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Defining the Optimal Prognostic Window for Cardiopulmonary Exercise Testing in Patients With Heart Failure

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Background—Ventilatory efficiency (V_E/V_{CO_2} slope) and peak oxygen consumption (V_O) provide robust prognostic information in patients with heart failure undergoing cardiopulmonary exercise testing (CPX). The purpose of this study is to assess the change in prognostic characteristics of CPX at different time intervals.

Methods and Results—Seven hundred ninety-one subjects (74% male, mean age: 60.7±12.9 years, ejection fraction: 34.6±15.0%, ischemic etiology: 51%) underwent CPX and were tracked for major cardiac events over a 4-year period. All event-free subjects were tracked for at least 3 years. Mean V_E/V_{CO_2} slope and peak V_{O_2} were 35.0±10.0 and 16.0±6.4 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$, respectively. There were a total of 263 major cardiac events (199 deaths, 45 transplants, and 19 left ventricular assist device implantations). Both continuous and dichotomous expressions of the V_E/V_{CO_2} slope and peak V_{O_2} were prognostically significant up to 18 months post-CPX. Continuous and dichotomous expressions of the V_E/V_{CO_2} slope remained prognostically significant up to 36 months post-CPX, whereas peak V_{O_2} was not predictive during the third and fourth year of follow-up. In a multivariate analysis, the V_E/V_{CO_2} slope was consistently the superior prognostic marker, whereas peak V_{O_2} added predictive value and was retained in the regression up to 18 months post-CPX.

Conclusions—These results indicate that commonly assessed CPX variables retain prognostic value for at least 2 years. The V_E/V_{CO_2} slope is the superior predictor of adverse events throughout follow-up, although peak V_{O_2} provides additive prognostic information during the first 2 years of follow-up. **(*Circ Heart Fail*. 2010;3:405-411.)**

Key Words: exercise ■ heart failure ■ oxygen ■ prognosis ■ ventilation

Cardiopulmonary exercise testing (CPX) is a well-accepted evaluation technique in patients with heart failure (HF), as indicated by position stands put forth by American[1] and European[2] organizations. The premise for the strong level of support for the application of CPX in this chronic disease population is the robust body of scientific evidence, now spanning >25 years, consistently demonstrating the prognostic value provided by variables attained from ventilatory expired gas analysis.[3] From CPX, the minute ventilation/carbon dioxide production (V_E/V_{CO_2}) slope and peak oxygen consumption (V_O) are the most frequently assessed variables for prognostic purposes and, although the former seems to provide superior predictive information, multivariate modeling including both measures is recommended.[3]

Clinical Perspective on p 411

From the entire HF population, it seems that those patients being actively considered for heart transplantation are most often referred for CPX to assist in determining whose prognosis is least favorable and therefore in the greatest need of surgical intervention. Although clinicians afford a high level of predictive credibility to information obtained from CPX, little consideration is given to the length of time the data provide valid insight into which patients are at greatest risk for adverse events. Our group has attempted to address this issue in the past, finding the prognostic strength of both the V_E/V_{CO_2} slope and peak V_{O_2} is diminished >1 year after CPX.[4] This initial investigation was performed in a relatively small cohort (n=258) with a limited amount of hard end points (45 cardiac-related deaths).

Although this initial investigation indicated that there was a finite period of time that CPX data should be considered for prognostic purposes in patients with HF, additional analysis is needed. Given the fluid nature of this chronic disease, from asymptomatic left ventricular dysfunction to refractory HF, the prognostic applications of CPX should not be considered indefinite. However, the optimal window for applying CPX data in a

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prognostic context has not been well defined. Clarifying this window would have implications for the frequency with which patients with HF should be referred for CPX and would further optimize the application of this procedure. The purpose of this investigation was to further define an optimal prognostic window for CPX responses in patients with HF.

Methods

This study is a multicenter analysis including patients with HF from the exercise testing laboratories at San Paolo Hospital, Milan, Italy; Wake Forest University Baptist Medical Center, Winston-Salem, NC; LeBauer Cardiovascular Research Foundation, Greensboro, NC; VA Palo Alto Health Care System, Palo Alto, Calif; and Virginia Commonwealth University, Richmond, Va. A total of 791 patients with chronic HF were included. Inclusion criteria were a diagnosis of HF[5] and evidence of left ventricular dysfunction by 2-dimensional echocardiography obtained within 1 month of data collection. All subjects completed a written informed consent and institutional review board approval was obtained at each institution.

CPX Procedures

Symptom-limited CPX was performed on all subjects and pharmacological therapy was maintained during exercise testing. Conservative ramping protocols were used at all centers, and ventilatory expired gas analysis was performed using a metabolic cart (Medgraphics CPX-D and Ultima, Minneapolis, Minn, Sensormedics Vmax29, Yorba Linda, Calif, or Parvomedics TrueOne 2400, Sandy, Utah). A treadmill and lower extremity ergometer were used as the exercise mode in 69% and 31% of the tests, respectively. Before each test, the equipment was calibrated in standard fashion using reference gases. Minute ventilation (V_E), oxygen uptake (V_O), and carbon dioxide output (V_{CO_2}) were acquired breath-by-breath and averaged over 10-second intervals. Peak V_{O_2} and peak respiratory exchange ratio (RER) were expressed as the highest 10-second averaged sample obtained during the last 20 seconds of testing. V_E and V_{CO_2} values, acquired from the initiation of exercise to peak, were input into spreadsheet software (Microsoft Excel, Microsoft Corp., Bellevue, Wash) to calculate the V_E/V_{CO_2} slope using least squares linear regression ($y=mx+b$, m=slope). Previous studies have shown that this method of calculating the V_E/V_{CO_2} slope to be prognostically optimal.[3]

End Points

In the overall cohort, subjects were followed up for major cardiac events (mortality, left ventricular device implantation, urgent heart transplantation) via medical chart review. Subjects were followed up 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 used in this study. Any death with a cardiac-related discharge diagnosis was considered an event. Subjects in the overall group who did not have a major cardiac event were tracked for a minimum of 3 years.

Statistical Analysis

Statistical software packages (SPSS 17.0, Chicago, Ill and StudySize 2.0, Vastra Frolunda, Sweden) were used to perform all analyses. Continuous data are reported as mean±standard deviation. One-way ANOVA was used to assess differences in continuous variables between subjects who remained event free or had a major cardiac event at 6-month intervals for the overall group tracked for 3 years. Post hoc analysis was performed by Tukey's honestly significant difference test. Chi-square analysis assessed distribution differences of categorical data among groups. Independent t tests were used to assess differences in CPX variables between subgroups of subjects who remained event free for 4 years or had a major cardiac event either between 36 and 42 or between 42 and 48 months. In subjects experiencing a major cardiac event, Pearson product-moment correlation analysis was used to assess the relationship between both peak V_O and the V_E/V_{CO_2} slope and time to event. A series of Cox proportional hazard models were performed to assess the prognostic value of peak V_O and the V_E/V_{CO_2} slope, both as continuous and dichotomous expressions (V_E/V_{CO_2} slope: $<36/\geq 36$; peak V_O: $<10/\geq 10$ mL · kg^{-1} · min^{-1}), during the 4-year tracking period. The first was a traditional time-to-event analysis with the date of CPX serving as the baseline time point. Subsequent proportional hazard models began follow-up time at succeeding 6-month intervals post-CPX. Subjects having an event in the preceding 6 months were removed from the next analysis. Dichotomous thresholds for both CPX variables were based on previous investigations demonstrating their prognostic significance.[3] By using all cardiac events, a post hoc power analysis was conducted for both CPX variables (continuous expressions) for all Cox proportional hazard models. Derived hazard ratios and total number of cardiac events were used to calculate power. Kaplan–Meier analysis assessed event-free survival of the V_E/V_{CO_2} slope and peak V_O according to the 4 level Ventilatory[6] and Weber[7] classification systems, respectively. Multivariate Cox regression (forward stepwise method; entry and removal value 0.05 and 0.10, respectively) assessed the combined prognostic value of peak V_O and the V_E/V_{CO_2} slope as continuous expressions. Multivariate survival analysis was used to assess the combined prognostic value of all variables listed in Table 1 in addition to the aforementioned CPX variables. For this latter analysis, major cardiac events were considered for the first 3 years after CPX. Finally, univariate Cox regression assessed the prognostic value of CPX at each of the 5 laboratories included in the analysis and based on mode of exercise as well as a peak RER threshold of $<1.00/\geq 1.00$. A P value of <0.05 was considered statistically significant for all tests.

Results

The characteristics of the clinical and cardiac events of the 791 subjects included in this analysis are listed in Table 1. Five hundred sixty subjects remained event free for 3 years, whereas the remaining 231 subjects experienced a major cardiac event during that time period (annual event rate: 9.9%). None of the subjects who remained event free for 3 years post-CPX was lost to follow-up over that time period. One hundred thirteen subjects were lost to follow-up during the fourth year of tracking. Over the first 3 years of tracking, 168 events were cardiac-related mortality (annual mortality rate: 7.3%). Several significant differences existed according to event status. Of note, New York Heart Association class was significantly lower and the left ventricular ejection fraction was significantly higher in subjects who were event free compared with those subjects having a major cardiac event during the first 2 years after CPX. Both variables were comparable between subjects who were event free and those having a major cardiac event during the third year after CPX.

CPX characteristics are listed in Table 2. Peak RER was comparable among groups, indicating similar effort. Peak V_{O_2} was significantly higher in subjects who remained event free compared with those who had a major cardiac event during the first 2 years after CPX (Figure 1). The V_E/V_{CO_2} slope was significantly lower in subjects who remained event free compared with those having a major cardiac event during the first 2½ years after CPX. Moreover, the V_E/V_{CO_2} slope was significantly higher in subjects having a major cardiac event in the first 6 months compared with subjects having a major cardiac event from 6 to 12, 12 to 18, and 30 to 36 months (Figure 2).

Four hundred ninety-nine subjects were tracked and remained event free for 42 months, whereas 13 had a major cardiac event between 36 and 42 months. The difference in peak V_{O_2} (no event: 17.5±6.6 versus event: 17.8±8.7 mL · kg^{-1} · min^{-1}, $P=0.98$) and peak RER (no event:

Table 1. Baseline Characteristics and Therapy Distribution

	Overall Group (n=791)	No. Events (n=560)	0 to 6 mo (n=76)	6 to 12 mo (n=51)	12 to 18 mo (n=39)	18–24 mo (n=30)	24–30 mo (n=20)	30–36 mo (n=15)
Baseline characteristics								
Age, y	60.7±12.9	61.5±11.9*	55.7±14.5	59.7±12.6	56.1±17.5	62.9±14.2	64.8±15.6	61.7±12.5
Sex, % male	80	80†	74	80	72	87‡	80	93§
Etiology, % ischemic/nonischemic	51/49	51/49	49/51	56/44	46/54	54/46	53/47	62/38‖
NYHA class	2.4±0.67	2.2±0.65¶	2.9±0.72	2.8±0.64	2.7±0.49	2.7±0.51	2.6±0.53	2.3±0.61#
LVEF, %	34.6±15.0	38.8±14.1**	23.2±11.6	25.4±13.0	26.6±12.3	27.3±12.3	31.1±16.4	33.4±13.5
Event type: death/transplant/LVAD	168/44/19	0/0/0	35/33/8	40/7/4	35/1/3	25/2/3	19/1/0	14/0/1
Therapy distribution, %								
ACE inhibitor	67	64	63	88††	83‡‡	66	67	58§§
Diuretic	59	49‖‖	86	80	83	85	81	64¶¶
β-blocker	52	49	64	69##	58	53	33***	54

NYHA indicates New York Heart Association; LVAD, left ventricular assist device.
*No event group younger than 0- to 6-month event group ($P<0.01$).
†Male % in the no-event group higher than the 0- to 6- and 12- to 18-month event groups ($P<0.01$).
‡Male % in the 18- to 24-month event group higher than the no-event, 0- to 6-month, and 18- to 24-month event groups ($P<0.01$).
§Male % in the 30- to 36-month event group higher than all others with exception of the 18- to 24-month event group ($P<0.05$).
‖Heart failure etiology distribution different in the 30- to 36-month event group compared with no-event and the 0- to 6-month event groups ($P<0.05$).
¶NYHA class in the no-event group lower compared with the 0- to 6-, 6- to 12-, 12- to 18-, and 18- to 24-month event groups ($P<0.05$).
#NYHA class in the 30- to 36-month event group lower compared with the 0- to 6-month event group ($P<0.05$).
**Left ventricular ejection fraction higher in the no-event group compared with the 0- to 6-, 6- to 12-, 12- to 18-, and 18- to 24-month event groups ($P<0.01$).
††ACE inhibitor use higher in the 6- to 12-month event group compared with all other groups with the exception of the 12- to 18-month event group ($P<0.05$).
‡‡ACE inhibitor use higher in the 12- to 18-month event group compared with the no-event, 0- to 6-, 18- to 24-, and 30- to 36-month event groups ($P<0.05$).
§§ACE inhibitor use higher in the no-event group compared with the 30- to 36-month event group ($P<0.01$).
‖‖Diuretic use lower in the no-event group compared with all other groups ($P<0.05$).
¶¶Diuretic use lower in the 30- to 36-month group compared with all other groups having an event ($P<0.05$).
##β-blocker use higher in the 6- to 12-month group compared with the no-event and the 24- to 30-month event group ($P<0.05$).
***β-blocker use lower in the 24- to 30-month event group compared with all other groups with the exception of the 30- to 36-month event group ($P<0.05$).

1.09±0.17 versus event: 1.12±0.18, $P=0.56$) was not significantly different, whereas the V_E/V_{CO_2} slope (no event: 32.0±7.7 versus event: 38.0±17.8, $P=0.008$) was significantly higher in subjects having a cardiac event. In addition, 428 subjects were tracked and remained event free for 48 months, whereas 19 died because of cardiac event between 42 and 48 months. During the last 6 months of the fourth year, the differences in peak V_{O_2} (no event: 17.7±6.6 versus event: 15.7±6.4 $mL \cdot kg^{-1} \cdot min^{-1}$, $P=0.26$), peak RER (no event: 1.09±0.17 versus event: 1.12±0.19, $P=0.48$), and the V_E/V_{CO_2} slope (no event: 31.9±7.7 versus event: 35.3±10.1, $P=0.06$) were not significant according to event status.

In the subjects experiencing a major cardiac event over the 4-year tracking period (n=263), Pearson product-moment correlation revealed that the V_E/V_{CO_2} slope ($r=-0.24$, $P<0.001$) and peak Vo ($r=0.32$, $P<0.001$) were both significantly correlated with time to event.

CPX variables of interest were significant predictors ($P<0.05$) of adverse events irrespective of: CPX laboratory, exercise mode, or a peak threshold of $<1.00/\geq 1.00$. In each instance, the V_E/V_{CO_2} slope was the superior prognostic marker. Kaplan–Meier analysis revealed the 4-level Weber[7] (Figure 3) and Ventilatory[6] (Figure 4) classification systems clearly delineated risk over the 3 years after CPX.

Cox proportional hazards models are listed in Table 3. Both continuous and dichotomous expressions of the V_E/V_{CO_2} slope were significant predictors of major cardiac events and cardiac mortality at each 6-month interval for the

Table 2. CPX Data

	Overall Group (n=791)	No. Events (n=560)	0 to 6 mo (n=76)	6 to 12 mo (n=51)	12 to 18 mo (n=39)	18–24 mo (n=30)	24–30 mo (n=20)	30–36 mo (n=15)
Peak V_{O_2}, $mL \cdot kg^{-1} \cdot min^{-1}$	16.0±6.4	17.4±6.6*	11.4±3.7	13.1±4.7	12.9±4.1	12.4±4.4	15.2±4.3	14.9±4.6
V_E/V_{CO_2} slope	35.0±10.0	32.2±10.0†	45.6±12.1‡	39.7±8.8	39.9±12.0	40.2±11.4	41.1±9.8	36.1±3.4
Peak RER	1.09±0.17	1.09±0.17	1.08±0.18	1.13±0.19	1.08±0.13	1.06±0.11	1.07±0.12	1.12±0.18

*Peak V_{O_2}: no-event group greater than 0- to 6-, 6- to 12-, 12- to 18-, and 18- to 24-month event groups ($P<0.001$).
†The V_E/V_{CO_2} slope: no-event group less than 0- to 6-, 6- to 12-, 12- to 18-, 18- to 24-, and 24- to 30-month event groups ($P<0.001$).
‡The V_E/V_{CO_2} slope was greater for the 0- to 6-month group than for the 6- to 12-, 12- to 18-, and 30- to 36-month event groups ($P<0.05$).

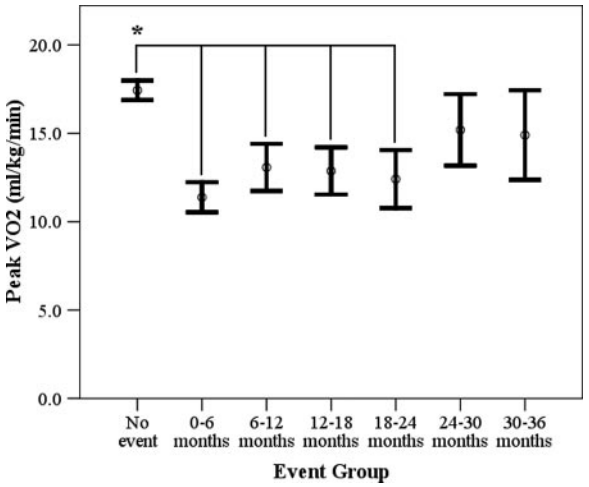

Figure 1. Difference in peak V_{O_2} according to event status. *$P<0.001$.

first 3½ years after CPX. Power calculations for survival analysis using the V_E/V_{CO_2} slope remained above 90% up to 30 months post-CPX and dropped to 79% and 61% for the 36- and 42-month post-CPX analyses, respectively. The continuous expression of peak V_{O_2} was a significant predictor of major cardiac events and cardiac mortality up to and including the 24-month post-CPX hazards model, whereas dichotomous expression was no longer significant after 12 months post-CPX. Neither expression of peak V_{O_2} identified subjects at increased risk from 30 months post-CPX to the end of tracking. When considering peak V_{O_2} as the prognostic variable, power was >90% up to 18 months post-CPX, dropped to 64% 24 months CPX, and declined to <50% thereafter.

Multivariate Cox regression results revealed that the V_E/V_{CO_2} slope and peak V_{O_2} were both retained in the model when considering all events and up to 18 months post-CPX. The V_E/V_{CO_2} slope was the superior prognostic marker in each instance, whereas peak V_{O_2} added predictive value (residual χ^2: ≥4.2, $P<0.05$). The V_E/V_{CO_2} slope was the only variable retained in the regression from 24 to 36 months post-CPX. Neither the V_E/V_{CO_2} slope nor peak V_O was entered into the

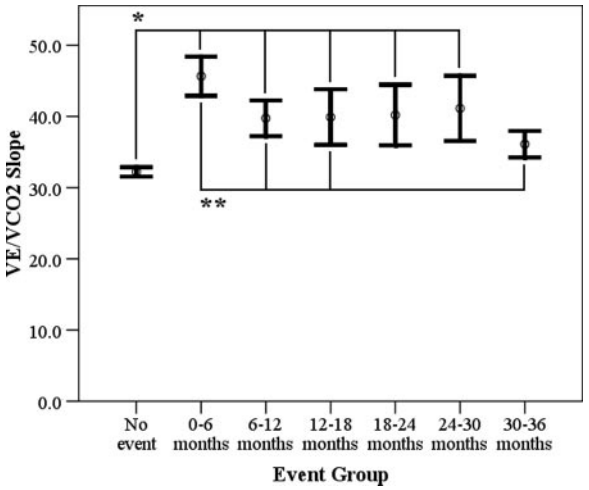

Figure 2. Difference in the V_E/V_{CO_2} slope according to event status. *$P<0.001$, **$P<0.05$.

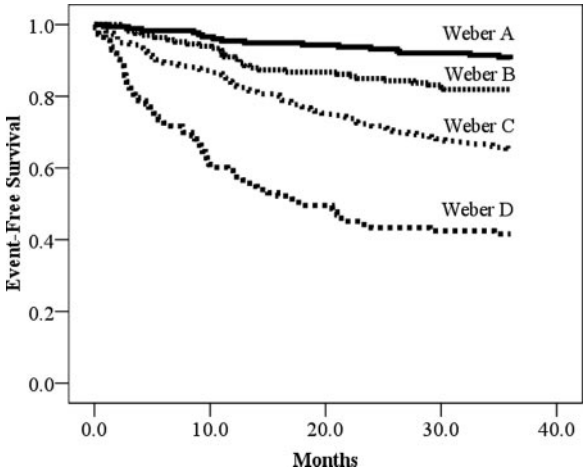

Figure 3. Kaplan–Meier analysis according to Weber class.

multivariate regression at 42 months post-CPX. When combining these CPX variables with all variables listed in Table 1, the V_E/V_{CO_2} slope remained the strongest prognostic marker (χ^2: 197.6, $P<0.001$). Left ventricular ejection fraction, New York Heart Association class, age and peak V_O added prognostic value and were retained (residual $\chi^2 \geq 5.0$, $P<0.05$).

Discussion

The prognostic power of CPX in HF is firmly supported by a wealth of original research.[6,8,9] Peak V_{O_2} and the V_E/V_{CO_2} slope are the most thoroughly investigated variables and are therefore afforded a high degree of clinical recognition and acceptance.[10] This is particularly true for peak V_{O_2}, although evidence now supports the prognostic superiority of the V_E/V_{CO_2} slope in the HF population,[3] a finding confirmed in this investigation. Historically, prognostic analyses have tracked events after CPX without considering the potential influence time past the initial assessment has on the prognostic ability of peak V_{O_2} and the V_E/V_{CO_2} slope. Our group addressed this previously, demonstrating the ability of both CPX variables to accurately predict that an increased risk for cardiac mortality and hospitalization was substantially higher within the first year of tracking compared with a longer time frame.[4] This initial analysis included a relatively small cohort (<300) and small number of events (<45

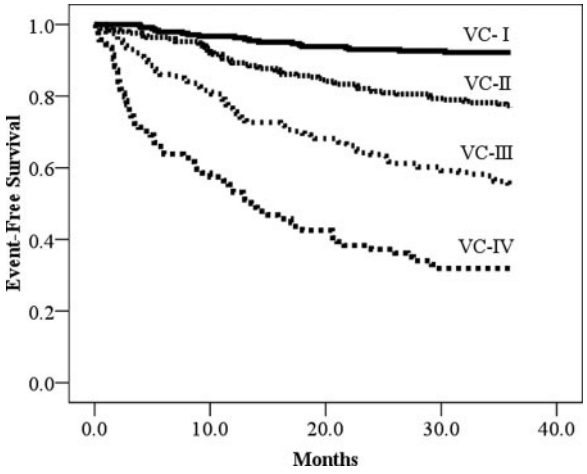

Figure 4. Kaplan–Meier analysis according to ventilatory class.

Table 3. Cox Proportional Hazards Models for CPX Variables According to Time Past Baseline Assessment

	All Cardiac Events				Cardiac Mortality			
	Hazard Ratio (95% CI) Continuous	*P*	Hazard Ratio (95% CI) Dichotomous*	*P*	Hazard Ratio (95% CI) Continuous	*P*	Hazard Ratio (95% CI) Dichotomous*	*P*
V_E/V_{CO_2} slope								
Overall (263 events; 199 deaths)	1.06 (1.05 to 1.07)	<0.001	4.1 (3.2 to 5.3)	<0.001	1.05 (1.04 to 1.06)	<0.001	3.5 (2.7 to 4.7)	<0.001
6 mo post CPX (187 events; 164 deaths)	1.05 (1.04 to 1.06)	<0.001	3.3 (2.5 to 4.4)	<0.001	1.05 (1.04 to 1.06)	<0.001	3.2 (2.3 to 4.4)	<0.001
12 mo post CPX (136 events; 124 deaths)	1.06 (1.04 to 1.07)	<0.001	3.4 (2.4 to 4.8)	<0.001	1.05 (1.04 to 1.07)	<0.001	3.3 (2.3 to 4.7)	<0.001
18 mo post CPX (95 events; 89 deaths)	1.06 (1.04 to 1.07)	<0.001	3.4 (2.3 to 5.1)	<0.001	1.06 (1.04 to 1.07)	<0.001	3.5 (2.3 to 5.3)	<0.001
24 mo post CPX (67 events; 64 deaths)	1.05 (1.04 to 1.07)	<0.001	3.4 (2.1 to 5.5)	<0.001	1.05 (1.04 to 1.07)	<0.001	3.5 (2.2 to 5.8)	<0.001
30 mo post CPX (47 events; 45 deaths)	1.05 (1.02 to 1.07)	<0.001	2.6 (1.5 to 4.7)	0.001	1.05 (1.02 to 1.07)	<0.001	2.9 (1.6 to 5.2)	<0.001
36 mo post CPX (32 events; 31 deaths)	1.05 (1.02 to 1.08)	0.001	2.4 (1.2 to 4.8)	0.01	1.05 (1.02 to 1.08)	0.001	2.5 (1.2 to 5.1)	0.01
42 mo post CPX (19 events; 19 deaths)	1.05 (1.00 to 1.09)	0.05	2.2 (0.90 to 5.6)	0.08	1.05 (1.00 to 1.09)	0.05	2.2 (0.90 to 5.6)	0.08
Peak V_{O_2}								
Overall (263 events; 199 deaths)	0.88 (0.86 to 0.91)	<0.001	3.2 (2.4 to 4.2)	<0.001	0.91 (0.88 to 0.93)	<0.001	2.3 (1.6 to 3.2)	<0.001
6 mo post CPX (187 events; 164 deaths)	0.90 (0.88 to 0.93)	<0.001	2.6 (1.8 to 3.7)	<0.001	0.91 (0.89 to 0.94)	<0.001	2.2 (1.5 to 3.3)	<0.001
12 mo post CPX (136 events; 124 deaths)	0.91 (0.88 to 0.94)	<0.001	2.0 (1.3 to 3.2)	0.002	0.92 (0.88 to 0.95)	<0.001	1.8 (1.1 to 3.0)	0.02
18 mo post CPX (95 events; 89 deaths)	0.92 (0.89 to 0.96)	<0.001	1.7 (0.95 to 3.1)	0.07	0.93 (0.89 to 0.96)	<0.001	1.7 (0.93 to 3.2)	0.08
24 mo post CPX (67 events; 64 deaths)	0.96 (0.91 to 1.00)	0.03	1.1 (0.45 to 2.5)	0.82	0.95 (0.91 to 1.00)	0.03	1.2 (0.5 to 2.7)	0.73
30 mo post CPX (47 events; 45 deaths)	0.96 (0.91 to 1.01)	0.10	1.3 (0.53 to 3.4)	0.53	0.96 (0.91–1.01)	0.10	1.4 (0.56 to 3.6)	0.47
36 mo post CPX (32 events; 31 deaths)	0.97 (0.92 to 1.03)	0.34	1.6 (0.57 to 4.7)	0.36	0.98 (0.92 to 1.04)	0.44	1.7 (0.59 to 4.9)	0.32
42 mo post CPX (19 events; 19 deaths)	0.95 (0.88 to 1.03)	0.26	2.2 (0.63 to 7.5)	0.22	0.95 (0.88 to 1.03)	0.26	2.2 (0.63 to 7.5)	0.22

*Thresholds: V_E/V_{CO_2} slope $</\geq 36$, peak V_{O_2} $</\geq 10$ mL · kg^{-1} · min^{-1}.

deaths, 19 within the first year and 26 over the next 5 years), limiting our ability to perform a more detailed analysis on the effect time post-CPX has on prognostic significance. This investigation attempted to rectify the limitations of our initial analysis and, to our knowledge, is the first one addressing this issue in a detailed manner.

HF is a dynamic condition in which clinical status has the potential to markedly deteriorate over a short time period. It is estimated that 80% of men and 70% of women diagnosed with HF younger than 65 die within 8 years of their diagnosis.[11] It is therefore not surprising that the prognostic value of CPX may not be maintained indefinitely because disease severity will worsen in a majority of these patients in <10 years. Importantly, peak V_{O_2} may lose its prognostic value in patients with HF 2 years post-CPX. The V_E/V_{CO_2} slope seems to retain prognostic value for 3½ years after CPX. In the latter half of the fourth year of tracking, the V_E/V_{CO_2} slope also seems to begin to lose prognostic value. These observations suggest the following: (1) when peak V_{O_2} and the V_E/V_{CO_2} slope are assessed from a prognostic perspective without consideration of time post-CPX, both are highly prognostic, which is consistent with the previous research[3]; (2) the prognostic strength of peak V_{O_2} and the V_E/V_{CO_2} slope may depend on time post-CPX. In combination, peak V_{O_2} and the V_E/V_{CO_2} slope can be considered for up to 2 years after CPX with a high degree of confidence. The V_E/V_{CO_2} slope may continue to provide prognostic insight into the fourth year after CPX, although its ability to predict risk for adverse events diminishes after 42 months; (3) neither peak V_{O_2} nor the V_E/V_{CO_2} slope may provide reliable prognostic information during the latter half of the fourth year post-CPX. Although the analysis was not extended into the fifth year after CPX, it is reasonable to hypothesize that the trends of diminished predictive value in the fourth year would continue. However, it should be noted that statistical power began to diminish for the V_E/V_{CO_2}

slope during the fourth year of tracking. The results of this study during this time period should therefore be viewed as compelling but in need of future studies to address this issue. Even so, attaining a cohort with enough events in a short time interval to demonstrate these CPX variables is not prognostic after an extended period, and generating a power of at least 80% may be challenging. In addition, the V_E/VCO_2 slope maintained prognostic significance for a longer period of time despite the lower event rate into the fourth year. This indicates the lack of prognostic significance for peak V_{O_2} during this period does portend a potentially important clinical message.

In 62 patients with HF, Florea et al[12] performed 2 CPX evaluations that were at least 4 months apart (mean: 19 months). In the 22 subjects having a major cardiac event, there was a significant reduction in peak V_{O_2} from the first to second test (18.3 versus 13.9 $mL \cdot kg^{-1} \cdot min^{-1}$, $P<0.05$), whereas there was no change in subjects who were event free (18.1 versus 20.8 $mL \cdot kg^{-1} \cdot min^{-1}$). The difference in peak V_O between groups according to event status was not significant during the baseline CPX but differed at the follow-up evaluation ($P<0.001$). The V_E/VCO_2 slope increased in subjects having a major cardiac event in this analysis (44.4 versus 50.0) but did not reach statistical significance. The difference in the V_E/VCO_2 slope in event-free subjects was more stable between the 2 tests (34.3 versus 35.9) and was significantly lower compared with the group having an adverse event at both the baseline and follow-up tests ($P<0.001$). This previous investigation underscores the fact that CPX responses vary with time and tend to worsen among subjects who subsequently experience an adverse event. This is particularly true for peak V_O, which was significantly reduced at follow-up in subjects having an adverse event. The V_E/VCO_2 slope seems to be more stable among subjects eventually having an adverse event, exhibiting a significantly higher value at both baseline and follow-up. This stability also seems to be the case for subjects who were event free, where the V_E/VCO_2 slope was significantly lower and comparable between baseline and follow-up assessments. The ability of the latter CPX variable to reflect longitudinal disease severity with greater stability during a cross-sectional analysis may be a primary reason for its prognostic superiority in comparison with peak V_O.[3] Even so, the prognostic window for the V_E/VCO_2 slope after CPX is not indefinite, and subjects initially presenting with a more favorable response will eventually have a higher incidence of adverse events. This is reflected by the statistically significant, albeit weak, correlation between CPX variables and time to event in this study (ie, CPX response improves in subjects having an adverse event at a longer time point from the assessment).

Numerous scientific statements from respected national and international organizations support the use of CPX for prognostic purposes in patients with HF.[1,13–15] Moreover, the American Heart Association guidelines for the diagnosis and management of patients with HF recommend the use of CPX to identify high-risk individuals being considered for heart transplantation or other advanced therapies.[16] However, none of these documents address the length of time CPX data maintain prognostic value, an important consideration given the fluid nature of HF etiology and disease progression. Given the results of this investigation, we propose the following: (1) as a conservative estimate, the current results support the prognostic utility of peak V_{O_2} and the V_E/VCO_2 slope for up to 2 years after the exercise assessment; (2) these variables should be assessed in combination over this time period, with progressively higher V_E/VCO_2 slope values in combination with progressively lower peak V_{O_2} values (VC-IV and Weber D), portending the greatest risk for major cardiac events; (3) irrespective of the time frame, subjects initially presenting with a poor CPX response should be considered at high risk for adverse events and monitored accordingly; (4) repeating the CPX every 2 years in patients with HF who initially have a peak V_{O_2} and V_E/VCO_2 slope that places them in the intermediate (Weber B/C and VC-II/III) risk categories is warranted; and (5) patients who are in Weber A and VC-I classes on initial CPX tend to remain at extremely low risk for a longer period. Repeating a CPX every 3 to 4 years may therefore be acceptable in this latter category.

Although the overall number of subjects and events in this investigation is relatively large for this area of study, removing preceding events at 6-month intervals diminishes the ability to perform extensive multivariate analyses. Ten events per predictor variable is a minimal recommended threshold for survival analyses.[17] This threshold was surpassed in all of the univariate analyses and either met or surpassed it for the multivariate analyses during the first 3½ years after CPX. Even so, statistical power diminished during the third and fourth year of tracking, limiting the strength of conclusions that can be drawn from this portion of the analysis. Moreover, other variables included in standardized prognostic models, such as the Seattle Heart Failure model,[18] were not available in this data set. However, although these variables are certainly valuable, previous investigations have demonstrated that CPX variables, particularly the V_E/VCO_2 slope, are among the strongest prognostic markers available.[6,8] This assertion was confirmed in this study, demonstrating the V_E/VCO_2 slope remained the single best predictor of adverse events over the entire 3-year period when all baseline variables listed in Table 1 were considered. Nevertheless, future investigations should determine whether the time-dependent predictive trends for CPX variables in this study extend to other important clinical measures. Changes in the clinical management of the subjects included in this analysis during the follow-up period were not tracked. It is therefore possible that the addition of medications such as β-blockers or devices such as an implantable cardioverter defibrillator would alter prognosis and thus diminish the predictive ability of the CPX variables assessed. Previous research, however, has found that both peak V_{O_2} and the V_E/VCO_2 slope remain prognostic irrespective of β-blocker use.[3,6] In addition, analysis of the prognostic value of CPX has produced consistent results for >25 years, supporting the hypothesis that an abnormal CPX response portends a higher adverse event risk irrespective of treatment strategies. Finally, there is a referral bias that should be considered with respect to the characteristics of patients referred for CPX that likely differ from the overall HF population.

In conclusion, peak V_{O_2} and the V_E/VCO_2 slope are well-established prognostic markers in patients with HF. Although this investigation affirms the overall prognostic strength of both peak V_{O_2} and the V_E/VCO_2 slope, there seems to be a time

constraint on their predictive utility, reflecting the variable nature of HF severity over time. Depending on the baseline CPX response, clinicians may want to consider repeating CPX over a 2- to 4-year time period to more accurately identify change in adverse event risk.

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CLINICAL PERSPECTIVE

Previous investigations have consistently demonstrated the prognostic value of cardiopulmonary exercise testing (CPX) in patients with heart failure (HF). The robust body of literature in this area has primarily assessed prognostic value of this assessment technique without considering the effect time post-CPX may have on the clinical information provided. This study demonstrates that, without consideration of time post-CPX, peak oxygen consumption (V_O) and the minute ventilation/carbon dioxide production (V_E/V_{CO_2}) slope are both strong prognostic markers, with the latter variable providing superior predictive information. This finding is consistent with the majority of previous investigations in this area. However, the prognostic value of both peak V_{O_2} and the V_E/V_{CO_2} slope begin to diminish as more time passes after CPX. This seems to be at least partially attributed to the fact that a greater proportion of individuals who initially have a favorable CPX response experience an adverse event over a prolonged period of time. This finding is not surprising given the fluid nature of cardiac stability in patients with HF (ie, progression to decompensated/refractory HF in previously stable patients). Specifically, this investigation found that peak V_{O_2} maintains prognostic value for 2 years, whereas the V_E/V_{CO_2} slope provides significant predictive information for 3½ years. In conclusion, clinicians responsible for the interpretation of CPX in patients with HF should consider the time period in which the data maintains prognostic validity and when repeat testing is warranted.