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# Exercise ventilatory inefficiency in heart failure and chronic obstructive pulmonary disease

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ABSTRACT

*Background:* Dyspnea on exertion is common to both heart failure (HF) and chronic obstructive pulmonary disease (COPD), and it is important to discriminate whether symptoms are caused by HF or COPD in clinical practice. The ventilatory equivalent for carbon dioxide ($V_E/VCO_2$) slope and $V_E$ intercept (a reflection of pulmonary dead space) are two candidate non-invasive indices that could be used for this purpose. Thus, we compared non-invasive indexes of ventilatory efficiency in patients with HF and preserved or reduced ejection fraction (HFpEF and HFrEF, respectively) or COPD.

*Methods:* Patients with HFpEF ($n = 21$), HFrEF ($n = 20$), and COPD ($n = 22$) patients performed cardiopulmonary exercise testing to volitional fatigue. $V_E$ and gas exchange were measured via breath-by-breath open circuit spirometry. All data from rest to peak exercise were used to calculate $V_E/VCO_2$ slope and $V_E$ intercept using linear regression. Receiver operating characteristic (ROC) curves were constructed to determine optimized cutoffs for $V_E/VCO_2$ slope and $V_E$ intercept to discriminate HFpEF and HFrEF from COPD.

*Results:* HFrEF patients had a greater $V_E/VCO_2$ slope than HFpEF and COPD patients (HFrEF: 40 ± 9; HFpEF: 32 ± 7; COPD: 32 ± 7) ($p < 0.01$). COPD patients had a greater $V_E$ intercept than HFpEF and HFrEF patients (COPD: 3.32 ± 1.66; HFpEF: 0.77 ± 1.23; HFrEF: 1.28 ± 1.19 L/min) ($p < 0.01$). A $V_E$ intercept of 2.64 L/min discriminated COPD from HF patients (AUC: 0.88, $p < 0.01$), while $V_E/VCO_2$ slope did not ($p = 0.11$).

*Conclusion:* These findings demonstrate that $V_E$ intercept, not $V_E/VCO_2$ slope, may discriminate COPD from both HFpEF and HFrEF patients.



## 1. Introduction

Patients with heart failure with preserved (HFpEF) or reduced ejection fraction (HFrEF) and chronic obstructive pulmonary disease (COPD) present with overlapping symptoms such as dyspnea on exertion, exercise intolerance, muscle weakness, and fatigue [1]. Furthermore, HF and COPD patients can exhibit multiple co-morbidities necessitating differentiating indices to align the most appropriate treatment strategy. The ventilatory equivalent for carbon dioxide ($V_E/VCO_2$) slope, determined from cardiopulmonary exercise testing (CPET), has been used as a prognostic tool in HF [2–4] as well as to assess disease progression and identify possible comorbidities including COPD [5–7].

Higher $V_E/VCO_2$ slope is indicative of greater disease severity and worse outcomes in HF [4], which is in contrast to COPD, where decreases in $V_E/VCO_2$ slope are associated with worsening COPD severity due to pulmonary abnormalities and mechanical constraints [7]. Thus, the $V_E/VCO_2$ slope would theoretically be useful to differentiate HF from COPD. However, patients with HF also exhibit pulmonary abnormalities similar to COPD (e.g., impaired lung diffusion capacity and mechanical constraints) [8–11], which may mask the differentiating impact of the $V_E/VCO_2$ slope. To this point, previous studies investigating the ability of $V_E/VCO_2$ slope to discriminate HFrEF and COPD have been inconclusive [12,13].

The ventilatory intercept ($V_E$ intercept) is a novel parameter derived from the $V_E$ to $VCO_2$ relationship during exercise, which theoretically equates to dead space and is not influenced by pulmonary mechanical constraints [7,14]. Unlike $V_E/VCO_2$ slope, $V_E$ intercept increases with greater disease severity in COPD [7], and COPD patients have a greater $V_E$ intercept than HFrEF patients [12,13]. To date, $V_E/VCO_2$ slope and $V_E$ intercept have been exclusively investigated in HFrEF and COPD patients. Because HFpEF comprises ~50% of the HF population, it is important to understand these ventilatory inefficiency indices in HFpEF. In fact, our lab and others have found that ventilatory efficiency (and the components of the alveolar air equation) can differ between HFrEF and HFpEF where HFrEF patients exhibit worse ventilatory efficiency (i.e. greater $V_E/VCO_2$ slope) [2,15].

The purpose of this study was to compare the $V_E/VCO_2$ slope and $V_E$ intercept in patients with COPD, HFpEF, or HFrEF. We hypothesized that

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1) COPD patients will have a greater $V_E$ intercept compared to HF patients and 2) HFrEF patients will exhibit a greater $V_E/VCO_2$ slope compared to COPD and HFpEF patients.

## 2. Methods

### 2.1. Participants

Patients with HFpEF (n = 21), HFrEF (n = 20), or COPD (n = 22) were referred to our study by their primary cardiologist or pulmonologist. HFrEF was defined by left ventricular ejection fraction (LVEF) ≤40% and HFpEF was defined by a LVEF ≥50%, clinical symptoms (e.g., exertional dyspnea) and elevated left heart filling pressures at rest and/or with exercise in accordance with established guidelines [16]. COPD patients with GOLD stages 1–4 were recruited.

Participants were excluded using the following criteria: primary pulmonary hypertension, diagnosed pulmonary disease (in HF patients), diagnosed heart failure (in COPD patients), significant coronary artery disease (stenosis ≥ 50%), cor pulmonale, primary renal or hepatic disease, valvular heart disease (any stenosis, >mild regurgitation, etc.), hypertrophic or infiltrative cardiomyopathy, constrictive pericarditis, or deep vein thrombosis. All participants provided written informed consent after being provided a written and verbal description of the study requirements. All aspects of this study were approved by the Mayo Clinic Institutional Review Board and conformed to principles outlined in the Declaration of Helsinki.

### 2.2. Echocardiography

Resting two-dimensional and tissue Doppler echocardiography according to guidelines of the American Society of Echocardiography were used to assess LVEF, morphology, and function (i.e. early transmitral flow velocity (E), late transmitral flow velocity (A), E/A ratio, early diastolic mitral annular velocity (e′), and peak E to e′ ratio) in HF patients [16].

### 2.3. Pulmonary function tests

Patients performed standard pulmonary function tests according to the ATS/ERS guidelines. All HFrEF and COPD patients as well as a subset (n = 12) of the HFpEF patients performed the pulmonary function tests. Forced expiratory volume in 1 s ($FEV_1$), forced vital capacity (FVC), and $FEV_1$/FVC are reported. $FEV_1$ and FVC are reported as percent (%) predicted values.

### 2.4. CPET protocol

Patients performed the CPET while remaining on standard pharmacologic therapy. Patients performed cycling exercise at an initial workload of 15–20 W with an increasing

**Table 1**
Patient characteristics.

| | COPD | HFpEF | HFrEF | p-Value |
|---|---|---|---|---|
| n | 22 | 21 | 20 | |
| Age (years) | 58 ± 8 | 63 ± 9 | 58 ± 7 | 0.07 |
| Sex (men/women) | 16/6[b] | 7/14 | 17/3[b] | <0.01 |
| Height (cm) | 170 ± 8 | 168 ± 10 | 173 ± 8 | 0.13 |
| Weight (kg) | 91 ± 25 | 101 ± 20 | 86 ± 14 | 0.07 |
| Body mass index (kg/m$^2$) | 31 ± 8 | 36 ± 7[c] | 29 ± 4 | <0.01 |
| Body surface area (m$^2$) | 2.1 ± 0.3 | 2.2 ± 0.3 | 2.0 ± 0.2 | 0.25 |
| $FEV_1$ (% predicted) | 52 ± 14 | 75 ± 18[a] | 80 ± 17[a] | <0.01 |
| FVC (% predicted) | 79 ± 14 | 80 ± 15 | 81 ± 16 | 0.89 |
| $FEV_1$/FVC (%) | 53 ± 14 | 74 ± 7[a] | 77 ± 5[a] | <0.01 |
| LV ejection fraction (%) | | 63 ± 6[c] | 22 ± 7 | <0.01 |
| GOLD stage, n (%) | | | | |
| 1 | 1 (5) | | | |
| 2 | 12 (55) | | | |
| 3 | 8 (36) | | | |
| 4 | 1 (5) | | | |
| NYHA class, n (%) | | | | |
| II | | 6 (29) | 11 (55) | 0.09 |
| III | | 14 (67) | 9 (45) | 0.17 |
| IV | | 1 (5) | 0 (0) | 0.34 |
| Weber-Janicki class [peak $VO_2$], n (%) | | | | |
| C, 10–16 mL/kg/min | | 3 (14) | 6 (30) | 0.24 |
| D, <10 mL/kg/min | | 18 (86) | 14 (70) | 0.24 |
| Hemoglobin (g/dL) | | 12.2 ± 1.5[c] | 13.7 ± 1.7 | <0.01 |
| Creatinine (mg/dL) | | 1.24 ± 0.29 | 1.46 ± 0.44 | 0.07 |
| eGFR (mL/min/1.73 m$^2$) | | 48 ± 17 | 52 ± 14 | 0.58 |
| Drug therapy, n (%) | | | | |
| Steroid | 13 (59) | 0 (0)[a] | 0 (0)[a] | <0.01 |
| Bronchodilator | 15 (68) | 0 (0)[a] | 0 (0)[a] | <0.01 |
| ACE I or ARB | 6 (27) | 14 (67)[a] | 14 (70)[a] | <0.01 |
| Antiarrhythmic | 0 (0) | 4 (19) | 9 (45)[a] | <0.01 |
| β-Blocker | 4 (18) | 16 (76)[a] | 17 (85)[a] | <0.01 |
| $Ca^{2+}$ channel blocker | 1 (5) | 6 (29) | 0 (0) | <0.01 |
| Digoxin | 0 (0) | 2 (10)[c] | 12 (60)[a] | <0.01 |
| Nitrate (oral, SL, or topical) | 0 (0) | 7 (33) | 6 (30) | 0.01 |
| Aspirin | 5 (23) | 15 (71)[a] | 15 (75)[a] | <0.01 |
| Diuretics | 5 (23) | 9 (43)[c] | 18 (90)[a] | <0.01 |
| Echocardiography | | | | |
| LA volume (mL) | | 76 ± 27[c] | 114 ± 42 | <0.01 |
| LA volume index (mL/m$^2$) | | 37 ± 13[c] | 56 ± 21 | <0.01 |
| Mitral E-wave VEL (cm/s) | | 95.4 ± 24.6 | 88.9 ± 37.7 | 0.53 |
| Mitral A-wave VEL (cm/s) | | 74.7 ± 19.7 | 71.3 ± 37.6 | 0.75 |
| Mitral E/A ratio | | 1.4 ± 0.7 | 1.5 ± 1.0 | 0.67 |
| Mitral septal tissue Doppler VEL (e′) (cm/s) | | 6.7 ± 2.1[c] | 4.3 ± 1.1 | <0.01 |
| Mitral E/e′ ratio | | 15.9 ± 8.0[c] | 22.5 ± 10.8 | 0.04 |
| IV septum thickness (mm) | | 10.3 ± 1.2 | 9.5 ± 1.3 | 0.06 |
| Posterior wall thickness (mm) | | 9.9 ± 1.7 | 9.9 ± 1.3 | 0.99 |

Mean ± SD. $FEV_1$, FVC, and $FEV_1$/FVC are from 12 of 21 HFpEF patients.
[a] Significantly different from COPD.
[b] Significantly different from HFpEF.
[c] Significantly different from HFrEF.

workload of 15–20 W every 3 min until volitional fatigue. Heart rate and rhythm were continuously monitored using a 12-lead electrocardiogram.

### 2.5. Ventilation and gas exchange

Breath-by-breath open circuit spirometry (MedGraphics, St. Paul, MN) was used to continuously measure ventilation and gas exchange throughout the CPET. The final 30 s of rest and of the final completed exercise stage (i.e., peak oxygen uptake ($\dot{V}O_2$peak)) were used for data analyses. Criteria for achievement of $\dot{V}O_2$peak included one of the following: heart rate <10 beats/min of the age-predicted maximum, plateau in $\dot{V}O_2$ (<150 mL/min) with increases in workload, respiratory exchange ratio >1.1, or rating of perceived exertion >17. Percent (%) predicted $\dot{V}O_2$peak was calculated from Hansen et al. (predicted $\dot{V}O_2$peak = weight (kg) ∗ (50.75 − 0.372 ∗ age)) [17]. Data acquired included $\dot{V}O_2$, $\dot{V}CO_2$, respiratory exchange ratio (RER), breathing frequency ($F_b$), tidal volume ($V_T$), ventilatory equivalents for $\dot{V}O_2$ and $\dot{V}CO_2$ ($\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$, respectively), inspiratory time (Ti), expiratory time (Te), and $V_T$/Ti (an index of ventilatory drive). The ventilatory efficiency response was expressed as a linear regression by plotting $\dot{V}_E$ (ordinate) and $\dot{V}CO_2$ (abscissa) using data at rest and $\dot{V}O_2$peak and the slope (i.e. $\dot{V}_E/\dot{V}CO_2$ slope) and y-intercept (i.e. $\dot{V}_E$ intercept) were determined for each patient as previously done [2–4,15,18,19]. Using all exercise data to derive these ventilatory efficiency parameters is clinically relevant and prognostically superior to determining ventilatory efficiency parameters with exercise data prior to the respiratory compensation threshold in HF patients [15,19].

### 2.6. Statistical analyses

Values are reported as mean ± standard deviation (SD). Statistical analyses were performed by using SigmaStat 2.0 (Jandel Scientific, San Rafael, CA). All data were checked for normal distribution using the Shapiro-Wilk test and, if normality was not met, data were reciprocally transformed. Participant characteristics and peak exercise data were compared using a one-way analysis of variance, unpaired *t*-tests, and Kruskal-Wallis one-way analysis of variance (for categorical data) when appropriate. Tukey post-hoc tests were used when significant *F*-tests were found. Linear regression was used to determine $\dot{V}_E/\dot{V}CO_2$ slope and $\dot{V}_E$ intercept. The receiver operating characteristic (ROC) curve model performed with JMP (JMP, Cary, NC) was used to determine area under the curve (AUC) and different cutoffs for $\dot{V}_E/\dot{V}CO_2$ slope and $\dot{V}_E$ intercept to discriminate patients with HFpEF and HFrEF from COPD patients. Statistical significance was set at $p < 0.05$.

## 3. Results

### 3.1. Participant characteristics

Age was similar in the groups but HFpEF had a greater BMI than HFrEF (Table 1). COPD patients had a lower $FEV_1$ (% predicted) and $FEV_1$/FVC than the HFpEF and HFrEF patients. Resting echocardiography measurements indicate there were increased filling pressures in HFpEF and HFrEF patients. All participants completed all aspects of this study in the absence of adverse events.

**Table 2**
Peak exercise data.

| | COPD | HFpEF | HFrEF | p-value |
|---|---|---|---|---|
| Workload (W) | 84 ± 35 | 40 ± 13[a] | 40 ± 12[a] | <0.01 |
| $\dot{V}O_2$ (mL/kg/min) | 17 ± 4 | 8 ± 2[a] | 9 ± 3[a] | <0.01 |
| $\dot{V}O_2$ (% predicted) | 59 ± 13 | 31 ± 9[a] | 30 ± 8[a] | <0.01 |
| $\dot{V}O_2$ (mL/min) | 1516 ± 431 | 825 ± 220[a] | 770 ± 203[a] | <0.01 |
| $\dot{V}CO_2$ (mL/min) | 1562 ± 551 | 860 ± 247[a] | 756 ± 217[a] | <0.01 |
| RER | 1.01 ± 0.10 | 1.04 ± 0.13 | 1.07 ± 0.09 | 0.33 |
| HR (beats/min) | 130 ± 22 | 102 ± 14[a] | 103 ± 26[a] | <0.01 |
| $\dot{V}_E$ (L/min) | 53 ± 17 | 28 ± 9[a] | 31 ± 9[a] | <0.01 |
| $F_b$ (breaths/min) | 34 ± 5 | 28 ± 9[a] | 28 ± 7[a] | <0.01 |
| $V_T$ (L) | 1.6 ± 0.5 | 1.0 ± 0.3[a] | 1.1 ± 0.4[a] | <0.01 |
| $\dot{V}_E/\dot{V}O_2$ | 35 ± 6[b] | 34 ± 9[b] | 44 ± 12 | <0.01 |
| $\dot{V}_E/\dot{V}CO_2$ | 35 ± 7[b] | 33 ± 6[b] | 41 ± 9 | <0.01 |
| Ti (s) | 0.58 ± 0.10 | 0.75 ± 0.22[a] | 0.85 ± 0.24[a] | <0.01 |
| Te (s) | 1.21 ± 0.22 | 1.62 ± 0.54 | 1.46 ± 0.80 | 0.07 |
| Ti/Ttot | 0.32 ± 0.05[b] | 0.32 ± 0.06[b] | 0.38 ± 0.07 | <0.01 |
| $V_T$/Ti | 2683 ± 614 | 1443 ± 409[a] | 1354 ± 309[a] | <0.01 |
| $O_2$ saturation (%) | 96 ± 3 | 94 ± 3 | 95 ± 4 | 0.15 |

Mean ± SD.
[a] Significantly different from COPD.
[b] Significantly different from HFrEF.

### 3.2. Peak exercise

COPD patients exhibited a greater workload, relative and absolute $\dot{V}O_2$, $\dot{V}CO_2$, HR, $\dot{V}_E$, $V_T$, $F_b$, Ti, and $V_T$/Ti compared to HFpEF and HFrEF patients during peak exercise (Table 2). At peak exercise, HFrEF patients had a greater $\dot{V}_E/\dot{V}CO_2$ ratio, $\dot{V}_E/\dot{V}O_2$ ratio, and Ti/Ttot compared to COPD and HFpEF patients.

### 3.3. Ventilatory inefficiency parameters

HFrEF patients had a greater $\dot{V}_E/\dot{V}CO_2$ slope than HFpEF and COPD patients (HFrEF: 40 ± 9; HFpEF: 32 ± 7; COPD: 32 ± 7) ($p < 0.01$) (Fig. 1A). COPD patients had a greater $\dot{V}_E$ intercept compared to HFpEF and HFrEF patients (COPD: 3.32 ± 1.66; HFpEF: 0.77 ± 1.23; HFrEF: 1.28 ± 1.19 L/min) ($p < 0.01$) (Fig. 1B). Importantly, these group differences in $\dot{V}_E/\dot{V}CO_2$ slope and $\dot{V}_E$ intercept were still present after adjustment for sex and BMI (all, $p < 0.01$). Significant inverse relationships were observed between $\dot{V}_E/\dot{V}CO_2$ slope and $\dot{V}_E$ intercept in HFpEF ($r^2 = 0.40$, $p < 0.01$), but not COPD ($r^2 = 0.11$, $p = 0.17$) or HFrEF ($r^2 = 0.00$, $p = 0.78$).

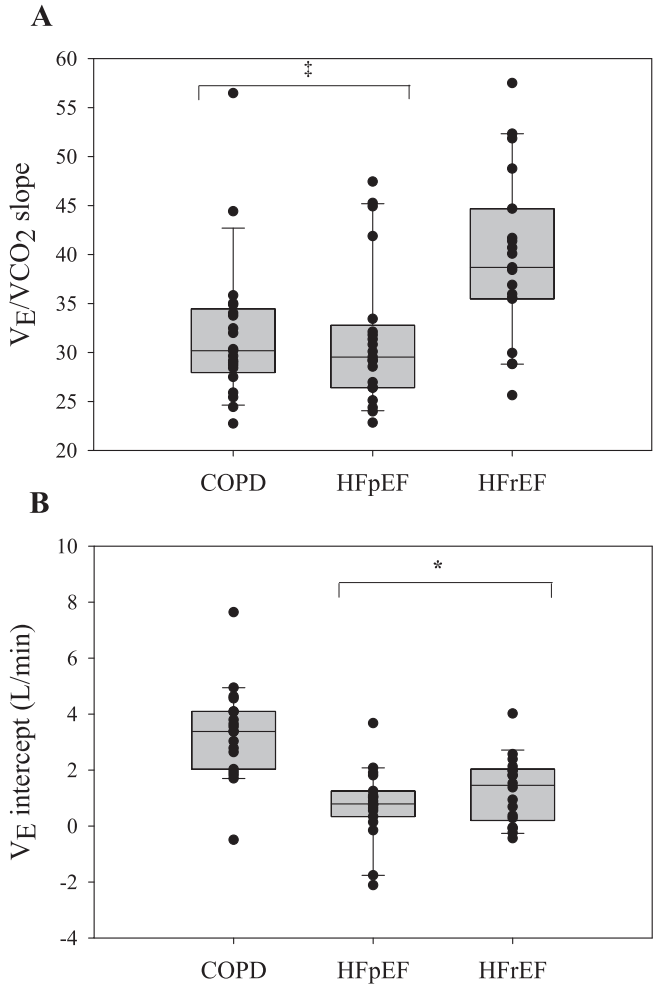


**Fig. 1.** $\dot{V}_E/\dot{V}CO_2$ slope and $\dot{V}_E$ intercept in COPD, HFpEF, and HFrEF patients. HFrEF patients had a greater $\dot{V}_E/\dot{V}CO_2$ slope compared to COPD and HFpEF patients ($p < 0.01$). COPD patients had a greater $\dot{V}_E$ intercept compared to HFpEF and HFrEF patients ($p < 0.01$). ‡, significantly different from HFrEF patients. *, significantly different from COPD patients. Data are reported as median and 25–75 interquartile range.

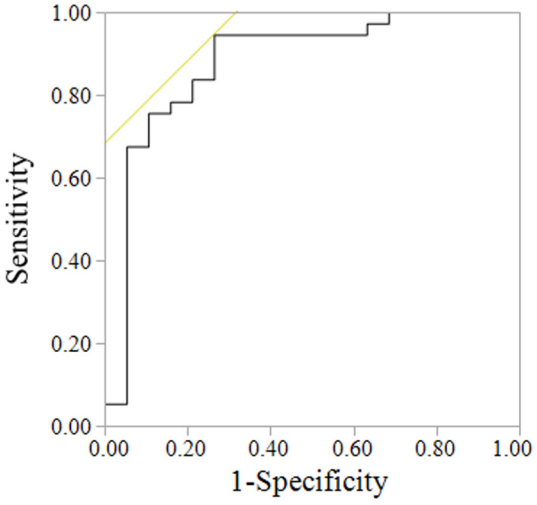


**Fig. 2.** ROC curve analysis considering all HF and COPD patients. The ROC curve identified a cutoff for $V_E$ intercept of ≥2.64 L/min to indicate patients with a high probability of having COPD (AUC: 0.88; $p < 0.01$).

### 3.4. ROC curves

A ROC curve analysis considering COPD and all HF patients identified a cutoff for $V_E$ intercept of ≥2.64 L/min to indicate patients with a high probability of having COPD (AUC: 0.88; $p < 0.01$) (Fig. 2) (Table 3), with 74% of COPD and 5% of HF patients exceeding this value. When considering COPD and HFpEF patients, ROC curve analysis identified a cutoff for $V_E$ intercept of ≥1.82 L/min to indicate patients with a high probability of having COPD (AUC: 0.90; $p < 0.01$). Using this cutoff, 89% of COPD and 16% of HFpEF patients had a $V_E$ intercept ≥1.36 L/min. For COPD and HFrEF patients, a ROC curve analysis identified a cutoff for $V_E$ intercept of ≥2.64 L/min to indicate patients with a high probability of having COPD (AUC: 0.85; $p < 0.01$). Using this cutoff, 74% of COPD and 6% of HFrEF patients had a $V_E$ intercept of ≥2.64 L/min. A ROC curve analysis considering COPD and HFrEF patients identified cutoff for $V_E/VCO_2$ slope of ≤35 to indicate patients with a high probability of having COPD (AUC: 0.79; $p < 0.01$). Using this cutoff, 86% of COPD and 21% of HFrEF patients had a $V_E/VCO_2$ slope ≤ 35.

## 4. Discussion

This is the first study comparing non-invasive indices of ventilatory efficiency during incremental exercise (i.e., $V_E/VCO_2$ slope and $V_E$ intercept) across COPD, HFpEF and HFrEF patients. Our major findings confirm the study hypothesis that $V_E$ intercept is greater in COPD patients compared to both HF groups with no differences between HFpEF and HFrEF. Furthermore, we found that the $V_E/VCO_2$ slope was greater in HFrEF compared to COPD and HFpEF patients (while no differences were present between the latter). Lastly, we found that COPD patients have a greater likelihood of having a $V_E$ intercept ≥2.64 L/min than both HF groups. Taken together, these findings are the first to demonstrate that $V_E$ intercept, not $V_E/VCO_2$ slope, can discriminate COPD from both HFpEF and HFrEF patients. This is clinically important given the high volume of patients presenting with unexplained dyspnea and/or co-morbid disease states including HF and COPD. Furthermore, because HF patients often demonstrate pulmonary abnormalities and COPD patients often demonstrate cardiac output impairment, these data allows us to begin to understand different patterns of data presented by patients with these diseases which influence both aspects of the cardiopulmonary system. Subsequently, this will allow clinicians the ability to differentiate the clinical treatment priority and align treatment strategies which will have the greatest impact.

**Table 3**
ROC analysis.

| | COPD and all HF | | COPD and HFpEF | | COPD and HFrEF | |
|---|---|---|---|---|---|---|
| | $V_E/VCO_2$ slope | $V_E$ intercept | $V_E/VCO_2$ slope | $V_E$ intercept | $V_E/VCO_2$ slope | $V_E$ intercept |
| AUC | 0.62 | 0.88 | 0.54 | 0.90 | 0.79 | 0.85 |
| p-Value | 0.11 | <0.01 | 0.85 | <0.01 | <0.01 | <0.01 |
| Cutoff | | 2.64 | | 1.82 | 35 | 2.64 |
| Sensitivity | | 0.74 | | 0.89 | 0.86 | 0.74 |
| Specificity | | 0.95 | | 0.84 | 0.79 | 0.94 |

The ability to non-invasively distinguish HF and COPD patients has important clinical utility as HF and COPD have overlapping symptoms (e.g., dyspnea on exertion, exercise intolerance, muscle weakness, fatigue) [1]. Therefore, alternative indices are required to differentiate COPD from HFpEF and HFrEF. The $V_E$ intercept, a measure of ventilatory efficiency quantified from CPET, has been found to be an important and useful parameter in COPD as it is not confounded by mechanical abnormalities and constraints [7]. An important novel finding of the present study was that the $V_E$ intercept was effective in differentiating COPD from HFpEF and HFrEF patients. This is clinically relevant given no currently available tools can non-invasively discriminate between HFpEF and COPD. These findings are consistent with and extend previous studies that have reported a greater $V_E$ intercept in COPD compared to HFrEF patients [12,13]. The elevated $V_E$ intercept in COPD patients theoretically equates to increased dead space (i.e. increased $V_E$ when metabolic demand is null) [20] and likely results from an altered breathing strategy (increased breathing frequency to compensate for reduced $V_T$ secondary to greater mechanical constraints) and/or a progressive ventilation-perfusion mismatch in COPD patients [21].

Importantly, the ROC curve analysis identified a significant cutoff for $V_E$ intercept (i.e. 2.64 L/min), but not $V_E/VCO_2$ slope when all HF patients were included in the analysis. Moreover, $V_E$ intercept AUC was significant for HFpEF patients, while $V_E$ intercept and $V_E/VCO_2$ slope AUCs were significant for HFrEF. These findings suggest that the $V_E/VCO_2$ relationship is important for both HF groups; however, the $V_E$ intercept component provides clinical value for HFpEF, while both $V_E$ intercept and $V_E/VCO_2$ provide clinical value for HFrEF. In the present study, the $V_E$ intercept cutoff value for the HFrEF patients (i.e. 2.64 L/min) is lower than previously reported (2.72–4.07 L/min) [12,13] likely due to the methodology used to derive the $V_E/VCO_2$ slope and $V_E$ intercept as well as the severity of disease in the HF and COPD patients [7,12,22,23].

An elevated $V_E/VCO_2$ slope has been found in several clinical populations including HFpEF, HFrEF, and COPD. However, disease severity in HF and COPD has opposing effects on $V_E/VCO_2$ slope. Because of these divergent responses, the $V_E/VCO_2$ slope has been found to be greater in HFrEF or not different compared to COPD patients [12,13]. In the present study, we found that the $V_E/VCO_2$ slope was greater in HFrEF compared to HFpEF and COPD, while not different between the latter. Our finding of a greater ventilatory inefficiency as indicated by a higher $V_E/VCO_2$ slope in HFrEF than HFpEF patients is consistent with previous studies [2,15]. Furthermore, the $V_E/VCO_2$ slope in HFpEF patients in the present study (~32) is consistent with the $V_E/VCO_2$ slope (~33) reported in HFpEF patients of a similar age [18]. The heightened ventilatory response in HFrEF likely arises from increased physiological dead space, neural ventilatory drive, and/or activation of group III/IV locomotor muscle afferents during exercise [24,25]. Furthermore, the exaggerated ventilatory response in HFrEF has important implications in blood flow redistribution during exercise [26,27] as well as possibly influencing the ventilatory efficiency in patients with HFrEF and co-existing COPD. Specifically, HFrEF patients with co-existing COPD have a higher $V_E/VCO_2$ slope than COPD alone [23].

There are several methodological factors to consider when interpreting our findings. First, we acknowledge the relatively small

sample size in the present investigation. Studies with larger sample sizes may be necessary to confirm our findings. Second, echocardiography measurements were not performed in the COPD patients. Third, the physiologic mechanisms responsible for the ventilatory inefficiency in HF and COPD patients were outside the scope of the present non-invasive study. Future studies are warranted using invasive techniques (e.g., arterial blood gas measurements, locomotor muscle neural feedback inhibition, etc.) in combination with interventions such as altering central-peripheral hemodynamics (e.g. via inorganic nitrite supplementation [28,29]) and modifying dead space [20] to better understand the underlying pathophysiology of ventilatory inefficiency in these populations.

In summary, we have demonstrated that $V_E$ intercept, determined non-invasively from a CPET, can discriminate HFpEF and HFrEF from COPD patients. These results demonstrate the importance of quantifying CPET metrics in HF and COPD patients while providing additional support for the use of the $V_E$ intercept as a ventilatory efficiency parameter. In contrast, $V_E/VCO_2$ slope was only sufficient in distinguishing HFrEF from COPD patients. Future studies are warranted to determine if $V_E$ intercept is capable of distinguishing HFpEF with concurrent COPD diagnoses from HFpEF patients.

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## Conflict of interest

No conflicts of interest are reported.

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