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ORIGINAL ARTICLE

Artificial Heart (Clinical)

# VE/VCO2 slope predicts RV dysfunction and mortality after left ventricular assist device: a fresh look at cardiopulmonary stress testing for prognostication

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**Abstract**
Preoperative cardiopulmonary exercise testing (CPET) is well validated for prognostication before advanced surgical heart failure therapies, but its role in prognostication after LVAD surgery has never been studied. VE/VCO2 slope is an important component of CPET which has direct pathophysiologic links to right ventricular (RV) performance. We hypothesized that $VE/VCO_2$ slope would prognosticate RV dysfunction after LVAD. All CPET studies from a single institution were collected between September 2009 and February 2019. Patients who ultimately underwent LVAD implantation were selectively analyzed. Peak VO2 and VE/VCO2 slope were measured for all patients. We evaluated their association with hemodynamic, echocardiographic and clinical markers of RV dysfunction as well mortality. Patients were stratified into those with a ventilatory class of III or greater. (VE/VCO2 slope of $\geq 36$, $n=43$) and those with a VE/VCO2 slope $<36$ ($n=27$). We compared the mortality between the 2 groups, as well as the hemodynamic, echocardiographic and clinical markers of RV dysfunction. 570 patients underwent CPET testing. 145 patients were ultimately referred to the advanced heart failure program and 70 patients later received LVAD implantation. Patients with VE/VCO2 slope of $\geq 36$ had higher mortality (30.2% vs. 7.4%, $p=0.02$) than patients with VE/VCO2 slope $<36$ ($n=27$). They also had a higher incidence of clinically important RVF (Acute severe 9.3% vs. 0%, Severe 32.6% vs 25.9%, $p=0.03$). Patients with a VE/VCO2 slope $\geq 36$ had a higher CVP than those with a lower VE/VCO2 slope ($11.2 \pm 6.1$ vs. $6.0 \pm 4.8$ mmHg, $p=0.007$), and were more likely to have a RA/PCWP $\geq 0.63$ (65% vs. 19%, $p=0.008$) and a PAPI $\leq 2$ (57% vs. 13%, $p=0.008$). In contrast, peak VO2 $<12$ ml/kg/min was not associated with postoperative RV dysfunction or mortality. Elevated preoperative VE/VCO2 slope is a predictor of postoperative mortality, and is associated with postoperative clinical and hemodynamic markers of impaired RV performance.

**Keywords** LVAD · Right ventricular failure · Cardiopulmonary stress testing · VE/VCO2

## Introduction

Left ventricular assist device (LVAD) support has become a cornerstone in the treatment regimen for advanced heart failure patients who are either not candidates for cardiac transplantation or who are otherwise too ill to proceed directly to transplantation. Overall survival trends continue to improve following LVAD implantation with one year combined survival of 83% and survival out to two years in the bridge to transplantation (BTT) population of 80% [1]. Despite improvements in survival, LVAD-related complications remain a limitation of the technology. In particular, right ventricular (RV) dysfunction and failure (RVF) frequently complicate LVAD implantation and can lead to increased morbidity and mortality [2]. Reported rates of RVF following LVAD range from 5% to 60.7% depending on the definition of RVF used [3, 4]. In an attempt to unify the definition of RVF, The Interagency Registry for Mechanical

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Circulatory Support (INTERMACS) established standardized definitions of RFV [5].

Several risk scores, using a combination of patient clinical, echocardiographic, laboratory, and hemodynamic data, have been developed to help predict RVF after LVAD placement [3, 6–15]. Unfortunately, these models have been limited as many of the studies were conducted in the era of pulsatile flow devices and before a unified definition of RVF was disseminated. Accordingly, there is a lack of correlation in the most widely used risk scores [16].

Cardiopulmonary exercise testing (CPET) is a mainstay of the preoperative risk stratification process for advanced heart failure patients [17, 18]. The VE/VCO2 slope, also known as the ventilatory efficiency, is readily calculated as the rate of change of minute ventilation (VE) as compared to ventilatory carbon dioxide (VCO2). Elevations in VE/VCO2 slope above 36 are associated with elevated short and moderate-term risk and can be useful in determining timing for advanced heart failure therapies [18]. A VE/VCO2 slope cutoff above 36 represents the transition from ventilatory class II to III which nearly doubles the risk of 2-year major adverse events from approximately 15–30% [19, 20]. An elevated VE/VCO2 slope has been associated with a reduction in tricuspid annular plane systolic excursion (TAPSE) and a reduction in RF ejection fraction in a general heart failure population [21, 22].

We hypothesized that an elevated VE/VCO2 prior to LVAD implantation would predict postimplant RVF, need for RVAD and death.

## Methods

### Patient population and endpoints

This study was approved by the MedStar Washington Hospital Center Institutional Review Board. Gas exchange and exercise metrics from all patients who underwent CPET evaluation at Washington Hospital Center between September 2009 and February 2019 were extracted. Patients who later underwent LVAD implantation made up the study cohort. These patients were analyzed for clinical echocardiographic and hemodynamic evidence of RV dysfunction and overall morbidity and mortality. RVF was defined using the INTERMACS definition: patients had to have signs of elevated right-sided pressures and clinical symptoms, then the severity of RVF was determined based on the duration of inotropic and/or inhaled pulmonary vasodilator support as well as the need for RVAD support or death. RVF was classified as mild ($\leq$7 days of inotropes); moderate (8–14 days of inotropes); severe ($\geq$14 days of inotropes and/or $\geq$48 h of pulmonary vasodilators); or acute severe (need for RVAD and/or death due to RVF) [23]. The primary outcome was the rate of acute severe RVF. Secondary clinical endpoints included all cause death and index hospitalization disposition outcome. Echocardiographic and hemodynamic data, when available, was analyzed for additional evidence of RV dysfunction. Right heart catheterization (RHC) at our institution is performed in patients with a clinical concern or those undergoing transplant evaluation. Secondary hemodynamic endpoints included metrics of RV dysfunction including elevated central venous pressure (CVP), elevated right atrial pressure to pulmonary capillary wedge pressure (RA/PCWP) > 0.63, pulmonary artery pulsatility index (PaPI) < 2, and RV stroke work index (RVSWI) < 0.3 mmHg × L/m$^2$. Completely transthoracic echocardiography (TTE) is routinely performed following LVAD implantation and the first ambulatory TTE after implant was used for analysis. Additional secondary echocardiographic endpoints included measures of RV dysfunction including TAPSE, RV size, and tricuspid regurgitation (TR) severity. In addition to quantitative assessment of RV function, a qualitative assessment was also performed (normal = 0, mild dysfunction = 1, mild/moderate = 1.5, moderate = 2, moderate/severe = 2.5, severe = 3). Qualitative TR severity was similarly assessed (none = 0, trace = 0.5, mild = 1, mild/moderate = 1.5, moderate = 2, moderate/severe = 2.5, severe = 3).

### Statistical methods

Continuous variables were analyzed with *t* tests if they were normally distributed and reported as means with standard deviation (SD). Non-normally distributed variables were expressed as medians with interquartile range and compared with the Mann–Whitney (Wilcoxon) test. Categorical variables were reported as numbers and percentages and analyzed using a Chi$^2$ test. Statistical significance was determined by a two-sided *p* value of $\leq$0.05. VE/VCO2 was compared with peak ventilatory oxygen utilization (Peak VO2) for the above endpoints. Receiver-operator characteristic (ROC) curves were used to determine the appropriate cutoff value for VE/VCO2 and Peak VO2 to for the primary endpoint. Kaplan–Meier time-to-event analysis was generated to describe time to death, and then tested using log rank tests. Stata 14.2 (StataCorp, College Station, Texas, USA) was used for data analysis.

## Results

Five hundred seventy patients underwent CPET testing between September 2009 and February 2019. Average age for the entire cohort was 55 ± 13, 66% were males and 62% were black. One hundred and forty-five patients were ultimately referred to the advanced heart failure program and 70 patients later received LVAD implantation. LVAD recipients were on

average, 56 ± 12 years old, 70% male and 71% black. Patients receiving an LVAD were able to achieve a lower workload with exercise (91 ± 39 watts vs. 104 ± 47 watts, $p = 0.02$) and had a lower peak VO2 (11.9 ± 3.7 ml/kg/min vs. 14.1 ± 5.9 ml/kg/min, $p = 0.001$) and higher VE/VCO2 slope (40.1 ± 9.7 vs. 35.3 ± 19.2, $p = 0.04$) than patients who did not undergo LVAD. Age, gender, and race as well as major comorbidities were similar between those with a ventilatory class III or greater (VE/VCO2 slope ≥ 36, $n = 43$) when compared with those with VE/VCO2 slope < 36 ($n = 27$) (Table 1), with the notable exception of diabetes (42% vs 15%, $p = 0.02$), CAD (47% vs. 22%, $p = 0.05$), INR (1.3 ± 0.2 vs 1.2 ± 0.1, $p = 0.04$), and albumin (3.1 ± 0.6 vs 3.4 ± 0.4, $p = 0.01$). The time from CPET to LVAD implant was the same between both groups (469 ± 547 days vs. 566 ± 797 days, $p = 0.55$).

## Clinical endpoints

Patients with a VE/VCO2 slope ≥ 36 had greater higher mortality (30.2% vs. 7.4%, $p = 0.02$) than patients with VE/VCO2 slope < 36. Kaplan–Meyer analysis revealed a 17% cumulative mortality in patients with an elevated VE/VCO2 slope vs 4% mortality in those with a lower VE/VCO2 slope at 1 year with survival curves which continued to diverge over time ($p = 0.11$) (Fig. 1). Patients with an elevated VE/VCO2 slope ≥ 36 were more likely to have acute severe or severe (9.3% and 32.6% respectively) RVF than those with a lower VE/VCO2 slope (0% and 25.9% respectively, $p = 0.03$) (Fig. 2). During the index admission after LVAD implant, patients with an elevated VE/VCO2 slope were more likely to be discharged to rehab (58.5% vs 26.9%, $p = 0.01$) and less likely to be discharged to home (31.7% vs. 73.1%, $p < 0.001$) as compared to those with a VE/VCO2 slope < 36 (Fig. 3). ROC analysis revealed that a VE/VCO2 slope cutoff of 50 could predict the need for RV mechanical support or death related to RHF with a sensitivity of 75%, specificity of 90% and area under the curve (AUC) of 0.84. Conversely, peak VO2 was poorly associated with the primary endpoint (AUC 0.36) (Fig. 4).

## Hemodynamic endpoints

Patients with a VE/VCO2 slope ≥ 36 had a higher CVP than those with a lower VE/VCO2 slope (11.2 ± 6.1 vs. 6.0 ± 4.8 mmHg, $p = 0.007$), a higher RA/PCWP (0.85 ± 0.44 vs. 0.52 ± 0.40, $p = 0.02$), and a lower PaPI (2.6 ± 1.7 vs. 6.2 ± 5.8, $p = 0.007$) (Fig. 5a). Patients with a VE/VCO2 slope ≥ 36 were also more likely to have a CVP > 15 (35% vs 6%, $p = 0.06$) RA/PCWP ≥ 0.63 (65% vs. 19%, $p = 0.008$) and a PAPI ≤ 2 (57% vs. 13%, $p = 0.008$) (Fig. 5b). Timing from LVAD implant to RHC was the same for those with a high and low VE/VCO2 slope (262 ± 285 days vs. 215 vs. 190 days, $p = 0.57$). By comparison, when the cohort was stratified according to peak VO2 above and below 12 ml/kg/min, there was no difference in CVP or RA/PCWP between the 2 groups, and there was no difference in the percentage of patients with an elevated RA/PCWP > 0.63 or PAPI < 2 (Fig. 5a, b).

**Table 1** Baseline characteristics for the LVAD cohort

| | VE/VCO2 < 36 (*N*: 27) | VE/VCO2 ≥ 36 (*N*: 43) | *p* value |
|---|---|---|---|
| Age at implant (yrs) | | | |
| BMI at implant | 30.8 ± 6 | 28.5 ± 6 | 0.06 |
| Male gender | 78% (21) | 65% (28) | 0.30 |
| African American | 70% (19) | 72% (31) | 0.22 |
| Hypertension | 44% (12) | 60% (26) | 0.22 |
| Hyperlipidemia | 52% (14) | 47% (20) | 0.81 |
| Diabetes | 15% (4) | 42% (18) | 0.02 |
| CAD | 22% (6) | 47% (20) | 0.05 |
| CABG | 4% (1) | 14% (6) | 0.24 |
| PVD | 11% (3) | 7% (3) | 0.67 |
| NICM | 85% (23) | 67% (29) | 0.16 |
| History of VT | 26% (7) | 21% (9) | 0.77 |
| History of Afib/Aflutter | 30% (8) | 47% (20) | 0.21 |
| Previous sternotomy | 7% (2) | 16% (7) | 0.47 |
| Hypothyroidism | 11% (3) | 14% (6) | 1.00 |
| COPD/asthma | 22% (6) | 12% (5) | 0.32 |
| Intention to treat | | | 0.36 |
| Bridge to transplant | 48% (13) | 42% (18) | |
| Destination therapy | 33% (9) | 49% (21) | |
| Bridge to decision | 19% (5) | 9% (4) | |
| VAD type | | | 0.58 |
| HeartMate 3 | 19% (5) | 30% (13) | |
| HeartMate II | 22% (6) | 21% (9) | |
| HVAD | 59% (16) | 21% (49) | |
| INTERMACS | | | 0.96 |
| Class 1 and 2 | 41% (11) | 48% (20) | |
| Class 3 | 44% (12) | 38% (16) | |
| Class 4 | 15% (4) | 14% (6) | |
| Na | 136 ± 4 | 137 ± 4 | 0.11 |
| BUN | 24 ± 14 | 28 ± 19 | 0.16 |
| Creatinine | 1.3 ± 0.4 | 1.6 ± 1.7 | 0.15 |
| AST | 31 ± 32 | 31 ± 24 | 0.48 |
| ALT | 45 ± 81 | 43 ± 58 | 0.89 |
| Bilirubin | 1.0 ± 0.4 | 1.4 ± 1.9 | 0.12 |
| INR | 1.2 ± 0.1 | 1.3 ± 0.2 | 0.04 |
| Albumin | 3.4 ± 0.4 | 3.1 ± 0.6 | 0.01 |

*BMI* body mass index, *CAD* coronary artery disease, *CABG* coronary artery bypass grafting, *PVD* peripheral vascular disease, *ICD* implantable cardioverter–defibrillator, *NICM* nonischemic cardiomyopathy, *VAD* ventricular assist device, *INTERMACS* interagency registry for mechanically assisted circulatory support, *Na* sodium, *AST* aspartate transaminase, *ALT* alanine transaminase, *INR* international normalized ratio, *BUN* blood urea nitrogen

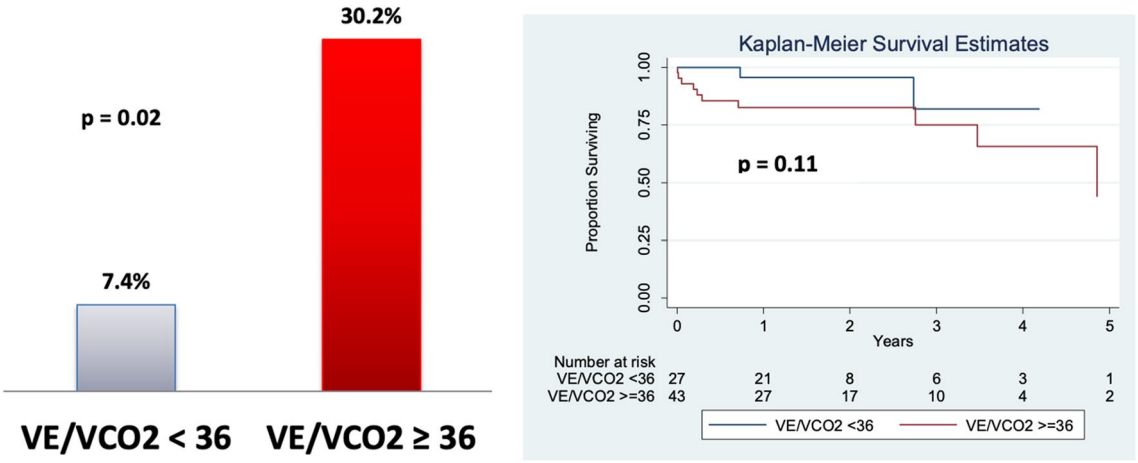
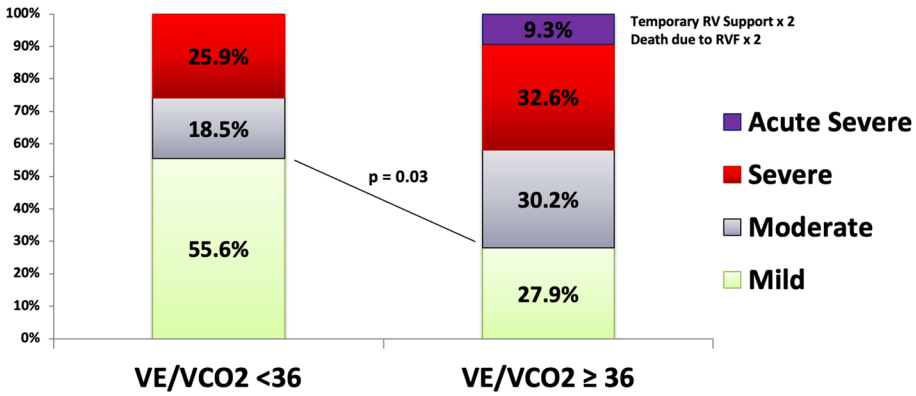
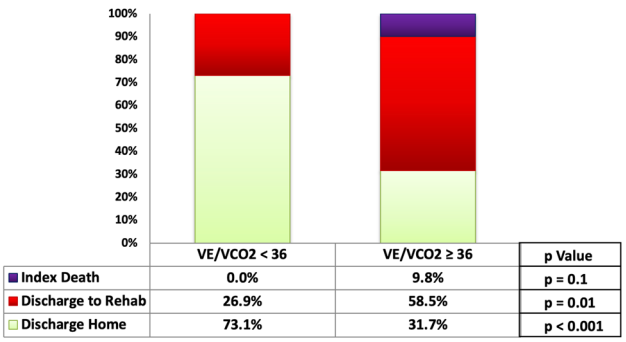



**Fig. 1** Overall death rate stratified by VE/VCO2 slope

**Fig. 2** Rates of mild, moderate, severe and acute severe RVF stratified by VE/VCO2 slope



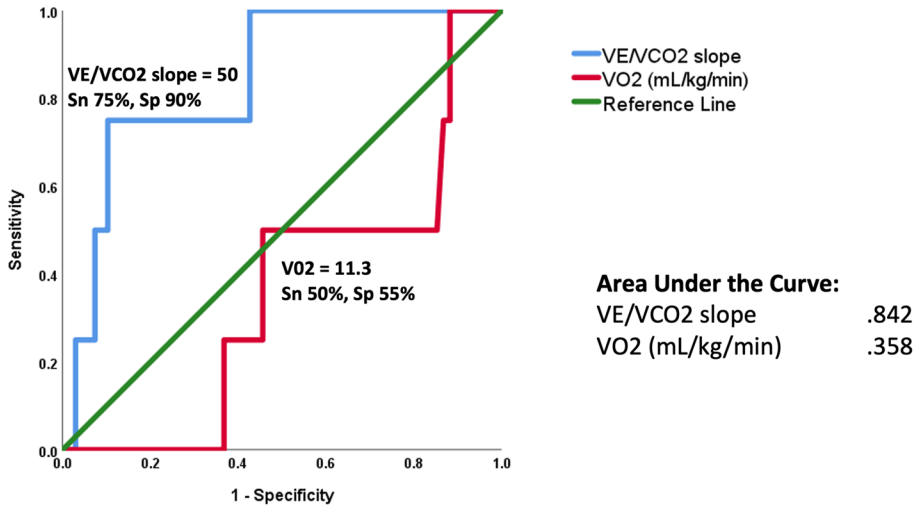




| | VE/VCO2 < 36 | VE/VCO2 ≥ 36 | p Value |
|---|---|---|---|
| Index Death | 0.0% | 9.8% | p = 0.1 |
| Discharge to Rehab | 26.9% | 58.5% | p = 0.01 |
| Discharge Home | 73.1% | 31.7% | p < 0.001 |

**Fig. 3** Index hospitalization outcomes after LVAD stratified by VE/VCO2 slope

## Echocardiographic endpoints

An elevation in VE/VCO2 slope above 36 was associated with several echocardiographic findings consistent with RV dysfunction. Mean TAPSE was lower for those with a VE/VCO2 slope of ≥ 36 compared to those with a lower slope (7.5 ± 3.2 mm vs 10.8 ± 3.5 mm, $p = 0.008$). Qualitative assessment of RV function also favored more dysfunction in those with an elevated VE/VCO2 slope as compared to those with reduced slope although this was not quite significant (2.4 ± 0.7 vs. 2.0 ± 0.8, $p = 0.06$). Numerically, the RV was more dilated in those with an elevated VE/VCO2 slope although this was not significant (5.0 ± 0.8 cm vs. 4.6 ± 0.6 cm, $p = 0.62$). The left ventricular end diastolic dimension (LVEDD) was smaller in those with a VE/VCO2 slope ≥ 36 compared to those with a lower slope (5.8 ± 1.1 cm vs. 6.3 ± 1.1 cm, $p = 0.002$). Tricuspid regurgitation was more severe in those with an elevated VE/VCO2 slope (1.0 ± 0.5 vs. 0.7 ± 0.2, $p = 0.04$) (Fig. 6). There was no difference in timing of TTE relative to LVAD implant between the two groups (64 ± 32 days vs. 73 ± 27 days, $p = 0.59$).



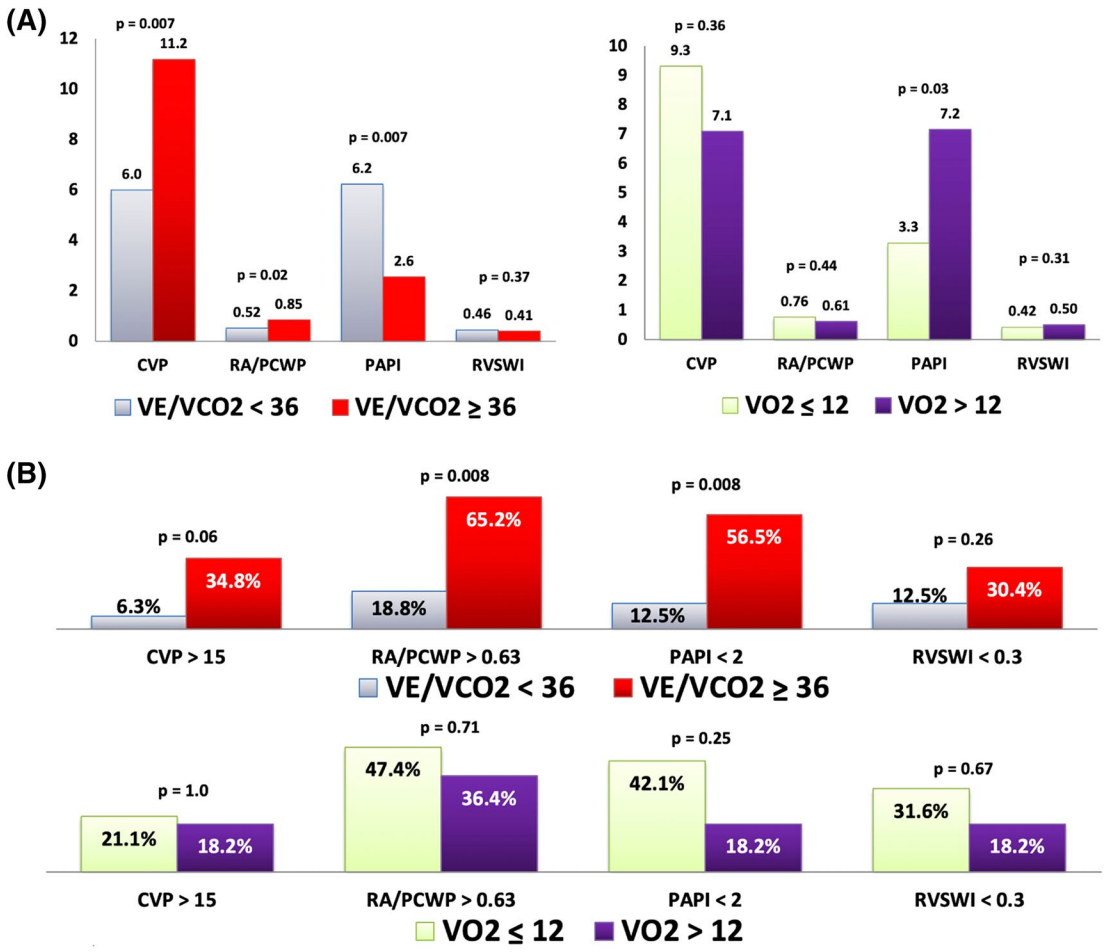




**Fig. 4** ROC analysis of VE/VCO2 slope and VO2 to predict acute severe RVF

**Fig. 5** (**a**) Hemodynamic metrics of RV dysfunction stratified by VE/VCO2 Slope and VO2. (**b**) Clinically relevant thresholds of RV dysfunction stratified by VE/VCO2 Slope and VO2

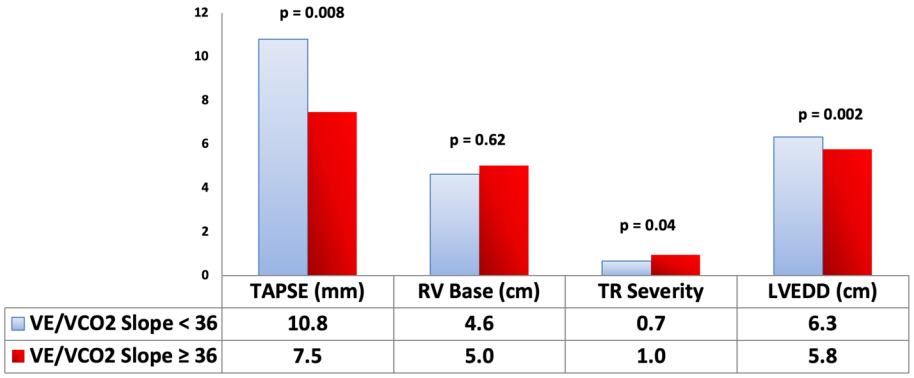



**Fig. 6** Echocardiographic metrics of RV dysfunction stratified by VE/VCO2 slope

## Discussion

In this study, we evaluated the prognostic role of VE/VCO2 slope obtained during routine cardiopulmonary stress testing for subsequent post-LVAD morbidity and mortality. The main findings of this study are as follows: (1) Elevation in preoperative VE/VCO2 slope predicts clinical RVF as well as hemodynamic and echocardiographic evidence of RV dysfunction after LVAD and (2) Peak VO2, another important CPET metric, failed to have the same prognostic capabilities as VE/VCO2 slope.

VE/VCO2 is dependent on the dead space ventilation (VD/VT) as follows [24]:

$$VE/VCO2 = 863/[(1 - VD/VT) \times PaCO2]$$

VE/VCO2 and thus VE/VCO2 slope will thus rise with any condition that increases dead space ventilation, such as alveolar fibrosis, pulmonary edema, hypoxic vasoconstriction, and the adaptive changes of pulmonary embolism and pulmonary hypertension among others (Fig. 7) [21]. VD/VT and thus VE/VCO2 are therefore markers of RV afterload. The right ventricle is exquisitely sensitive to changes in afterload [25]. Given the direct relationship between VE/VCO2 slope, VD/VT and RV afterload, elevations in VE/VCO2 slope preoperatively reflect a state of heightened demand on the right ventricle that can become exacerbated postoperatively leading to RV dysfunction and related morbidity and mortality after LVAD implant. Although peak VO2 is an important prognostic marker in general advanced heart failure patients, its role in predicting post-LVAD related morbidity and mortality does not appear as robust as VE/VCO2 slope. Several studies have shown that peak VO2 does not improve following LVAD implantation despite a clear survival benefit after LVAD [26, 27].

Several anatomic and functional changes occur to the right ventricle after LVAD implantation that can exacerbate RF dysfunction. RV function is intimately associated with RV morphology and changes to septal position after LVAD implantation has been proposed as one mechanism of RF dysfunction [28]. In addition, RV preload increases following LVAD support which may be a challenge for a struggling RV to overcome and may contribute to tricuspid annular dilation and exacerbate tricuspid regurgitation [29]. The pro-inflammatory state prior to and after LVAD implant, which can be exacerbated by perioperative bleeding has also been implicated in the mechanism of RV dysfunction [30]. Here we show that that an elevated VE/VCO2 slope not only predicts clinical RVF but also is associated with impaired hemodynamics and structural changes of RV dysfunction as capture by echocardiography. Notably, zero patients with a VE/VCO2 slope < 36 required an RVAD or died from RVF.

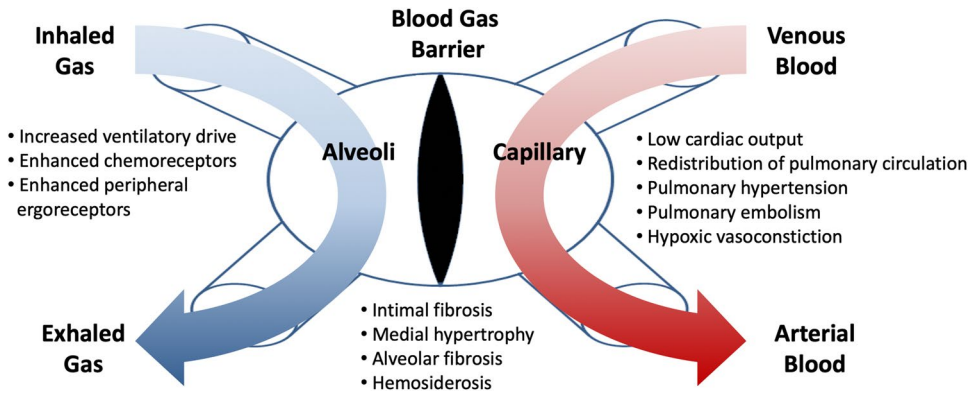



**Fig. 7** Relationship between VE/VCO2, dead space and adaptive changes of heart failure and pulmonary disease

Right ventricular dysfunction and failure following LVAD implantation remains a major source of morbidity and mortality and thus tools that allow for the timely recognition of patients at risk for this complication is of the utmost importance. Early identification of RVF, ideally even before LVAD implantation, may be able to mitigate downstream maladaptive RV remodeling and improve patient outcomes. Upfront right ventricular assist device (RVAD) implantation has been associated with lower in-hospital mortality, need for renal replacement therapy and stroke than delayed, provision RVAD implantation [31]. Unlike many other predictive studies that have preceded our current analysis, our study was performed in the continuous LVAD era and used the INTERMACS standardized definition. We are also the first study to include CPET data in the RV risk stratification. CPET is already part of the routine preoperative evaluation process in most advanced heart failure centers.

### Limitations

This study was retrospective and thus there was variation in timing between preoperative CPET and postoperative TTE and RHC. However, there was no difference in timing of CPET, TTE or RHC relative to LVAD implant between the low and high VE/VCO2 groups. There was a long time in delay between CPET date and LVAD implant date, but once could argue that this adds strength to the prognostic role of VE/VCO2 slope as the variable was able to stand the test of time. This study was conducted at a single center and thus institutional biases need to be accounted for. This is of particular importance when considering the rates of mild and moderate RVF as defined by INTERMACS as the decision of whether to leave a patient on inotropes can sometimes be subjective. Conversely, severe and acute severe RV failure has more objectivity in the classification and institutional bias therefore has less of an impact. Here we show that the rates of severe and acute severe RVF as well as death are higher in those with an elevated VE/VCO2 slope.

## Conclusion

Elevated preoperative VE/VCO2 slope is a predictor of postoperative mortality and acute severe RVF and is associated with postoperative clinical, echocardiographic and hemodynamic markers of impaired RV performance. A prospective study investigating VE/VCO2 slope on post-LVAD outcomes is warranted.

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## Declarations

**Conflict of interest** Grinstein—Consultant for Medtronic and Speakers Bureau for Abbott; Sawalha, Medvedofsky, Ahmad, Hofmeyer, Rodrigo, Kadakkal, Barnett, Kalantari, Talati, Zaghol and Molina—none; Sheikh—institutional research support from Abbott; Najjar—research support and consultant for Abbott.

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