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 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 (\(\dot{V}O_2\)) in stratifying risk in chronic HF patients. Although several studies published during the 1980s deserve mention, the study by Mancini et al is considered to be the cornerstone of the documentation of the prognostic power of peak \(\dot{V}O_2\). In the study, 116 male chronic HF patients were divided into the following three groups: group 1, patients with peak \(\dot{V}O_2\) of < 14 mL/kg/min who had been accepted for heart transplantation; group 2, patients with peak \(\dot{V}O_2\) of \(\geq\) 14 mL/kg/min who had transplant deferred; and group 3, patients with peak \(\dot{V}O_2\) of < 14 mL/kg/min but...
with significant comorbid 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 $\leq10$ mL/kg/min, $>10$ to $\leq14$ mL/kg/min, $>14$ to $\leq18$ 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 $\leq10$ mL/kg/min, and was almost identical among those with peak VO$_2$ values of $>10$ to $\leq14$ mL/kg/min, $>14$ to $\leq18$ 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 (i.e., 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 VO₂, 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 VO₂ with age, in healthy subjects and chronic HF populations, the authors reasoned that peak VO₂ corrected for lean body mass would reflect a more accurate picture of cardiopulmonary function during exercise. Lean peak VO₂, either as a continuous variable or using a cutoff value of ≤ 19 mL/kg/min, was a better predictor of outcome than unadjusted peak VO₂ 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 (VE) and carbon dioxide output (VCO₂), expressed as the VE/VCO₂ slope, is associated with a poor outcome.20–28 Chua et al20 reported that a VE/VCO₂ slope of > 34 was associated with worse prognosis in 173 chronic HF patients, and Kleber et al21 selected a VE/VCO₂ slope that was > 130% of the age-adjusted and sex-adjusted value as the best predictive cutoff point in 142 patients. Francis et al22 certified the prognostic information of VE/VCO₂ slope over a wide range of values, from 30 to 55, whereas MacGowan et al23 substantiated that the combination of a peak VE/VCO₂ slope of > 50 and a peak VO₂ of ≤ 15 mL/kg/min was associated with an 82% mortality rate in 104 chronic HF patients. Finally, Robbins et al24 found that a VE/VCO₂ slope of ≥ 44.7 at peak exercise was superior to a peak VO₂ of ≤ 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.25–27 Moreover, we demonstrated that oscillatory ventilation during exercise, defined as cyclic fluctuations in VE at rest that persist during effort lasting for ≥ 60% of the exercise

![Figure 1](image_url)  
**Figure 1.** The prognosticating algorithm for the individual patient with chronic HF according to peak VO₂ and VAT identification.

<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>Stelken et al15/1996</td>
<td>181</td>
<td>16.3 ± 5.9</td>
<td>24</td>
<td>Percent achieved of predicted peak VO₂</td>
</tr>
<tr>
<td>Cohen-Solal et al16/1997</td>
<td>178</td>
<td>17.6 ± 5.6</td>
<td>19</td>
<td>Percent achieved of predicted peak VO₂</td>
</tr>
<tr>
<td>Osada et al17/1998</td>
<td>500</td>
<td>12.0 ± 2.0</td>
<td>26</td>
<td>Peak SBF and percent achieved of predicted peak VO₂</td>
</tr>
<tr>
<td>Osman et al18/2000</td>
<td>225</td>
<td>16.0 ± 5.9</td>
<td>13</td>
<td>Adjusted peak VO₂ to lean body mass</td>
</tr>
</tbody>
</table>

*SBF = systolic BP.
†Values given as mean ± SD.
duration, with an amplitude $\geq 15\%$ of the average resting value, is not unusual in chronic HF patients (ie, 12\% of 323 patients), and has independent and additional prognostic power,26.

Beside gas exchange parameters, other exercise variables have been investigated to further stratify chronic HF patients undergoing CPX (Table 3). Osada et al29 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 $\dot{V}O_2$ of $<50\%$ were selected as significant additional and independent variables in patients with a peak $\dot{V}O_2$ of $\leq 14$ 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 $\beta$-blockers. Chronotropic incompetence was measured by calculating the proportion of heart rate (HR) reserve, applying the method of Wilkoff and Miller,30 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 $\dot{V}O_2$ 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 $\dot{V}O_2$, $<10$ 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 $\dot{V}O_2$, mL/kg/min</th>
<th>Event Rate, %</th>
<th>CPX Variables Related to Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacGowan et al19/1997</td>
<td>104</td>
<td>NA</td>
<td>19</td>
<td>Peak $\dot{V}CO_2$ in pts with peak $\dot{V}O_2 \leq 15$ mL/kg/min</td>
</tr>
<tr>
<td>Chua et al20/1997</td>
<td>155</td>
<td>18.5 ± 7.3</td>
<td>24</td>
<td>$\dot{V}CO_2$ slope</td>
</tr>
<tr>
<td>Robbins et al21/1999</td>
<td>470</td>
<td>13.0 ± 7.0</td>
<td>15</td>
<td>Peak $\dot{V}CO_2$ and low HR response</td>
</tr>
<tr>
<td>Kleber et al22/2000</td>
<td>142</td>
<td>15.2 ± 4.7</td>
<td>29</td>
<td>$\dot{V}CO_2$ slope</td>
</tr>
<tr>
<td>Francis et al23/2000</td>
<td>303</td>
<td>17.8 ± 6.6</td>
<td>30</td>
<td>Peak $\dot{V}O_2$ and $\dot{V}CO_2$ slope</td>
</tr>
<tr>
<td>Arena and Humphrey24/2002</td>
<td>37</td>
<td>13.3 ± 4.5</td>
<td>51†</td>
<td>$\dot{V}CO_2$ slope</td>
</tr>
<tr>
<td>Mejlert et al25/2002</td>
<td>67</td>
<td>11.7 ± 3.6</td>
<td>21</td>
<td>Peak $\dot{V}CO_2$</td>
</tr>
<tr>
<td>Corrè et al26/2002</td>
<td>323</td>
<td>14.0 ± 3.0</td>
<td>16</td>
<td>Oscillatory exertional ventilation</td>
</tr>
<tr>
<td>Corrè et al27/2002</td>
<td>600</td>
<td>14.8 ± 4.0</td>
<td>15</td>
<td>$\dot{V}CO_2$ slope in pts with peak $\dot{V}O_2 &gt; 10$–18 mL/kg/min</td>
</tr>
<tr>
<td>Mezzani et al28/2003</td>
<td>570</td>
<td>14.5 ± 4.0</td>
<td>12</td>
<td>Peak RER in pts with peak $\dot{V}O_2 &lt; 10$ mL/kg/min</td>
</tr>
</tbody>
</table>

*Pts = 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 $\dot{V}O_2$, mL/kg/min</th>
<th>Event Rate, %</th>
<th>CPX Variables Related to Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osada et al29/1998</td>
<td>500</td>
<td>12.1 ± 2.0</td>
<td>26</td>
<td>Peak SBP and percent achieved of predicted peak $\dot{V}O_2$</td>
</tr>
<tr>
<td>Robbins et al30/1999</td>
<td>470</td>
<td>13.0 ± 7.0</td>
<td>15</td>
<td>Peak $\dot{V}CO_2$ and low HR response</td>
</tr>
<tr>
<td>Williams et al31/2001</td>
<td>219</td>
<td>23.0 ± 9.2</td>
<td>12</td>
<td>Peak cardiac power</td>
</tr>
<tr>
<td>Cohen-Solal et al32/2002</td>
<td>175</td>
<td>20.3 ± 5.6</td>
<td>16</td>
<td>Circulatory power</td>
</tr>
<tr>
<td>Scharf et al33/2002</td>
<td>154</td>
<td>18.8 ± 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 $\dot{V}O_2$; exercise cardiac power = product of peak SBP and percent achieved of predicted peak $\dot{V}O_2$. See Table 1 for abbreviations not used in the text.

†Values given as mean ± SD.
sional value of peak \( V_o \) in patients with a peak \( V_o \) 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 \( \leq 1.05 \) (in order to exclude poor motivation). Patients were stratified into the following four groups according to functional capacity: peak \( V_o \) \( \leq 10 \) mL/kg/min; peak \( V_o > 10 \) to \( \leq 14 \) mL/kg/min; peak \( V_o > 14 \) to \( < 18 \) mL/kg/min; and peak \( V_o \geq 18 \) 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 \( V_o \) of \( \leq 10 \) mL/kg/min died, as opposed to only 3 of those patients with peak \( V_o \) of \( \geq 18 \) 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 \( V_o > 10 \) to \( \leq 14 \) mL/kg/min, 17%; patients with peak \( V_o > 14 \) to \( 18 \) mL/kg/min 11%). In this cohort of patients with intermediate functional capacity (ie, a mean \( \pm SD \) peak \( V_o \), 13.9 \( \pm 2 \) mL/kg/min), the VE/\( V_{\text{co2}} \) 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 \( V_o \), \( V_o \) at VAT, and detectable VAT. The best cutoff value for VE/\( V_{\text{co2}} \) slope was 35. Patients with a VE/\( V_{\text{co2}} \) slope of \( \geq 35 \) had a significantly higher mortality rate than did those with a VE/\( V_{\text{co2}} \) slope of \( < 35 \) (30% vs 10%, respectively; \( p < .0001 \)), but a similar one to those with peak \( V_o \) of \( \leq 10 \) mL/kg/min (30% vs 37%, respectively). We postulated that the broad range of VE/\( V_{\text{co2}} \) 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 \( V_o \) and VE/\( V_{\text{co2}} \) slope in chronic HF patients is summarized in Figure 2. A threshold peak \( V_o \) value of \( \leq 10 \) mL/kg/min identifies high-risk patients, whereas a cutoff value of \( \geq 18 \) mL/kg/min categorizes patients with a fairly good long-term prognosis. A peak \( V_o \) 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 VE/\( V_{\text{co2}} \) slope of \( \geq 35 \) allows the identification of those with the worst outcomes, with a total mortality rate comparable to that detected among those with a peak \( V_o \) of \( \leq 10 \) mL/kg/min.

**Patients With Severe Exercise Intolerance**

Patients with severe exercise intolerance (ie, peak \( V_o < 10 \) mL/kg/min) become increasingly less...
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/VCO₂ slope, and peak RER. Indeed, commencing with peak VO₂, a threshold of peak VO₂ of ≤ 10 mL/kg/min identifies high-risk patients, a cutoff 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/VCO₂ 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/VCO₂ 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 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 (ie, selected middle-aged men with severe HF) who had an up-to-date therapeutic armamentarium (with the exception of β-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 β-blockers has been evaluated in small series of patients, with different β-blocker agents, leading to contradictory results that should be interpreted considering severity of disease, type and duration of β-blocker treatment, and heart transplantation candidacy.46–49 Patients who receive therapy with β-blockers are usually in a lower New York Heart Association class, have a higher mean left ventricular ejection fraction and peak Vo2, 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 β-blockers have very low peak Vo2 values and generate disarrangement signals to the ventilatory control system, resulting in an abnormal exertional ventilatory response (ie, high Ve/Vco2 slope). On the other hand, long-term β-blocker therapy interferes with hemodynamic and metabolic adaptations and with ion balance during exercise, but pharmacologic differences among β-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 Vo2 of ≤ 10 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 Vo2 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 β-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 β-blockers,53 but the inconclusive results, due to study population differences and the

![Diagram](image-url)
lack of an accepted standard for the assessment of Vo$_2$ 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 Vo$_2$ 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 Vo$_2$ 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**


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