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The Prognostic Utility of Cardiopulmonary Exercise Testing Stands the Test of Time in Patients With Heart Failure

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Abstract

INTRODUCTION: While the medical management strategy for patients with heart failure (HF) has dramatically changed, cardiopulmonary exercise testing (CPX) procedures and the data obtained have remained relatively stable. We are unaware of any previous investigation that has assessed differences in the prognostic utility of CPX in HF according to time period, reflecting differences in the clinical management of systolic HF.

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The authors declare no conflicts of interest.

METHODS: Subjects ($n = 381$) underwent CPX between April 1, 1993, and December 31, 2005, and the remaining 511 were tested between January 1, 2006, and October 28, 2010. Peak oxygen uptake ($\dot{V}O_2$) and the minute ventilation/carbon dioxide production ($\dot{V}_E/\dot{V}CO_2$) slope were ascertained for all tests.

RESULTS: Both the $\dot{V}_E/\dot{V}CO_2$ slope and peak $\dot{V}O_2$ were strong univariate predictors of adverse events in both subgroups. In the multivariate analysis, the $\dot{V}_E/\dot{V}CO_2$ slope was the strongest predictive marker while peak $\dot{V}O_2$ added predictive value and was retained in the regression for all scenarios. In subjects undergoing CPX before 2006, a $\dot{V}_E/\dot{V}CO_2$ slope 45 or greater and a peak $\dot{V}O_2$ of less than $10 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ generated a hazard ratio of 4.2 (95% CI: 1.9–9.1, $P < .001$) when considering only mortality as an endpoint. In subjects undergoing CPX after 2006, a $\dot{V}_E/\dot{V}CO_2$ slope 45 or greater and a peak $\dot{V}O_2$ of less than $10 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ generated a hazard ratio of 8.2 (95% CI: 4.7–14.3, $P < .001$) when considering only mortality as an endpoint.

CONCLUSION: The results of this study indicate that CPX continues to be a valuable clinical assessment in the present-day HF management.

Keywords

expired gas; heart disease; survival; ventilation

Since the seminal publication by Mancini et al¹ in 1991, which convincingly demonstrated the prognostic value of peak oxygen uptake ($\dot{V}O_2$), cardiopulmonary exercise testing (CPX) has become the clinical gold standard for functional assessment in patients with systolic heart failure (HF). Over the past 20 years, numerous studies demonstrating the prognostic significance of key CPX variables, the most notable being peak $\dot{V}O_2$ and the minute ventilation ($\dot{V}_E$)/carbon dioxide production ($\dot{V}CO_2$) relationship, have solidified its clinical acceptance and application.^{2–4} However, while the medical management strategy for patients with HF has dramatically changed since the 1991, CPX procedures and the data obtained have remained relatively stable, although O'Neill et al⁵ facilitated reconsideration of optimal threshold values for aerobic capacity according to β -blockade use. Even so, this shift in peak $\dot{V}O_2$ assessment for prognostic purposes was subtle. Similar work has assessed the prognostic value of the $\dot{V}_E/\dot{V}CO_2$ slope according to β -blocker use, finding that the predictive value of this CPX variable is unaffected.⁶ These investigations support the continued use of CPX as a prognostic assessment in the current β -blockade era. However, the evolution of systolic HF management, which is reflected by current clinical practice patterns, extends well beyond a single pharmacologic approach. Therefore, while the prognostic utility of CPX in systolic HF continues to enjoy strong support, additional issues requiring investigation persist. In particular, we are unaware of any previous investigation that has assessed differences in the prognostic utility of CPX in HF according to time period, reflecting differences in the clinical management of systolic HF. Such a query is needed to demonstrate that CPX continues to be prognostically viable in present-day clinical practice and is therefore the impetus of the current investigation. We hypothesize that key CPX variables will demonstrate consistent prognostic patterns and strength, irrespective of the time period the exercise assessment took place.

METHODS

This study was a multicenter analysis including HF patients from 6 well-established CPX laboratories: LeBauer Cardiovascular Research Foundation, Greensboro, NC; Stanford University, Palo Alto, CA; VA Palo Alto Health Care System, Palo Alto, CA; Brigham and Women's Hospital, Boston, MA; Virginia Commonwealth University, Richmond, VA; and San Paolo Hospital, Milan, Italy. A total of 892 patients with systolic HF underwent CPX, using a conservative protocol on either a treadmill or lower extremity ergometer. The inclusion criteria consisted of a diagnosis of HF⁷ and evidence of left ventricular systolic dysfunction by 2-dimensional echocardiography obtained within 1 month of data collection. All subjects completed a written informed consent and the institutional review board approval was obtained at each institution.

CPX Procedures

Symptom-limited CPX was performed on all subjects and pharmacologic therapy was maintained during exercise testing. Progressive exercise testing protocols 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). Before each test, the equipment was calibrated in a standard fashion using reference gases. Minute ventilation, $\dot{V}_{O_2}$, and $\dot{V}_{CO_2}$ were acquired breath by breath and averaged over 10-second intervals. Peak $\dot{V}_{O_2}$ and respiratory exchange ratio were defined as the highest 10-second averaged value obtained during the final 30 seconds of CPX. Minute ventilation and $\dot{V}_{CO_2}$ values, acquired from the initiation of exercise to peak, were input into spreadsheet software (Microsoft Excel, Microsoft Corp, Bellevue, WA) to calculate the $\dot{V}_E/\dot{V}_{CO_2}$ slope via least squares linear regression ($y = mx + b$, where m slope).

Endpoints

Subjects were followed by the HF programs at their respective institutions. Major cardiac events (mortality, LVAD implantation, and urgent heart transplantation) were tracked via medical chart review for 3 years post-CPX. All subjects either were tracked for the entire 3-year duration post-CPX or had a major cardiac event during that time period.

Subgroup Designation

For comparative purposes, subjects were divided into 2 subgroups: (1) those tested between April 1, 1993, and December 31, 2005, and (2) those tested between January 1, 2006, and October 28, 2010. This date threshold was chosen because the last American Heart Association guideline for HF management was published in the latter half of 2005.⁸

Statistical Analysis

Statistical analysis was performed using SPSS 19.0 (SPSS, Chicago, IL). Unpaired t -testing (for continuous variables) and χ^2 testing (for dichotomous variables) were used to compare baseline and CPX characteristics of HF subgroups according to testing time period. Univariate and multivariate (Forward stepwise method; entry and removal values 0.05 and 0.10, respectively) Cox regression analysis was used to assess the prognostic value of peak

$\dot{V}_{O_2}$ and the $\dot{V}_E/\dot{V}_{CO_2}$ slope as continuous variables. Next, Cox regression was used to generate hazard ratios for subjects according to a $\dot{V}_E/\dot{V}_{CO_2}$ slope threshold of <45 or ≥ 45 , and a peak $\dot{V}_{O_2}$ threshold of <10 or $\geq 10 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Subjects designated as having an unfavorable response had to demonstrate both a $\dot{V}_E/\dot{V}_{CO_2}$ slope threshold of ≥ 45 and a peak $\dot{V}_{O_2}$ threshold of $\geq 10 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. For this latter survival analysis, only mortality was considered as an event. A P value $< .05$ was considered statistically significant for all tests.

RESULTS

Subjects ($n = 381$) underwent CPX between April 1, 1993, and December 31, 2005, and the remaining 511 subjects were tested between January 1, 2006, and October 28, 2010. Baseline and CPX characteristic comparisons between the time-dependent subgroups are listed in Table 1. A number of characteristics were significantly different between subgroups including age, gender, New York Heart Association (NYHA) class, HF etiology distribution, resting left ventricular ejection fraction, β -blocker use, and CPX performance.

There were 83 major cardiac events (74 deaths, 7 transplants, and 2 LVAD implantations) in the group tested before 2006. The overall annual event rate was 7.2%. When only considering mortality as an endpoint, the annual event rate was 6.5%. There were 162 major cardiac events (71 deaths, 57 transplants, and 34 LVAD implantations) in the group tested after 2006. The overall annual event rate was 13.5%. When only considering mortality as an endpoint, the annual event rate was 6.2%. Survival analysis results are listed in Table 2. Both the $\dot{V}_E/\dot{V}_{CO_2}$ slope and peak $\dot{V}_{O_2}$ were strong univariate predictors of both composite major cardiac events and mortality in both subgroups. In the multivariate analysis, the $\dot{V}_E/\dot{V}_{CO_2}$ slope was the strongest predictive marker while peak $\dot{V}_{O_2}$ added predictive value and was retained in the regression for all scenarios. In subjects undergoing CPX before 2006, a $\dot{V}_E/\dot{V}_{CO_2}$ slope ≥ 45 and a peak $\dot{V}_{O_2}$ of $<10 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ generated a hazard ratio of 4.2 (95% CI: 1.9–9.1, $P < .001$) when considering only mortality as an endpoint. In subjects undergoing CPX after 2006, a $\dot{V}_E/\dot{V}_{CO_2}$ slope ≥ 45 and a peak $\dot{V}_{O_2} \geq 10 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ generated a hazard ratio of 8.2 (95% CI: 4.7–14.3, $P < .001$) when considering only mortality as an endpoint.

DISCUSSION

Cardiopulmonary exercise testing has enjoyed strong endorsement as a primary clinical assessment for patients with systolic HF for more than a decade,^{9,10} a position that continues to be reflected in recent position papers.^{4,11–13} This support is substantiated by the wealth of original research investigations demonstrating the prognostic value of CPX in this patient population.^{3,14} Admittedly, the treatment approach in patients with systolic HF has changed dramatically during this time period. This evolution in treatment over the past 2 decades, in conjunction with the relatively stable approach to CPX interpretation during the same time period, logically leads one to hypothesize that the clinical utility of this exercise assessment may be impacted. The current investigation appears to be the first analysis that has compared the prognostic utility of CPX during 2 distinct time periods that reflected significantly different approaches to treatment in systolic HF. The fact that subjects who remained event-

free were tracked for the same period of time in the current investigation is an additional strength of the current analysis.

Characteristics listed in Table 1 indicate that the type of patient with systolic HF referred for CPX has significantly changed. Specifically, more recent CPX referrals were younger, more likely to be female, have a more heterogeneous mix of systolic HF etiology, and a higher level of disease severity as indicated by New York Heart Association class and LVEF. Moreover, CPX performance is poorer in the current referral base, further substantiating a higher degree of disease severity in patients currently being referred for this exercise assessment. In addition, more subjects being currently referred for CPX are receiving a β -blocking agent and have eventually received a heart transplant or LVAD implantation, all of which are reflective of current pharmacologic and surgical practice patterns in patients with systolic HF. The significant differences in patient characteristics during these 2 time periods were not necessarily an anticipated observation but encouraging nonetheless. While CPX likely provides prognostic insight for the entire population with systolic HF, such a broad approach is neither feasible nor considered necessary. It is widely held that only those systolic HF patients with advanced disease severity, still functionally mobile, and being considered for advanced surgical interventions (ie, transplantation or LVAD implantation), be referred for CPX. The data presented in Table 1, supporting advanced disease severity in the cohort tested after 2006, indicate that clinicians referring patients for CPX are more closely following this mindset in present-day clinical practice. However, while the percentage of female patients with systolic HF referred for CPX was significantly higher in the more recent cohort, approximately three quarters of those tested after 2006 were male. Given that the prevalence of HF is approximately equal in men and women,¹⁵ greater efforts should be made to ensure that appropriate female patients are referred for CPX.

Despite these dramatic differences in subject characteristics and exercise performance between the 2 time periods assessed, the prognostic value of the 2 primary CPX variables remains remarkably consistent and robust. Perhaps the strongest indication of this consistency was the survival analyses only considering death as an endpoint, which equilibrated the type of event and annual event rate between subgroups. This finding is not surprising, given that the ability of these CPX variables to reflect the level of HF-induced pathophysiology is not likely to be impacted by the approach to clinical management.¹⁴ In addition, given the near doubling of the hazard ratio, it appears that currently proposed $\dot{V}_E/\dot{V}_{CO_2}$ slope and peak $\dot{V}_{O_2}$ threshold values for defining acceptable criteria for transplant listing or LVAD implantation⁴ are even more relevant in present-day clinical practice.

As in any investigation, the current analysis possesses weaknesses that require consideration. First, while the current investigation included several variables presented in Table 1 that would indicate differences in disease severity according to time period, it would have been optimal to have additional data to support this hypothesis, including neurohormonal blood markers, renal function, and invasive hemodynamic data. This information was unfortunately not available. In addition, the evolution of HF management is more continuous than dichotomous in nature. Therefore, there are subjects within each cohort that certainly received similar management, particularly in those undergoing CPX in close approximation to either side of the 2006 threshold. Although arbitrary, dividing the group according to CPX

before or after 2006 seemed to be a reasonable rationale, given the last AHA update of the HF management guidelines published in the latter part of 2005.⁸ Moreover, the mean and percentage values presented in Table 1 support the notion that the subgroups possessed different characteristics and were managed differently as a whole. Second, other CPX variables, such as the oxygen uptake efficiency slope and exercise oscillatory ventilation, have been shown to provide prognostic value, and their addition to the current analysis would have been valuable.⁴ Unfortunately, capture of these additional CPX variables in this cohort was inconsistent, necessitating their exclusion.

In conclusion, the current analysis supports the continued use of CPX as a valuable prognostic tool in patients with systolic HF for the foreseeable future. This type of analysis should continue to be conducted at future time points as HF management will certainly continue to evolve. Moreover, as new CPX variables demonstrating that prognostic value emerge and become established as important clinical markers, they too should be included in future analyses of this nature.

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Table 1 •

Subject Characteristics According to CPX Time Period

	CPX: 1993-2005 (n = 381)	CPX: 2006-2010 (n = 511)	P Value
Age, y	58.4 ± 13.8	54.2 ± 13.1	<.001
Gender, % male	83	73	<.001
BMI, kg/m ²	28.2 ± 6.0	28.9 ± 6.5	.24
HF etiology, % ischemic/nonischemic	53/47	33/67	<.001
NYHA class	2.3 ± 0.78	2.6 ± 0.82	<.001
Resting LVEF, %	31.0 ± 9.7	25.2 ± 9.1	<.001
β-Blocker, % prescribed	59	85	<.001
ACE inhibitor, % prescribed	66	68	.37
Peak $\dot{V}O_2$, mL · kg ⁻¹ · min ⁻¹	16.4 ± 6.2	14.7 ± 5.9	<.001
Peak RER	1.09 ± 0.17	1.14 ± 0.14	<.001
$\dot{V}E/\dot{V}CO_2$ slope	33.9 ± 8.8	36.2 ± 10.2	<.001

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; CPX, cardiopulmonary exercise testing; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RER, respiratory exchange ratio; $\dot{V}O_2$, oxygen uptake; $\dot{V}E/\dot{V}CO_2$, minute ventilation/carbon dioxide production.

Table 2 •

Univariate and Multivariate Cox Regression Analysis According to CPX Time Period

	CPX: 1993-2005 (n = 381)		CPX: 2006-2010 (n = 511)	
	Major Cardiac Events (n = 83)		Major Cardiac Events (n = 162)	
	Only Death (n = 74)		Only Death (n = 71)	
Univariate analysis ^a				
$\dot{V}E/\dot{V}CO_2$ slope	1.07 (1.06–1.09) ^c	1.07 (1.05–1.09) ^c	1.06 (1.05–1.07) ^c	1.06 (1.05–1.08) ^c
Peak $\dot{V}O_2$	0.90 (0.86–0.94) ^c	0.90 (0.86–0.94) ^c	0.82 (0.79–0.86) ^c	0.76 (0.71–0.82) ^c
Multivariate analysis ^b				
$\dot{V}E/\dot{V}CO_2$ slope	80.7 ^c	62.6 ^c	114.7 ^c	52.4 ^c
Residual χ^2				
Peak $\dot{V}O_2$	4.2 ^d	4.3 ^d	34.2 ^c	27.4 ^c

Abbreviations: CPX, cardiopulmonary exercise testing; $\dot{V}E$, minute ventilation; $\dot{V}CO_2$, carbon dioxide production; $\dot{V}O_2$, oxygen uptake.

^aReported as hazard ratio and 95% confidence interval.

^bReported as χ^2 and residual χ^2

^c $P < .001$.

^d $P < .05$.