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Use of 'ideal' alveolar air equations and corrected end-tidal PCO₂ to estimate arterial PCO₂ and physiologic dead space during exercise in patients with heart failure

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Abstract

Background—Arterial CO₂ tension (PaCO₂) and physiologic dead space (V_D) are not routinely measured during clinical cardiopulmonary exercise testing (CPET). Abnormal changes in PaCO₂ accompanied by increased V_D directly contribute to impaired exercise ventilatory function in heart failure (HF). Because arterial catheterization is not standard practice during CPET, this study tested the construct validity of PaCO₂ and V_D prediction models using 'ideal' alveolar air equations and basic ventilation and gas-exchange measurements during CPET in HF.

Methods—Forty-seven NYHA class II/III HF (LVEF=21±7%; age=55±9 years; male=89%; BMI=28±5 kg/m²) performed step-wise cycle ergometry CPET to volitional fatigue. Breath-by-breath ventilation and gas-exchange were measured continuously. Steady-state PaCO₂ was measured at rest and peak exercise via radial arterial catheterization. Construct V_D was calculated via 'ideal' alveolar equations, whereas PaCO₂ or V_D models were based on end-tidal CO₂ tension (P_{ET}CO₂), tidal volume (V_T), and/or weight.

Results—Criterion measurements of PaCO₂ (38±5 vs. 33±5 mmHg, $P<0.01$) and V_D (0.26±0.07 vs. 0.41±0.15 L, $P<0.01$) differed at rest vs. peak exercise. The equation, $5.5+0.90\times P_{ET}CO_2 - 0.0021\times V_T$, was the strongest predictor of PaCO₂ at rest and peak exercise (bias ±95%LOA=-3.24±6.63 and -0.98±5.76 mmHg; $R^2=0.57$ and 0.75 , $P<0.001$, respectively). This equation closely predicted V_D at rest and peak exercise (bias±95%LOA=-0.03±0.06 and -0.02±0.13 L; $R^2=0.86$ and 0.83 , $P<0.001$, respectively).

Conclusions—These data suggest predicted PaCO₂ and V_D based on breath-by-breath gasexchange and ventilatory responses demonstrate acceptable agreement with criterion measurements at peak exercise in HF patients. Routine assessment of PaCO₂ and V_D can be used to improve interpretability of exercise ventilatory responses in HF.

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These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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Keywords

HFrEF; reduced ejection fraction heart failure; arterial carbon dioxide partial pressure; end-tidal carbon dioxide partial pressure; PETCO₂; exercise intolerance

1. INTRODUCTION

A hallmark feature of human heart failure (HF) is an abnormal ventilatory response to exercise [1-7]. There are immediate clinical implications associated with an exaggerated rate mediated rise in ventilation during exercise in HF [1-7]. Cardiopulmonary exercise testing (CPET) including basic measurements of breath-by-breath ventilation and gas exchange has been established as an important diagnostic tool to objectively assess exercise ventilatory function and clinical status in HF patients [8]. The interpretive value of clinical CPET can be further strengthened when accompanied by invasive measures of arterial blood gases [1-7]. Measurement of arterial carbon dioxide tension (PaCO₂) in the context of 'ideal' alveolar equations [9] can be used to improve the integrative physiologic interpretation of ventilatory responses such as the ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}_{CO_2}$) [1-7].

While measurements of breath-by-breath ventilation and gas exchange can be routinely measured during CPET in clinical and research settings using standard metabolic cart systems, concomitant sampling of arterialized blood is not routinely available. Likewise, because HF patients may demonstrate pulmonary impairments independent or secondary to HF (e.g., ↓ lung diffusion capacity, $\dot{V}_A/\dot{Q}$ mismatching, etc. [10-13]), absolute measures of end-tidal carbon dioxide tension (P_{ET}CO₂) cannot be assumed to inherently translate to absolute levels of PaCO₂ during exercise in these individuals [7, 14].

By contrast, it has been demonstrated that by correcting P_{ET}CO₂ via prediction modeling derived from arterial sampling, rest and/or exercise PaCO₂ may be estimated with high-fidelity in healthy adults across the aging spectrum [15-17]. While others have assumed PaCO₂ levels [18] or have applied models to estimate PaCO₂ during exercise in HF [19], the construct validity of such applications has not been clearly determined. Using alternative approaches, others have developed prediction equations for assessing physiologic dead space (V_D) combined with classical Bohr and/or 'ideal' alveolar air equations to approximate PaCO₂ in healthy adults [20-23]. However, without proper construct validation testing, it cannot be assumed this method of assessing PaCO₂ derived from predicted V_D translates to HF.

There are important clinical implications for which our ability to study the components of the ventilatory response to exercise in HF patients is critical. Therefore, this study aimed to test the construct validity of PaCO₂ [15-17] and V_D [20-23] prediction models in patients with HF across rest and exercise conditions. This is clinically relevant since clarifying the validity of prediction equations for PaCO₂ and V_D responses during exercise may help avoid misuse of such applications and alternatively will provide an additional technical means to study the physiologic underpinnings of ventilatory impairments contributing to exercise intolerance in these patients.

2. Methods

2.1 Participants

Patients with reduced ejection fraction (HFrEF) (N=47) were referred by their primary cardiologist for CPET as part of a comprehensive HF evaluation at Mayo Clinic, Rochester, MN (characteristics, Table 1). Inclusion criteria was consistent with the European Society of Cardiology identification of HFrEF [24]. Additional exclusion criteria included: significant coronary artery disease (stenosis $\geq 50\%$), cor pulmonale, diagnosed pulmonary disease independent or secondary to HF, primary renal or hepatic disease, valvular heart disease (any stenosis, $>$ mild regurgitation), hypertrophic/infiltrative cardiomyopathy, or constrictive pericarditis. The study was approved by the Mayo Clinic Institutional Review Board and all aspects of this study complied with the Declaration of Helsinki. All participants provided written informed consent prior to participation in this study.

2.2 Pulmonary function

All participants performed upright seated resting airway function testing via flow-volume loop spirometry (CPFS system spirometer, Medical Graphics, St. Paul, MN) according to guidelines of the American Thoracic Society [25]. Measured variables included forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1), whereas FEV_1/FVC was derived. Percent (%) of predicted FVC, FEV_1 , and FEV_1/FVC were calculated according to equations of Crapo et al. [26]. Ventilatory reserve was calculated as the quotient of peak exercise $\dot{V}_E$ and maximum voluntary ventilation (MVV) times 100, whereby MVV was computed as the product of FEV_1 and 35 [27]. Additionally, single breath lung diffusing capacity for carbon monoxide (DL_{CO}) was performed according to guidelines of the American Thoracic Society [28], whereas % predicted DL_{CO} was calculated from Crapo and Morris [29].

2.3 Exercise protocol

Step-wise CPET to volitional fatigue was performed via cycle ergometry at a cadence of 60-65 rpm. Participants began with a 3 min rest transitioning immediately to a workload of 20-W for 3 min, increasing by 10-W every 3 min thereafter until exhaustion [27]. All participants were continually encouraged to exercise until they could not go any longer. Subjective participant effort during CPET was assessed via rating of perceived exertion (RPE, Borg 6 to 20 scale) at the end of each stage, which was used as an index to suggest peak exercise (RPE ≥ 17) was attained [27].

2.4 Ventilation and gas exchange measurements and arterial sampling

Participants respired through a mouthpiece connected to a pneumotachograph whereby volumes, flows, and gases were measured/sampled breath-by-breath via open-circuit spirometry (CPX/D, MGC Diagnostics, St. Paul, MN) throughout CPET. This system was calibrated according to manufacturer guidelines for flows and precision grade gases of known concentrations immediately prior to each CPET. All measurements accounted for equipment related dead space. All data was analyzed over the final 30 s of each completed stage. Measured variables included: pulmonary oxygen uptake ($\dot{V}O_2$), $\dot{V}CO_2$, RER,

respiratory rate (f_B), V_T , $\dot{V}_E$, $P_{ET}CO_2$, and end-tidal oxygen tension ($P_{ET}O_2$). Percent predicted peak $\dot{V}O_2$ was calculated from Hansen et al. [30].

Arterial blood samples were drawn during the 15-20 s mid-portion of the last 30 s of each exercise stage to align with ventilation and gas exchange measurements. Blood draws occurred using standard techniques at the left radial artery via percutaneous insertion of a 20-gauge catheter whereby samples were collected in 3 mL heparinized glass syringes, rolled, and placed in ice. Samples were immediately transported to the Mayo Clinic institutional Clinical Core Laboratory (meets all routine standards of clinical blood-gas laboratory [31]) where standard processing techniques occurred for arterial measurements of $PaCO_2$ and oxygen saturation (SaO_2).

2.5 'Ideal' alveolar equations

All elements necessary for the traditional calculation of V_D based on direct measurements of $PaCO_2$ and breath-by-breath ventilation and gas exchange were derived using principles of 'ideal' alveolar equations [2, 6, 9]:

$$\frac{V_D}{V_T} = \left(1 - \frac{863 \times \dot{V}CO_2}{\dot{V}_E \times PaCO_2}\right);$$

where 863 converts gas concentration to tension while correcting for $\dot{V}CO_2$ expressed as a dry gas volume at standard temperature (0°C), pressure (760 mm Hg), and dry (0% water vapor) (STPD) and ventilation expressed as a wet gas volume at body temperature, pressure, and saturation (BTPS).

2.6 $PaCO_2$ prediction models

$PaCO_2$ prediction models tested in this study include [15-17]:

$$PaCO_2 = 5.2 + 0.82 \times P_{ET}CO_2 \quad (1)$$

$$PaCO_2 = 5.5 + 0.90 \times P_{ET}CO_2 - 0.0021 \times V_T \quad (2)$$

2.7 V_D prediction models

V_D prediction models tested in this study include [20-23]:

$$V_D = 64.56 \times V_T + 138.73 \quad (3)$$

$$V_D = 0.077 \times V_T \div 138.4 \quad (4)$$

$$V_D = 0.049 \times V_T + 1.54 \times \text{weight} \quad (5)$$

$$V_D = 0.285 \times V_T - 64 \quad (6)$$

Additionally, using the Bohr equation below, V_D was calculated using $P_{ET}CO_2$ as a substitute for $PaCO_2$.

2.8 $PaCO_2$ estimated from predicted V_D

To calculate estimates of $PaCO_2$ using V_D from equations 3 to 6 [20-23], the Bohr equation was used while solving for $PaCO_2$:

$$\frac{V_D}{V_T} = \frac{PaCO_2 - PECO_2}{PaCO_2}$$

where mixed-expired CO_2 ($PECO_2$) equaled the quotient of 863 and $\dot{V}_E/\dot{V}CO_2$ [32].

3. Statistical Analyses

Continuous data are presented as mean $\pm$ SD where appropriate. To assess whether differences occurred between any one of the different prediction methods versus the criterion (e.g., measured $PaCO_2$), two-tailed unpaired Student's *t*-tests were used. Because of multiplicity of pairwise comparisons (e.g., estimated versus measured $PaCO_2$) and to minimize the potential for Type I error, resultant *P*-values were corrected for the total number of comparisons performed. Two-tailed statistical significance was determined using an alpha level of 0.01. Two-tailed paired Student's *t*-tests were used to assess rest to peak exercise differences for variables of interest.

Construct validity of prediction models was assessed using the following tests [33]: 1) Univariate ordinary least squares linear regressions (coefficient of determination, R^2) were performed separately for each prediction equation at time periods of rest and peak exercise; 2) Goodness of model fit equations (i.e., $y=mx+b$) and R^2 from each linear regression model were used as the basis to derive the construct validity index [33] termed standard error of estimate [$SEE=SD \times \sqrt{1-R^2}$]. For each SEE, the 95% limits of agreement (LOA, $\pm 1.96 \times SD$ of the practical-criterion difference, i.e., mean bias) and the agreement ratio ($\times/\div$) (95% confidence limits (CL)) were calculated; 3) Data plots were constructed to assess the uniformity of residuals against predictions computed from linear regression and SEE models. Ideal residuals are considered uniform if their mean is equal to zero accompanied by a uniform scattering across the range of predicted values.

Power of regression models and standard interpretation of R^2 were based on thresholds of Cohen [34]: modest $R^2=0.02$, moderate $R^2=0.15$, and strong $R^2 \geq 0.25$; power ≥ 0.80 . Unless otherwise noted, two-tailed significance was determined using an alpha level of 0.05.

Statistical analyses were performed using SAS statistical software v.9.4 (SAS Institute, Cary, NC).

4. Results

The phenotype of the sample detailed in Table 1 was consistent with European Society Guidelines for the diagnosis of HFrEF. The age range of participants was 41-74 years, 89% were males, left ventricular ejection fraction range was 8-41%, and 40% were New York Heart Association functional class II whereas the remaining patients were class III. Hemoglobin (Hb) levels were normal, whereas measures of renal function were within ranges consistent with HFrEF. The most common pharmacologic therapy included ACE inhibitors, β -blockers, digoxin, aspirin, and diuretics each at 70% of patients; whereas ARBs, antiarrhythmic, nitrates, and statins each occurred at <60% of patients. Compared to normal ranges, resting absolute and % of predicted FVC and FEV₁ were reduced, while only absolute FEV₁/FVC and % of predicted DL_{CO} were reduced.

Compared to peak exercise responses in Table 1 where RPE was 17 ± 1 , resting $\dot{V}O_2$ (2.8 ± 0.6 mL/kg/min), $\dot{V}CO_2$ (0.21 ± 0.05 L/min), RER (0.90 ± 0.11), f_B (18 ± 4 breaths/min), V_T (0.56 ± 0.15 L), $\dot{V}_E$ (10 ± 2 L/min), $PECO_2/P_{ET}CO_2$ (0.61 ± 0.06), $PaCO_2$ (Figure 1), and V_D (Table 2) were lower (all $P < 0.01$); whereas resting $P_{ET}CO_2$ (32 ± 5 mm Hg), $PECO_2$ (20 ± 3 mm Hg), and SaO_2 (95 ± 4 %) did not differ versus peak exercise. Consistent with increased $\dot{V}_E/\dot{V}CO_2$ slope in Table 1, ventilatory reserve was above lower normal limits of 15%. Compared to rest, peak exercise $PaCO_2$ (measured and all predicted) differed in Figure 1 ($P < 0.01$). Lastly, in comparing absolute measured $PaCO_2$ to estimated $PaCO_2$ at both rest and peak exercise, prediction models where $PaCO_2$ was derived secondary to predicted V_D consistently under-estimated $PaCO_2$ (except Eq.4, which over-estimated $PaCO_2$) (Figure 1).

4.1 Construct Validation Testing

Bias $\pm$ 95%LOA presented in Figure 1 for both rest and peak exercise responses showed that predicted $PaCO_2$ (or using $P_{ET}CO_2$) was consistently less than measured $PaCO_2$ except for Eq.4 (where $PaCO_2$ was predicted secondary to predicting V_D). However, consistent with all predictive models except for, Eq.4, bias $\pm$ 95%LOA between estimated and measured $PaCO_2$ improved from rest to peak exercise, with nearly no bias for Eq. 2 at peak exercise (Figure 1).

Corresponding with bias $\pm$ 95%LOA at rest in Figure 1B, resting linear regressions with respective residual plots and SEE in Figures 1 and 2 demonstrate concurrent validity was strongest when predicting $PaCO_2$ using either $P_{ET}CO_2$ (Figures 1C and 1D) or Eq. 1 and 2, which were not dependent on predicted V_D . As bias $\pm$ 95%LOA improved from rest to peak exercise in Figure 1 (panel B vs. F, respectively), so too did respective linear regressions, residual plots, and SEE at peak exercise presented in Figures 1 and 2. Models (i.e., $P_{ET}CO_2$ or Eq. 1 and 2) demonstrating the strongest validity at rest were more robust in predicting $PaCO_2$ at peak exercise in Figures 1 and 2. Provoked by decreased $PaCO_2$ (rest to peak exercise, $P < 0.01$), the gradient between $P_{ET}CO_2$ and $PaCO_2$ (i.e., illustrated as bias in Figure 1) was less negative at peak exercise (Figure 1F) compared to rest (Figure 1B) ($P < 0.01$).

Lastly, consistent with lower strength of validity associated with PaCO₂ prediction models involving predicted V_D (i.e., Eq. 3 to 6), V_D calculated in the absence of accounting for measured or predicted PaCO₂ (i.e., Eq. 1 or 2) consistently demonstrated the weakest R², SEE, and bias±95%LOA, particularly when compared to the overall strength of Eq.2 in predicting V_D at both rest and peak exercise (Table 2). Nevertheless, all V_D (both measured and predicted, except for Eq. 5) increased from rest to peak exercise in Table 2 ($P<0.01$).

5. Discussion

While the prediction models tested in this study have been previously validated for use in estimating PaCO₂ [15-17] and V_D [20-23] at rest and/or during exercise in healthy adults, translation of those observations to HF have not been defined. Although PaCO₂ and V_D are not routinely measured during clinical CPET, these variables play a critical role in both quantifying and interpreting ventilatory efficiency (e.g., $\dot{V}_E/\dot{V}_{CO_2}$ slope) in HF patients [1-4, 6]. Therefore, it is immediately clinically relevant to clarify whether prediction models used to assess PaCO₂ and V_D demonstrate agreement with criterion measurements during exercise in HF patients.

These data suggest that predicted PaCO₂ primarily based on P_{ET}CO₂, or predicted PaCO₂ secondary to indirectly estimating V_D should be interpreted with caution at rest and to a lesser extent at peak exercise in HF. Likewise, the inhomogeneous alignment of V_D derived using measured PaCO₂ and ‘ideal’ alveolar air equations compared to predicted V_D estimated either independent of PaCO₂ or dependent on predicted PaCO₂ suggests modeled V_D and PaCO₂ responses should be confirmed with ‘Gold’ standard methodology when major clinical decisions are involved. Nevertheless, consistent with Guazzi et al. [35] who tested the validity of the prediction model of Jones et al. [15] (Eq.2 in this study), we support and further extend those observations by demonstrating: 1) of the seven prediction models tested in this study, PaCO₂ and V_D estimated using Eq.2 consistently demonstrated the closest agreement with criterion measurements, particularly at peak exercise; 2) it cannot be assumed PaCO₂ and V_D can be uniformly predicted across models previously validated in other populations despite being derived using similar factors (e.g., PaCO₂, P_{ET}CO₂, etc.) [15-17, 20-23]; and 3) the magnitude of validity supporting use of these indirect approaches for quantifying PaCO₂ and V_D is less consistent at rest versus peak exercise in HF patients.

While the original model of Jones et al. [15] (Eq.2) was derived in a small sample of healthy young adults for predicting PaCO₂ during exercise, Eq.2 tested in this study was the single model which compared favorably with tests of this equation reported by Guazzi et al. [35] in HF and Williams and Babb [16] in healthy young or late-adulthood individuals. With this close agreement between corrected P_{ET}CO₂ and measured PaCO₂ across exercise studies, these data suggest contributions from $\dot{V}_A/\dot{Q}$ mismatching (>1.0) cannot independently explain the augmented rate-mediated rise in exercise ventilation in HF patients as suggested by others [1, 4, 7, 18].

A $\dot{V}_A/\dot{Q} > 1.0$ during exercise can be attributed to impaired pulmonary perfusion, which may lead to, for example, increased $\dot{V}_E/\dot{V}_{CO_2}$ driven by high V_D/V_T (due to ↑ V_D) in HF [1, 4, 7, 18]. However, given the manner by which estimated PaCO₂ (Eq.2) converged toward

measured PaCO_2 from rest to peak exercise in this study, we hypothesize that blunted pulmonary perfusion is not likely to explain our observations. While changes in P_{ETCO_2} are influenced by airway compartment factors such as dead space (both anatomic and physiologic), gas trapping, etc. [14, 32], it is also relevant that expired CO_2 and, hence, P_{ETCO_2} is co-dependent on gas transfer across the alveolar-capillary membrane barrier and adequate pulmonary capillary perfusion shifts during exercise. In the absence of sufficiently perfused ventilated alveoli ($\dot{V}_A/\dot{Q} > 1.0$ [1, 4, 7, 18]) pulmonary CO_2 transfer would not be expected to match changes in PaCO_2 across a timecourse (as demonstrated in this study) if CO_2 from mixed venous blood were not available at ventilated alveoli. While increased metabolic demand makes pulmonary CO_2 exchange more sensitive to integrated diffusion and perfusion dynamics, it has been proposed that because of unique properties of CO_2 (e.g., high diffusing capacity, reactivity with Hb, and blood solubility) and the relationship CO_2 shares with $\dot{V}_A/\dot{Q}$ that it is not until the presence of moderate-to-severe membrane diffusion limitations coupled with $\dot{V}_A/\dot{Q} > 1.0$ where pulmonary CO_2 transfer might be appreciably impaired [36, 37].

When exhalation of CO_2 exceeds pulmonary hemodynamic delivery of CO_2 it could be expected that P_{ETCO_2} might decrease. By contrast, independent of exaggerated ventilation, it is possible that P_{ETCO_2} may decrease simply due to impaired $\dot{Q}$ (i.e., what is not delivered cannot be blown off and therefore, PaCO_2 would not be expected to markedly decrease) [14, 32]. Thus, in the absence of marked dissociation between peak exercise P_{ETCO_2} and PaCO_2 , our data suggest increased ventilation (i.e., expired CO_2) was indeed accompanied by an adequate level of global pulmonary hemodynamic delivery of CO_2 in HF patients (i.e., $\dot{V}_A/\dot{Q} > 0.0$). The reduction in PaCO_2 demonstrated in this study is consistent with suitable transport of CO_2 to and throughout the pulmonary system via traditional pathways [2, 6]. If ventilation so grossly exceeded pulmonary hemodynamic delivery of CO_2 where abated perfusion of ventilated alveoli is completely driving increased $\dot{V}_E/\dot{V}_{\text{CO}_2}$ slope via high V_D/V_T , it is reasonable to suggest that we should have observed a pronounced drop in P_{ETCO_2} paralleled by a lesser reduction in PaCO_2 , which did not occur.

Likewise, if present, an effect of under-perfused ventilated alveoli ($\dot{V}_A/\dot{Q} > 1.0$) on ventilation may be recognizable because of a diluting effect of dead space (anatomic and/or physiologic) on P_{ETCO_2} . At the global lung level, the dilution of P_{ETCO_2} attributable to physiologic constraints (i.e., alveolar dead space) may be readily observed by examining PECO_2 and the ratio of PECO_2 to P_{ETCO_2} . A reduction in $\text{PECO}_2/\text{P}_{\text{ETCO}_2}$ (i.e., 0.70) as demonstrated in this study is suggested to be caused airway defects, whereas increased $\text{PECO}_2/\text{P}_{\text{ETCO}_2}$ (i.e., > 0.70) would suggest attenuated pulmonary perfusion [32].

While we acknowledge that the peak exercise P_{ETCO_2} - PaCO_2 gradient in this study is more negative than that of healthy individuals in later-adulthood reported by Williams and Babb [16], we also demonstrate in this study that the P_{ETCO_2} - PaCO_2 gradient became less negative from rest to peak exercise. To a certain degree, blunted pulmonary perfusion may have played a role in explaining the discrepancy between these data and Williams and Babb [16]. However, it is also likely that effects of exercise mediated increased CO_2 production contrasted by smaller V_T (e.g., due to decreased lung/chest compliance [38]) and other factors such as dynamic instability of alveolar CO_2 tension [11, 39] also contributed to this

negative gradient. As such, the convergence of $P_{ET}CO_2$ toward $PaCO_2$ at peak exercise appears attributable to reductions in $PaCO_2$, and not large shifts in $P_{ET}CO_2$. If impaired pulmonary perfusion were to have been responsible for these data, measured $PaCO_2$ should have markedly exceeded $P_{ET}CO_2$. In contrast to our observations, such an exaggerated $P_{ET}CO_2$ - $PaCO_2$ gradient would not likely to have been overcome when predicting $PaCO_2$ from $P_{ET}CO_2$ even when using the correction factor as referenced in Eq.2 [15].

We suggest that the $PaCO_2$ prediction equation of Jones et al. [15] (Eq.2) demonstrates value as a noninvasive approach to routinely quantify $PaCO_2$ and subsequent derivation of V_D/V_T aimed to improve interpretability of ventilatory function during CPET in HF.

6. Limitations

Although these data are consistent with observations of Williams and Babb [16], we did not include age, gender, and body sized matched healthy controls in this study to confirm their results in that population. We also did not include invasive techniques (e.g., no mixed venous sampling) in this study to directly account for potential factors such as extra-pulmonary shunt, differences in alveolar to end-pulmonary capillary gas tensions, and venous admixture. Future studies should include those advanced invasive methods to confirm impaired perfusion and subsequent $\dot{V}_A/\dot{Q}$ mismatch is not independently responsible for unaccounted variance between predicted versus criterion measures of $PaCO_2$. Finally, while a major goal in providing validation data to support the use or disuse of $PaCO_2$ and V_D prediction equations is to understand the clinical utility of such alternative approaches in HF patients, the longitudinal prognostic implications of using criterion versus estimated $PaCO_2$ or V_D exercise responses in the present cohort are not available at this time.

7. Conclusions

These data suggest that noninvasive indirect quantification of $PaCO_2$ and V_D based on the $PaCO_2$ prediction equation of Jones et al. [15] (Eq.2) demonstrates acceptable levels of construct validity during CPET in patients with HF. However, compared to peak exercise, these data suggest that interpretation of resting data when using any of the prediction models for quantifying $PaCO_2$ and V_D should be conducted with caution. Because of the immediate clinical implications associated with an impaired ventilatory response to exercise in HF, these data provide encouraging evidence-based support for a noninvasive approach to advance our understanding of the role that abnormal changes in $PaCO_2$ and V_D contribute to the pathophysiology of exercise ventilatory limitations in patients with HF.

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Figure 1.

Comparisons of arterial carbon dioxide tension (PaCO₂) responses measured (criterion) or indirectly estimated at rest or peak exercise in patients with heart failure. **Panels A to D)** PaCO₂ responses at rest. **Panel A**, data presented as interquartile range with mean of the sample represented as (+). *Different compared to measured PaCO₂, $P < 0.01$. **Panel B**, bias $\pm$ 95% limits of agreement (LOA) of responses between measured PaCO₂ and predicted PaCO₂ using equations: Eq.1, Jones et al. [15], $\text{PaCO}_2 = 5.2 + 0.82 \times \text{PETCO}_2$; Eq.2, Jones et al. [15], $\text{PaCO}_2 = 5.5 + 0.90 \times \text{PETCO}_2 - 0.0021 \times V_T$; Eq.3, Asmussen and Nielsen [20], $V_D = 64.56 \times V_T + 138.73$; Eq.4, Jones in Paterson and Cunningham [21], $V_D = 0.077 \times V_T + 138$; Eq.5, Godfrey and Davies [22], $V_D = 0.049 \times V_T + 1.54 \times \text{weight}$; Eq.6, Shephard and Bar-Or

[23], $V_D=0.285 \times V_T - 64$; or end-tidal carbon dioxide tension (P_{ETCO_2}). Data presented as mean $PaCO_2$ of predicted (practical) minus measured (criterion) with bars representing lower and upper 95% LOA. **Panel C**, univariate ordinary least squares regressions between P_{ETCO_2} (independent, abscissa) and criterion $PaCO_2$ (dependent, ordinate) at rest. Solid black line is model goodness of fit line for the regression equation, whereas grey dashed line is the line of identity. Presented in brackets next to coefficient of determination (R^2) are 95% CL. **Panel D**, predicted $PaCO_2$ using the model goodness of fit equation from Panel C versus residuals [i.e., measured (criterion) $PaCO_2$ minus P_{ETCO_2} (practical)]. Dispersion of prediction errors occurring when predicting $PaCO_2$ from the regression using P_{ETCO_2} is quantified using the standard error of estimate (SEE) with lower and upper 95% CL in brackets. **Panels E to H**: $PaCO_2$ responses at peak exercise. All tests described above for rest were mirrored for peak exercise.

Figure 2.

Tests of concurrent validity for predicting arterial carbon dioxide tension (PaCO_2) in patients with heart failure. **Panels A to F**, for all univariate ordinary least squares regressions, measured PaCO_2 (criterion) is the dependent variable to be predicted while being set on the ordinate. **A)** Eq.1, Jones et al. [15], $\text{PaCO}_2 = 5.2 + 0.82 \times \text{PETCO}_2$; **B)** Eq.2, Jones et al. [15], $\text{PaCO}_2 = 5.5 + 0.90 \times \text{PETCO}_2 - 0.0021 \times V_T$; **C)** PaCO_2 was derived indirectly using equation from Eq.3, Asmussen and Nielsen [20], $V_D = 64.56 \times V_T + 138.73$; **D)** PaCO_2 was derived indirectly using equation from Eq.4, Jones in Paterson and Cunningham [21], $V_D = 0.077 \times V_T \pm 138$; **E)** PaCO_2 was derived indirectly using equation from Eq.5, Godfrey and Davies [22], $V_D = 0.049 \times V_T + 1.54 \times \text{weight}$; **F)** PaCO_2 was derived indirectly using equation from Eq.6, Shephard and Bar-Or [23], $V_D = 0.285 \times V_T - 64$. Solid black line is model goodness of fit line for the regression equation at peak exercise, whereas dashed black line is model goodness of fit line for the regression equation at rest. Grey dashed line is the line of identity. Presented in brackets next to coefficient of determination (R^2) are 95% CL. **Panels G to L)** Predicted values of PaCO_2 using respective model goodness of fit equations from Panels A to F versus residuals [i.e., measured (criterion) PaCO_2 minus predicted PaCO_2 (practical)]. Dispersion of prediction errors occurring when predicting PaCO_2 using regression equations from Panels A to F is quantified using the standard error of estimate (SEE) with lower and upper 95% CL in brackets. Open grey circles represent rest, whereas open black circles represent peak exercise.

Table 1

Characteristics of heart failure patients

Variable	N = 47
Age, years	55 ± 9
Gender, male/female	42/5
Left ventricular ejection fraction, %	21 ± 7
NYHA class, II/III	19/28
Height, cm	174 ± 8
Weight, kg	86 ± 15
Body mass index, kg/m ²	28 ± 5
Body surface area, m ²	2.04 ± 0.20
Hemoglobin, g/dL	14.1 ± 1.7
Creatinine, mg/dL	1.36 ± 0.44
eGFR, mL/min per 1.73 m ²	58 ± 18
Drug Therapy, n (%)	
ACE inhibitor	33 (70)
ARBs	7 (15)
Antiarrhythmic	15 (32)
β-blocker (β ₁ -selective or non-selective)	40 (85)
Digoxin	33 (70)
Nitrate (oral, SL, or topical)	11 (23)
Aspirin	34 (72)
Diuretics	43 (91)
Statin	26 (55)
Resting Pulmonary function	
Forced vital capacity (FVC), L	3.62 ± 1.02
FVC, % of predicted	80 ± 18
Forced expiratory volume in 1 s (FEV ₁), L	2.67 ± 0.86
FEV ₁ , % of predicted	74 ± 19
FEV ₁ /FVC	0.73 ± 0.09
FEV ₁ /FVC, % of predicted	95 ± 11
Lung diffusing capacity carbon monoxide (DL _{CO}), mL/min/mm Hg	19 ± 5
DL _{CO} , % of predicted	68 ± 15
Maximum voluntary ventilation, L/min	93 ± 30
Peak exercise function	
Oxygen uptake (V̇O ₂), mL/kg/min	8.52 ± 2.72
V̇O ₂ % of predicted	31 ± 8
Carbon dioxide output (V̇O ₂), L/min	0.76 ± 0.25
Respiratory exchange ratio	1.07 ± 0.11
Respiratory rate (f _B), breaths/min	30 ± 7
Tidal volume (V _T), L	1.11 ± 0.35

Variable	N = 47
Minute ventilation ($\dot{V}_E$), L/min	32 ± 10
Ventilatory reserve, %	38 ± 14
$\dot{V}_E/\dot{V}_{CO_2}$ slope	43 ± 12
End-tidal CO ₂ tension (P _{ET} CO ₂), mm Hg	30 ± 6
Mixed expired CO ₂ tension (PECO ₂), mm Hg	21 ± 5
PECO ₂ /P _{ET} CO ₂	0.69 ± 0.04
Arterial oxygen saturation (SaO ₂), %	96 ± 4

Data are mean $\pm$ SD, or otherwise noted.

Table 2

Physiologic dead space derived from measured arterial carbon dioxide tension or estimated via prediction equations at rest or peak exercise in heart failure

Variable	V _D (L)	R ² (95% CL)	SEE (95% CL)	Bias (95% LOA)
Rest				
Measured	0.26 ± 0.07	-	-	-
Eq. 1	0.21 ± 0.04 [‡]	0.84 (0.74 to 0.91) [*]	0.03 (0.02 to 0.03)	-0.06 (-0.13 to 0.01)
Eq. 2	0.23 ± 0.05	0.86 (0.77 to 0.92) [*]	0.03 (0.02 to 0.03)	-0.03 (-0.09 to 0.03)
Eq. 3	0.17 ± 0.01 [‡]	0.69 (0.51 to 0.81) [*]	0.04 (0.03 to 0.05)	-0.09 (-0.21 to 0.03)
Eq. 4	0.31 ± 0.08 [‡]	0.69 (0.51 to 0.81) [*]	0.04 (0.03 to 0.05)	0.05 (-0.04 to 0.14)
Eq. 5	0.13 ± 0.02 [‡]	0.00 (0.00 to 0.00)	0.07 (0.06 to 0.09)	-0.13 (-0.27 to 0.01)
Eq. 6	0.10 ± 0.04 [‡]	0.69 (0.51 to 0.81) [*]	0.04 (0.03 to 0.05)	-0.17 (-0.25 to -0.09)
P _{ET} CO ₂	0.21 ± 0.09 [‡]	0.78 (0.63 to 0.87) [*]	0.03 (0.02 to 0.04)	-0.05 (-0.13 to 0.03)
Peak exercise				
Measured	0.41 ± 0.15 [§]	-	-	-
Eq. 1	0.33 ± 0.10 ^{§‡}	0.69 (0.51 to 0.81) [*]	0.06 (0.05 to 0.07)	-0.08 (-0.22 to 0.05)
Eq. 2	0.39 ± 0.12 [§]	0.83 (0.71 to 0.90) [*]	0.06 (0.05 to 0.08)	-0.02 (-0.15 to 0.11)
Eq. 3	0.21 ± 0.02 ^{§‡}	0.54 (0.32 to 0.71) [*]	0.10 (0.09 to 0.13)	-0.20 (-0.47 to 0.06)
Eq. 4	0.62 ± 0.20 ^{§‡}	0.54 (0.32 to 0.71) [*]	0.10 (0.09 to 0.13)	0.21 (-0.06 to 0.47)
Eq. 5	0.13 ± 0.02 [‡]	0.11 (0.00 to 0.32)	0.14 (0.12 to 0.18)	-0.28 (-0.56 to 0.01)
Eq. 6	0.25 ± 0.10 ^{§‡}	0.54 (0.32 to 0.71) [*]	0.10 (0.09 to 0.13)	-0.16 (-0.36 to 0.04)
P _{ET} CO ₂	0.33 ± 0.09 ^{§‡}	0.70 (0.52 to 0.82) [*]	0.08 (0.07 to 0.11)	-0.09 (-0.26 to 0.09)

Data are means ± SD or otherwise noted. V_D=physiologic dead space; P_{ET}CO₂=end-tidal carbon dioxide tension; R²=coefficient of determination from linear regression between measured V_D (dependent) vs. predicted V_D (independent); CL=confidence limits; SEE=standard error of estimate; Bias=mean difference between estimated minus measured V_D; LOA=limits of agreement. Names in tables denote from where equations were referenced to estimate V_D as follows: Eq.1, Jones et al. (15), PaCO₂=5.2+0.82×P_{ET}CO₂; Eq.2, Jones et al. (15), PaCO₂=5.5+0.90×P_{ET}CO₂ - 0.0021×V_T; Eq.3, Asmussen and Nielsen (20), V_D=64.56×V_T+138.73; Eq.4, Jones in Paterson and Cunningham (21), V_D=0.077×V_T÷138; Eq.5, Godfrey and Davies (22), V_D=0.049×V_T+1.54×weight; Eq.6, Shephard and Bar-Or (23), V_D=0.285×V_T-64.

[‡]Different from measured V_D at rest, *P*<0.01;

[‡]Different from measured V_D at peak exercise, *P*<0.01.

^{*}Significant, *P*<0.01.

[§]Different from rest, *P*<0.01.