Cardiopulmonary Exercise Testing and Prognosis in Chronic Heart Failure*: A Prognosticating Algorithm for the Individual Patient

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The identification of individuals who are at high risk of chronic heart failure (HF) is a medical art of growing concern. Cardiopulmonary exercise stress testing (CPX) has become an important clinical tool to predict outcome. The value of peak oxygen consumption rests in the fact that it integrates elements of cardiac adaptations, and skeletal muscle, pulmonary, and endothelial dysfunctions more than other traditional prognostic indicators of chronic HF. Recently, exercise-related ventilatory abnormalities have gained attention, stimulating scientific debate and an innovative perspective. This review, through a critical examination of previous experiences, will focus on the prognostic application of CPX, defining a proficient outline of treatment for the individual patient.

Key words: cardiopulmonary exercise testing; heart failure; prognosis

Abbreviations: CPX = cardiopulmonary exercise stress testing; HF = heart failure; HR = heart rate; RER = respiratory exchange ratio; VAT = ventilatory anaerobic threshold; V̇\textsubscript{CO}\textsubscript{2} = carbon dioxide output; V\textsubscript{E} = minute ventilation; V̇\textsubscript{O}\textsubscript{2} = oxygen consumption

The identification of individuals who are at high risk of chronic heart failure (HF) is a medical art of burgeoning interest, reflecting the increasing confidence about effective pharmacologic therapies, as well as innovative surgical and device-related treatments. 

Cardiopulmonary exercise stress testing (CPX), when properly performed, provides an objective measurement of peak functional capacity, and has become an important clinical tool with which to define disease severity and to predict outcome in patients with chronic HF due to left ventricular systolic dysfunction. Thus, CPX plays a pertinent role in decision-making about the workup of the chronic HF patient.

This review will focus on the clinical application and interpretation of CPX with specific reference to prognosis, defining an algorithm for use in the individual patient.

Peak Oxygen Consumption

There is overwhelming evidence of the role played by peak oxygen consumption (V\textsubscript{O}2) in stratifying risk in chronic HF patients. Although several studies published during the 1980s deserve mention, the study by Mancini et al \textsuperscript{10} is considered to be the cornerstone of the documentation of the prognostic power of peak V\textsubscript{O}2. In the study, 116 male chronic HF patients were divided into the following three groups: group 1, patients with peak V\textsubscript{O}2 of < 14 mL/kg/min who had been accepted for heart transplantation; group 2, patients with peak V\textsubscript{O}2 of \geq 14 mL/kg/min who had transplant deferred; and group 3, patients with peak V\textsubscript{O}2 of < 14 mL/kg/min but...
with significant comorbidity that precluded heart transplantation. The 1-year survival rates in groups 1, 2, and 3 were 48%, 94%, and 47%, respectively. Of note, a peak VO$_2$ of $<10$ mL/kg/min was associated with significantly poorer predicted survival. The results of the study by Mancini et al$^{10}$ were adopted by the American Heart Association/American College of Cardiology consensus statement on the selection and treatment of candidates for heart transplantation,$^{11}$ which affirmed that, once maximal therapy has been instituted and maintained, peak VO$_2$ has a predictive role, and that “...for patients with VO$_2$ max $<14$ mL/kg/min, it is important to prove that exercise testing was truly maximal by documenting achievement of the anaerobic threshold at approximately 50% to 70% of VO$_2$ max.”

Thus, a simple but somewhat dogmatic approach has been formulated. When the ventilatory anaerobic threshold (VAT) is detected, a peak VO$_2$ of $<14$ mL/kg/min identifies patients who are at high risk, whereas at values above that threshold the patient is considered to have a fairly good prognosis.

The VAT

Exercise tolerance in chronic HF patients is notoriously hard to quantify because the end point for the test usually is subjective and may depend on the motivation of the patient or the examiner. The anaerobic threshold has been proposed as a submaximal index of exercise capacity, independent of the patient’s motivation, and has been classically defined as the point where lactate increases in plasma during exercise, as a consequence of the transition from total aerobic to aerobic plus anaerobic metabolism. The mechanism for lactate increase is controversial,$^{12}$ but the gas exchange consequences of the exertional lactate production and homeostasis adjustments can be monitored during CPX. A failure to reach the VAT strongly suggests poor motivation or noncardiovascular limitation of exercise tolerance.

In daily clinical practice, VAT goes undetected in a large proportion of chronic HF patients,$^{13}$ especially in those with reduced exercise tolerance, restricting the prognostic and decisional value of peak VO$_2$. Opasich et al$^{14}$ evaluated the predictive role of peak VO$_2$ in 505 male chronic HF patients (64%) in whom VAT had and had not been identified. When the VAT was identified, the cardiac event rates were 59%, 32%, 32%, and 15% in patients with peak VO$_2$ values of $\leq 10$ mL/kg/min, $>10$ to $\leq 14$ mL/kg/min, $>14$ to $\leq 18$ mL/kg/min, and $>18$ mL/kg/min, respectively. When VAT was not detected, the event rate was 46% in patients with peak VO$_2$ of $\leq 10$ mL/kg/min, and was almost identical among those with peak VO$_2$ values of $>10$ to $\leq 14$ mL/kg/min, $>14$ to $\leq 18$ mL/kg/min, and $>18$ mL/kg/min (29%, 23%, and 22%, respectively).

Thus, when VAT is detected, patients with a peak VO$_2$ of $<10$ mL/kg/min have a high event rate, whereas those with a peak VO$_2$ of $>18$ mL/kg/min have a good prognosis. Patients with intermediate functional capacity (ie, peak VO$_2$ between 10 and 18 mL/kg/min) fall into an arbitrary prognostic region in which peak VO$_2$ does not provide predictive or decisional information. When the VAT is undetectable, the following dichotomy is suggested: for patients with peak VO$_2$ of $<10$ mL/kg/min, there is a high risk of events; and for those who exceed this cutoff, the risk stratification is considered to be inconclusive and the replication of CPX is recommended (Fig 1).

Beyond Peak VO$_2$

While there is much faith in peak VO$_2$ as a predictive parameter, most clinicians do not realize that a multiplicity of factors influence any given value. Peak VO$_2$ is traditionally expressed as milliliters per minute or as milliliters per kilogram per minute, but it is well-known that peak VO$_2$ is affected by age, gender, body weight, muscle mass, and conditioning status. Thus, a peak VO$_2$ value adjusted for these factors should theoretically improve the predictive accuracy (Table 1). Based on this assumption, Stelken et al$^{15}$ retrospectively studied 181 chronic HF patients in order to compare the percentage achieved of the predicted peak VO$_2$, taking into account age, gender, and weight, with the traditionally used absolute peak VO$_2$ measured in milliliters per kilogram per minute. During the 12-month follow-up, nonsurvivors achieved a lower percentage of the predicted peak VO$_2$ and a lower absolute peak VO$_2$ than survivors, and multivariate analysis revealed that $<50\%$ predicted of the peak VO$_2$ was the strongest predictor of cardiac events, superior to the cutoff absolute value of peak VO$_2$ of $<14$ mL/kg/min. Aaronson and Mancini$^{16}$ refuted these results, measuring the percentage of predicted peak VO$_2$ derived from the standard formulas of Wasserman et al$^{17}$ (incorporating age, weight, height, and gender) and Astrand$^{18}$ (incorporating only age and gender). Neither method of determining the percentage of peak VO$_2$ significantly improved the prediction of survival over peak VO$_2$, as the areas under the receiver operating curves constructed for the absolute peak VO$_2$ normalized for body weight and percentage of predicted peak VO$_2$ were roughly equal.

Osman et al$^{19}$ have documented that the adjustment of peak VO$_2$ to lean body weight provides greater prognostic strength than the traditionally
reported standard peak \( \dot{V}O_2 \), expressed in milliliters per kilogram per minute. As body fat is a metabolically inactive mass, and the variability in body fat may contribute to the decline in peak \( \dot{V}O_2 \) with age, in healthy subjects and chronic HF populations, the authors reasoned that peak \( \dot{V}O_2 \) corrected for lean body mass would reflect a more accurate picture of cardiopulmonary function during exercise. Lean peak \( \dot{V}O_2 \), either as a continuous variable or using a cutoff value of \( \geq 19 \) ml/kg/min, was a better predictor of outcome than unadjusted peak \( \dot{V}O_2 \) in 225 chronic HF patients.

Over the past 5 years, research has revealed that ventilatory expired gas parameters obtained from symptom-limited CPX embody prognostic value in chronic HF patients (Table 2). An abnormally high relationship between minute ventilation (\( V_e \)) and carbon dioxide output (\( V_{CO_2} \)), expressed as the \( V_e/V_{CO_2} \) slope, is associated with a poor outcome. Chua et al\(^{20} \) reported that a \( V_e/V_{CO_2} \) slope of \( > 34 \) was associated with worse prognosis in 173 chronic HF patients, and Kleber et al\(^{21} \) selected a \( V_e/V_{CO_2} \) slope that was \( > 130\% \) of the age-adjusted and sex-adjusted value as the best predictive cutoff point in 142 patients. Francis et al\(^{22} \) certified the prognostic information of \( V_e/V_{CO_2} \) slope over a wide range of values, from 30 to 55, whereas MacGowan et al\(^{23} \) substantiated that the combination of a peak \( V_e/V_{CO_2} \) slope of \( > 50 \) and a peak \( \dot{V}O_2 \) of \( \leq 15 \) ml/kg/min was associated with an 82% mortality rate in 104 chronic HF patients. Finally, Robbins et al\(^{24} \) found that a \( V_e/V_{CO_2} \) slope of \( \geq 44.7 \) at peak exercise was superior to a peak \( \dot{V}O_2 \) of \( \leq 13.9 \) ml/kg/min in predicting 18-month survival. The predictive power of ventilatory parameters is clearly valuable also in selected middle-aged to very elderly chronic HF patients. Moreover, we demonstrated that oscillatory ventilation during exercise, defined as cyclic fluctuations in \( V_e \) at rest that persist during effort lasting for \( \geq 60\% \) of the exercise

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**Table 1—Clinical Studies Documenting the Relationship Between Peak \( \dot{V}O_2 \) Adjusted Value and Prognosis in Chronic HF Patients Undergoing Symptom-Limited CPX**

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Patients, No.</th>
<th>Peak ( \dot{V}O_2 ), ml/kg/min</th>
<th>Event Rate, %</th>
<th>CPX Variables Related to Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stelken et al(^{15} )/1996</td>
<td>181</td>
<td>16.3 ± 5.9</td>
<td>24</td>
<td>Percent achieved of predicted peak ( \dot{V}O_2 )</td>
</tr>
<tr>
<td>Cohen-Solal et al(^{16} )/1997</td>
<td>178</td>
<td>17.6 ± 5.6</td>
<td>19</td>
<td>Percent achieved of predicted peak ( \dot{V}O_2 )</td>
</tr>
<tr>
<td>Osada et al(^{17} )/1998</td>
<td>500</td>
<td>12.0 ± 2.0</td>
<td>26</td>
<td>Peak SBF and percent achieved of predicted peak ( \dot{V}O_2 )</td>
</tr>
<tr>
<td>Osman et al(^{18} )/2000</td>
<td>225</td>
<td>16.0 ± 5.9</td>
<td>13</td>
<td>Adjusted peak ( \dot{V}O_2 ) to lean body mass</td>
</tr>
</tbody>
</table>

\(^{a}\)Systolic BP.
\(^{b}\)Values given as mean ± SD.
duration, with an amplitude ≥ 15% of the average resting value, is not unusual in chronic HF patients (ie, 12% of 323 patients), and has independent and additional prognostic power.25

Beside gas exchange parameters, other exercise variables have been investigated to further stratify chronic HF patients undergoing CPX (Table 3). Osada et al26 performed a multivariate analysis using all noninvasive exercise parameters obtained during CPX in 500 chronic HF patients who had been referred for heart transplantation to identify the 3-year prognostic risk. Peak systolic BP of < 120 mm Hg and a VO₂ of < 50% were selected as significant additional and independent variables in patients with a peak VO₂ of ≤ 14 mL/kg/min. Robbins et al24 studied 470 consecutive chronic HF patients who had been referred for functional evaluation who were not receiving therapy with β-blockers. Chronotropic incompentence was measured by calculating the proportion of heart rate (HR) reserve, applying the method of Wilkoff and Miller,27 based on the linear relation between HR and metabolic work. The chronotropic index was considered to be abnormal if it was in the lowest 25th percentile of the patient cohort. At multivariate analysis, low chronotropic index (ie, ≤ 0.51) was selected as an independent predictor of death due to any cause.

Indeed, several respiratory gas exchange and exercise variables obtained during symptom-limited CPX have been proposed to improve outcome prediction in chronic HF patients. Each single exertional parameter awards additional outcome discrimination, with the appeal of providing, for clinicians, a convenient "high risk/low risk" categorization. In reality, such a dichotomous approach that forces patients into one of two categories tends to oversimplify the issue and is of limited relevance in patients with chronic HF, which is a complex, heterogeneous clinical condition. Thus, it seems more useful to substantiate whether these parameters yield complementary prognostic information in addition to peak VO₂ in subgroups of functional capacity chronic HF patients, in particular in patients with an intermediate exercise ability range compared to those with severe exercise intolerance (ie, peak VO₂ < 10 mL/kg/min). In the former, the selection of a unique and optimal threshold has been unfruitful and discordant,14,22,31–35 and the limited prognostic and deci-

Table 2—Clinical Studies Documenting Relationship Between Ventilatory Parameters and Prognosis in Chronic HF Patients Undergoing Symptom-Limited CPX*

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Patients, No.</th>
<th>Peak VO₂, mL/kg/min</th>
<th>Event Rate, %</th>
<th>CPX Variables Related to Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacGowan et al1997</td>
<td>104</td>
<td>NA</td>
<td>19</td>
<td>Peak Ve/VO₂ in pts with peak VO₂ ≤ 15 mL/kg/min</td>
</tr>
<tr>
<td>Chua et al1997</td>
<td>155</td>
<td>18.5 ± 7.3</td>
<td>24</td>
<td>Ve/VO₂ slope</td>
</tr>
<tr>
<td>Robbins et al1999</td>
<td>470</td>
<td>13.0 ± 7.0</td>
<td>15</td>
<td>Peak Ve/VO₂ and low HR response</td>
</tr>
<tr>
<td>Kleber et al2000</td>
<td>142</td>
<td>15.2 ± 4.7</td>
<td>29</td>
<td>Ve/VO₂ slope</td>
</tr>
<tr>
<td>Francis et al2000</td>
<td>303</td>
<td>17.8 ± 6.6</td>
<td>30</td>
<td>Peak VO₂ and Ve/VO₂ slope</td>
</tr>
<tr>
<td>Arena and Humphrey2002</td>
<td>37</td>
<td>13.3 ± 4.5</td>
<td>51†</td>
<td>Ve/VO₂ slope</td>
</tr>
<tr>
<td>Meijert et al2002</td>
<td>67</td>
<td>11.7 ± 3.6</td>
<td>21</td>
<td>Peak Ve/VO₂</td>
</tr>
<tr>
<td>Corrè et al2002</td>
<td>323</td>
<td>14.0 ± 3.0</td>
<td>16</td>
<td>Oscillatory exertional ventilation</td>
</tr>
<tr>
<td>Mezzani et al2003</td>
<td>600</td>
<td>14.8 ± 4.0</td>
<td>15</td>
<td>Ve/VO₂ slope in pts with peak VO₂ &gt; 10–18 mL/kg/min</td>
</tr>
</tbody>
</table>

*p = patients; NA = not applicable.
†Values given as mean ± SD.
Includes hospitalizations.

Table 3—Clinical Studies Documenting Relationship Between Noninvasive Exercise Variables and Prognosis in Chronic HF Patients Undergoing Symptom-Limited CPX*

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Patients, No.</th>
<th>Peak VO₂, mL/kg/min</th>
<th>Event Rate, %</th>
<th>CPX Variables Related to Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osada et al1998</td>
<td>500</td>
<td>12.1 ± 2.0</td>
<td>26</td>
<td>Peak SBP and percent achieved of predicted peak VO₂</td>
</tr>
<tr>
<td>Robbins et al1999</td>
<td>470</td>
<td>13.0 ± 7.0</td>
<td>15</td>
<td>Peak Ve/VO₂ and low HR response</td>
</tr>
<tr>
<td>Williams et al2001</td>
<td>219</td>
<td>23.0 ± 9.2</td>
<td>12</td>
<td>Peak cardiac power</td>
</tr>
<tr>
<td>Cohen-Solal et al2002</td>
<td>175</td>
<td>20.3 ± 5.6</td>
<td>16</td>
<td>Circulatory power</td>
</tr>
<tr>
<td>Scharf et al2002</td>
<td>154</td>
<td>19.8 ± 0.4</td>
<td>21</td>
<td>Exercise cardiac power</td>
</tr>
</tbody>
</table>

*Peak cardiac power = product of peak SBP and peak rebreathing cardiac output; circulatory power = product of peak SBP and peak VO₂; exercise cardiac power = product of peak SBP and percent achieved of predicted peak VO₂. See Table 1 for abbreviations not used in the text.
†Values given as mean ± SD.
sional value of peak \( \dot{V}O_2 \) in patients with a peak \( \dot{V}O_2 \) of 10 to 18 mL/kg/min is aggravated by the fact that the majority of patients referred for heart transplantation fall into this intermediate group. The latter patients are at high risk to experience cardiac events, and demand complex and costly therapy. Thus, the identification of objective indexes of maximal effort is crucial.

**Patients With Intermediate Exercise Capacity**

We recently studied a cohort of 600 chronic HF patients who had the ability to perform CPX until exhaustion with a peak respiratory exchange ratio (RER) of ≤ 1.05 (in order to exclude poor motivation). Patients were stratified into the following four groups according to functional capacity: peak \( \dot{V}O_2 \) ≤ 10 mL/kg/min; peak \( \dot{V}O_2 \) > 10 to ≤ 14 mL/kg/min; peak \( \dot{V}O_2 \) > 14 to < 18 mL/kg/min; and peak \( \dot{V}O_2 \) ≥ 18 mL/kg/min. The primary end points were cardiovascular death and heart transplantation in status 1. Twenty-six patients from among those with a peak \( \dot{V}O_2 \) of ≤ 10 mL/kg/min died, as opposed to only 3 of those patients with peak \( \dot{V}O_2 \) of ≥ 18 mL/kg/min (p < 0.0001). No significant difference in the total mortality rate was found among the 403 patients with intermediate exercise capacity (patients with peak \( \dot{V}O_2 \) > 10 to ≤ 14 mL/kg/min, 17%; patients with peak \( \dot{V}O_2 \) > 14 to 18 mL/kg/min, 11%). In this cohort of patients with intermediate functional capacity (ie, a mean [± SD] peak \( \dot{V}O_2 \), 13.9 ± 2 mL/kg/min), the \( \dot{V}E/\dot{V}CO_2 \) slope resulted as the strongest independent predictor of major cardiac events at multivariate analysis adjusted for New York Heart Association functional class, left ventricular ejection fraction, peak systolic BP, chronotropic adaptation (ie, maximal HR – resting HR), percentage of predicted \( \dot{V}O_2 \), \( \dot{V}O_2 \) at VAT, and detectable VAT. The best cutoff value for \( \dot{V}E/\dot{V}CO_2 \) slope was 35. Patients with a \( \dot{V}E/\dot{V}CO_2 \) slope of ≥ 35 had a significantly higher mortality rate than did those with a \( \dot{V}E/\dot{V}CO_2 \) slope of < 35 (30% vs 10%, respectively; p < .0001), but a similar one to those with peak \( \dot{V}O_2 \) of ≤ 10 mL/kg/min (30% vs 37%, respectively). We postulated that the broad range of \( \dot{V}E/\dot{V}CO_2 \) slope (22 to 60) among patients with intermediate exercise capacity may represent a proper descriptor of the heterogeneity of hemodynamic and neurohormonal adaptations to exercise and disorders of ventilatory reflex control.

The prognostic and decisional impact of peak \( \dot{V}O_2 \) and \( \dot{V}E/\dot{V}CO_2 \) slope in chronic HF patients is summarized in Figure 2. A threshold peak \( \dot{V}O_2 \) value of ≤ 10 mL/kg/min identifies high-risk patients, whereas a cutoff value of ≥ 18 mL/kg/min categorizes patients with a fairly good long-term prognosis. A peak \( \dot{V}O_2 \) ranging from 10 to 18 mL/kg/min indicates a moderate risk of cardiac events, and in this subset of patients, irrespective of VAT detection, a \( \dot{V}E/\dot{V}CO_2 \) slope of ≥ 35 allows the identification of those with the worst outcomes, with a total mortality rate comparable to that detected among those with a peak \( \dot{V}O_2 \) of ≤ 10 mL/kg/min.

**Patients With Severe Exercise Intolerance**

Patients with severe exercise intolerance (ie, peak \( \dot{V}O_2 \), < 10 mL/kg/min) become increasingly less

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**Figure 2.** The prognostic and decisional impact of peak \( \dot{V}O_2 \) and \( \dot{V}E/\dot{V}CO_2 \) slope in chronic HF patients with intermediate functional capacity.
used to accomplishing strenuous daily activities with clinical progression of the disease, and their motivation to reach maximal effort and to experience symptoms during an exercise test may be lacking. Indeed, objective indexes of maximal effort are needed in order to ensure a peak VO₂ reliability and to avoid inappropriate prognostic stratification due to poor motivation.

Mezzani et al evaluated 570 chronic HF patients, 273 of whom had a peak VO₂ of ≤ 14 mL/kg/min (peak VO₂ > 10 to ≤ 14 mL/kg/min, 193 patients; peak VO₂ ≤ 10 mL/kg/min, 80 patients). The composite end point of the study was death due to cardiovascular causes or the need for urgent heart transplantation. Twenty-two patients (4%) were not able to reach an RER of 1 at peak effort, and peak RERs of at least 1, 1.05, 1.10, and 1.15, respectively, were reached by 96%, 89%, 74%, and 57% of patients. The composite end point was reached in 78 patients (14%) from among the whole study group. The 2-year mortality rates were 7%, 17%, and 31%, respectively, in patients with peak VO₂ values of > 14, > 10 to ≤ 14, and ≤ 10 mL/kg/min (p < 0.0001). In the group with a peak VO₂ of ≤ 10 mL/kg/min, at multivariate analysis the ability to attain a peak RER of ≥ 1.15 was the only independent predictor of the composite end point, with a relative risk of 1.65. Indeed, in the group with a peak VO₂ of ≤ 10 mL/kg/min, patients who were unable to reach a peak RER of ≥ 1.15 (41 patients) showed a 2-year mortality rate of 17%, which was far higher than that of those able to reach such a peak RER value (39 patients [48%]; p < .0001), but was similar to the rate observed in patients with peak VO₂ of > 10 to ≤ 14 mL/kg/min. Altogether, these results suggest that chronic HF patients with severely reduced exercise tolerance should be encouraged to exercise as close as possible up to an RER of 1.15, in order to ascertain their motivation and to ensure peak VO₂ prognostic reliability. In the case of peak RER values of < 1.15, a cautious use of peak VO₂ in clinical decision making is recommended (Fig 3).

**Recommended Prognosticating Algorithm**

In summary, the risk stratification procedure with symptom-limited CPX in chronic HF patients, traditionally based on peak VO₂ and VAT, should be replaced by a new prognosticating algorithm (Fig 4) that is structured on a multiparametric decoding scrutiny employing the stepwise introduction of peak VO₂, VE/VO₂ slope, and peak RER. Indeed, commencing with peak VO₂, a threshold of peak VO₂ of ≤ 10 mL/kg/min identifies high-risk patients, a cut-off value of ≥ 18 mL/kg/min indicates patients with a fairly good long-term prognosis, while peak VO₂ between 10 and 18 mL/kg/min indicates a moderate risk of cardiac events. In this latter subset of patients, a VE/VO₂ slope of ≥ 35 allows for the identification of those patients with worse outcomes. In chronic HF patients with a peak VO₂ of ≤ 10 mL/kg/min, the peak RER can correctly discriminate outcome, as those reaching an RER of at least 1.15 at peak effort have a higher risk, whereas those unable to attain a peak RER of 1.15 have a prognosis comparable to that of patients with a better functional capacity. As VE/VO₂ slope yields an efficient predictive contribution for almost one fourth of patients with moderate chronic HF, and as the attainment of a peak RER of ≥ 1.15 allows the identification of nearly half of patients with severe exercise intolerance with “true” low peak aerobic power, who are thus at high risk, the stepwise process that we are recommending can assist physicians in clinical decision making by describing a reliable risk for the individual patient.

**Limitations**

This review was conceived to analyze noninvasive gas exchange and exercise parameters, thus we deliberately excluded data derived from the direct assessment of the hemodynamic response during exercise that may also contribute to improve the prognostic evaluation of chronic HF patients. A number of noninvasive surrogates of cardiac output have been investigated in chronic HF patients undergoing symptom-limited CPX. Cohen-Solal et al stated that “circulatory power,” calculated as the product of VO₂ and peak systolic BP, strengthens the prognostic value of CPX, especially in patients with a low peak VO₂ and a low BP, whereas Scharf et al documented that exercise cardiac power, defined as the product of the achieved percent predicted peak VO₂ and peak VAT, provides a reliable index of functional capacity and prognosis.
\( \dot{V}O_2 \) and peak systolic BP, < 5,000% mm Hg indicates a poor 1-year mortality rate. Although the assessment of these new, easily available, and accurate parameters can improve risk stratification, and can avoid the measurement of invasive hemodynamic variables (Table 3), further studies are warranted to confirm their potential risk prediction power.

Moreover, the results of the studies reviewed in this article are robust and unambiguous, but are not generalizable, since they were conducted for the most part in "stereotypic" heart transplant candidates (i.e., selected middle-aged men with severe HF) who had an up-to-date therapeutic armamentarium (with the exception of \( \beta \)-blockers) at their disposal and were in sinus rhythm. Few studies included women, elderly patients, or patients with atrial fibrillation or comorbidity. Up to now, the applicability and prognostic role of CPX in chronic HF cohorts treated with \( \beta \)-blockers has been evaluated in small series of patients, with different \( \beta \)-blocker agents, leading to contradictory results that should be interpreted considering severity of disease, type and duration of \( \beta \)-blocker treatment, and heart transplantation candidacy.46–49

Patients who receive therapy with \( \beta \)-blockers are usually in a lower New York Heart Association class, have a higher mean left ventricular ejection fraction and peak \( \dot{V}O_2 \), and are, in brief, in a clinical condition that generally is not associated with severe functional impairment or neuroautonomic instability. Thus, a limited number of patients treated with \( \beta \)-blockers have very low peak \( \dot{V}O_2 \) values and generate disarrangement signals to the ventilatory control system, resulting in an abnormal exertional ventilatory response (i.e., high VE/VCO\(_2\) slope). On the other hand, long-term \( \beta \)-blocker therapy interferes with hemodynamic and metabolic adaptations and with ion balance during exercise, but pharmacologic differences among \( \beta \)-blocker agents in the degree of antiadrenergic activity can result in meaningful dissimilarities in maximal exercise capacity in chronic HF patients.50 We have documented that chronic HF patients treated with carvedilol have a low risk of cardiac events, and that peak \( \dot{V}O_2 \) of \( \leq 10 \text{ mL/kg/min} \) allows the identification of patients with moderately worse prognosis, whereas above this threshold a mild risk of cardiac events is expected. The role of symptom-limited CPX is limited as no additional gas exchange parameters yielded supplementary prognostic advice in carvedilol patients with a peak \( \dot{V}O_2 \) of > 10 mL/kg/min.47 Thus, until now, we have thought that this new prognosticating algorithm should not be recommended for the general, highly heterogeneous chronic HF population and for those treated with \( \beta \)-blockers.

Finally, two distinct groups have investigated the prognostic role of gas exchange kinetics at low-intensity (submaximal) work rate, either alone or in combination with peak exercise parameters.51–53 This is a promising area for risk stratification that may be applicable when maximal exercise is contraindicated or is not achievable. Prospectively, submaximal variables, which are obtainable with one single exercise test, may have a predictive role in patients with intermediate functional capacity and in those treated with \( \beta \)-blockers,53 but the inconclusive results, due to study population differences and the

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**Figure 4.** A new prognosticating algorithm that is structured on a multiparametric decoding scrutiny employing the stepwise introduction of peak \( \dot{V}O_2 \), VE/VCO\(_2\) slope, and peak RER. The dotted line indicates that patients with intermediate exercise capacity (i.e., peak \( \dot{V}O_2 \) of > 10 and < 18 mL/kg/min) and excessive ventilatory response (i.e., VE/VCO\(_2\) slope of \( \geq 35 \)) have a total mortality rate that is comparable to that detected with a peak \( \dot{V}O_2 \) of \( \leq 10 \text{ mL/kg/min} \) (whole population).
lack of an accepted standard for the assessment of VO₂ kinetics, actually suggest a word of caution.

**Final Considerations**

Notwithstanding its almost unbounded appeal, prognostic definition in chronic HF patients is a complex, demanding, and sometimes contradictory area of scientific interest. If clinical stability is guaranteed and maximal medical treatment is instituted, peak VO₂ is a convincing, strong, and independent predictor of outcome, supporting the value of CPX as a clinical tool in chronic HF management. However, in the last few years we have discovered that a single arbitrary cut point value for peak VO₂ is unlikely to describe the true risk of events, and that a multiparametric stepwise approach may be more fruitful. Specific research is needed to broadcast the importance of a multiparametric interpretation of CPX because, while the challenge of modifying the standard dichotomous prognosticating algorithm has been an intrepid one, changing physicians’ management of chronic HF patients in the light of this innovative approach (eg, in the selection of heart transplantation candidates) may well be an even greater challenge. Nevertheless, it is important to underline that, as every patient is unique, the ultimate judgment regarding management and therapeutic strategy must be made by the physician in the light of all the circumstances that are relevant to that patient.

**REFERENCES**

5 Benjaminovitz A, Mancini DM. The role of exercise-based prognosticating algorithms in the selection of patients for heart transplantation. Curr Opin Cardiol 1999; 4:114–120
16 Aaronson KD, Mancini DM. Is percentage of predicted maximal exercise oxygen consumption a better predictor of survival than peak exercise oxygen consumption for patients with severe heart failure. J Heart Lung Transplant 1995; 14:981–989
18 Astrand P. Human physical fitness with special reference to sex and age. Physiol Rev 1956; 36(suppl):307–335
exercise testing identifies low risk patients with heart failure and severely impaired exercise capacity considered for heart transplantation. J Am Coll Cardiol 1998; 31:577–582


# Cardiopulmonary Exercise Testing and Prognosis in Chronic Heart Failure*: A Prognosticating Algorithm for the Individual Patient

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