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Prognostic Value of Capnography During Rest and Exercise in Patients With Heart Failure

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Abstract

New variables obtained from cardiopulmonary exercise testing (CPX) have received attention in recent years, in particular the partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$). The purpose of this study was to therefore comprehensively assess the ability of resting and exercise $P_{ET}CO_2$ to predict major cardiac events in a heart failure (HF) cohort referred for CPX. A total of 963 patients with systolic HF undergoing symptom-limited CPX were included in the analysis. Resting and exercise $P_{ET}CO_2$ along with other CPX variables were determined, and patients were followed for major adverse events. With regard to resting measures, multivariate analysis revealed that left ventricular ejection fraction was the most robust prognostic marker ($P < .001$) while resting $P_{ET}CO_2$ added significant predictive value and was retained in the regression ($P < .001$). When exercise data were considered, the multivariate analysis revealed that the $P_{ET}CO_2$ apex during exercise added predictive value and was retained ($P < .05$). In what is the largest evaluation of $P_{ET}CO_2$ in the assessment of systolic HF patients to date, the authors substantiate prior (smaller) studies showing prognostic utility of $P_{ET}CO_2$, both as a resting measure (an important potential

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screening tool) and during exercise. These data add to the rationale to incorporate $P_{ET}CO_2$ as a routine monitoring component in HF management."

Given the elevated risk of adverse events in patients with heart failure (HF), identifying clinical variables with prognostic value that are also easily obtainable and cost-efficient is a high priority. Cardiopulmonary exercise testing (CPX), which incorporates ventilatory expired gas analysis, is a proven and widely accepted clinical assessment in the HF population. Of the numerous variables that can be obtained from CPX, peak oxygen consumption (VO_2), and the minute ventilation/carbon dioxide production (VE/CO_2) relationship have historically garnered the greatest recognition.¹ However, other ventilatory expired gas variables have received attention in recent years, in particular the partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$).

The partial pressure of end-tidal CO_2 , both at rest and during exercise, has been shown to accurately reflect disease severity and cardiac function in patients with HF.²⁻⁴ Moreover, our group and others have demonstrated $P_{ET}CO_2$, both at rest and during exercise, is a significant predictor of adverse events in this chronic disease population.⁵⁻⁷ Therefore, $P_{ET}CO_2$ may have particular clinical value given the noninvasive and cost-effective manner by which this particular measure can be ascertained. While the currently available investigations demonstrating the prognostic value of $P_{ET}CO_2$ are promising, they are limited from the perspective of relatively small sample sizes and number of events. Moreover, we are unaware of any previous investigation that has comprehensively assessed the prognostic differences of $P_{ET}CO_2$ calculations (ie, static measures as well as change scores) at rest and during exercise.

The purpose of the current study was to therefore comprehensively assess the ability of resting and exercise $P_{ET}CO_2$ to predict major cardiac events in a large HF cohort referred for CPX. A secondary aim was to determine which $P_{ET}CO_2$ calculation(s) provide optimal prognostic insight with multivariate modeling. Given previous investigations in this area, we hypothesized that $P_{ET}CO_2$ would provide independent and complementary risk information to more established indices of prognosis in patients with HF.

METHODS

The current investigation was a multicenter analysis that included HF patients from the exercise testing laboratories at San Paolo Hospital, Milan, Italy; LeBauer Cardiovascular Research Foundation, Greensboro, NC; Stamford University, Palo Alto, CA; VA Palo Alto Health Care System, Palo Alto, CA; Brigham and Women's Hospital, Boston, MA; and Virginia Commonwealth University, Richmond, VA. A total of 963 patients with systolic HF were included in the current analysis. All patients were in a compensated state at the time of CPX. The inclusion criteria consisted of a diagnosis of HF,⁸ evidence of left ventricular systolic dysfunction by 2-dimensional echocardiography obtained within 1 month of data collection, New York Heart Association class I through III, and no coexisting diagnosis of significant pulmonary disease, as per chart review/CPX referral documentation. Mean age and left ventricular ejection fraction (LVEF) were 55 ± 13 years and $28\% \pm 10\%$, respectively. Etiology of HF was ischemic in 38% of the patients and nonischemic in the remaining 62%.

Seventy-five percent of the patients were men. Lastly, 77% and 71% of the cohort was prescribed a β -blocker and angiotensin-converting enzyme inhibitor at the time of CPX, respectively. All patients completed a written informed consent and institutional review board approval was obtained at each institution.

CPX Procedures

Symptom-limited CPX was performed on all patients and pharmacologic therapy was maintained during exercise testing. Progressive exercise testing protocols that were conservative in nature with respect to workload titration were employed at all centers and ventilatory expired gas analysis was performed using a metabolic cart (Medgraphics CPX-D and Ultima, Minneapolis, MN; Sensormedics Vmax29, Yorba Linda, CA or Parvomedics TrueOne 2400, Sandy, UT). The mode of exercise was a treadmill in 67% of the tests and a lower extremity ergometer in the remaining 33%. Previous research has demonstrated CPX variables are comparably prognostic using either of these exercise modes.⁹ Before each test, the equipment was calibrated in standard fashion using reference gases and a 3-l syringe. Minute ventilation (VE), oxygen uptake (VO_2), and carbon dioxide output (VCO_2) were acquired breath-by-breath, and averaged over 10-second intervals. Resting P_{ETCO_2} was defined as the average value (2 minute) obtained in the seated position prior to CPX. The highest 10-second averaged P_{ETCO_2} during submaximal exercise (ie, highest 10-second averaged increase from the resting value) was considered the apex value (ie $\text{P}_{\text{ETCO}_{2\text{apex}}}$). The 10-second averaged P_{ETCO_2} at maximal exercise was also determined (ie $\text{P}_{\text{ETCO}_{2\text{max}}}$). Lastly, the change in P_{ETCO_2} from rest to $\text{P}_{\text{ETCO}_{2\text{apex}}}$ ($\text{P}_{\text{ETCO}_2-1}$) and from this submaximal apex value to $\text{P}_{\text{ETCO}_{2\text{max}}}$ ($\text{P}_{\text{ETCO}_2-2}$) was calculated. Peak VO_2 and the peak respiratory exchange ratio (RER) were expressed as the highest 10-second averaged sample obtained during the last 20 seconds of testing. VE and VCO_2 values, acquired from the initiation of exercise to maximal exertion, were input into spreadsheet software (Microsoft Excel; Microsoft Corp, Bellevue, WA) to calculate the VE/ VCO_2 slope via least-squares linear regression ($y=mx+b$, $m=\text{slope}$).

End Points

In the overall cohort, patients were followed for major cardiac events (mortality, left ventricular assist device implantation, urgent heart transplantation) via medical chart review for up to 4 years post-CPX. Patients were followed by the HF programs at their respective institution providing a high likelihood that all events were captured. External means of tracking events, such as the Social Security Death Index, were not utilized in the present study. Any death with a cardiac-related discharge diagnosis was considered an event.

Statistical Analysis

A statistical software package (SPSS 19.0, SPSS, IBM, Armonk, NY) was used to perform all analyses. Continuous and categorical data are reported as mean $\pm$ standard deviation and percentages, respectively. Independent t tests and chi-square tests were used to assess differences in CPX variables between patients who remained event free or experienced a major cardiac event during the tracking period. Receiver operating characteristic (ROC) curve analysis assessed the prognostic classification schemes for all P_{ETCO_2} variables. Univariate and multivariate (forward stepwise method; entry and removal value 0.05 and

0.10, respectively) Cox regression analysis was used to assess the prognostic value of key resting and CPX variables. A P value $<.05$ was considered statistically significant for all tests.

RESULTS

There were 179 major cardiac events (120 deaths, 22 left ventricular assist device implantations, and 37 transplantations) during the 4-year tracking period. The mean tracking period for the entire cohort was 22.4 ± 14.4 months. None of the patients were lost to follow-up. The average yearly event rate was 8.9%. Table I lists CPX variables according to major cardiac event status. There were significant differences for all variables with the exception of peak RER and $P_{ET}CO_2-2$.

Resting LVEF was also significantly higher in patients who were event-free compared with those who experienced an event ($29 \pm 9\%$ vs $23 \pm 9\%$, $P < .001$) while there was no difference in age (55 ± 13 vs 56 ± 14 years, $P = .26$). The percentage of patients with an ischemic etiology was significantly higher in the group who experienced a major cardiac event (46% vs 36%, $P = .007$). The distribution of men and women in event-free vs major cardiac event subgroups was not significantly different (73/27% vs 78/22%, $P = .17$).

The Figure illustrates the ROC results for all $P_{ET}CO_2$ expressions. With the exception of $P_{ET}CO_2-2$, all prognostic classification schemes were statistically significant.

Table II lists the univariate Cox regression analyses for all expressions of $P_{ET}CO_2$. With the exception of $P_{ET}CO_2-2$, all other variables were prognostically significant.

Table III lists the univariate and multivariate Cox regression analyses for key resting variables. Heart failure etiology, LVEF, and resting $P_{ET}CO_2$ were all significant univariate predictors of adverse events. Multivariate analysis revealed that LVEF was the most robust prognostic marker while resting $P_{ET}CO_2$ added significant predictive value and was retained in the regression. HF etiology was not a significant multivariate marker while age was neither a significant univariate nor multivariate prognostic marker. In a univariate analysis, a previously established resting $P_{ET}CO_2$ prognostic threshold of < 33 mm Hg¹⁰ produced a hazard ratio of 2.4 (95% confidence interval [CI], 1.8–3.3; $P < .001$).

Table IV lists the univariate and multivariate Cox regression analyses for key resting and CPX variables. All variables considered were significant univariate predictors of survival. The multivariate analysis revealed that the VE/VCO_2 slope was the strongest predictor of adverse events while LVEF, peak VO_2 , and $P_{ET}CO_{2apex}$ were also retained in the regression. In a univariate analysis, using the minimal normal increase of 3 mm Hg during progressive exercise, a $P_{ET}CO_{2apex}$ of < 36 mm Hg¹¹ produced a hazard ratio of 2.8 (95% CI, 2.1–3.8; $P < .001$).

When only key resting and $P_{ET}CO_2$ variables were included in a multivariate survival analysis, $P_{ET}CO_{2apex}$ was the strongest predictor (chi-square, 67.3; $P < .001$) and both LVEF (residual chi-square, 47.7; $P < .001$) and $P_{ET}CO_{2max}$ (residual chi-square, 4.0; $P < .05$) were retained in the regression.

DISCUSSION

Assessing $P_{ET}CO_2$ both at rest and during exercise has recently been shown to provide diagnostic² and prognostic^{5,7} value in patients with HF. The results of the present study support the prognostic value of $P_{ET}CO_2$ at rest and during exercise in, to our knowledge, the largest HF cohort to date. Previous research has demonstrated a significant relationship between $P_{ET}CO_2$ and cardiac function in patients with HF.^{2,4} While indices of cardiac function should in principle be the most reliable predictors of risk, cardiac function is difficult to measure directly and can vary considerably for patients with similar degrees of HF. The demonstrated link between $P_{ET}CO_2$ and central function is important in that $P_{ET}CO_2$ is noninvasive, easy to measure, and strongly related to prognosis.

During resting assessments, $P_{ET}CO_2$ was an independent prognostic marker and was retained in the multivariate model with LVEF. This finding is consistent with previous investigations demonstrating the clinical utility of resting $P_{ET}CO_2$ both as a diagnostic^{5,12} and prognostic⁷ marker. The potential clinical value of resting $P_{ET}CO_2$ is notable in the sense that it can be quantified in a noninvasive, quick (2-minute averaged data), reliable,¹³ and relatively inexpensive manner. In particular, the use of capnography to assess a patient's clinical status, both acutely and longitudinally, may be particularly attractive in the outpatient and home health settings. In both of these settings, there is a need for objective information on HF stability (compensation vs decompensation), progression of disease, and prognosis. Moreover, given the ease by which resting $P_{ET}CO_2$ can be obtained, there may be self-monitoring applications for this technology in the context of HF home-based monitoring programs. However, the ability of resting $P_{ET}CO_2$ to track changes in clinical status longitudinally has not been investigated at this time. As such, future research should be directed toward assessing the utility of resting $P_{ET}CO_2$ to longitudinally monitor clinical status in these and other settings in the HF population.

While all but one expression of $P_{ET}CO_2$ were significant univariate markers of risk in the current study, only the $P_{ET}CO_{2\text{apex}}$ during submaximal exercise was retained in the multivariate regression including other established CPX variables. When only key resting and $P_{ET}CO_2$ variables (ie, excluding peak VO_2 and the VE/VCO_2 slope) were included in a multivariate regression, both $P_{ET}CO_{2\text{apex}}$ and $P_{ET}CO_{2\text{max}}$ were retained along with LVEF. This latter finding holds relevance given that $P_{ET}CO_2$ can be independently obtained with a hand-held device. Thus, when a complete ventilatory expired gas analysis system is not available during exercise testing, $P_{ET}CO_2$ monitoring in conjunction with traditional exercise testing procedures (ie, heart rate, hemodynamics, and subjective symptoms) may provide valuable clinical information. Previous investigations have demonstrated $P_{ET}CO_2$ during exercise reflects cardiac function and disease severity^{2-4,14} as well as prognosis^{6,15} in patients with HF. Additional research supports the clinical utility of exercise $P_{ET}CO_2$ for gauging disease severity in patients with pulmonary arterial hypertension, reinforcing the clinical applicability of this variable.¹⁶⁻¹⁹

Future research is needed to confirm the independent value of $P_{ET}CO_2$ during exercise. In fact, our results indicate the VE/VCO_2 slope and peak VO_2 are important prognostic markers in HF, providing greater predictive resolution in multivariate modeling compared

with $P_{ET}CO_2$ alone. These particular CPX variables have garnered a wealth of data supporting their prognostic value and should continue to be central in the analysis of exercise testing data in the HF population.^{1,20–22} However, $P_{ET}CO_{2apex}$ was retained in the multivariate prognostic model in the current study, warranting consideration of expanding the list of CPX variables assessed in patients with HF. Moreover, while the information obtained from exercise testing with full ventilatory expired gas analysis is clearly valuable, broad application of CPX is not feasible given the cost of equipment, time commitment and personnel needed to conduct the assessment. In this context, the use of simplified exercise testing approaches with exclusive monitoring of $P_{ET}CO_2$ may allow for a larger portion of the HF population to undergo a functional assessment, which clearly provides valuable information. For example, $P_{ET}CO_2$ values during low-intensity, submaximal exercise testing have demonstrated prognostic value in patients with HF.¹⁵ This type of submaximal testing procedure, akin to the 6-minute walk test with refined monitoring, may be particularly attractive to an outpatient HF management clinic, allowing for valuable exertional data to be obtained in a large number of patients in an economically feasible and time-efficient manner. It is important to note that the authors of the current analysis still strongly recommend that HF patients who are being considered for transplant candidacy or device implantation be referred for a full, symptom-limited, CPX. However, patients who are not being considered for these end-stage surgical interventions, and would not typically be referred for a CPX, may benefit from submaximal testing with $P_{ET}CO_2$ analysis.

Study Limitations

There are several limitations to this study that require consideration. All of the patients were clinically referred for CPX, introducing a potential selection bias. We also did not have access to other key baseline variables that would be valuable to assess in multivariate modeling, such as, for example, renal function and the use of cardiac resynchronization device therapy. Thus, while there are initial findings to indicate the value of $P_{ET}CO_2$ monitoring in HF patients not selected for CPX,⁵ additional research, including more relevant clinical variables, is needed to support broader application of $P_{ET}CO_2$ in this population. The prognostic information $P_{ET}CO_2$ adds to other variables during CPX may be limited by overlapping with what is already provided by other variables such as peak VO_2 and the VE/VCO_2 slope. Thus, for resting and exercise $P_{ET}CO_2$ to demonstrate true clinical utility, it must do so as a “stand-alone” measure used in settings that would benefit from an additional rapid, noninvasive assessment to gauge patient status and prognosis. Moreover, the application of our findings to patients with HF and preserved LVEF and/or women requires further analysis. There are data to suggest CPX responses are valuable in female HF patients as well as those with preserved LVEF and thus expansion of this research to include $P_{ET}CO_2$ in ^{23–25} cohorts with these characteristics is warranted. Lastly, other CPX variables, such as exercise oscillatory ventilation and the oxygen uptake efficiency slope, have also demonstrated prognostic value in HF. Unfortunately, the dataset used in the current analysis did not include these variables. It would therefore be worthwhile for future analyses to perform a more comprehensive multivariate CPX analysis.

CONCLUSIONS

Data supporting the potential clinical utility of $P_{ET}CO_2$, both at rest and during exercise, continue to accumulate in patients with HF. The results of our study are consistent with previous findings and support the concept that $P_{ET}CO_2$ is a useful prognostic marker in these patients. Further research is needed to determine the utility of this marker in broader groups of patients with HF and to determine the applications of routinely monitoring $P_{ET}CO_2$ via a hand-held device.

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References

1. Balady GJ, Arena R, Sietsema K, et al. Clinician's guide to cardiopulmonary exercise testing in adults. A scientific statement from the American Heart Association. *Circulation*. 2010;122:191–225. [PubMed: 20585013]
2. Matsumoto A, Itoh H, Eto Y, et al. End-tidal CO₂ pressure decreases during exercise in cardiac patients: association with severity of heart failure and cardiac output reserve. *J Am Coll Cardiol*. 2000;36:242–249. [PubMed: 10898441]
3. Myers J, Gujja P, Neelagaru S, et al. End-tidal CO₂ pressure and cardiac performance during exercise in heart failure. *Med Sci Sports Exerc*. 2009;41:19–25. [PubMed: 19092707]
4. Tanabe Y, Hosaka Y, Ito M, et al. Significance of end-tidal P(CO₂) response to exercise and its relation to functional capacity in patients with chronic heart failure. *Chest*. 2001;119:811–817. [PubMed: 11243962]
5. Klemen P, Golub M, Grmec S. Combination of quantitative capnometry, N-terminal pro-brain natriuretic peptide, and clinical assessment in differentiating acute heart failure from pulmonary disease as cause of acute dyspnea in pre-hospital emergency setting: study of diagnostic accuracy. *Croat Med J*. 2009;50:133–142. [PubMed: 19399946]
6. Arena R, Guazzi M, Myers J. Prognostic value of end-tidal carbon dioxide during exercise testing in heart failure. *Int J Cardiol*. 2007;117:103–108. [PubMed: 16843545]
7. Arena R, Myers J, Abella J, et al. The partial pressure of resting end-tidal carbon dioxide predicts major cardiac events in patients with systolic heart failure. *Am Heart J*. 2008;156:982–988. [PubMed: 19061716]
8. Radford MJ, Arnold JM, Bennett SJ, et al. ACC/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with chronic heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Heart Failure Clinical Data Standards): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Failure Society of America. *Circulation*. 2005;112:1888–1916. [PubMed: 16162914]
9. Arena R, Guazzi M, Myers J, Ann PM. Prognostic characteristics of cardiopulmonary exercise testing in heart failure: comparing American and European models. *Eur J Cardiovasc Prev Rehabil*. 2005;12: 562–567. [PubMed: 16319546]
10. Myers J, Arena R, Dewey F, et al. A cardiopulmonary exercise testing score for predicting outcomes in patients with heart failure. *Am Heart J*. 2008;156:1177–1183. [PubMed: 19033016]
11. Wasserman K, Hansen JE, Sue DY, et al. Normal values In: Weinberg R, ed. *Principles of Exercise Testing and Interpretation*, 4th ed Philadelphia, PA: Lippincott Williams and Wilkins; 2005: 160–182.
12. Grmec S, Golub M, Klemen P, Cander D. Utility of the quantitative capnometry (QC) and rapid bedside test for N-terminal pro-brain natriuretic peptide (pro-BNP) in the evaluation of respiratory distress in prehospital setting – preliminary results. *J Emerg Med*. 2007;33: 322.

13. Arena R, Peberdy MA. Reliability of resting end-tidal carbon dioxide in chronic heart failure. *J Cardiopulm Rehabil.* 2005;25:177–180. [PubMed: 15931023]
14. Hansen JE, Ulubay G, Chow BF, et al. Mixed-expired and end-tidal CO₂ distinguish between ventilation and perfusion defects during exercise testing in patients with lung and heart diseases. *Chest.* 2007;132:977–983. [PubMed: 17573506]
15. Arena R, MacCarter D, Olson TP, et al. Ventilatory expired gas at constant-rate low-intensity exercise predicts adverse events and is related to neurohormonal markers in patients with heart failure. *J Cardiac Fail.* 2009;15:482–488.
16. Yasunobu Y, Oudiz RJ, Sun XG, et al. End-tidal PCO₂ abnormality and exercise limitation in patients with primary pulmonary hypertension. *Chest.* 2005;127:1637–1646. [PubMed: 15888840]
17. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation.* 2001;104:429–435. [PubMed: 11468205]
18. Sun X, Hansen JE, Oudiz RJ, Wasserman K. Gas exchange detection of exercise-induced right-to-left shunt in patients with primary pulmonary hypertension. *Circulation.* 2002;105:54–60. [PubMed: 11772876]
19. Arena R, Lavie CJ, Milani RV, et al. Cardiopulmonary exercise testing in patients with pulmonary arterial hypertension: an evidence-based review. *J Heart Lung Transplant.* 2010;29:159–173. [PubMed: 19969471]
20. Arena R, Myers J, Guazzi M. The clinical and research applications of aerobic capacity and ventilatory efficiency in heart failure: an evidence-based review. *Heart Fail Rev.* 2008;13:245–269. [PubMed: 17987381]
21. Arena R, Myers J, Abella J, et al. Development of a ventilatory classification system in patients with heart failure. *Circulation.* 2007; 115:2410–2417. [PubMed: 17452607]
22. Francis DP, Shamim W, Davies LC, et al. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO₂(2)slope and peak VO₂. *Eur Heart J.* 2000;21:154–161. [PubMed: 10637089]
23. Guazzi M, Myers J, Arena R. Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. *J Am Coll Cardiol.* 2005;46:1883–1890. [PubMed: 16286176]
24. Guazzi M, Myers J, Peberdy MA, et al. Cardiopulmonary exercise testing variables reflect the degree of diastolic dysfunction in patients with heart failure-normal ejection fraction. *J Cardiopulm Rehabil Prev.* 2010;30:165–172. [PubMed: 20216325]
25. Guazzi M, Arena R, Myers J. Comparison of the prognostic value of cardiopulmonary exercise testing between male and female patients with heart failure. *Int J Cardiol.* 2006;113:395–400. [PubMed: 16650490]

	Area Under the Curve	95% Confidence Interval	p-value
Resting $P_{ET}CO_2$	0.64	0.60-0.69	<0.001
$P_{ET}CO_{2apex}$	0.67	0.63-0.72	<0.001
$P_{ET}CO_{2max}$	0.67	0.63-0.72	<0.001
$\Delta P_{ET}CO_2-1$	0.60	0.56-0.64	<0.001
$\Delta P_{ET}CO_2-2$	0.54	0.49-0.58	0.15

FIGURE.

Receiver operating characteristic curve analysis for $P_{ET}CO_2$. $P_{ET}CO_2$ indicates partial pressure of end-tidal carbon dioxide production; $P_{ET}CO_2-1$, change in $P_{ET}CO_2$ from rest to apex; $P_{ET}CO_2-2$, change in $P_{ET}CO_2$ from apex to max.

TABLE I.

Differences in CPX Variables According to Major Cardiac Event Status

	Event-Free (n=820)	Major Cardiac Event (n=179)	P Value
Peak VO_2 , $\text{mlO}_2/\text{kg}/\text{min}$	16.0±5.3	12.9±4.2	<.001
Peak RER	1.11±0.13	1.1±0.15	.31
VE/ VCO_2 slope	33.8±8.3	40.2±10.4	<.001
Resting P_{ETCO_2} , mm Hg	34.2±4.4	32.1±4.4	<.001
$\text{P}_{\text{ETCO}_2\text{apex}}$, mm Hg	37.7±5.7	34.5±5.0	<.001
$\text{P}_{\text{ETCO}_2\text{max}}$, mm Hg	34.3±6.8	30.6±5.5	<.001
$\text{P}_{\text{ETCO}_2-1}$, mm Hg	3.6±4.0	2.4±3.1	<.001
$\text{P}_{\text{ETCO}_2-2}$, mm Hg	-3.4±5.0	-3.9±3.4	.18

Abbreviations: PETCO_2 , partial pressure of end-tidal carbon dioxide production; PETCO_2-1 , change in PETCO_2 from rest to apex;

PETCO_2-2 , change in PETCO_2 from apex to max; RER, respiratory exchange ratio; VE/ VCO_2 , minute ventilation/carbon dioxide production; VO_2 , oxygen consumption.

TABLE II.Univariate Survival Analysis for $P_{ET}CO_2$ Variables

	Chi-Square	Hazard Ratio (95% CI)	P Value
Resting $P_{ET}CO_2$	40.8	0.91 (0.88–0.93)	<.001
$P_{ET}CO_{2\text{apex}}$	67.3	0.90 (0.88–0.92)	<.001
$P_{ET}CO_{2\text{max}}$	64.2	0.90 (0.88–0.92)	<.001
$P_{ET}CO_{2-1}$	18.0	0.93 (0.89–0.96)	<.001
$P_{ET}CO_{2-2}$	0.91	0.98 (0.94–1.02)	.33

Abbreviations: CI, confidence interval; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide production; $P_{ET}CO_{2-1}$, change in $P_{ET}CO_2$ from rest to apex; $P_{ET}CO_{2-2}$, change in $P_{ET}CO_2$ from apex to max.

TABLE III.**Survival Analysis for Key Resting Variables**

	Chi-Square	Hazard Ratio (95% CI)	P Value
Univariate analysis			
Age	0.59	1.00 (0.99–1.02)	.44
HF etiology	5.2	1.41 (1.04–1.89)	<.05
LVEF	67.5	0.93 (0.92–0.95)	<.001
Resting P _{ET} CO ₂	40.8	0.91 (0.88–0.93)	<.001
Multivariate analysis			
	Chi-square		
LVEF	67.5		<.001
	Residual chi-square		
Resting P _{ET} CO ₂	28.1		<.001
HF etiology	3.4		.07
Age	0.71		.40

Abbreviations: CI, confidence interval; HF, heart failure; LVEF, left ventricular ejection fraction; P_{ET}CO₂, partial pressure of end-tidal carbon dioxide production.

TABLE IV.

Survival Analysis for Key Resting and CPX Variables

	Chi-Square	Hazard Ratio (95% CI)	P Value
Univariate analysis			
HF Etiology	5.2	1.41 (1.04–1.89)	<.05
LVEF	67.5	0.93 (0.92–0.95)	<.001
Resting P _{ET} CO ₂	40.8	0.91 (0.88–0.93)	<.001
VE/VCO ₂ slope	106.6	1.06 (1.05–1.07)	<.001
Peak VO ₂	52.0	0.87 (0.84–0.90)	<.001
P _{ET} CO ₂ apex	67.3	0.90 (0.88–0.92)	<.001
P _{ET} CO ₂ max	64.2	0.90 (0.88–0.92)	<.001
P _{ET} CO ₂ -1	18.0	0.93 (0.89–0.96)	<.001
Multivariate analysis			
	Chi-square		
VE/VCO ₂ slope	106.6		<.001
	Residual chi-square		
LVEF	45.0		<.001
Peak VO ₂	16.5		<.001
P _{ET} CO ₂ apex	4.9		.03
HF etiology	1.1		.29
Resting P _{ET} CO ₂	0.60		.44
P _{ET} CO ₂ -1	0.60		.44
P _{ET} CO ₂ max	0.48		.49

Abbreviations: CI, confidence interval; HF, heart failure; LVEF, left ventricular ejection fraction; P_{ET}CO₂, partial pressure of end-tidal carbon dioxide production; VE/VCO₂, minute ventilation/carbon dioxide production; VO₂, oxygen consumption; P_{ET}CO₂-1, change in P_{ET}CO₂ from rest to apex.