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A M E R I C A N C O L L E G E O F  
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# Influence of Heart Failure Etiology on the Prognostic Value of Peak Oxygen Consumption and Minute Ventilation/Carbon Dioxide Production Slope\*

Ross Arena, PhD, PT; Jonathan Myers, PhD; Joshua Abella, MD; and Mary Ann Peberdy, MD

**Background:** Peak oxygen consumption ( $\dot{V}O_2$ ) and minute ventilation ( $\dot{V}_E$ )/carbon dioxide production ( $\dot{V}CO_2$ ) slope have been widely demonstrated to have strong prognostic value in patients with heart failure (HF). In the present study, we investigated the effect of HF etiology on the prognostic applications of peak  $\dot{V}O_2$  and  $\dot{V}_E/\dot{V}CO_2$  slope.

**Methods:** Two hundred sixty-eight subjects underwent symptom-limited cardiopulmonary exercise testing (CPX). The population was divided into ischemic (115 men and 22 women) and nonischemic (108 men and 23 women) subgroups. The occurrence of cardiac-related events over the year following CPX was compared between groups using receiver operating characteristic curve (ROC) analysis

**Results:** Mean age  $\pm$  SD was significantly higher ( $61.0 \pm 10.0$  years vs  $50.3 \pm 16.2$  years) while mean peak  $\dot{V}O_2$  was significantly lower ( $15.0 \pm 5.2$  mL/kg/min vs  $17.5 \pm 6.7$  mL/kg/min) in the ischemic HF group ( $p < 0.05$ ). ROC curve analysis demonstrated that both peak  $\dot{V}O_2$  and  $\dot{V}_E/\dot{V}CO_2$  slope were significant predictors of cardiac events in both the ischemic group (peak  $\dot{V}O_2$ , 0.74;  $\dot{V}_E/\dot{V}CO_2$  slope, 0.76;  $p < 0.001$ ) and the nonischemic group (peak  $\dot{V}O_2$ , 0.75;  $\dot{V}_E/\dot{V}CO_2$  slope, 0.86;  $p < 0.001$ ). Optimal prognostic threshold values for peak  $\dot{V}O_2$  were 14.1 mL/kg/min and 14.6 mL/kg/min in the ischemic and nonischemic groups, respectively. Optimal prognostic threshold values for the  $\dot{V}_E/\dot{V}CO_2$  slope were 34.2 and 34.5 in the ischemic and nonischemic groups, respectively.

**Conclusions:** Baseline and exercise characteristics were different between ischemic and nonischemic patients with HF. However, the prognostic power of the major CPX variables was strikingly similar. Different prognostic classification schemes based on HF etiology may therefore not be necessary when analyzing CPX responses in clinical practice. (CHEST 2005; 128:2812–2817)

**Key words:** hospitalization; mortality; prognosis; ventilatory expired gas

**Abbreviations:** CPX = cardiopulmonary exercise testing; HF = heart failure; LVEF = left ventricular ejection fraction; RER = respiratory exchange ratio; ROC = receiver operating characteristics;  $\dot{V}_E$  = minute ventilation;  $\dot{V}CO_2$  = carbon dioxide production;  $\dot{V}O_2$  = oxygen consumption

Numerous mechanisms have been identified that underlie the development of heart failure (HF). One of these mechanisms involves the etiology of HF; dichotomization into ischemic and nonischemic subgroups is one important consideration for risk

stratifying these patients. For example, Likoff et al<sup>1</sup> reported that the presence of ischemic HF independently predicted increased risk for mortality compared to patients with idiopathic HF. Myers et al<sup>2</sup> likewise found patients with ischemic HF had a lower survival rate compared to patients with nonischemic HF. Webb-Peploe et al<sup>3</sup> reported a higher complication rate and lower exercise capacity in a group of patients with ischemic HF compared to patients with idiopathic HF.

In recent years, the prognostic power of cardiopulmonary exercise testing (CPX) has emerged as an important tool in the risk paradigm in HF; the guidelines on HF include the application of CPX for optimizing risk assessment in HF, particularly for the evaluation of transplant candidates.<sup>4,5</sup> Numerous in-

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vestigations<sup>2,6-9</sup> have demonstrated the diagnostic and prognostic value of CPX in this population. Of the variables obtained from CPX, peak oxygen consumption ( $\dot{V}O_2$ ) and minute ventilation ( $\dot{V}E$ )/carbon dioxide production ( $\dot{V}CO_2$ ) slope are the most frequently assessed variables in the clinical setting. The application of these two indexes has evolved from numerous studies demonstrating the prognostic power of peak  $\dot{V}O_2$ <sup>6,7,10</sup> and  $\dot{V}E/\dot{V}CO_2$  slope.<sup>7,8,11</sup>

The application of CPX and the threshold values applied for determining risk<sup>4,6,10</sup> have largely been done without consideration of the etiology underlying HF. We recently observed that exercise testing responses and prognostic characteristics differed significantly between groups with ischemic and nonischemic HF.<sup>12</sup> Given these differences,<sup>1,2</sup> it is reasonable to hypothesize that optimal threshold values for stratifying risk would also differ by etiology. The purpose of the present study was to compare the prognostic characteristics of peak  $\dot{V}O_2$  and  $\dot{V}E/\dot{V}CO_2$  slope between patients with ischemic and nonischemic HF etiology.

## MATERIALS AND METHODS

Two hundred sixty-eight patients assessed between April 1, 1993, and March 24, 2004, were included in the study. One hundred fifty-one patients underwent exercise testing and were subsequently followed up by the Veterans Affairs Health Care System in Palo Alto, CA. The remaining 117 patients were tested and followed up by the HF program at the Medical College of Virginia in Richmond. The entire sample was divided into two subgroups based on underlying etiology. Patients with a history of coronary artery disease and/or myocardial infarction were classified as having ischemic HF. Patients with no history of coronary artery disease were classified as having nonischemic HF. Ischemic HF was diagnosed in 137 patients, and nonischemic HF was diagnosed in the remaining 131 patients. Idiopathic cardiomyopathy was diagnosed in the majority of patients in the nonischemic group (approximately 70%). All patients were tested on an outpatient basis. The exercise tests were conducted as part of a standard clinical evaluation or as part of a research study. Regardless of the reason for testing, all procedures, including the exercise protocol and mode, monitoring, and data collection, were consistent in the data set. Written informed consent was obtained from all patients prior to testing. Approval from the respective institutional review board was obtained for those patients undergoing an exercise test as part of a prospective research project. Patient and pharmacologic characteristics are listed in Table 1.

Inclusion criteria consisted of a diagnosis of HF and evidence of left ventricular dysfunction by echocardiography or cardiac catheterization. Ten patients who received regular or emergent care at a facility other than those mentioned in the previous paragraph were excluded. The latter exclusion criteria helped ensure that all end points were captured. The sample was a consecutive series of patients evaluated over the specified period provided the inclusion criteria were met. Selection bias was therefore not a concern at either center.

**Table 1—Patient Characteristics\***

Characteristics	Ischemic HF	Nonischemic HF
Patients, No.	137	131
Male	115	108
Female	22	23
Age, yr†	61.1 ± 10.0	50.3 ± 16.2
LVEF, %	32.6 ± 11.9	31.4 ± 13.0
Angiotensin-converting enzymes	87 (63.5)	98 (74.8)
Cardiac glycosides	64 (46.7)	85 (64.9)
Diuretics	74 (54)	97 (74)
β-Blockers	58 (42.3)	54 (41.2)

\*Data are presented as mean ± SD of No. of patients (%).

†p < 0.001 between ischemic and nonischemic groups.

### Equipment Calibration

Ventilatory expired gas analysis was obtained through one of several metabolic systems depending on the clinic and time frame for exercise testing (CPX-D; Medgraphics; Minneapolis, MN/Vmax29; SensorMedics; Yorba Linda, CA/CS-100; Schiller; Baar, Switzerland/Ozca; Orca Diagnostics; Santa Barbara, CA). The oxygen and carbon dioxide sensors were calibrated using gases with known oxygen, nitrogen, and carbon dioxide concentrations prior to each test. The flow sensor was also calibrated before each test.

### Testing Procedure and Data Collection

Symptom-limited exercise testing with ventilatory expired gas analysis was conducted using a treadmill or cycle ergometer. The treadmill was the only mode of exercise used at the Medical College of Virginia Hospital. The Veterans Affairs Hospital likewise used a treadmill in the majority (approximately 90%) of exercise tests. Both centers solely employ ramping protocols for exercise testing, which were similar in stage time and incremental workload adjustments. Monitoring consisted of continuous ECG, manual BP measurements, heart rate recordings every minute via the ECG, and rating of perceived exertion (Borg 6 to 20 scale) at each stage. Test termination criteria were followed in accordance with American College of Sports Medicine guidelines.<sup>13</sup>

$\dot{V}O_2$ ,  $\dot{V}CO_2$ , and  $\dot{V}E$  were measured throughout the exercise test. Peak  $\dot{V}O_2$  and peak respiratory exchange ratio (RER) were expressed as the highest 10-s average value obtained during the last stage of the exercise test. Ten-second averaged  $\dot{V}E$  and  $\dot{V}CO_2$  data, from the initiation of exercise to peak exercise, were input into spreadsheet software (Microsoft Excel; Microsoft; Bellevue, WA) to calculate the  $\dot{V}E/\dot{V}CO_2$  slope via least-squares linear regression ( $y = mx + b$ ,  $m = \text{slope}$ ). Previous work by our group<sup>14</sup> has shown this method of calculating the  $\dot{V}E/\dot{V}CO_2$  slope to be prognostically optimal.

### End Points

Patients were followed up for cardiac-related events (mortality or hospitalization) for 1 year following exercise testing via medical chart review and the Social Security Death Index. Cardiac-related mortality was defined as death directly resulting from failure of the cardiac system. Cardiac-related hospitalization was defined as a hospital admission directly resulting from cardiac dysfunction requiring inpatient care to correct. Any death or hospital admission with a cardiac-related discharge diagnosis confirmed by diagnostic tests or autopsy was considered an event. The most common causes

of mortality, as per discharge diagnosis, were cardiac arrest, myocardial infarction, and HF. The most common causes of hospitalization were decompensated HF and coronary artery disease. Patients in whom mortality or hospitalization were of a noncardiac etiology were treated as censored cases.

### Statistical Analysis

Unpaired *t* testing was used to compare differences in age, left ventricular ejection fraction (LVEF), peak  $\dot{V}O_2$ , and  $\dot{V}E/\dot{V}CO_2$  slope between the ischemic and nonischemic groups as well as subgroup analyses of interest (comparisons of patients with a cardiac-related event vs those without a cardiac-related event).

Kaplan-Meier analysis was used to assess differences in cardiac-related events between the ischemic and nonischemic groups. The log-rank test was used to determine if the difference in event-free survival was significant between groups. Receiver operating characteristic (ROC) curves were constructed for peak  $\dot{V}O_2$  and  $\dot{V}E/\dot{V}CO_2$  slope classification schemes for the overall, ischemic, and nonischemic HF groups. Optimal threshold values (highest combination of sensitivity/specificity) were identified for the 1-year end points via ROC curve analysis and used in univariate and multivariate Cox regression analysis.

Using the optimal threshold values determined by ROC curve analysis, univariate Cox regression analysis assessed the ability of peak  $\dot{V}O_2$  and  $\dot{V}E/\dot{V}CO_2$  slope to predict 1-year cardiac-related events, and to derive a hazard ratio for both variables in the overall group as well as ischemic and nonischemic groups. The prognostic value of HF etiology was also assessed via univariate Cox regression analysis in the overall group.

Multivariate Cox regression analysis (forward stepwise method) using peak  $\dot{V}O_2$  and  $\dot{V}E/\dot{V}CO_2$  slope was used to assess the combined effect of these variables in predicting 1-year cardiac-related events in the overall group and both etiologies. HF etiology was also entered into the multivariate Cox regression analysis for the overall group. Entry and removal *p* values for the multivariate analyses were set at 0.05 and 0.10, respectively. All data are reported as mean values  $\pm$  SD. Statistical tests with a *p* value  $<$  0.05 were considered significant.

## RESULTS

Unpaired testing revealed the ischemic group was significantly older than the nonischemic group ( $p <$  0.001), while LVEF was not significantly different between groups ( $p =$  0.41). These results are listed in Table 1. There were a total of 89 cardiac-related events (77 hospitalizations and 12 deaths) in the overall group. Fifty-three cardiac-related events occurred in the ischemic group (46 hospitalizations and 7 deaths) and 36 cardiac-related events occurred in the nonischemic group (31 hospitalizations and 5 deaths). The mean tracking periods for patients with a cardiac-related event in the ischemic and nonischemic HF groups were  $3.4 \pm 2.9$  months and  $4.7 \pm 3.3$  months, respectively. The difference in time to first event approached, but did not reach, statistical significance ( $p =$  0.07). Kaplan-Meier analysis results are illustrated in Figure 1. The difference in event rate between groups was significantly higher in the ischemic group.

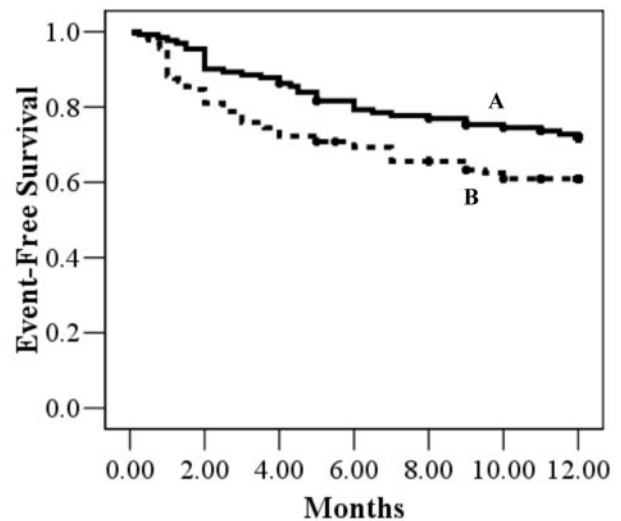


FIGURE 1. Kaplan-Meier analysis for 1-year cardiac-related events for the nonischemic group (A) [n = 131; 36 events; 72.5% event free] and the ischemic group (B) [n = 137; 53 events; 61.3% event free]. Log rank = 4.6;  $p =$  0.03. ● = censored cases.

Age remained significantly higher in the ischemic subgroup with a cardiac-related event ( $59.9 \pm 10.3$  years vs  $48.7 \pm 16.2$  years,  $p <$  0.001) as well as the subgroup who remained event free during the tracking period ( $61.7 \pm 9.8$  years vs  $50.9 \pm 16.2$  years,  $p <$  0.001). Conversely, LVEF was not significantly different between ischemic and nonischemic subgroups who had an event ( $29.9 \pm 12.5\%$  vs  $27.3 \pm 12.4\%$ ,  $p =$  0.34) or in the subgroups who remained event free during the tracking period ( $34.3 \pm 11.2\%$  vs  $32.9 \pm 13.0\%$ ,  $p =$  0.44).

CPX results for the ischemic and nonischemic groups as well as subgroups dichotomized by the occurrence of an event are listed in Table 2. Peak  $\dot{V}O_2$  was significantly higher in the nonischemic group and the event-free subgroup. The difference in peak  $\dot{V}O_2$  in the ischemic and nonischemic subgroups experiencing an event was not significant. The difference in the  $\dot{V}E/\dot{V}CO_2$  slope between the ischemic and nonischemic subgroups was not statistically significant in any of the analyses. Although the mean peak RER was  $>$  1.0 in both groups, it was significantly higher in the ischemic group and event-free subgroup.

For the overall group, ROC curve analysis demonstrated that peak  $\dot{V}O_2$  (area under the curve, 0.75;  $p <$  0.001) and  $\dot{V}E/\dot{V}CO_2$  slope (area under the curve, 0.80;  $p <$  0.001) prognostic classification schemes were both statistically significant. Optimal prognostic threshold values for peak  $\dot{V}O_2$  and  $\dot{V}E/\dot{V}CO_2$  slope were  $\geq 14.2$  mL/kg/min (sensitivity, 71%; specificity, 67%) and  $\geq 34.2$  (sensitivity, 78%; specificity, 72%), respectively.

ROC curve analysis results for the ischemic and nonischemic groups are listed in Table 3. The peak  $\dot{V}O_2$

**Table 2—CPX Values for the Ischemic HF and Nonischemic HF Groups\***

Variables	Overall Groups			Event-Free Patients			Patients With Cardiac-Related Events		
	Ischemic HF (n = 137)	Nonischemic HF (n = 131)	p Value	Ischemic HF (n = 84)	Nonischemic HF (n = 95)	p Value	Ischemic HF (n = 53)	Nonischemic HF (n = 36)	p Value
Peak $\dot{V}O_2$ , mL/kg/min	15.0 ± 5.2	17.5 ± 6.7	p = 0.001†	16.7 ± 4.9	19.1 ± 6.8	p = 0.009†	12.3 ± 4.5	13.4 ± 4.6	p = 0.24
$\dot{V}E/\dot{V}CO_2$ slope	34.8 ± 10.1	32.7 ± 8.2	p = 0.06	31.2 ± 7.2	30.0 ± 6.5	p = 0.10	39.8 ± 11.9	39.9 ± 8.0	p = 0.99
Peak RER	1.12 ± 0.18	1.07 ± 0.15	p = 0.008†	1.13 ± 0.17	1.08 ± 0.15	p = 0.03†	1.11 ± 0.18	1.05 ± 0.17	p = 0.11

\*Data are presented as mean ± SD.

†Ischemic vs nonischemic groups.

and  $\dot{V}E/\dot{V}CO_2$  slope classification schemes were statistically significant for both the ischemic and nonischemic groups. Optimal threshold values were likewise similar between etiologies for both peak  $\dot{V}O_2$  and  $\dot{V}E/\dot{V}CO_2$  slope.

Using the optimal prognostic threshold values derived from ROC curve analysis, univariate Cox regression analysis revealed that hazard ratios for peak  $\dot{V}O_2$  and  $\dot{V}E/\dot{V}CO_2$  slope were 3.6 (95% confidence interval, 2.3 to 5.5) and 5.3 (95% confidence interval, 3.4 to 8.4), respectively (p < 0.001 for both). The hazard ratio for HF etiology was also significant, with ischemic HF conferring a higher risk (hazard ratio, 1.6; 95% confidence interval, 1.0 to 2.4; p = 0.04). In the multivariate Cox regression analysis,  $\dot{V}E/\dot{V}CO_2$  slope was the superior prognostic variable ( $\chi^2 = 57.8$ , p < 0.001). Peak  $\dot{V}O_2$  added additional prognostic value and was retained (residual  $\chi^2 = 8.8$ , p = 0.003). HF etiology did not add additional prognostic value and was removed from the regression (residual  $\chi^2 = 2.1$ , p = 0.15).

Hazard ratios from the univariate Cox regression analysis for the ischemic and nonischemic groups are listed in Table 4. As expected, optimal threshold values for peak  $\dot{V}O_2$  and  $\dot{V}E/\dot{V}CO_2$  slope derived from ROC curve analysis produced statistically significant hazard ratios (p < 0.001). Multivariate Cox regression analysis revealed that  $\dot{V}E/\dot{V}CO_2$  slope was the superior prognostic marker in both the ischemic ( $\chi^2 = 26.9$ , p < 0.001) and nonischemic ( $\chi^2 = 44.5$ , p < 0.001) groups. Peak  $\dot{V}O_2$  added significant prognostic value in the ischemic group and was retained in the regression (residual  $\chi^2 = 5.2$ , p = 0.02). Peak  $\dot{V}O_2$ , however, did not add

significant prognostic value in the nonischemic group and was removed (residual  $\chi^2 = 3.2$ , p = 0.07).

## DISCUSSION

The results of the present study indicate HF etiology impacts baseline characteristics as well as the response to CPX. Specifically, patients with ischemic HF were, as a whole, older and demonstrated a significantly lower aerobic capacity compared to patients with nonischemic HF. The higher  $\dot{V}E/\dot{V}CO_2$  slope value observed in the ischemic group approached statistical significance, while LVEF was similar between groups. While age remained significantly higher in the ischemic HF patients who had a cardiac-related event, peak  $\dot{V}O_2$  and  $\dot{V}E/\dot{V}CO_2$  slope values were similar to the subjects in the nonischemic group who had an event. In the ischemic and nonischemic patients who did not have a cardiac-related event, age was again significantly higher and peak  $\dot{V}O_2$  was significantly lower in the ischemic subgroup. While  $\dot{V}E/\dot{V}CO_2$  slope was not significantly different, the difference in mean values was greater between the event-free ischemic and nonischemic subgroups. The difference in CPX variables between ischemic and nonischemic groups was only apparent in those subjects who remained event free. Conversely, the CPX characteristics of patients with a cardiac-related event were similar, irrespective of HF etiology.

The ischemic group demonstrated a worse prognosis during the 1-year tracking period as evidenced by Kaplan-Meier and Cox regression analyses. These find-

**Table 3—ROC Curve Analysis Results**

Groups	Area Under ROC Curve	p Value	Optimal Threshold Value	Sensitivity, %	Specificity, %
Ischemic HF					
Peak $\dot{V}O_2$ , mL/kg/min	0.74	< 0.001	≤ 14.1	73	64
$\dot{V}E/\dot{V}CO_2$ slope	0.76	< 0.001	≥ 34.2	75	72
Nonischemic HF					
Peak $\dot{V}O_2$ , mL/kg/min	0.75	< 0.001	≤ 14.6	67	72
$\dot{V}E/\dot{V}CO_2$ slope	0.86	< 0.001	≥ 34.5	83	72

**Table 4—Univariate Cox Regression Analysis Results Using Optimal Threshold Values Determined by ROC Curve Analysis**

Groups	$\dot{V}E/\dot{V}CO_2$ slope		Peak $\dot{V}O_2$ , mL/kg/min	
	Threshold	Hazard Ratio (95% Confidence Interval)	Threshold	Hazard Ratio (95% Confidence Interval)
Ischemic HF	$\geq 34.2$	4.3 (2.4–7.8)*	$\leq 14.1$	3.3 (1.9–5.8)*
Nonischemic HF	$\geq 34.5$	8.2 (3.9–17.2)*	$\leq 14.6$	4.3 (2.1–8.9)*

\* $p < 0.001$ .

ings are in agreement with previous investigations<sup>1,2,15</sup> reporting a greater risk for adverse events in patients with ischemic HF. In addition, the decreased time to a cardiac-related event in the ischemic group approached statistical significance ( $p = 0.07$ ). These results collectively indicate the ischemic group had a poorer prognosis compared to their nonischemic counterparts.

Despite differences in baseline characteristics and CPX values as well as event-free survival between the ischemic and nonischemic groups, the prognostic characteristics of peak  $\dot{V}O_2$  and  $\dot{V}E/\dot{V}CO_2$  slope were strikingly similar. The  $\dot{V}E/\dot{V}CO_2$  slope was the superior prognostic marker, although peak  $\dot{V}O_2$  did add additional prognostic value. HF etiology, while a significant univariate predictor of events, did not add additional prognostic value to the  $\dot{V}E/\dot{V}CO_2$  slope and peak  $\dot{V}O_2$  in the multivariate analysis. In the separate etiology-based analysis, peak  $\dot{V}O_2$  and  $\dot{V}E/\dot{V}CO_2$  slope remained significant predictors of cardiac-related events. However,  $\dot{V}E/\dot{V}CO_2$  slope was the superior prognostic marker in both etiologies. In the multivariate model, peak  $\dot{V}O_2$  added prognostic value in the ischemic group. In those subjects with nonischemic HF, peak  $\dot{V}O_2$  did not add prognostic value to  $\dot{V}E/\dot{V}CO_2$  slope, although the residual  $\chi^2$  was nearly statistically significant. Irrespective of these minor differences, optimal prognostic threshold values derived via ROC curve analysis were nearly identical (Table 3). An optimal/recommended prognostic threshold value of 14.0 mL/kg/min for peak  $\dot{V}O_2$ <sup>6,16</sup> and 34.0 for  $\dot{V}E/\dot{V}CO_2$  slope has also been reported by other investigators.<sup>8,17</sup> Additionally, several investigators<sup>18–22</sup> have similarly found  $\dot{V}E/\dot{V}CO_2$  slope to be a superior prognostic marker when compared to peak  $\dot{V}O_2$ , and our findings confirm these previous analyses.

Why patients with an ischemic etiology have poorer outcomes is unknown. Detrimental alterations to left ventricular size and function are a hallmark of the chronic adaptation to HF. There is evidence to suggest such changes in cardiac architecture secondary to HF are not consistent across different etiologies. Gasparini et al<sup>23</sup> hypothesized that scarring from previous myocardial infarction limits the effectiveness of cardiac resynchronization therapy in ischemic patients, whereas this is not the case in nonischemic patients. In

their study,<sup>23</sup> LVEF, 6-min walk distance, and New York Heart Association classification improved significantly in both groups following cardiac resynchronization therapy. However, improvements were significantly greater in the nonischemic group compared to the ischemic group. Perhaps the unique changes in cardiac structure and function brought about by HF secondary to ischemia contribute to the poorer CPX performance and prognosis that has been observed in the present and previous investigations.<sup>23</sup>

In the present study, we included hospitalization for cardiac reasons as an end point and limited the follow-up period to 1 year. Irrespective of etiology, individuals with HF can shift from a stable to an uncompensated status (or *vice versa*) rather abruptly. Limiting the follow-up period to 1 year may be clinically optimal given the fluid nature of cardiac function in the HF patient. We recently completed an analysis of the impact of time past CPX on the prognostic characteristics of  $\dot{V}E/\dot{V}CO_2$  slope and peak  $\dot{V}O_2$  in subjects with HF.<sup>24</sup> This analysis indicated that the sensitivity for predicting outcomes rose modestly while specificity dramatically fell for both CPX variables after  $> 1$  year after exercise testing. A 1-year tracking period may therefore represent an appropriate balance between avoiding outdated information and the economic constraints of multiple exercise tests. In addition, most research examining the prognostic value of CPX has not used hospitalization as an end point. Given that HF is the primary hospital diagnostic-related group among Medicare patients,<sup>25</sup> analysis of measures predicting hospitalization in this population seems warranted. The ability of  $\dot{V}E/\dot{V}CO_2$  slope and peak  $\dot{V}O_2$  to effectively predict hospitalization may help identify high-risk patients and provide appropriate interventions on an outpatient basis thereby preventing nonfatal adverse events (hospitalization) and reducing health-care costs.

There are numerous mechanisms by which an individual can acquire nonischemic HF. A primary limitation of the present study was the inability to perform subgroup analyses in particular nonischemic groups. The majority of nonischemic patients in the present study were classified as having idiopathic cardiomyopathy (approximately 70%). Future research utilizing larger subject samples should be conducted to deter-

mine whether the prognostic characteristics of CPX are consistent across the different mechanisms leading to nonischemic HF.

## CONCLUSION

CPX continues to be a widely accepted clinical procedure in the HF population. This practice is justified given the growing body of data demonstrating its prognostic value. However, the potential influence of HF etiology on the prognostic characteristics of CPX has not been fully explored. The present results indicate that while there were clear differences in baseline characteristics, CPX values, and event rates between individuals with ischemic and nonischemic HF, the prognostic characteristics of  $\dot{V}E/\dot{V}CO_2$  slope and peak  $\dot{V}O_2$  were similar. Thus, a distinction between an ischemic and nonischemic etiology does not appear to be necessary when applying CPX responses in stratifying risk in patients with HF.

## REFERENCES

- 1 Likoff MJ, Chandler SL, Kay HR. Clinical determinants of mortality in chronic congestive heart failure secondary to idiopathic dilated or to ischemic cardiomyopathy. *Am J Cardiol* 1987; 59:634–638
- 2 Myers J, Gullestad L, Vagelos R, et al. Clinical, hemodynamic, and cardiopulmonary exercise test determinants of survival in patients referred for evaluation of heart failure. *Ann Intern Med* 1998; 129:286–293
- 3 Webb-Peploe KM, Chua TP, Harrington D, et al. Different response of patients with idiopathic and ischaemic dilated cardiomyopathy to exercise training. *Int J Cardiol* 2000; 74:215–224
- 4 Gibbons RJ, Balady GJ, Timothy BJ, et al. ACC/AHA 2002 guideline update for exercise testing: summary article; a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *J Am Coll Cardiol* 2002; 40:1531–1540
- 5 Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary; a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *Circulation* 2001; 104:2996–3007
- 6 Mancini DM, Eisen H, Kusmaul W, et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991; 83:778–786
- 7 Arena R, Myers J, Aslam SS, et al. Peak  $\dot{V}O_2$  and  $\dot{V}E/\dot{V}CO_2$  slope in patients with heart failure: a prognostic comparison. *Am Heart J* 2004; 147:354–360
- 8 Chua TP, Ponikowski P, Harrington D, et al. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol* 1997; 29:1585–1590
- 9 Reindl I, Wernecke KD, Opitz C, et al. Impaired ventilatory efficiency in chronic heart failure: possible role of pulmonary vasoconstriction. *Am Heart J* 1998; 136:778–785
- 10 Myers J, Gullestad L, Vagelos R, et al. Cardiopulmonary exercise testing and prognosis in severe heart failure: 14 mL/kg/min revisited. *Am Heart J* 2000; 139:78–84
- 11 MacGowan GA, Panzak G, Murali S. Exercise-related ventilatory abnormalities are more specific for functional impairment in chronic heart failure than reduction in peak exercise oxygen consumption. *J Heart Lung Transplant* 2001; 20:1167–1173
- 12 Arena R, Tevald M, Peberdy MA. Influence of etiology on ventilatory expired gas and prognosis in heart failure. *Int J Cardiol* 2005; 99:217–223
- 13 Balady G, Berra KA, Lawrence A et al. Clinical exercise testing. In: Franklin BA, Whaley MH, Howley ET, eds. *ACSM guidelines for exercise testing and prescription*. Baltimore, MD: Lippincott Williams and Wilkins, 2000; 91–114
- 14 Arena R, Myers J, Aslam S, et al. Technical considerations related to the minute ventilation/carbon dioxide output slope in patients with heart failure. *Chest* 2003; 124:720–727
- 15 Bettencourt P, Ferreira A, Dias P, et al. Predictors of prognosis in patients with stable mild to moderate heart failure. *J Cardiac Fail* 2000; 6:306–313
- 16 Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA guidelines for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *J Am Coll Cardiol* 1997; 30:260–311
- 17 Fink LI, Wilson JR, Ferraro N. Exercise ventilation and pulmonary artery wedge pressure in chronic stable congestive heart failure. *Am J Cardiol* 1986; 57:249–253
- 18 MacGowan GA, Murali S. Ventilatory and heart rate responses to exercise: better predictors of heart failure mortality than peak exercise oxygen consumption. *Circulation* 2000; 102:E182
- 19 Francis DP, Shamim W, Davies LC, et al. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from  $\dot{V}E/\dot{V}CO_2$  slope and peak  $\dot{V}O_2$ . *Eur Heart J* 2000; 21:154–161
- 20 Davies LC, Francis DP, Piepoli M, et al. Chronic heart failure in the elderly: value of cardiopulmonary exercise testing in risk stratification. *Heart* 2000; 83:147–151
- 21 Kleber FX, Vietzke G, Wernecke KD, et al. Impairment of ventilatory efficiency in heart failure: prognostic impact. *Circulation* 2000; 101:2803–2809
- 22 Ponikowski P, Francis DP, Piepoli MF, et al. Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. *Circulation* 2001; 103:967–972
- 23 Gasparini M, Mantica M, Galimberti P, et al. Is the outcome of cardiac resynchronization therapy related to the underlying etiology? *Pacing Clin Electrophysiol* 2003; 26:175–180
- 24 Myers J, Arena R, Guazzi M. Impact of time past exercise testing on prognostic variables in patients with heart failure. *Eur J Cardiovasc Prev Rehabil* 2004; 11(suppl):67
- 25 Parmley WW. Heart failure awareness week: February 14–21. *J Am Coll Cardiol* 2000; 35:534

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