate in the hypocapnic group was associated with similar  $V_T$  (Figure 3A) but greater respiratory frequency (Figure 3B) (i.e., the respiratory frequency/ $V_T$  ratio was systematically higher compared with the nonhypocapnic 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

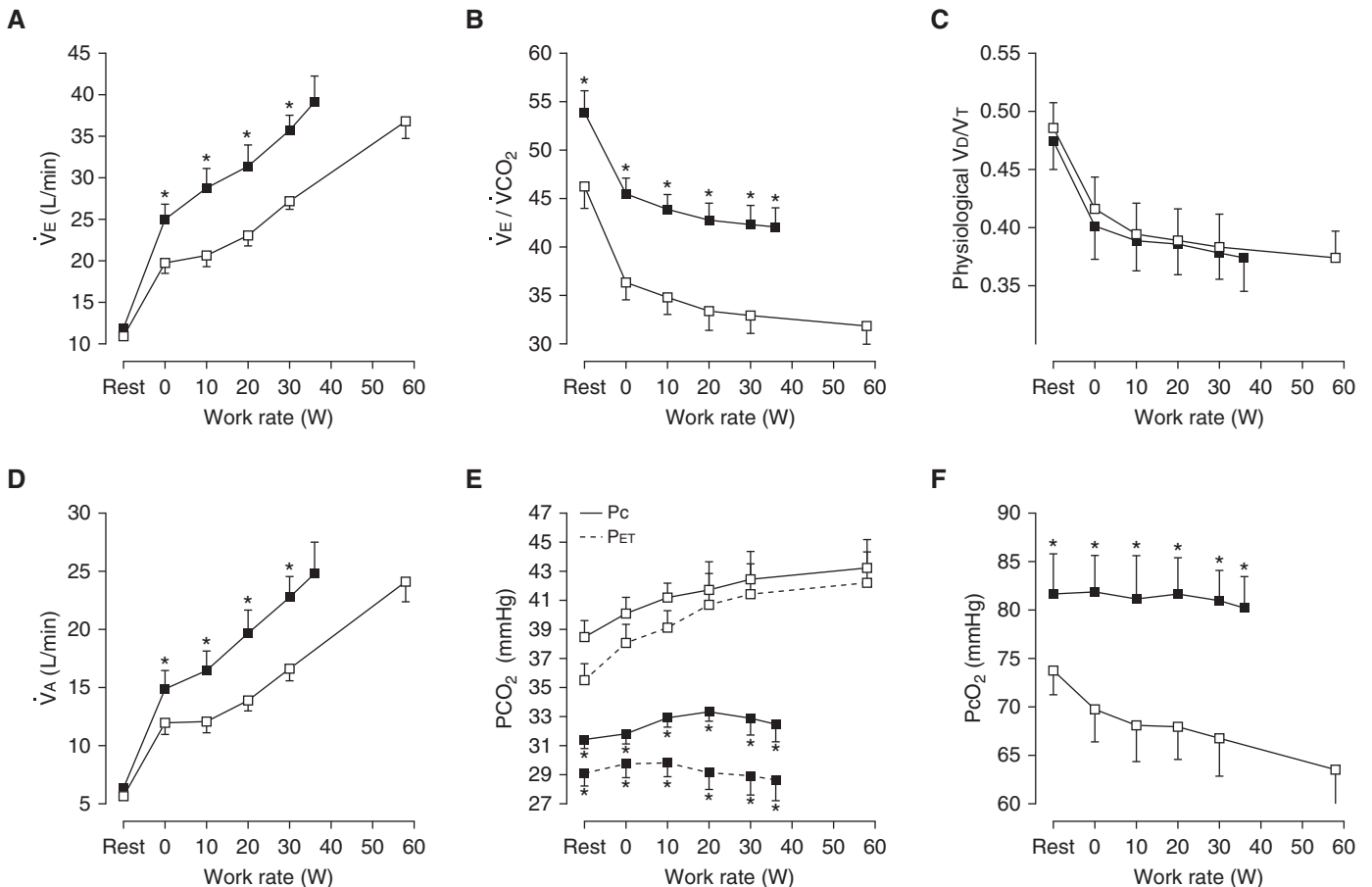
**Table 3.** Physiologic and Sensory Responses to Step-wise, Progressive Incremental Cardiopulmonary Exercise Testing

	Hypocapnic Group (n = 10)	Nonhypocapnic Group (n = 12)
Peak WR, W	43 ± 12*	58 ± 14
Metabolic/cardiovascular responses		
Peak $\dot{V}O_2$ , L/min	0.94 ± 0.18*	1.18 ± 0.15
Peak $\dot{V}O_2$ , ml/min/kg	12.1 ± 3.1*	16.0 ± 2.9
Peak RER	1.08 ± 0.08	1.10 ± 0.07
$\Delta \dot{V}O_2 - \Delta WR$ slope, ml/min/W	9.7 ± 2.6	9.9 ± 2.8
Peak HR, bpm	114 ± 18	111 ± 25
Ventilatory responses		
Peak $\dot{V}_E/MVV$ , %	75.5 ± 11.9	73.4 ± 9.9
Peak $V_T$ , L	1.12 ± 0.64	1.23 ± 0.80
Peak f, rpm	34 ± 12	31 ± 10
Peak $\dot{V}_E/\dot{V}_{CO_2}$	43 ± 4*	32 ± 6
$\dot{V}_E/\dot{V}_{CO_2}$ nadir	42 ± 5*	33 ± 6
%predicted	152 ± 28*	118 ± 37*
$\Delta V_E - \Delta V_{CO_2}$ slope	43 ± 6*	27 ± 7
%predicted	147 ± 24*	110 ± 31*
$\Delta V_E - \Delta V_{CO_2}$ intercept, L/min	1.1 ± 2.1*	5.1 ± 2.9
Peak-rest IC, L	-0.48 ± 0.37*	-0.28 ± 0.30
Peak EILV/TLC, %	0.83 ± 0.06*	0.78 ± 0.08
Peak EELV/TLC, %	0.70 ± 0.08*	0.66 ± 0.07
Pulmonary gas exchange responses		
Peak $P_{ETCO_2}$ , mm Hg	28 ± 4*	41 ± 5
Peak $P_{cCO_2}$ , mm Hg	32 ± 3*	43 ± 4
Peak $P(c-ET)CO_2$ , mm Hg	-4 ± 4	-2 ± 4
Peak $V_D/V_T$	0.37 ± 0.07	0.38 ± 0.06
Peak $P(A-c)O_2$ , mm Hg	38.5 ± 7.7	39.3 ± 6.7
Peak $Sp_{O_2}$ , %	96 ± 3*	92 ± 3
Sensory responses		
Peak dyspnea score	8.5 (3 to 10)*	5 (2 to 8)
Peak leg effort score	5.5 (2 to 8)	6 (1 to 8)
Peak dyspnea - leg effort scores	3 (5 to 1)	-1 (2 to -4)
Peak dyspnea > leg effort scores, n	8*	3

*Definition of abbreviations:* bpm = beats per minute; EELV = end-expiratory lung volume; EILV = end-inspiratory lung volume; f = respiratory rate; HR = heart rate; IC = inspiratory capacity; MVV = maximal voluntary ventilation;  $P_c$  = capillary pressure;  $P_{ET}$  = end-tidal partial pressure; RER = respiratory exchange ratio; rpm = respirations per minute;  $Sp_{O_2}$  = oxygen saturation by pulse oximetry; TLC = total lung capacity; WR = work rate.

Values are mean ± SD, n, or median (range).

\* $P < 0.05$ .



**Figure 2.** Ventilatory (A–D) and pulmonary gas exchange (E and F) responses to incremental cardiopulmonary exercise testing in chronic obstructive pulmonary disease–heart failure patients separated by presence ( $n = 10$ ) or not ( $n = 12$ ) of exercise hypocapnia (solid 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  $\pm$  SEM. Pc = capillary (arterialized) partial pressure; PET = end-tidal partial pressure.

rate (Figure 3D). Consequently,  $V_T/IC$  ratio was greater at higher exercise intensities (Figure 4B). Higher end-expiratory lung volume but similar  $V_T$  led the patients with hypocapnia to reach earlier critical inspiratory constraints (Figures 3E and 3F). Of note, mean inspiratory flow ( $V_T$ /inspiratory time ratio) and the duty cycle (inspiratory/total time ratio) were both higher in this group (Figures 4C and 4D).

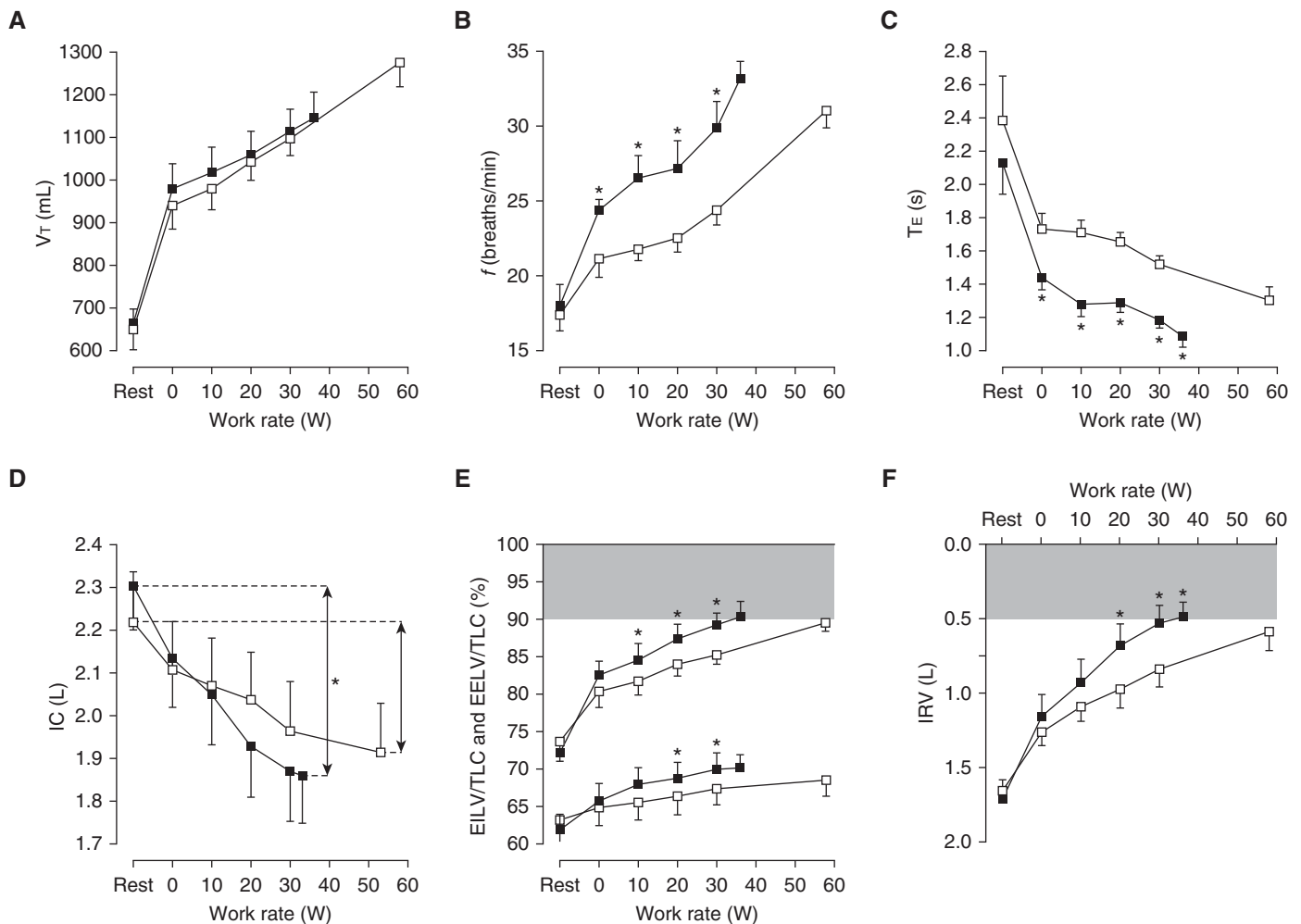
Patients in the hypocapnic group reported higher dyspnea ratings at all submaximal work rates and at peak exercise compared with their counterparts (Figure 5A). There was no significant between-group differences in ratings of exertional leg discomfort at submaximal exercise (data not shown) or end-exercise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

## Discussion

The main original finding of this study involving stable patients with COPD–heart failure overlap indicates that heightened ventilatory stimulation was instrumental to explain exercise ventilatory inefficiency. Thus, patients with lower  $P_{aCO_2}$  had to overcome an enlarged physiologic dead space to (alveolar) hyperventilate. Excessive ventilation helped to preserve arterial oxygenation but at the expense of dynamic hyperinflation, earlier mechanical constraints, greater dyspnea, and reduced exercise capacity. These results indicate that breathlessness and poor exercise tolerance in overlapping COPD–heart failure are strongly influenced by interpatient 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  $\dot{V}_E/\dot{V}_{CO_2}$  relationship) is a key exercise pathophysiologic 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 (8–10) and others (11, 12) in patients with COPD presenting with heart failure as comorbidity. 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 (physiologic  $V_D/V_T$ ). Although patients with worse ventilatory inefficiency (i.e., the hypocapnic group) did not present with increased physiologic  $V_D/V_T$  compared with their counterparts, the effect of a given decrement in  $P_{CO_2}$  in increasing  $\dot{V}_E/\dot{V}_{CO_2}$



**Figure 3.** Pattern and timing of breathing (A–C) and operating lung volume (D–F) during incremental exercise in cardiopulmonary exercise testing in chronic obstructive pulmonary disease–heart failure patients separated by presence ( $n = 10$ ) or not ( $n = 12$ ) of exercise hypocapnia (*solid* and *open* symbols, respectively). *Shaded areas* in E and F represent the volumes typically associated with critical inspiratory constraints in chronic obstructive pulmonary disease (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  $\pm$  SEM. EELV = end-expiratory lung volume; EILV = end-inspiratory lung volume;  $f$  = respiratory rate; IC = inspiratory capacity; IRV = inspiratory reserve volume; TLC = total lung capacity;  $T_E$  = expiratory time.

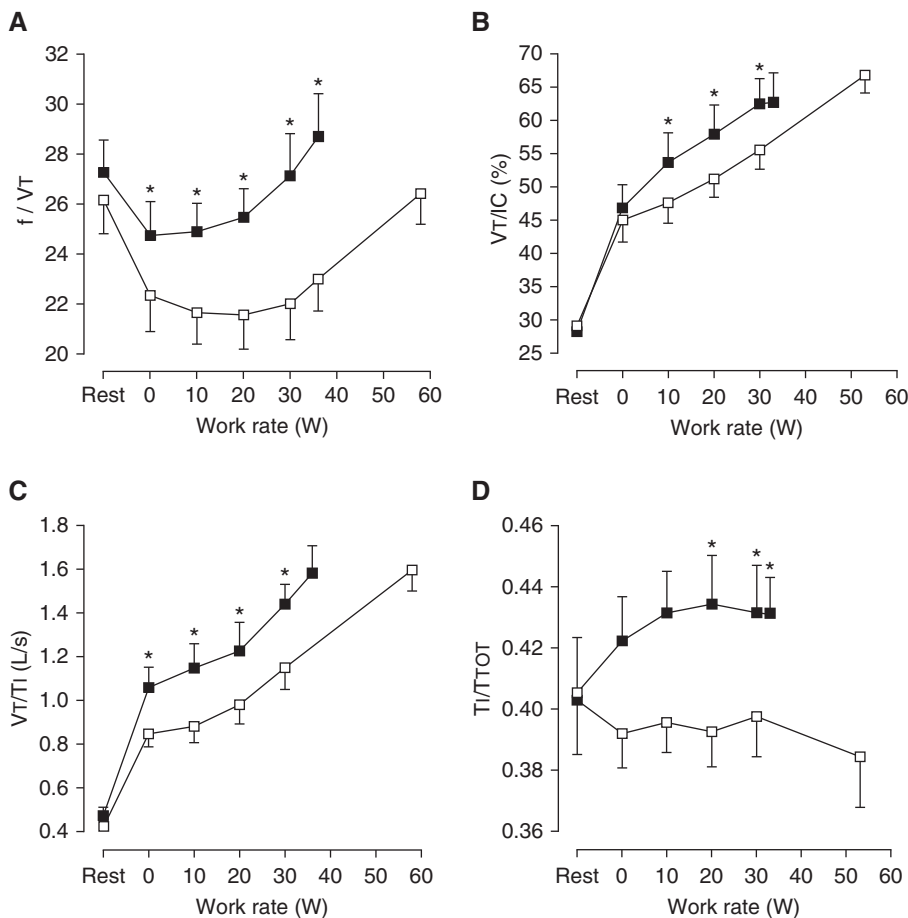
was amplified by the presence of larger “wasted” ventilation. The resulting alveolar hyperventilation downwardly displaced the level at which  $P_{cCO_2}$  was chronically regulated, a self-perpetuating consequence of a high ventilatory drive (33). Consequently, a hyperbolic decrease in  $P_{cCO_2}$  as a function of  $\dot{V}_A/\dot{V}_{CO_2}$  ratio (Figure 1C) is highly consistent with a tight control of arterial  $CO_2$  tension in patients showing ample differences in  $\dot{V}_D/\dot{V}_T$  (Figure 1A) (7, 8).

In this context, it is noteworthy that patients without hypocapnia maintained exercise  $P_{cCO_2}$  close to the resting eucapnic level or allowed it to raise despite starting exercise with seemingly similar mechanical-

ventilatory reserves than the patients with hypocapnia (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  $P_{cCO_2}$  reduced the ventilatory needs and, potentially, the work performed by the respiratory muscles). In other words, the respiratory controller of patients without hypocapnia opted “not to fight” 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 because patients maintained better arterial oxygenation than their counterparts (Figure 2F) despite similar efficiency in intrapulmonary oxygenation [i.e., same  $P_{(A-c)O_2}$ ] (Table 3).

The dichotomous behavior regarding exercise  $P_{cCO_2}$  trajectory showed in Figure 2 resembles that long described in pink puffers (type A) versus blue bloaters (type B) patients with COPD (35, 36). Although there was a trend for patients with hypocapnia 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



**Figure 4.** Breathing pattern (A and B), mean inspiratory flow (C), and timing of breathing (D) in chronic obstructive pulmonary disease–heart failure patients separated by presence (n = 10) or not (n = 12) of exercise hypocapnia (solid 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  $\pm$  SEM. f = respiratory rate; IC = inspiratory capacity;  $T_I$  = inspiratory time;  $T_{TOT}$  = total respiratory cycle time.

patients (35, 36). Thus, it is conceivable that the well-established consequences of heart failure on ventilatory drive (21, 23, 37) had a dominant role in inducing a low  $P_{cCO_2}$  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  $O_2$  delivery in face of a failing heart (38). It should be acknowledged, however, that oxygen saturation as measured by pulse oximetry was typically greater than 90% in the nonhypocapnic group; thus, oxygen delivery was well-maintained in both groups. Owing to similar  $V_D/V_T$  (Figure 2C) and higher  $P_{cCO_2}$  (Figure 2F) compared with the nonhypocapnic, higher wasted ventilation (39) and increased stimulation of carotid bodies by hypoxemia

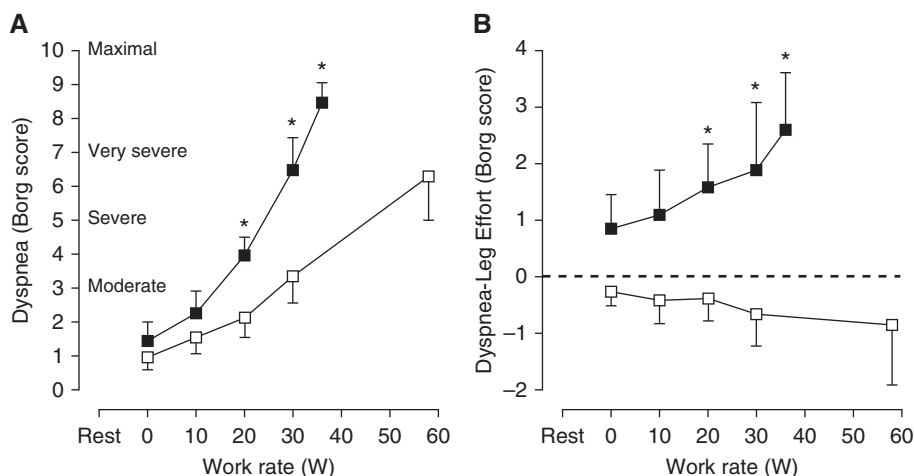
(37) seems unlikely. Sympathetic overstimulation, lacticidosis, and increased stimulation or a heightened sensitivity of central chemoreceptors and peripheral muscle ergoreceptors might be involved (as reviewed in Reference 38). Of note, resting TAPSE/PASP ratio was significantly lower in patients with worse ventilatory inefficiency (Table 2) suggesting right ventricle–pulmonary circulation uncoupling. Lower  $DL_{CO}$  in this group also suggests more extensive pulmonary microvascular abnormalities. In fact, Guazzi and coworkers (40) found a close relationship between low TAPSE/PASP and increased  $\dot{V}_E/\dot{V}_{CO_2}$  in patients with heart failure. Although the underlying mechanisms are unclear, they might involve higher afferent stimulation from cardiopulmonary 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

Because of larger inspiratory volume reserves compared with 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) (Figures 3D–3F). For instance, inspiratory reserve volume at 30 W in this group was, on average, almost half of that observed in the nonhypocapnic 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 ( $V_T/IC$  ratio  $\sim 0.7$  and peak inspiratory reserve volume  $\sim 0.5$  L) (30),  $V_T$  tended to stabilize (Figure 3B) and  $\dot{V}_E$  increased mainly because of 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 5.** (A and B) Exertional symptoms (Borg scale ratings) during incremental cardiopulmonary exercise testing in chronic obstructive pulmonary disease–heart failure patients separated by presence ( $n = 10$ ) or not ( $n = 12$ ) of exercise hypocapnia (solid 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  $\pm$  SEM.

(Figure 4C), an index of increased ventilatory drive (30).

The patients with hypocapnia paid a too-high sensory “price” to preserve exertional  $P_{CO_2}$ . For instance, this group presented with consistently higher dyspnea scores throughout exercise (Figure 5B) and at exercise cessation (Table 3) compared with 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  $\dot{V}_E$  *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, patients with hypocapnia 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). In contrast, the relative contribution of leg effort to exercise limitation was significantly higher in the nonhypocapnic 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 cardiopulmonary 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 subgroup 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 ergopulmonary and cardiopulmonary receptors) (21, 23, 37, 40). Moreover, patients with poorer ventilatory efficiency are likely to benefit mostly from rehabilitative strategies associated with low-to-minimal ventilatory stress, such as 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<sub>1</sub> (15–17), 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 physiologic information,

which is clinically relevant to contemporary COPD management. ■

**Author disclosures** are available with the text of this article at [www.atsjournals.org](http://www.atsjournals.org).

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