A cardiopulmonary exercise testing score for predicting outcomes in patients with heart failure

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Objective The aim of this study is to evaluate the predictive accuracy of a cardiopulmonary exercise test (CPX) score.

Background Cardiopulmonary exercise test responses, including peak VO_2, markers of ventilatory inefficiency (eg, the VE/VCO_2 slope and oxygen uptake efficiency slope [OUES]), and hemodynamic responses, such as heart rate recovery (HRR) and chronotropic incompetence (CRI) are strong predictors of outcomes in patients with heart failure (HF). However, there is a need for simplified approaches that integrate the additive prognostic information from CPX.

Methods At 4 institutions, 710 patients with HF (568 male/142 female, mean age 56 ± 13 years, resting left ventricular ejection fraction 33 ± 14%) underwent CPX and were followed for cardiac-related mortality and separately for major cardiac events (death, hospitalization for HF, transplantation, left ventricular assist device implantation) for a mean of 29 ± 25 months. The age-adjusted prognostic power of peak VO_2, VE/VCO_2 slope, OUES ($VO_2 = a \log_{10} VE + b$), resting end-tidal carbon dioxide pressure ($PetCO_2$), HRR, and CRI were determined using Cox proportional hazards analysis, optimal cutpoints were determined, the variables were weighted, and a multivariate score was derived.

Results There were 175 composite outcomes. The VE/VCO_2 slope (≥34) was the strongest predictor of risk and was attributed a relative weight of 7, with weighted scores for abnormal HRR (≤6 beats at 1 minute), OUES (>1.4), $PetCO_2$ (<33 mm Hg), and peak VO_2 (≤14 mL kg^{-1} min^{-1}) having scores of 5, 3, 3, and 2, respectively. Chronotropic incompetence was not a significant predictor and was excluded from the score. A summed score >15 was associated with an annual mortality rate of 27% and a relative risk of 7.6, whereas a score <5 was associated with a mortality rate of 0.4%. The composite score was the most accurate predictor of cardiovascular events among all CPX responses considered (concordance indexes 0.77 for mortality and 0.75 for composite outcome composed of mortality, transplantation, left ventricular assist device implantation, and HF-related hospitalization). The summed score remained significantly associated with increased risk after adjusting for age, gender, body mass index, ejection fraction, and cardiomyopathy type.

Conclusion A multivariable score based on readily available CPX responses provides a simple and integrated method that powerfully predicts outcomes in patients with HF. (Am Heart J 2008;156:1177-83.)

Although mortality from cardiovascular disease in general has continued to decline in recent years, the prevalence of chronic heart failure (CHF) has risen over the last decade.[1] Accurately estimating prognosis for patients with this condition is therefore one of the important challenges facing clinicians who treat CHF. In recent years, the cardiopulmonary exercise test (CPX) has become an established tool in the management of these patients. Consensus statements on CHF management from the United States, Europe, and elsewhere have supported this technology and its applications for quantifying functional capabilities, establishing the severity of CHF, evaluating therapy, prescribing exercise, and most notably, stratifying risk.[2-4] Maximal oxygen uptake (peak VO_2) achieved from the CPX has been the most commonly used response to help make decisions regarding medical management and interventions, including transplantation.[2-5] The available consensus guidelines have focused on the application of specific cutpoints for peak VO_2 in stratifying patients with CHF into low- and high-risk categories.[2-4]

More recently, the emphasis of prognostic studies has shifted to a focus on ventilatory inefficiency, in lieu of or in combination with peak VO_2, in estimating risk. The most widely studied index of ventilatory inefficiency has been the minute ventilation/carbon dioxide production (VE/VCO_2) slope. A growing body of studies over the last decade has demonstrated that among patients with CHF, the VE/VCO_2 slope more powerfully predicts mortality,

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hospitalization, or both, than peak VO_2.[6-12] There have also been other expressions of ventilatory inefficiency associated with poor outcomes in CHF, including the oxygen uptake efficiency slope (OUES),[12,13] VO_2 kinetics,[14] end-tidal carbon dioxide pressure ($PetCO_2$) at rest and during exercise,[15,16] VO_2 in recovery from exercise,[17] and oscillatory ventilation.[18] Exercise test responses not involving ventilatory gas exchange have also been shown to predict risk in patients with CHF, including impaired heart rate recovery (HRR),[19] blunted systolic blood pressure,[20] and an impaired heart rate response (termed chronotropic incompetence).[21]

Most previous studies have taken a binary approach to estimating risk, for example, applying a peak VO_2 achieved <14 mL kg^{-1} min^{-1} to define a group at high risk. Unlike this approach, the development of multivariable scores permits the quantification of risk using a spectrum of increasingly abnormal findings.[22] The use of multivariable risk models integrating the full range of CPX responses has not been fully explored. For example, few studies have applied peak VO_2 in combination with indices of ventilatory inefficiency to estimate risk. Although there have been a small number of multivariate approaches using the CPX for prognostic purposes,[20,23-26] these approaches are limited for several reasons. First, they have generally focused on the top performing variable, disregarding the potential value of the independent, additive value of the multitude of exercise test variables in predicting risk. Other studies have used statistical models that are unattractive as routine clinical tools because they tend to be cumbersome, often requiring a calculator. Finally, these studies have generally not incorporated newer CPX markers of risk that have recently been recognized to powerfully predict outcomes in HF.

The purpose of this study was to develop a multivariate score based on CPX responses to facilitate risk stratification in patients with CHF. Our objective was to integrate newer indices of ventilatory inefficiency in addition to established markers of risk from the exercise test to provide a simple and graded score that can be easily applied.

Methods

This study was a multicenter analysis including patients with HF from the exercise laboratories at the VA Palo Alto Health Care System and Stanford University, Palo Alto, CA; San Paolo Hospital, Milan, Italy; Virginia Commonwealth University, Richmond, VA; and the LeBauer Cardiovascular Research Foundation, Greensboro, NC. A total of 710 patients with chronic HF (568 males and 142 females), tested between March 18, 1993 and March 5, 2007, were included. Inclusion criteria consisted of a diagnosis of CHF[2] and evidence of left ventricular systolic (ejection fraction <40%) and/or diastolic dysfunction by 2-dimensional echocardiography obtained within 1 month of exercise testing. Diastolic dysfunction was considered to be present if the ejection fraction was normal (>45%) and the subject had a history of decompensated CHF. Subjects received routine follow-up care at the 4 institutions included in the study. The subjects completed a written informed consent, and institutional review board approval was obtained at each institution.

Cardiopulmonary exercise test procedure and data collection

Symptom-limited CPX was performed on all patients using treadmill or cycle ergometer ramping protocols.[27] A treadmill was used for testing in the American centers, whereas a cycle ergometer was used in the European center. We previously observed that optimal peak VO_2 and VE/VCO_2 slope threshold values for estimating prognosis are similar irrespective of mode of exercise in patients with CHF.[28]

Minute ventilation (VE, BTPS), oxygen uptake (VO_2, STPD), carbon dioxide production (VCO_2, STPD), and other CPX variables were acquired breath by breath and averaged over 10- or 15-second intervals. VE and VCO_2 responses throughout exercise were used to calculate the VE/VCO_2 slope via least squares linear regression ($y = mx + b$, m = slope). Previous work by our group and others has shown this method of calculating the VE/VCO_2 slope to be optimal for estimating prognosis.[29,30] The OUES was calculated using [(VO_2 (L/min) = m ($\log_{10}$VE) + b, where m = OUES)].[12,31,32] Heart rate recovery was defined as (maximal heart rate minus heart rate at 1 minute in recovery).[19] Resting end-tidal carbon dioxide pressure ($PetCO_2$) was derived from the average of a 2-minute sitting resting period prior to the test.[15]

End points

The primary end point was cardiac-related mortality. Two composite end points including major cardiac events were also studied; the first included cardiac transplantation, left ventricular assist device (LVAD) implantation, and cardiac-related death (composite outcome 1), and the second included cardiac-related hospitalization, cardiac transplantation, LVAD implantation, and cardiac-related death (composite outcome 2). Subjects were followed for major cardiac-related events for 3 years after their exercise test using the Social Security Death Index and hospital and outpatient medical chart review. Follow-up was performed by the CHF program at each respective institution, providing a high likelihood that all major events were captured.

Statistical analysis

NCSS (Kayesville, UT), SPSS (Chicago, IL) software, and the 'Design' and 'Hmisc' libraries in S-Plus 7.0 (Seattle, WA) were used for statistical analyses. Unpaired t tests were used for comparisons of continuous variables, and χ^2 tests were used to compare categorical variables between those who experienced a cardiac event and those who did not. The receiver operating characteristic (ROC) curve analysis was used to define optimal threshold values for each CPX response. Z tests were used to compare the areas under the ROC curves for CPX responses. Proportional hazards analysis was used to determine age-adjusted hazard ratios for the 5 CPX variables included in the model, each expressed dichotomously using the threshold value. Optimal thresholds for each of the CPX variables were as follows: VE/VCO_2 slope (≥34) abnormal HRR (≤6 beats at 1 minute), OUES (>1.4), $PetCO_2$ (<33 mm Hg), and peak VO_2 (≤14 mL kg^{-1} min^{-1}).

Table I. Demographic and clinical characteristics of survivors and nonsurvivors

Characteristic	Survivors (n = 599)	Nonsurvivors (n = 111)	P
Age (y)	56.5 ± 13	55.1 ± 13	.31
BMI (kg/m^2)	29.0 ± 6.1	26.9 ± 5.0	<.001
Ejection fraction (%)	34.2 ± 13	25.8 ± 11	<.001
NYHA class	2.32 ± 0.80	2.53 ± 0.66	.07
Peak VO_2 (mL kg^{-1} min^{-1})	17.49 ± 6.6	14.0 ± 4.7	<.001
Medications, n (%)			
β-Blocker	377 (63)	61 (55)	.11
ACE inhibitor	457 (76)	76 (68)	.08
Diuretic	347 (58)	83 (75)	<.001

NYHA, New York Heart Association; *VO_2*, oxygen uptake.

Each variable was assigned a weight according to the hazard ratios and summed to calculate the composite score. The proportional hazard assumptions were confirmed for each variable using the log [–log (survival function)] plot.

Kaplan-Meier analysis was used to determine overall and cardiovascular event-free survival characteristics for the summed score classifications 0 to 5, 6 to 10, 11 to 15, and >15. This analysis was repeated in 2 prespecified subgroups, which were composed of subjects with left ventricular ejection fraction (LVEF) <30% (median value for the study population) and subjects with LVEF ≥30%. The log-rank test was used to determine statistical significance of the Kaplan-Meier analyses. Multivariable proportional hazards analysis adjusted for age, sex, body mass index (BMI), ejection fraction, and cardiomyopathy type and stratified by study site was then used to calculate hazard ratios for each summed score classification group.

The predictive accuracies of each of the CPX responses were determined using the right censored concordance index (C index) validated with 200 bootstrap samples. The predictive accuracy of the summed score was then evaluated via similar analysis in 4 prespecified subgroups: subjects with ischemic cardiomyopathy and nonischemic cardiomyopathy and subjects with LVEF <30% and >30%.

Results

Baseline characteristics and development of the summed score

The study sample is composed of 568 males and 142 females with CHF; 331 (49%) had an ischemic etiology. The BMI and ejection fraction were higher among those who survived versus those who died (Table I). Among CPX variables, peak VO_2 (17.5 ± 6.6 vs 14.0 ± 4.7 mL kg^{-1} min^{-1}), peak heart rate, HRR, OUES, and $PetCO_2$ were higher among those who survived. Conversely, the VE/VCO_2 slope and the CPX weighted summed score were lower among survivors ($P < .001$ for both) (Table II).

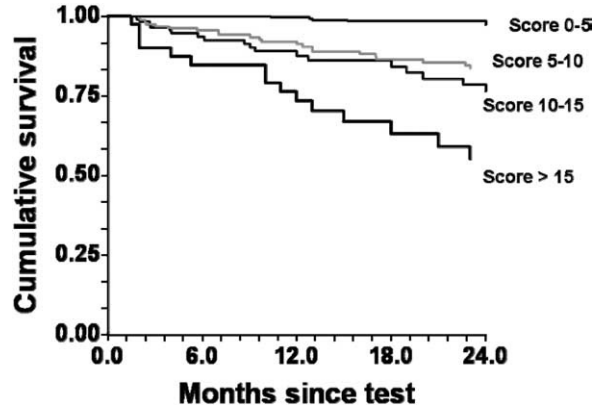
There were 175 total adverse events (91 deaths, 65 cardiac-related hospitalizations, 12 transplantations, and 7 LVAD implantations) over the mean 2.4 ± 2.1 year follow-up. Composite outcome 1 included 110 events, and composite outcome 2 included 143 events. By proportional hazards analysis, an abnormal VE/VCO_2 slope was the strongest predictor of the composite outcome, followed by HRR, OUES, $PetCO_2$, and peak VO_2. The weighted scores for each of these responses were 7, 5, 3, 3, and 2, respectively. When only those patients taking β-blockers were studied, the relative weights were similar, with the exception that there was a lower weight for HRR (weight = 2).

Table II. Exercise test responses in survivors and nonsurvivors

Characteristic	Survivors	Nonsurvivors	P
Resting heart rate (beat/min)	77 ± 16	78 ± 19	.66
Maximal heart rate (beat/min)	128 ± 25	117 ± 26	.001
Peak VO_2 (mL kg^{-1} min^{-1})	17.5 ± 6.6	14.0 ± 4.7	<.001
Peak RER	1.07 ± 0.17	1.05 ± 0.18	.31
HRR (beats)	19.2 ± 14	8.6 ± 9	<.001
VE/VCO_2 slope	32.4 ± 8.0	40.4 ± 10	<.001
OUES	1.79 ± 0.78	1.35 ± 0.67	.001
$PetCO_2$ (mm Hg)	35.1 ± 7.8	31.3 ± 6.1	<.001
Weighted summed score	4.0 ± 4.7	9.4 ± 5.3	<.001

RER, Respiratory exchange ratio.

Figure 1

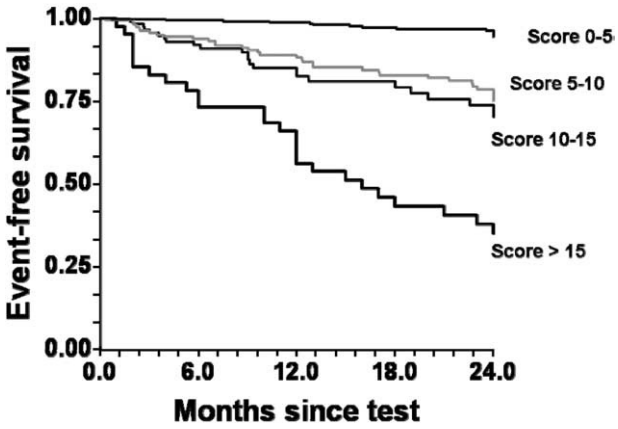


Cumulative survival by Kaplan-Meier analysis for composite risk scores. $P < .001$ by log-rank test.

Relationships between summed score and outcomes

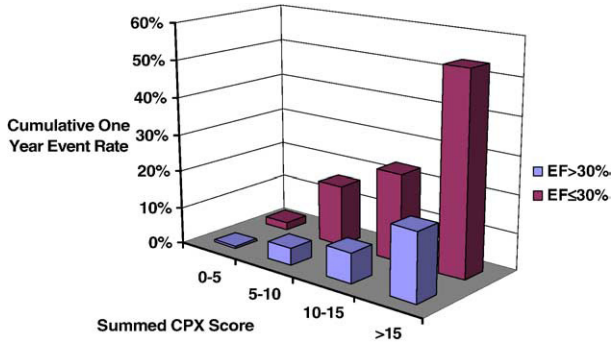
Overall and cardiovascular event-free Kaplan-Meier survival estimates according to summed score classification are presented in Figures 1 and 2, respectively. There were significant step-wise increases in both mortality and composite outcome rates associated with increasing weighted summed scores. The estimated 1-year death rates were 26.6% (95% confidence interval [CI] 12.4-40.8) for subjects with summed scores >15 and only 0.4% (0.0%-1.1%) for subjects with summed scores <5. Similarly, whereas subjects with summed scores >15 had estimated 1-year rates of death, transplantation, LVAD implantation, or CHF-related hospitalization of 44.0%

Figure 2



Cumulative cardiovascular event-free survival Kaplan Meier analysis for composite risk scores. Cardiovascular events were death, transplantation, LVAD implantation, and CHF hospitalization. $P < .001$ by log-rank test.

Figure 3

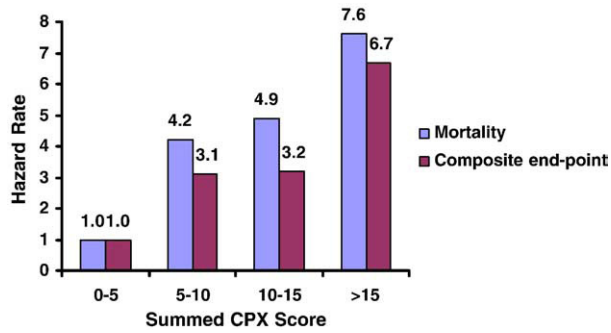


Cumulative 1 year rate of death, transplantation, LVAD implantation, or CHF hospitalization according to ejection fraction and composite CPX score.

(95% CI 28.2%-59.1%), subjects with summed scores <5 had rates of such events at 1 year of 1.2% (95% CI 0.1%-2.4%).

This step-wise increase in risk persisted in Kaplan-Meier subgroup analyses for both subjects with LVEF ≥30% and subjects with LVEF <30%, although subjects with LVEF ≥30% had lower overall event rates (Figure 3). Multivariable proportional hazards analysis adjusted for potential confounders (Figure 4) revealed similar associations between the summed score and event rates. In this model, subjects with weighted summed scores >15 had hazards for mortality and composite outcomes of 7.6 (95% CI 3.3-17.8) and 6.7 (95% CI 3.6-12.4), respectively, when compared with subjects who had summed scores <5.

Figure 4



Hazard ratios for mortality and composite end point (includes death, transplantation, LVAD implantation, and CHF hospitalization) by CPX risk score in multivariable analysis. The model included age, gender, BMI, ejection fraction, and cardiomyopathy type (ischemic vs nonischemic) and was stratified by study site. $P < .001$ for trend.

Table III. Predictive accuracy of cardiopulmonary exercise testing parameters and composite risk score

	Mortality	Composite outcome 1 *	Composite outcome 2 †
Variable	**C index**	**C index**	**C index**
Composite risk score	0.77	0.77	0.75
Ve/VCO_2 slope ≥34	0.71	0.71	0.71
Peak VO_2 ≤ 14 mL kg^{-1} min^{-1}	0.64	0.65	0.64
$PetCO_2$ ≤33 mm Hg	0.65	0.63	0.64
OUES >1.4	0.61	0.61	0.61
HRR ≤6 beat/min	0.57	0.58	0.56

C index indicates the bootstrap-validated right-censored concordance index.
*Composite outcome of death, transplantation, and LVAD implantation.
†Composite outcome of death, transplantation, LVAD implantation, and CHF-related hospitalization.

Predictive accuracy of CPX variables and summed score

The predictive accuracy of CPX responses and the weighted summed scores for mortality and the 2 composite outcomes are presented in Table III. The VE/VCO_2 slope was the most accurate predictor of outcomes of any individual CPX variable (C index 0.71 for all outcomes), followed by peak VO_2, $PetCO_2$, OUES, and HRR. The summed risk score was a more accurate predictor of outcomes than any individual CPX variable (C indexes 0.77 for mortality and composite end point 1 and 0.75 for composite end point 2, respectively). The predictive accuracy of the summed score for mortality and composite outcome 1 was similar in subjects with ischemic and nonischemic cardiomyopathy but differed for composite outcome 2 (C index 0.78 for ischemic cardiomyopathy

Table IV. Predictive accuracy of cardiopulmonary exercise testing risk score in selected subgroups

	Mortality	Composite outcome 1 *	Composite outcome 2 †
	C index	C index	C index
Cardiomyopathy type			
Ischemic	0.77	0.77	0.78
Nonischemic	0.76	0.77	0.73
Ejection fraction			
≤30%	0.77	0.76	0.74
>30%	0.73	0.73	0.70

C index represents bootstrap validated concordance right-censored concordance index.
*Composite outcome of death, transplantation, and LVAD implantation.
†Composite outcome of death, transplantation, LVAD implantation, and CHF-related hospitalization.

and 0.73 for nonischemic cardiomyopathy; Table IV). The summed score was consistently more accurate in predicting outcomes in subjects with an LVEF <30% than in subjects with an LVEF >30% (Table IV). The performance of the score was similar when patients tested on a cycle ergometer (23% of the sample) were removed.

Discussion

Beginning in the mid-1990s, consensus guidelines recommended the application of the CPX to supplement other clinical data in the management of patients with HF. However, these guidelines limited their recommendations to the application of peak VO_2 achieved in the context of selecting patients for transplantation. In recent years, a broader appreciation of the CPX has occurred, and an expanding number of responses from the test have been applied to predict risk in patients with HF. This has led to a shift in focus from peak VO_2 to indices of ventilatory inefficiency.[32] Most notably, the VE/VCO_2 slope has consistently been shown to more powerfully predict risk than peak VO_2.[6-12,32] Other CPX responses, including $PetCO_2$ and the OUES, have also recently been shown to be strong markers of risk in HF.[12,13,15,16] However, most studies have addressed these responses in isolation, largely disregarding the potential value of the independent, additive value of the multitude of exercise test variables that predict mortality risk. There is a growing awareness of the need to apply statistical techniques to develop evidence-based multivariable scores for improving clinical decision making.[22,33] Although there have been efforts to apply multivariable techniques to improve estimates of prognosis in HF, these approaches are generally cumbersome and have used models that were largely developed empirically.

In this study, we observed that a multivariable score using relatively easily derived CPX responses improves the estimation of risk in patients with HF. We incorporated variables that have recently been shown to be independent and strong predictors of outcomes in patients with HF.[6-16,19,20,32] The estimation of risk was incremental, with each response adding progressively and independently to the prediction of adverse outcomes. In contrast to more complex regression equations, a simple scoring approach was used,[22,33] requiring only the determination of whether a response exceeded an abnormal threshold and the summation of points. Although the score used only CPX responses, the strength of the model was similar to more detailed approaches requiring right heart catheterization data, measures of ventricular function, or both.[23,25] In evaluation of the model, we used a C index which, unlike the hazard ratio, estimates the predictive accuracy of a model.[34] The C index estimates the probability of concordance between predicted and observed responses; in the present context, it is the probability that of any 2 randomly selected patients, the patient who remains event-free for longer has a lower CPX score than the patient who experiences an event in a shorter amount of time. In our study population, the CPX score was the most accurate predictor of outcomes of all CPX responses considered. Moreover, we observed that the CPX score remained accurately associated with time-to-outcome in patients with both nonischemic and ischemic cardiomyopathy and in patients with LVEF >30% or ≤30%.

Although other CPX responses have recently been used for the estimation of prognosis in patients with HF (including oxygen kinetics, the ventilatory threshold, VO_2 in recovery, and oscillatory breathing patterns),[17,18,20,24,26] we limited the analysis to the 5 variables described above because (1) we[6,7,11,12,15,16,19,20,29] and others[5,8-10,13,26] have recently reported on the strength of these particular responses in predicting HF outcomes, and (2) each is easily obtained from the CPX summary report and requires no (or minimal) additional calculations; thus, the scoring system is kept as simple as possible. In accordance with recent studies from our group[6,11,12,15,16,19] and others,[8-10] the VE/VCO_2 slope was the most powerful predictor of risk, with an abnormal response ascribed a relative "weight" of 7 points, followed by abnormal HRR, with a score of 5 points. Importantly, each of the 5 responses added significant and independent prognostic information to predicting risk. In addition, the predictive accuracy of the score was similar regardless of type or severity of HF (Table IV).

Although resting $PetCO_2$ and HRR have not been widely applied in prognostic studies in patients with HF, we included these responses in the score. Reduced $PetCO_2$ at rest has been associated with impaired cardiac output under various conditions in the intensive care unit.[35,36] Because impaired cardiac output is an important mechanism underlying ventilation/perfusion

mismatching in the lung and therefore inefficient ventilation in HF,[33] it follows that $PetCO_2$ would predict prognosis. We recently observed that resting $PetCO_2$ strongly predicted mortality and hospitalization in HF[15]; in fact, when $PetCO_2$ was assessed multivariately with the VE/VCO_2 slope, peak VO_2 was not a significant predictor of these outcomes. Heart rate recovery is related to the capacity of the cardiovascular system to reverse autonomic nervous system (withdrawal of vagal activity) and baroreceptor (detection of changes in blood pressure and inhibition of sympathetic discharge) adaptations that occur during exercise, often termed *vagal reactivation*.[37] Autonomic dysfunction is a hallmark of HF,[38] and we recently observed that HRR is a powerful predictor of outcomes in these patients.[19] Although HRR has rarely been applied in previous multivariable models, the fact that HRR had the second highest weight in the score suggests that this response should be routinely included in risk stratification models in patients with HF.

Limitations

We did not have sufficient data to validate the score; to do so will require an independent sample. The application of the score requires validation before being applied at multiple centers. Most (80%) of our sample was men, and the severity of HF varied. Thus, the portability of this approach to women and other populations with HF requires further study. We did not include clinical or invasive hemodynamic indices of risk, and there are CPX markers of risk that we did not include in the score. However, our objective was to focus on the prognostic use of the CPX itself and to keep the score as simple as possible. In addition, our sample size limited the number of independent variables in the model.

Summary

This study further defines the important role of the CPX for predicting outcomes in patients with HF. Rather than relying strictly on peak VO_2, the simple summation of several easily obtained responses from the CPX can be used to more accurately describe the spectrum of risk for adverse events in these patients. By including indices that reflect abnormalities in several systems that are related to outcomes, including oxygen delivery and extraction (peak VO_2), ventilatory inefficiency (VE/VCO_2 slope and OUES), and autonomic function (HRR), application of the score described herein may be used to more appropriately facilitate clinical decision making in patients referred for evaluation of HF.

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