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Prognostic value of Cardiopulmonary Exercise Testing in Heart Failure with preserved Ejection Fraction. The Henry Ford Hospital CardioPulmonary EXercise Testing (FIT-CPX) Project

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Abstract

Background—Although cardiopulmonary exercise (CPX) testing in patients with heart failure and reduced ejection fraction (HFrEF) is well established, there is limited data on the value of CPX variables in patients with HF and preserved EF (HFpEF). We sought to determine the prognostic value of select CPX measures in patients with HFpEF.

Methods—This was a retrospective analysis of patients with HFpEF (EF ≥ 50%) who performed a CPX test between 1997 and 2010. Selected CPX variables included; peak oxygen uptake (VO₂), percent predicted maximum oxygen uptake (ppMVO₂), minute ventilation to carbon dioxide production (V_E/VCO₂) slope and exercise oscillatory ventilation (EOV). Separate Cox regression analyses were performed to assess the relationship between each CPX variable and a composite outcome of all-cause mortality or cardiac transplant (CTx).

Results—We identified 173 HFpEF patients (45% women; 58% non-white; age = 54±14 y) with complete CPX data. During a median follow-up of 5.2 y there were 42 deaths and 5 CTx. The 1, 3, and 5 y cumulative event-free survival was 96%, 90%, and 82% respectively. Based on the Wald statistic from the Cox regression analyses adjusted for age, sex, and beta-blockade therapy, ppMVO₂ was the strongest predictor of the endpoint (Wald χ^2 = 15.0, HR per 10% = $p < 0.001$), followed by peak VO₂ (Wald χ^2 = 11.8, $p = 0.001$). V_E/VCO₂ slope (Wald χ^2 = 0.4, $p = 0.54$) and EOV (Wald χ^2 = 0.15, $p = 0.70$) had no significant association to the composite outcome.

Conclusion—These data support the prognostic utility of peak VO₂ and ppMVO₂ in patients with HFpEF. Additional studies are needed to define optimal cut points to identify low and high risk patients.

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DISCLOSURES

None

Keywords

Prognosis; cardiopulmonary exercise test; Heart failure with preserved EF

Recent epidemiological data suggests that approximately half of patients with heart failure (HF) have a preserved ejection fraction (EF), with mortality and hospitalization rates that are similar to patients who have HF with reduced EF (HFrEF) (1). Despite the increased prevalence of HF with preserved EF (HFpEF), there has been little success in improving prognosis of these patients as compared to those with systolic dysfunction (2). This is partly because there is a paucity of evidence addressing how to best diagnose, risk stratify, and treat these patients (3).

Cardiopulmonary exercise (CPX) testing is a well established tool to help risk stratify and determine prognosis in patients with HFrEF (4). Many of the variables measured during such testing are strong and independent predictors of survival, including peak oxygen uptake (VO_2), percent predicted maximum oxygen uptake (ppMVO_2), minute ventilation to carbon dioxide production (V_E/VCO_2 slope), and exercise oscillatory ventilation (EOV) (5–8). Although the ability of these variables to predict prognosis has been well established in patients with HFrEF, data is only beginning to emerge regarding the prognostic utility of CPX testing in patients with HFpEF (9–11). Whether the above CPX-derived variables or other similar variables also predict mortality in HFpEF warrants further exploration (12).

Using a demographically diverse cohort of patients, this retrospective study describes the association between select CPX-derived variables and survival free from all-cause mortality or cardiac transplant (CTx) in patients with HFpEF.

METHODS

Study Cohort

Our study was designed as a retrospective observational study which included patients 18 y with a diagnosis of HFpEF who had undergone a *clinically-referred* CPX test at Henry Ford Hospital between January 1997 and December 2010. The Institutional Review Board of Henry Ford Health System approved the study and no extramural funding was used to support this work. Selection of the patients was made by a query of the Henry Ford Preventive Cardiology Outcomes (PRECO) database. PRECO contains prospectively collected CPX test data. A manual review of the electronic medical record was performed to confirm relevant data including, a physician diagnosis of ischemic or non ischemic cardiomyopathy and EF. Myocardial perfusion imaging, echocardiography or cardiac catheterization reports were reviewed to determine EF. To be included in this analysis an EF had to be measured 6 months prior or 2 months following the CPX test date. HFpEF was defined as an EF 50%. Patients were excluded if they underwent valve repair/replacement. The cohort was not limited by other criteria.

Cardiopulmonary Exercise Testing

The patients in our study cohort had undergone CPX testing mainly for assessment of their exercise tolerance. All CPX tests were completed per American College of Cardiology and the American Heart Association guidelines (13). During these CPX tests, patients were encouraged to exercise to their symptom-limited maximum capacity. Attainment of a maximum predicted heart rate or a pre-selected respiratory exchange ratio was not a reason to stop the tests.

Treadmill was the preferred exercise modality, using a protocol that increased work rate by 1 to 2 metabolic equivalents of task [METs] per 2 or 3 min stage. When clinically indicated, a leg ergometer was used in <2% of all patients. During exercise the electrocardiograph (ECG) was continuously monitored from the start until at least minute 6 of recovery. After 2 minutes of standing rest, heart rate and blood pressure were measured. Blood pressure was also recorded every 2 to 3 minutes during the exercise and regularly during recovery.

Gas Exchange Data Management

A MGC Diagnostics metabolic cart (Ultima, CPX/D, or CPX Express; St. Paul, Minnesota, USA) was utilized for respiratory gases analysis. Prior to each CPX test the gas and flow analyzers were calibrated according to the manufacturer recommendations. MGC Diagnostics' Breeze Suite 7.1 software was used to calculate the V_E/V_{CO_2} slope using all exercise data.

EOV was identified based on published criteria (14) by clinical exercise physiologists experienced in the interpretation of CPX data. $ppMVO_2$ was calculated using the Wasserman equation (15).

Endpoint Data

The US Centers for Disease Control and Prevention's National Death Index was used to determine mortality through 2011. Identifiers included name, gender, date of birth, and social security number and were present for the entire cohort. The National Death Index is a reliable source to accurately differentiate deceased versus alive patients when social security numbers are used along with other personal identifiers (16). CTx were identified from the hospital's clinic databases through 2011. A minimum of 1 y follow-up was available on the entire cohort.

Statistical Analysis

The primary outcome of our study was the combined endpoint of all-cause mortality or CTx. The index date was the date on which CPX test had been conducted. The follow-up time was calculated as days between the CPX test date and the endpoint date or December 31, 2011.

Life tables were used to calculate the cumulative event rate. The relationship between select CPX test variables (i.e., peak VO_2 , $ppMVO_2$, V_E/V_{CO_2} slope, and EOV) and event-free survival were assessed separately using univariate and multivariate (adjusted for age, gender and beta-blockade therapy) Cox regression analyses. Kaplan-Meier survival curves were

also constructed. Statistical significance was defined as an $\alpha < 0.05$. IBM SPSS version 22 (IBM, Somers, New York, USA) was utilized for all statistical analyses.

RESULTS

One hundred, eighty-eight patients were identified with HFpEF (EF $\geq 50\%$). Among these 177 patients had completed data for peak VO_2 , ppMVO_2 , V_E/VCO_2 slope, and EOV. Four patients out of the 177 patients had undergone an aortic or mitral valve surgery due to severe valvular disease. These patients were excluded from our analysis due to the assumption that their preserved EF was a consequence of their surgery. Out of the remaining 173 patients in our final study group, mostly were middle age (54 ± 14 y), male (65%), of African American (AA) race. Their most common cardiovascular risk factor was hypertension (53%). Details of the demographics and study characteristics can be found in Table 1.

During a median follow-up of 5.2 y (interquartile range [IQR] 3.4 – 7.9 y) there were 47 events (27%), which included 42 deaths and 5 CTx. Patients who experienced an event were more likely to be older and less likely to have an Implantable Cardioverter-Defibrillator (ICD) (Table 1). With regard to CPX testing, patients who experienced an event had a lower peak heart rate (118 vs. 128 $\text{beats} \cdot \text{min}^{-1}$) and lower peak VO_2 (14.0 vs. 17.9 $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). Table 2 shows details of data from the CPX tests.

The 1, 3, and 5 y cumulative event-free survival was $96 \pm 1\%$, $90 \pm 2\%$, and $82 \pm 3\%$, respectively. Results from the Cox regression analyses are shown in Tables 3 and 4. Based on the Wald statistic, ppMVO_2 was a stronger predictor than peak VO_2 . Neither V_E/VCO_2 slope nor EOV were significantly related to the outcome in univariate or multivariate analyses (Tables 3 and 4). There was no significant interaction observed by sex for peak VO_2 ($P = 0.444$), ppMVO_2 ($P = 0.682$), V_E/VCO_2 slope ($P = 0.971$), or EOV ($P = 0.746$).

There was a significant variation in cumulative survival between tertiles of ppMVO_2 (Figure 1-A) with patients with a $\text{ppMVO}_2 \geq 58\%$ experiencing 1, 3 and 5 y cumulative survival of $89 \pm 4\%$, $83 \pm 5\%$, and $67 \pm 6\%$, respectively. There was also a significant variation in cumulative survival between tertiles of peak VO_2 (Figure 1-B) with patients with a peak $\text{VO}_2 \geq 13.9 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ experiencing 1, 3 and 5 y cumulative survival of $91 \pm 4\%$, $84 \pm 5\%$, and $69 \pm 6\%$, respectively.

DISCUSSION

We showed that key CPX variables that have been associated with prognosis in HFrEF (peak VO_2 and ppMVO_2) were also significantly associated with a composite outcome of all-cause mortality or CTx in a diverse cohort of patients with HFpEF. Among these CPX variables, ppMVO_2 was found to be the best prognostic indicator, being associated with a 30% lower risk per 10% of ppMVO_2 achieved. This is comparable to risk association in patients with HFrEF (17). We are not aware of another study that has evaluated the prognostic utility of ppMVO_2 in patients with HFpEF.

Our study represents an analysis of commonly used CPX variables in a study group of 173 patients with HFpEF. From the previous literature, there are only three prior studies that

have studied the relationship of CPX variables with prognosis in HFpEF patients (4,18,19). In their 2005 study of 409 HF patients, Guazzi et al (4) reported that V_E/VCO_2 slope and peak VO_2 in patients with HFpEF were both significantly related to all-cause mortality and hospitalization; however, V_E/VCO_2 slope was stronger. In a 2008 study of 151 HFpEF patients, Guazzi et al (19) reported that EOV was the strongest predictor for cardiac events in a multivariable analysis of exercise data only (no demographic variables), followed by V_E/VCO_2 slope and peak VO_2 . In a 2013 paper evaluating peak VO_2 and V_E/VCO_2 slope in a study cohort of 224 HFpEF patients, Yan et al (18) concluded that V_E/VCO_2 slope (but not peak VO_2) was associated with all-cause mortality when adjusted for brain natriuretic peptide. In our study ppMVO₂ and peak VO_2 , were both significantly related to survival; however, V_E/VCO_2 slope and EOV were not related to survival. Our work confirms findings from other studies showing that select CPX variables such as peak VO_2 have a strong prognostic role in patients with HFpEF. Furthermore we studied the role of ppMVO₂ which has been shown to be an important prognostic indicator in HFrEF and found it to be the best prognostic indicator in our HFpEF patient group. Our findings differ slightly from previous studies relative to which CPX variable is 'better' as EOV and V_E/VCO_2 slope which were shown to be strongly linked to the outcomes (4,18,19), were not found to be significant in our study. This may be due to differences in the study follow up periods, different end points and type of patient selection; our study included a composite end point of CTx or mortality, had a longer follow-up period than previous studies and also included a more racially diverse patient cohort. Additional investigation is warranted in this area.

The CPX variable ppMVO₂ has been evaluated in dozens of studies as a possible predictor of survival in patients with HFrEF. In spite of having independent association with survival in several of these studies, ppMVO₂ has not received much attention (12,20). Whereas peak VO_2 accurately reflects the functional capacity of an individual, ppMVO₂ may be more appropriate because it describes a patient's functional capacity within the context of both age and gender, two factors that are known to influence measured values (17). ACC/AHA guidelines include a ppMVO₂ of 55 % as an indication to refer for cardiac transplantation (21).

Several studies have shown an increase in the prevalence of HFpEF (1), partly because of improved diagnosis and recognition of the disorder. Our study shows that select CPX-derived variables like peak VO_2 and ppMVO₂ that have been shown to be good prognostic tools in patients with HFrEF, can also provide reasonable prognostic insight in patients with HFpEF. Based on our data, 5-y survival rates for ppMVO₂ 58% and peak VO_2 13.9 is 67% and 69%, respectively. This may help stratify risk patients with HFpEF in a manner that is synonymous to patients with HFrEF. By being able to identify those patients with a higher risk profile, referral to specialists and vigilant follow up and education can be started sooner, which may improve long term survival. Furthermore, our findings may provide information that can help formulate and initiate further research that advances the clinical evaluation and care of patients with HFpEF.

The strengths of our work included the manual review of the medical records to identify patients with HFpEF and the gender and racial diversity of our cohort. Median time to follow up was longer than previously reported in other studies and more CPX variables were

included in our analyses. However, like all retrospective cohort studies ours was not without limitations. First, it is possible that there were residual confounders related to CPX variables and outcomes. Additionally, this was a single center experience and thus the external validity could be questioned, but our cohort and the larger population that they represent appears similar to other cohorts presenting with HFpEF (4).

We conducted a retrospective cohort study that included patients with HFpEF who had undergone CPX testing at our institution with more than 3 y of follow-up. We showed that CPX parameters are predictive of outcome among patients with HFpEF (similar to patients with HFrEF) and that the strongest single predictor of the primary end point derived from CPX testing was ppMVO_2 . Additional research is needed to further define the association between similar and other CPX test measures and prognosis in patients with HFpEF.

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Figure 1. Kaplan-Meier survival curves by tertiles of ppMVO₂ (%) and peak VO₂ (mL·kg⁻¹·min⁻¹)
(A) represents line graphs for survival as a function of ppMVO₂ values: 58%, 59%–76% and 77%.
(B) represents line graphs for survival as a function of peak VO₂ values: 13.9, 14.0–18.0 and 18.1 (mL·kg⁻¹·min⁻¹)
Peak VO₂, peak oxygen consumption; ppMVO₂, percent predicted maximum oxygen consumption;

Table 1

Demographic and clinical characteristics of the study cohort

Characteristics	All Subjects (n = 173)	Event-Free (n = 126)	Event (n = 47)
Age (y)	54 ± 14	53 ± 14	58 ± 13 *
Female	77 (45)	57 (45)	20 (43)
<i>Race</i>			
White	73 (42)	55 (44)	18 (38)
Black	91 (53)	64 (51)	27 (57)
Other	9 (5)	7 (6)	2 (4)
Body mass index (kg•m ⁻²)	32 ± 9	31 ± 8	33 ± 10
History of coronary artery disease	28 (16)	18 (14)	10 (21)
Ejection fraction (%)	56 ± 5	56 ± 5	56 ± 6
Implanted pacemaker	23 (13)	18 (14)	5 (11)
Implanted cardioverter-defibrillator, n (%)	23 (13)	21 (17)	2 (4) *
<i>Cardiovascular Risk Factors</i>			
Hypertension	117 (68)	86 (68)	31 (66)
Diabetes (type 1 or 2)	38 (22)	28 (22)	10 (21)
Tobacco use within last 2 y	24 (14)	18 (14)	6 (13)
<i>Medications</i>			
Beta-adrenergic blockade	131 (76)	101 (80)	30 (64) *
ACE or ARB	116 (67)	85 (68)	31 (66)
Diuretic	120 (69)	83 (66)	37 (79)

Data are mean ± standard deviation or n (%).

* P < 0.05, compared to patients who were event-free.

ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2

Cardiopulmonary exercise test data

Variables	All Subjects (n = 177)	Event-Free (n = 129)	Event (n = 48)
Rest heart rate (beats•min ⁻¹)	77 ± 14	77 ± 13	75 ± 16
Rest systolic blood pressure (mmHg)	117 ± 22	117 ± 22	118 ± 24
Rest diastolic blood pressure (mmHg)	71 ± 13	71 ± 12	70 ± 14
Peak heart rate (beats•min ⁻¹)	125 ± 26	128 ± 27	118 ± 22*
Peak systolic blood pressure (mmHg)	156 ± 30	157 ± 29	156 ± 31
Peak diastolic blood pressure (mmHg)	76 ± 14	76 ± 14	76 ± 16
Peak Oxygen Uptake			
mL•kg ⁻¹ •min ⁻¹	16.9 ± 6.3	17.9 ± 6.6	14.0 ± 4.1*
L•min ⁻¹	1.5 ± 0.6	1.6 ± 0.6	1.3 ± 0.5*
% predicted	68 ± 18	70 ± 18	60 ± 15*
Peak oxygen pulse (mL•beat ⁻¹)	12.3 ± 4.2	12.7 ± 4.3	11.1 ± 3.6*
V _E -VCO ₂ slope	30.2 ± 7.0	30.0 ± 6.3	31.2 ± 8.5
Exercise oscillatory ventilation	12 (7)	8 (6)	4 (9)
Peak respiratory exchange ratio	1.12 ± 0.13	1.12 ± 0.11	1.12 ± 0.16

Data are mean ± standard deviation or n (%).

* P value < 0.05, compared to patients who were event-free.

Table 3

Univariate Cox regression analyses to predict the composite endpoint of mortality or cardiac transplant (n = 173)

CPX Variables	χ^2	HR (95% CI)	P value
Peak VO_2 ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	14.2	0.86 (0.79, 0.93)	< 0.001
ppMVO ₂ (per 10%)	14.9	0.70 (0.58, 0.84)	< 0.001
V_E -VCO ₂ slope	3.2	1.04 (1.00, 1.08)	0.072
EOV	0.03	1.10 (0.39, 3.07)	0.855

CI, confidence interval; EOV, exercise oscillatory ventilation; HR, hazard ratio; ppMVO₂, percent predicted maximum oxygen uptake; peak VCO₂, peak volume of carbon dioxide production; VE, minute ventilation; VO₂, volume of oxygen uptake

Table 4

Multivariate Cox regression analyses to predict the composite endpoint of mortality or cardiac transplant (n = 173)

CPX Variables	χ^2	HR (95% CI)	P value
Peak VO ₂ (mL•kg ⁻¹ •min ⁻¹)	11.8	0.86 (0.79, 0.94)	0.001
ppMVO ₂ (per 10%)	15.0	0.66 (0.53, 0.81)	< 0.001
V _E -VCO ₂ slope	0.4	1.01 (0.97, 1.06)	0.54
EOV	0.15	0.81 (0.28, 2.33)	0.698

* Adjusted for age, gender and beta-blockade therapy. CI, confidence interval; EOV, exercise oscillatory ventilation; HR, hazard ratio; VCO₂, volume of carbon dioxide production; VE, minute ventilation; VO₂, volume of oxygen uptake