Validation of a Cardiopulmonary Exercise Test Score in Heart Failure

Myers et al: CPX Score In Heart Failure

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Abstract

Background—Cardiopulmonary exercise test (CPX) responses are strong predictors of outcomes in patients with heart failure (HF). We recently developed a CPX score that integrated the additive prognostic information from CPX. The purpose of this study was to validate the score in a larger, independent sample of patients.

Methods and Results—2,625 HF patients underwent CPX and were followed for cardiovascular (CV) mortality and major CV events (death, transplantation, LVAD implantation). Net reclassification improvement (NRI) for the score and each of its components were determined at 3 years. The VE/VCO2 slope was the strongest predictor of risk and was attributed a relative weight of 7, with weighted scores for abnormal heart rate recovery, OUES, PetCO2, and peak VO2 having scores of 5, 3, 3, and 2, respectively. A summed score >15 was associated with an annual mortality rate of 12.2% and a relative risk of 8.3, whereas a score <5 was associated with an annual mortality rate of 1.2%. The composite score was the most accurate predictor of CV events among all CPX responses considered (C indexes 0.70 for CV mortality and 0.72 for the composite outcome). Each component of the score provided significant NRI compared with peak VO2 (category-free NRI 0.61 to 0.77), and the score provided significant NRI above clinical risk factors for both CV events and mortality (NRI 0.63 and 0.65 for CPX score compared with clinical variables alone).

Conclusions—These results validate the application of a simple, integrated multivariable score based on readily available CPX responses.

Key Words: exercise testing, exercise physiology, heart failure, epidemiology, oxygen consumption
Recent advances in therapy have resulted in a reduction in mortality for most forms of cardiovascular disease (CVD). However, success in treating other forms of CVD along with aging of the population has resulted in an increase in the prevalence of chronic heart failure (HF) (1,2). HF is now the leading cause of hospitalization among those over the age of 65, accounting for approximately 20% of hospital admissions in this group (3). Therefore, a great deal of effort in recent years has been directed toward evaluation techniques designed to optimally stratify risk in these patients. A hallmark symptom of HF is exercise intolerance, typically evidenced by excessive shortness of breath, fatigue, or both. Over the last two decades, the cardiopulmonary exercise test (CPX) has become an important procedure for quantifying the degree of exercise intolerance. Numerous studies have demonstrated that CPX responses powerfully stratify risk in patients with HF (4,5). Once generally limited to the assessment of peak VO2, indices of ventilatory inefficiency, heart rate recovery, and other responses have more recently been demonstrated to provide clinically significant and independent information for estimating prognosis in patients with HF (4-6).

There remains debate regarding the optimal application of CPX variables for estimating risk for mortality, hospitalization, or other outcomes in patients with HF. Similar to many other clinical tools, researchers have tended to take a binary approach when applying the CPX for this purpose. For example, a peak VO2 achieved ≤14 ml•kg⁻¹•min⁻¹ has been widely applied to define HF patients at high risk for adverse events (4,7). More recently, there has been a growing awareness of the additional benefit of applying more complex statistical techniques and multivariate scores to predict risk in patients with CVD (8-10), and HF specifically (6,11). The advantage of these approaches is that they permit the quantification of risk across the spectrum of abnormal responses (10), and have been demonstrated to predict risk more accurately (6,10-12). These approaches have long been recommended for the standard exercise test to assist with the diagnosis of coronary artery
disease (8,9,13,14), and have recently been applied to CPX for estimating prognosis in patients with HF (6,11).

We recently developed a CPX score using a summation of readily available responses that improved the prognostic utility of the test (6). CPX responses recently shown to be strong and independent predictors of outcomes in patients with HF provided incremental, progressive, and independent information to the prediction of adverse outcomes. However, the sample employed was relatively small and a validation cohort for the score was not available. In addition, the association between a given risk marker and outcomes, despite generating a significant hazard, does not necessarily result in a higher reclassification of risk (15,16). Recently, statistical tests such as the net reclassification improvement (NRI) have been recommended to better quantify the ability of a measure to discriminate risk. The NRI improves upon more standard indices of predictive modeling, such as the area under the receiver-operating-characteristic curve (AUC) in that it more directly and incrementally evaluates the ability of new risk markers to classify subjects into higher or lower categories of risk (15-17). In the current study, we sought to: 1) validate a CPX score developed previously (6) in a larger, independent sample of patients with HF; and 2) determine the contributions of individual and combined components of the CPX to enhance risk classification in patients with HF.

Methods

This study was performed as part of a HF consortium; a multicenter, retrospective analysis including HF patients from the exercise laboratories at the VA Palo Alto Health Care System and Stanford University, Palo Alto, California, San Paolo Hospital, Milan, Italy, Virginia Commonwealth University, Richmond, Virginia, Brigham and Women’s Hospital, Boston, Massachusetts, and the LeBauer Cardiovascular Research Foundation, Greensboro, North
A total of 2,625 patients with chronic HF, tested between 1993 and 2010, were included. The sample included 1,974 males and 651 females, with a mean age of 56±14 years. Eighty nine percent of the subjects were independent from the original sample from which the score was developed. Inclusion criteria consisted of a diagnosis of HF (18) and evidence of left ventricular systolic (ejection fraction [EF] <40%) and/or HF with preserved EF by two-dimensional echocardiography obtained within one month of exercise testing. HF with preserved systolic function was considered to be present if the ejection fraction was normal (>45%) and the subject had a history of decompensated heart failure. Subjects received routine follow-up care at the five institutions included in the study. All subjects were stable and receiving optimal medical therapy at the time of testing. The subjects completed a written informed consent and institutional review board approval was obtained at each institution.

CPX Procedure and Data Collection. Symptom-limited CPX was performed on all patients using treadmill or cycle ergometer ramping protocols (19). A treadmill was used for testing in the American centers while a cycle ergometer was used in the European center. We previously observed that optimal peak VO2 and VE/VCO2 slope threshold values for estimating prognosis were similar irrespective of mode of exercise in patients with HF (20). Ventilatory expired gas analysis was performed using a metabolic cart at all five centers (Medgraphics CPX-D or ULTIMA PFX, Minneapolis, MN, Orca Diagnostics, Santa Barbara, CA, Parvo Medics TrueOne 2400, Sandy, UT or CareFusion Oxycon Pro, San Diego, CA). Before each test, the equipment was calibrated in standard fashion using reference gases. A standard 12-lead electrocardiogram was obtained at rest, each minute during exercise, and for at least 5 minutes during the recovery phase; blood pressure was measured using a standard cuff sphygmomanometer.

Minute ventilation (VE, BTPS), oxygen uptake (VO2, STPD), carbon dioxide
production (VCO2, STPD) and other CPX variables were acquired breath-by-breath and averaged over 10- or 15-second intervals. VE and VCO2 responses throughout exercise were used to calculate the VE/VCO2 slope via least squares linear regression \( y = mx + b \), \( m=\text{slope} \). Previous work by our group and others has shown this method of calculating the VE/VCO2 slope to be optimal for estimating prognosis (21,22). The OUES was calculated using \([\text{VO2 (l/min)} = m (\log_{10} \text{VE}) + b, \text{where } m=\text{OUES}]\) (23). Heart rate recovery was defined as [maximal heart rate minus heart rate at 1 minute in recovery] (24). Resting end-tidal CO2 pressure (PetCO2) was derived from the average of a two minute sitting resting period prior to the test (25).

**Endpoints.** The primary endpoint was cardiac-related mortality. A second composite endpoint including major cardiac events was also studied; this included cardiac transplantation, left ventricular assist device (LVAD) implantation and cardiac-related death. Subjects were followed for major cardiac-related events for three years after their exercise test using the Social Security Death Index and/or hospital and outpatient medical chart review. Follow-up was performed by the HF program at each respective institution, providing a high likelihood that all major events were captured. Individuals conducting the CPX were not involved in decisions regarding cause of death or heart transplant/LVAD implantation.

**Statistical Analysis.** NCSS (Kayesville, UT), software and the ‘Design’ and ‘Hmisc’ libraries in S-Plus 7.0 and R (Seattle, WA) were used for all statistical analyses. Unpaired t-tests were used for comparisons of continuous variables, and chi-square tests were used to compare categorical variables between those who experienced a cardiac event and those who did not. 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. Cox proportional hazards analysis was used to determine age-adjusted hazard ratios for the 5 CPX variables included in the model, each expressed

6
dichotomously using the threshold value. Optimal thresholds for each of the CPX variables were as follows: VE/VCO2 slope (≥ 34) abnormal HRR (≤6 beats at 1 min), OUES (≤1.4), PetCO2 (<33mmHg), and peak VO2 (≤14 ml•kg-1•min-1). Each variable was assigned a weight according to the hazard ratios, and summed to calculate the composite score. 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 0-5, 6-10, 11-15, and >15. This analysis was repeated in two pre-specified sub-groups, which comprised subjects with left ventricular ejection fraction (LVEF) < 30% and subjects with LVEF ≥ 30%. The log-rank test was used to determine statistical significance of the Kaplan-Meier analyses. Multivariable Cox proportional hazards analysis adjusted for age, sex, BMI, ejection fraction, and HF etiology was then used to calculate hazard ratios for each summed score classification group.

The predictive accuracy of each of the CPX responses were determined using both the right censored concordance index (C index) validated with 200 bootstrap samples, and the Akaike Information Criterion (AIC) method (26). The predictive accuracy of the summed score was then evaluated via similar analyses in four pre-specified subgroups: subjects with ischemic cardiomyopathy and non-ischemic cardiomyopathy, and subjects with LVEF < and ≥ 30%. To further evaluate the reclassification characteristics of individual components of the CPX score, as well as the composite CPX score in comparison with standard clinical risk factors (age, systolic blood pressure, heart failure etiology, body mass index, diuretic use, and LVEF), we calculated the category-free net reclassification improvement index (NRI), modified for right censored survival data according to the methods proposed by Pencina et al (27). The NRI was calculated for both cardiovascular-related mortality and major cardiovascular events. We corrected for over-optimism using 1000 bootstrap replicates and
report the median results and bootstrap estimated 95% confidence intervals.

**Results**

Baseline characteristics of the study population and development of the summed score. The study sample comprised 1,974 males and 651 females with HF; 35% had an ischemic etiology. The mean age of the cohort was 56±14 years and the mean body mass index (BMI) was 28.7±6.0. Subjects who died from cardiac causes were older and had a lower ejection fraction compared with subjects with no events (Table 1). Among CPX variables, peak VO2 (18.6±8.5 vs. 14.1±5.4 ml•kg⁻¹•min⁻¹), peak heart rate, HRR, OUES, and PetCO2 were higher among those with no events. Conversely, resting heart rate, the VE/VCO2 slope and the CPX weighted summed score were lower among in the no event group vs. those who died from cardiac causes. Peak VO2 was lowest while the VE/VCO2 slope and the weighted summed score were highest in patients who had a secondary outcome (LVAD or transplantation) vs. both the no event and cardiac mortality groups.

There were 412 total adverse events (290 deaths, 79 transplantations, and 43 LVAD implantations) over the mean 2.4±2.5 year follow-up. The weighted scores for abnormal CPX responses were derived from proportional hazards analysis and replicated from the previous score (6); weighted scores of 7, 5, 3, 3 and 2 were applied for the VE/VCO2 slope, HRR, OUES, PetCO2, and peak VO2, respectively. When only those patients taking beta blockers were studied, the relative weights were similar, with the exception that there was a lower weight for HRR (weight=2).

Predictors of adverse events. Age-adjusted univariate predictors of cardiovascular mortality, secondary events, and total events are presented in Table 2. Each of the CPX responses in the score was significantly associated with each of the outcomes, with an abnormal VE/VCO2 slope generating the highest risk (hazard ratios 3.2 [95% CI 2.5-4.3], 8.3
[95% CI 5.4-12.9] and 4.3 [95% CI 3.5-5.3], all p<0.001) for cardiovascular mortality, secondary events, and total events, respectively). With a weighted summed score of 0-5 as the reference group, risks for all event categories were significantly higher as the weighted summed score categories increased from 6-10, 11-15, and >15. For total events, a score >15 was associated with a hazard ratio >9. These results were similar among patients with preserved and reduced EF. Each CPX response and the composite score also significantly predicted risk when expressed as continuous variables.

Relationships between summed score and outcomes. Overall mortality and the composite event-free Kaplan-Meier survival estimates according to summed score classifications 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 one-year death rate was 12.2% for subjects with a summed score of greater than 15 and only 1.2% for subjects with a summed score less than 5. Similarly, whereas subjects with summed scores greater than 15 had estimated one-year rates of death, transplantation, or LVAD of 17%, subjects with summed scores less than 5 had rates of such events at one year of 2.8%. This step-wise increase in risk persisted in Kaplan-Meier sub-group analyses for both subjects with LVEF >30% and subjects with LVEF ≤30%, though subjects with LVEF >30% had lower overall event rates.

Predictive accuracy of CPX variables and summed score. The predictive accuracy of CPX responses and the weighted summed score for mortality and major events are presented in Table 3. The VE/VCO2 slope was the most accurate predictor of outcomes among individual CPX variables (C index 0.70 for major events), followed by peak VO2, OUES, PetCO2, and HRR. The summed risk score was a more accurate predictor of outcomes than any individual CPX variable (C indexes 0.70 for cardiac mortality and and 0.72 for major events, respectively). The predictive accuracy of the summed score for mortality and the
composite outcome was similar in subjects with ischemic and non-ischemic cardiomyopathy.

Table 4 presents age-adjusted AIC weights for each individual CPX response and the summed score. The summed score had the highest predictive value (0.73, indicating a 73% probability of being the strongest model). The score remained the most powerful after adjustment for beta blocker use and after applying different cutpoints for high risk.

Classification of risk. Table 5 presents category-free net reclassification improvement indexes (NRI) for major cardiovascular events at 36 months for individual components of the CPX score. The VE/VCO2 slope, OUES, end-tidal PetCO2, and HRR all provided significant overall incremental risk reclassification. The risk reclassification improvement provided by HRR was specific to individuals without cardiovascular events; all other components of the CPX score provided significant risk reclassification improvement both for subjects with cardiovascular events and those without cardiovascular events at 36 months. Table 6 presents category-free NRI for the CPX score in comparison to standard clinical risk factors (age, systolic blood pressure, heart failure etiology, body mass index, diuretic use, and left ventricular ejection fraction). The CPX score provided significant net reclassification improvement for both cardiovascular-related mortality (NRI = 0.65, 95% CI 0.61-0.69) and for cardiovascular events (NRI = 0.63, 95% CI 0.59-0.68) at 36 months.

Discussion

The current results provide a measure of validation for a previously developed CPX score (6) in group of patients with HF that is significantly larger than the sample from which the score was developed. The multivariate score employed common and easily derived CPX responses, and its application improved the classification risk for adverse events in patients with HF. The estimation of risk was incremental, with each component of the score adding progressively and independently to the prediction of outcomes. The composite CPX score
was the most accurate predictor of outcomes among all the CPX responses considered, and accurately predicted risk for adverse events among patients with both ischemic and non-ischemic cardiomyopathy and among both patients with LVEF >30% and ≤30%. The current data thus represent what is commonly termed a validation set, or a measure of cross-validation for the original score (28). These findings further refine the application of CPX for the estimation of risk in patients with HF, and may help to optimize the clinical decision making process when evaluating these patients.

We employed a novel index of risk classification, the NRI (15-17), to provide better insight into the individual components of CPX that are known to predict risk (4,6). The NRI reflects clinically meaningful improvement in risk classification achieved with each component of the score; it is calculated as the net change in risk among subjects after the addition of each marker to the baseline model (in the current case, standard clinical variables). Our results extend previous findings by demonstrating that each CPX response included in an integrated score (the VE/VCO2 slope, peak VO2, OUES, resting PetCO2, and HRR) added significant incremental improvement in risk reclassification. For example, adding individual components of the score to peak VO2 improved classification of subjects at risk (up or down) by approximately 70% (Table 5); similarly, adding the integrated CPX score to clinical variables improved the classification of subjects at risk by >60% (Table 6). Thus, the addition of the score to a simple model of clinical risk factors significantly improved risk classification. In addition, these findings suggest that the individual components of the score reflect separate maladaptive pathways in HF and that each contributes to adverse event risk.

While peak VO2 has been the most widely-used CPX variable to predict risk, reliance on any single factor or statistic is generally known to have limited accuracy (15,29). For example, multivariate scores have long been recommended to enhance the diagnostic and
prognostic accuracy of the standard exercise test and have been recommended in exercise testing guidelines (14). This is in part due to a growing awareness of the need to apply statistical techniques to develop evidence-based multivariable models for improving clinical decision making (10,12). The CPX score described herein is consistent with this approach, as it provides quantification of risk across the spectrum of abnormal responses. The performance of the score was similar to the original analysis (6) both in terms of its predictive accuracy and overall risk using cumulative scores (Tables 3 and 4, Figures 1 and 2). Patients with a summed score >15 had a more than 4-fold risk for cardiovascular mortality, a more than 12-fold risk for secondary events, and a more than 9-fold risk for total events. This is contrasted by the risk associated with, for example, an impaired peak VO2 alone, which had an age-adjusted hazard ratio of 2.0, and underscores the advantages of applying a multivariable approach as opposed to the commonly-applied binary method. The CPX score yielded a 73% probability that the model was superior, as compared to the negligible probability when using any one of the variables alone, or even when compared to the combination of peak VO2 and the VE/VCO2 slope (Table 4).

In recent years, our group (4,6,20,21,24,25) and others (4,5,22,30) have demonstrated significant and independent prognostic value for each of the components of the score. One explanation for the strong and incremental prognostic power we observed is that the components of the score reflect different pathologies that are characteristic of HF. While peak VO2 has long been recognized as an important prognostic marker in patients with HF, indices of ventilatory inefficiency have more recently been demonstrated to be important components of the risk paradigm (4,5), and their application is now advocated in guidelines on HF management (31,32). In particular, the VE/VCO2 slope has been widely studied and has been shown to be a more powerful predictor of risk than peak VO2 (4,6,31), which is consistent with the current study (Tables 2 and 3). Abnormalities in ventilatory efficiency have been
demonstrated to reflect ventilation/perfusion mismatching in the lungs (related in part to an impaired cardiac output response to exercise), early lactate accumulation, and abnormalities in respiratory control (4,5,31,32). Abnormal HRR is associated with autonomic dysfunction that is common in HF (reflected by impaired vagal reactivation), and has been shown to provide prognostic power independent of peak VO2 and the VE/VCO2 slope (24).

The present results extend previous findings from Aaronson et al (11) who employed peak VO2 along with several non-invasive clinical markers in a multivariate model to predict event-free survival in patients with HF (termed the Heart Failure Survival Score, or HFSS). Application of 7 non-invasive variables identified low and high-risk groups with 93% and 43% 1-year event free survival, respectively. The HFSS has outperformed peak VO2 alone in both US and European populations of patients with HF (11,33,34). While the HFSS has been validated (33) and widely used, it included only peak VO2 from CPX. Numerous recent studies have also incorporated one or more indices of ventilatory inefficiency in addition to peak VO2 to predict prognosis in HF (4-6); all of these studies have demonstrated improved risk stratification by documenting inefficient ventilation in addition to impaired peak VO2. However, we are unaware of other multivariate scores focusing specifically on CPX responses.

**Limitations.** By design, the CPX score focuses primarily on the ventilatory gas exchange response to exercise and does not include other clinical markers of risk in HF. There are other CPX responses that predict risk, particularly oscillatory breathing (4,31), which were not included in the score. In addition, while the score was compared with simple clinical variables, it should be noted that there are many other variables and biomarkers that have been used to define risk in HF. A more complex score including some of these markers may provide better precision for estimating risk. Some patients had LVAD or transplantation as their endpoint, and a given patients’ CPX responses likely influenced the decision to have
these procedures, raising a potential bias. Finally, the sample was 75% male, and the results
may not be as applicable to women.

Summary. The current results extend the many recent studies demonstrating the strong
prognostic value of CPX. Our findings validate a composite CPX score (6) for predicting risk
of adverse events in patients with HF; individual components of the score improved
reclassification of risk for mortality and adverse events. The simple summation of easily
derived responses from CPX can be applied to more accurately estimate risk in patients with
HF.

Disclosures

None.

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mortality in unselected patients presenting for exercise testing with symptoms of suspected
Table 1. Demographic and cardiopulmonary exercise test comparisons between survivors and non-survivors

<table>
<thead>
<tr>
<th>Variables</th>
<th>No Events (n = 2290)</th>
<th>Cardiac Mortality (n = 224)</th>
<th>Secondary Outcomes (Transplant/LVAD) (n=121)</th>
<th>p value††</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>55.6 ± 14</td>
<td>61.0 ± 13*</td>
<td>50.3 ± 13†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>28.7 ± 6.1</td>
<td>27.8 ± 5.6</td>
<td>27.7 ± 5.8*</td>
<td>0.022</td>
</tr>
<tr>
<td>Ejection Fraction (%)</td>
<td>36.7 ± 15.8</td>
<td>31.1 ± 13.4*</td>
<td>22.6 ± 11.7†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NYHA Class</td>
<td>2.32 ± 0.83</td>
<td>2.69 ± 0.77*</td>
<td>3.06 ± 0.69†</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Medications, n%
- β-Blocker: 1410 (66.1) vs. 112 (55.2)* vs. 88 (73.9)**, p = 0.001
- ACE inhibitor: 1261 (55.1) vs. 135 (60.3) vs. 72 (59.5)*, p = 0.229
- Diuretic: 1056 (54.5) vs. 93 (60.8) vs. 98 (82.4)*, p < 0.0001

Exercise test responses#
- Resting heart rate (b/min): 75 ± 14 vs. 80 ± 16* vs. 75 ± 15**, p < 0.0001
- Maximal heart rate (b/min): 130 ± 26 vs. 122 ± 22* vs. 110 ± 27†, p < 0.0001
- Peak VO2 (ml•kg⁻¹•min⁻¹): 18.8 ± 8.5 vs. 14.9 ± 5.6* vs. 12.1 ± 3.8†, p < 0.0001
- Peak RER: 1.10 ± 0.14 vs. 1.10 ± 0.17 vs. 1.14 ± 0.16†, p = 0.008
- HRR (beats): 20.1 ± 13.4 vs. 15.7 ± 10.3* vs. 15.9 ± 11.8*, p < 0.0001
- VE/VCO2 slope: 32.5 ± 8.6 vs. 37.6 ± 11.7* vs. 42.3 ± 11.7†, p < 0.0001
- OUES: 2.09 ± 0.89 vs. 1.60 ± 0.65* vs. 1.31 ± 0.61*, p < 0.0001
- PetCO2 (mmHg): 33.9 ± 4.6 vs. 32.6 ± 4.4* vs. 31.5 ± 3.9*, p < 0.0001
- Weighted summed score: 5.26 ± 4.3 vs. 7.4 ± 4.6* vs. 8.6 ± 4.2†, p < 0.0001

†† p value represents main effect
* p <0.05 vs. no events
** p <0.05 vs. cardiac mortality
† p <0.05 vs. no events and cardiac mortality

BMI – body mass index; NYHA – New York Heart Association; ACE – angiotensin receptor blocker; RER – respiratory exchange ratio; HRR – heart rate recovery at 1 minute; OUES – oxygen uptake efficiency slope; PetCO2 – end-tidal carbon dioxide pressure

#Using standard clinical indications, reasons for stopping exercise included 22% overall fatigue/exhaustion, 31% shortness of breath/dyspnea, 22% leg fatigue, 6% chest discomfort, 5% claudication, 0.4% knee pain, and 13.6% for other reasons.
Table 2. Age-adjusted univariate proportional hazards analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cardiac Mortality (n= 224)</th>
<th>LVAD/Transplant (n= 121)</th>
<th>Total Events (n= 412)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR  95 % CI  p Value</td>
<td>HR  95 % CI  p Value</td>
<td>HR  95 % CI  p Value</td>
</tr>
<tr>
<td>Age (y)</td>
<td>1.37 1.20 - 1.57 &lt; 0.0001</td>
<td>1.46 1.21 - 1.77 &lt; 0.0001</td>
<td>1.10 0.98 - 1.21 0.11</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>1.11 0.97 - 1.27 0.14</td>
<td>1.09 0.90 - 1.33 0.39</td>
<td>1.11 1.00 - 1.25 0.06</td>
</tr>
<tr>
<td>Ejection Fraction (%)</td>
<td>1.55 1.33 - 1.81 &lt; 0.0001</td>
<td>3.33 2.56 - 4.33 &lt; 0.0001</td>
<td>1.95 1.71 - 2.23 &lt; 0.0001</td>
</tr>
<tr>
<td>NYHA Class</td>
<td>1.92 1.39 - 2.66 &lt; 0.0001</td>
<td>3.90 2.65 - 5.75 &lt; 0.0001</td>
<td>2.53 1.99 - 3.21 &lt; 0.0001</td>
</tr>
<tr>
<td>Etiology (ischemic)</td>
<td>1.01 1.36 - 2.34 &lt; 0.0001</td>
<td>1.98 1.34 - 2.95 0.0007</td>
<td>1.72 1.40 - 2.10 &lt; 0.0001</td>
</tr>
<tr>
<td>Peak VO2 ≤ 14 ml·kg-1·min-1</td>
<td>1.98 1.52 - 2.57 &lt; 0.0001</td>
<td>6.07 4.06 - 9.05 &lt; 0.0001</td>
<td>3.10 2.54 - 3.77 &lt; 0.0001</td>
</tr>
<tr>
<td>HRR ≤ 6 beats at 1 min</td>
<td>1.75 1.09 - 2.79 0.02</td>
<td>2.04 0.99 - 4.22 0.054</td>
<td>2.14 1.55 - 2.96 &lt; 0.0001</td>
</tr>
<tr>
<td>VE/VCO2 slope ≥ 34</td>
<td>3.24 2.47 - 4.26 &lt; 0.0001</td>
<td>8.32 5.36 - 12.92 &lt; 0.0001</td>
<td>4.29 3.48 - 5.29 &lt; 0.0001</td>
</tr>
<tr>
<td>OUES ≤ 1.4</td>
<td>2.33 1.56 - 3.44 &lt; 0.0001</td>
<td>5.75 2.79 - 11.90 &lt; 0.0001</td>
<td>2.87 2.08 - 3.94 &lt; 0.0001</td>
</tr>
<tr>
<td>PetO2 &lt; 33 mmHg</td>
<td>1.77 1.25 - 2.51 0.001</td>
<td>3.11 1.96 - 4.95 &lt; 0.0001</td>
<td>2.38 1.86 - 3.04 &lt; 0.0001</td>
</tr>
<tr>
<td>Weighted Summed Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 5 (n= 1398)</td>
<td>1  (reference)</td>
<td>1  (reference)</td>
<td>1  (reference)</td>
</tr>
<tr>
<td>6 to 10 (n= 841)</td>
<td>2.33 1.72 - 3.16 &lt; 0.0001</td>
<td>5.21 3.26 - 8.33 &lt; 0.0001</td>
<td>2.74 2.16 - 3.48 &lt; 0.0001</td>
</tr>
<tr>
<td>10 to 15 (n= 335)</td>
<td>3.26 2.28 - 4.67 &lt; 0.0001</td>
<td>7.16 4.20 - 12.21 &lt; 0.0001</td>
<td>4.6 3.55 - 5.98 &lt; 0.0001</td>
</tr>
<tr>
<td>&gt; 15 (n= 38)</td>
<td>4.31 1.87 - 9.9 0.0005</td>
<td>12.4 4.72 - 32.57 &lt; 0.0001</td>
<td>9.25 5.75 - 14.88 &lt; 0.0001</td>
</tr>
</tbody>
</table>

*Includes: LVAD, Transplant, and all causes of death. Age, BMI, and ejection fraction are increments using SD. Abbreviations as in Table 1
<table>
<thead>
<tr>
<th>Variable</th>
<th>Cardiac Mortality C index</th>
<th>Major Events C index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO2 ≤ 14 ml•kg⁻¹•min⁻¹</td>
<td>0.61</td>
<td>0.67</td>
</tr>
<tr>
<td>HHR ≤ 6 beats at 1 minute</td>
<td>0.61</td>
<td>0.60</td>
</tr>
<tr>
<td>VE/VCO2 slope ≥ 34</td>
<td>0.66</td>
<td>0.70</td>
</tr>
<tr>
<td>OUES ≤ 1.4</td>
<td>0.62</td>
<td>0.65</td>
</tr>
<tr>
<td>PetCO2 &lt; 33 mmHg</td>
<td>0.58</td>
<td>0.61</td>
</tr>
<tr>
<td>Composite risk score</td>
<td>0.70</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Table 3. Predictive accuracy of CPX parameters and composite risk score
Table 4. Predictive accuracy of cardiopulmonary exercise testing parameters and composite risk score

<table>
<thead>
<tr>
<th>Predictive Model*</th>
<th>Mortality</th>
<th>AIC</th>
<th>AIC Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Peak VO2 ≤ 14 ml•kg⁻¹•min⁻¹</td>
<td>922</td>
<td>0.02</td>
</tr>
<tr>
<td>B</td>
<td>HRR ≤ 6 beats at 1 minute</td>
<td>944</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>VE/VCO₂ slope ≥ 34</td>
<td>916</td>
<td>0.49</td>
</tr>
<tr>
<td>D</td>
<td>OUES ≤ 1.4</td>
<td>925</td>
<td>0.005</td>
</tr>
<tr>
<td>E</td>
<td>PetCO₂ &lt; 33 mmHg</td>
<td>937</td>
<td>0</td>
</tr>
<tr>
<td>F</td>
<td>Peak VO2 ≤ 14 ml•kg⁻¹•min⁻¹ and VE/VCO₂ slope ≥ 34</td>
<td>908</td>
<td>26.7</td>
</tr>
<tr>
<td>G</td>
<td>Weighted summed score</td>
<td>906</td>
<td>72.7</td>
</tr>
</tbody>
</table>

*Age-adjusted;
AIC-Akaike information criterion
HRR – Heart rate recovery
OUES – Oxygen uptake efficiency slope
Table 5. Net re-classification improvement (NRI) for major events at 36 months according to components of CPX score

<table>
<thead>
<tr>
<th>Model</th>
<th>Event-free survival rate-all subjects</th>
<th>Event-free survival rate-subjects reclassified up††</th>
<th>Event-free survival rate-subjects reclassified down††</th>
<th>NRI-subjects with events</th>
<th>NRI-subjects without events</th>
<th>NRI-all subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO2 + VE/VCO2 slope</td>
<td>0.87</td>
<td>0.92 (293)</td>
<td>0.31 (0.27-0.34)</td>
<td>0.30 (0.29-0.31)</td>
<td>0.61 (0.57-0.64)</td>
<td></td>
</tr>
<tr>
<td>Peak VO2 + VE/VCO2 slope + OUES†</td>
<td>0.69 (131)</td>
<td>0.93 (347)</td>
<td>0.22 (0.18-0.25)</td>
<td>0.55 (0.54-0.56)</td>
<td>0.77 (0.73-0.80)</td>
<td></td>
</tr>
<tr>
<td>Peak VO2 + VE/VCO2 slope + OUES + PetCO2†</td>
<td>0.71 (188)</td>
<td>0.93 (290)</td>
<td>0.37 (0.33-0.40)</td>
<td>0.29 (0.28-0.30)</td>
<td>0.66 (0.62-0.69)</td>
<td></td>
</tr>
<tr>
<td>Peak VO2 + VE/VCO2 slope + OUES + PetCO2 + HRR†</td>
<td>0.63 (79)</td>
<td>0.92 (399)</td>
<td>-0.02 (-0.05-0.01)</td>
<td>0.76 (0.76-0.78)</td>
<td>0.74 (0.71-0.78)</td>
<td></td>
</tr>
</tbody>
</table>

* Compared with peak VO2 only.
†† Compared with model described in preceding row.
†† Numbers in parentheses represent numbers of subjects reclassified up or down.
Table 6. Net reclassification improvement for major cardiovascular events and cardiovascular-related mortality at 36 months according to CPX score

<table>
<thead>
<tr>
<th>Event-free survival rate-all subjects</th>
<th>Event-free survival rate-subjects reclassified up†</th>
<th>Event-free survival rate-subjects reclassified down†</th>
<th>NRI-subjects with events</th>
<th>NRI-subjects without events</th>
<th>NRI-all subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major cardiovascular events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical variables</td>
<td>0.80</td>
<td>--</td>
<td>--</td>
<td></td>
<td>--</td>
</tr>
<tr>
<td>Clinical variables + CPX score*</td>
<td>0.69 (585)</td>
<td>0.88 (826)</td>
<td>0.36 (0.32-0.39)</td>
<td>0.27 (0.26-0.29)</td>
<td>0.63 (0.59-0.68)</td>
</tr>
<tr>
<td>Cardiovascular-related mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical variables</td>
<td>0.88</td>
<td>--</td>
<td>--</td>
<td></td>
<td>--</td>
</tr>
<tr>
<td>Clinical variables + CPX score*</td>
<td>0.80 (568)</td>
<td>0.93 (842)</td>
<td>0.36 (0.33-0.40)</td>
<td>0.29 (0.28-0.31)</td>
<td>0.65 (0.61-0.69)</td>
</tr>
</tbody>
</table>

* Compared with model including clinical variables only: age, systolic blood pressure, heart failure etiology, body mass index, diuretic use, and left ventricular ejection fraction
† Numbers in parentheses represent numbers of subjects reclassified up or down
Figure Legends

**Figure 1.** Kaplan-Meier curves illustrating cumulative survival for increasing CPX scores. p<0.01 by log-rank test.

**Figure 2.** Kaplan-Meier curves illustrating event-free survival for the composite outcome (death, transplantation, and LVAD implantation) by increasing CPX scores. p<0.01 by log-rank test.
Event-Free Survival vs. Months follow-up for different score ranges:
- Score 0 - 5
- Score 5 - 10
- Score 10 - 15
- Score >15

Source: Circulation: Heart Failure
Validation of a Cardiopulmonary Exercise Test Score in Heart Failure
Jonathan Myers, Ricardo Oliveira, Frederick Dewey, Ross Arena, Marco Guazzi, Paul Chase, Daniel Bensimhon, Mary Ann Peberdy, Euan Ashley, Erin West, Lawrence P. Cahalin and Daniel E. Forman

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