exercise and the heart

Cardiopulmonary Exercise Testing and Prognosis in Chronic Heart Failure*

A Prognosticating Algorithm for the Individual Patient

Ugo Corrà, MD; Alessandro Mezzani, MD; Enzo Bosimini, MD; and Pantaleo Giannuzzi, MD

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. *(CHEST 2004; 126:942–950)*

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; $\dot{V}CO_2$ = carbon dioxide ouput; $\dot{V}E$ = minute ventilation; $\dot{V}O_2$ = 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.[1–4] 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.[5] 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.[6] Although several studies[7–9] published during the 1980s deserve mention, the study by Mancini et al[10] 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 ≥ 14 mL/kg/min who had transplant deferred; and group 3, patients with peak $\dot{V}O_2$ of < 14 mL/kg/min but

Correspondence to: Ugo Corrà, MD, Divisione di Cardiologia, Fondazione "S. Maugeri," Via per Revislate, 13, 28010 Veruno, Italy; e-mail: ucorra@fsm.it

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 $\dot{V}O_2$ 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 $\dot{V}O_2$ has a predictive role, and that "... for patients with $\dot{V}O_2$ 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 $\dot{V}O_2$ max."

Thus, a simple but somewhat dogmatic approach has been formulated. When the ventilatory anaerobic threshold (VAT) is detected, a peak $\dot{V}O_2$ 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 $\dot{V}O_2$. Opasich et al[14] evaluated the predictive role of peak $\dot{V}O_2$ 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 $\dot{V}O_2$ values of ≤ 10 mL/kg/min, > 10 to ≤ 14 mL/kg/min, > 14 to ≤ 18 mL/kg/min, and > 18 mL/kg/min, respectively. When VAT was not detected, the event rate was 46% in patients with peak $\dot{V}O_2$ of ≤ 10 mL/kg/min, and was almost identical among those with peak $\dot{V}O_2$ values of > 10 to ≤ 14 mL/kg/min, > 14 to ≤ 18 mL/kg/min, and > 18 mL/kg/min (29%, 23%, and 22%, respectively).

Thus, when VAT is detected, patients with a peak $\dot{V}O_2$ of < 10 mL/kg/min have a high event rate, whereas those with a peak $\dot{V}O_2$ of > 18 mL/kg/min have a good prognosis. Patients with intermediate functional capacity (*ie*, peak $\dot{V}O_2$ between 10 and 18 mL/kg/min) fall into an arbitrary prognostic region in which peak $\dot{V}O_2$ does not provide predictive or decisional information. When the VAT is undetectable, the following dichotomy is suggested: for patients with peak $\dot{V}O_2$ 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 $\dot{V}O_2$

While there is much faith in peak $\dot{V}O_2$ as a predictive parameter, most clinicians do not realize that a multiplicity of factors influence any given value. Peak $\dot{V}O_2$ is traditionally expressed as milliliters per minute or as milliliters per kilogram per minute, but it is well-known that peak $\dot{V}O_2$ is affected by age, gender, body weight, muscle mass, and conditioning status. Thus, a peak $\dot{V}O_2$ 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 $\dot{V}O_2$, taking into account age, gender, and weight, with the traditionally used absolute peak $\dot{V}O_2$ measured in milliliters per kilogram per minute. During the 12-month follow-up, nonsurvivors achieved a lower percentage of the predicted peak $\dot{V}O_2$ and a lower absolute peak $\dot{V}O_2$ than survivors, and multivariate analysis revealed that $< 50\%$ predicted of the peak $\dot{V}O_2$ was the strongest predictor of cardiac events, superior to the cutoff absolute value of peak $\dot{V}O_2$ of < 14 mL/kg/min. Aaronson and Mancini[16] refuted these results, measuring the percentage of predicted peak $\dot{V}O_2$ 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 $\dot{V}O_2$ significantly improved the prediction of survival over peak $\dot{V}O_2$, as the areas under the receiver operating curves constructed for the absolute peak $\dot{V}O_2$ normalized for body weight and percentage of predicted peak $\dot{V}O_2$ were roughly equal.

Osman et al[19] have documented that the adjustment of peak $\dot{V}O_2$ to lean body weight provides greater prognostic strength than the traditionally
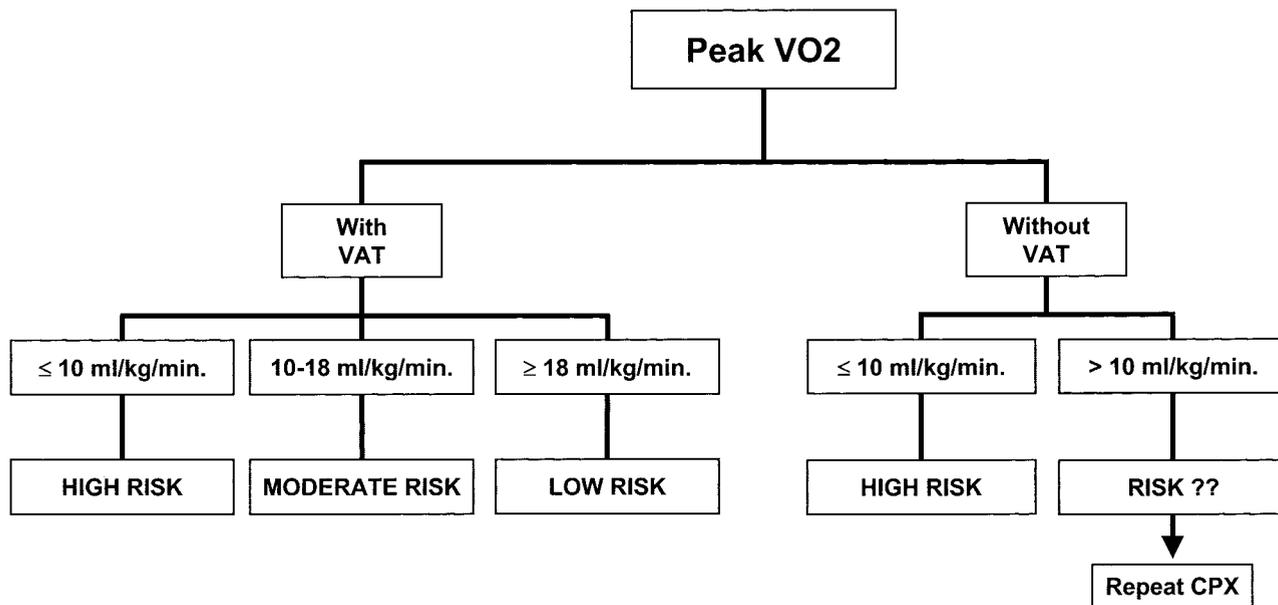
FIGURE 1. The prognosticating algorithm for the individual patient with chronic HF according to peak $\dot{V}O_2$ and VAT identification.

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 ≤ 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 ($\dot{V}E$) and carbon dioxide output ($\dot{V}CO_2$), expressed as the $\dot{V}E/\dot{V}CO_2$ slope, is associated with a poor outcome.[20–28] Chua et al[20] reported that a $\dot{V}E/\dot{V}CO_2$ slope of > 34 was associated with worse prognosis in 173 chronic HF patients, and Kleber et al[21] selected a $\dot{V}E/\dot{V}CO_2$ 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 $\dot{V}E/\dot{V}CO_2$ slope over a wide range of values, from 30 to 55, whereas MacGowan et al[23] substantiated that the combination of a peak $\dot{V}E/\dot{V}CO_2$ slope of > 50 and a peak $\dot{V}O_2$ of ≤ 15 mL/kg/min was associated with an 82% mortality rate in 104 chronic HF patients. Finally, Robbins et al[24] found that a $\dot{V}E/\dot{V}CO_2$ slope of ≥ 44.7 at peak exercise was superior to a peak $\dot{V}O_2$ 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 $\dot{V}E$ at rest that persist during effort lasting for $\geq 60\%$ of the exercise

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*

Study/Year	Patients, No.	Peak $\dot{V}O_2$,† mL/kg/min	Event Rate, %	CPX Variables Related to Outcome
Stelken et al[15]/1996	181	16.3 ± 5.9	24	Percent achieved of predicted peak $\dot{V}O_2$
Cohen-Solal et al[32]/1997	178	17.6 ± 5.6	19	Percent achieved of predicted peak $\dot{V}O_2$
Osada et al[29]/1998	500	12.0 ± 2.0	26	Peak SBP and percent achieved of predicted peak $\dot{V}O_2$
Osman et al[19]/2000	225	16.0 ± 5.9	13	Adjusted peak $\dot{V}O_2$ to lean body mass

*SBP = systolic BP.
†Values given as mean ± SD.

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

Study/Year	Patients, No.	Peak $\dot{V}O_2$,† mL/kg/min	Event Rate, %	CPX Variables Related to Outcome
MacGowan[23]/1997	104	NA	19	Peak $\dot{V}E/\dot{V}CO_2$ in pts with peak $\dot{V}O_2 \leq 15$ mL/kg/min
Chua et al[20]/1997	155	18.5 ± 7.3	24	$\dot{V}E/\dot{V}CO_2$ slope
Robbins et al[24]/1999	470	13.0 ± 7.0	15	Peak $\dot{V}E/\dot{V}CO_2$ and low HR response
Kleber et al[21]/2000	142	15.2 ± 4.7	29	$\dot{V}E/\dot{V}CO_2$ slope
Francis et al[22]/2000	303	17.8 ± 6.6	30	Peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope
Arena and Humphrey[25]/2002	37	13.3 ± 4.5	51‡	$\dot{V}E/\dot{V}CO_2$ slope
Mejhert et al[27]/2002	67	11.7 ± 3.6	21	Peak $\dot{V}E/\dot{V}CO_2$
Corrà et al[28]/2002	323	14.0 ± 3.0	16	Oscillatory exertional ventilation
Corrà et al[36]/2002	600	14.8 ± 4.0	15	$\dot{V}E/\dot{V}CO_2$ slope in pts with peak $\dot{V}O_2 > 10$–< 18 mL/kg/min
Mezzani et al[39]/2003	570	14.5 ± 4.0	12	Peak RER in pts with peak $\dot{V}O_2 < 10$ mL/kg/min

*pts = patients; NA = not applicable.
†Values given as mean $\pm$ SD.
‡Includes hospitalizations.

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.[28]

Beside gas exchange parameters, other exercise variables have been investigated to further stratify chronic HF patients undergoing CPX (Table 3). Osada et al[29] 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 ≤ 14 mL/kg/min. Robbins et al[24] studied 470 consecutive chronic HF patients who had been referred for functional evaluation who were not receiving therapy with β-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 3—*Clinical Studies Documenting Relationship Between Noninvasive Exercise Variables and Prognosis in Chronic HF Patients Undergoing Symptom-Limited CPX*

Study/Year	Patients, No.	Peak $\dot{V}O_2$,† mL/kg/min	Event Rate, %	CPX Variables Related to Outcome
Osada et al[29]/1998	500	12.1 ± 2.0	26	Peak SBP and percent achieved of predicted peak $\dot{V}O_2$
Robbins et al[24]/1999	470	13.0 ± 7.0	15	Peak $\dot{V}E/\dot{V}CO_2$ and low HR response
Williams et al[43]/2001	219	23.0 ± 9.2	12	Peak cardiac power
Cohen-Solal et al[44]/2002	175	20.3 ± 5.6	16	Circulatory power
Scharf et al[45]/2002	154	18.8 ± 0.4	21	Exercise cardiac power

*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 $\pm$ 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 $\dot{V}O_2 \geq 18$ mL/kg/min.[36] 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 a $\dot{V}O_2$ 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/mink 11%). In this cohort of patients with intermediate functional capacity (ie, a mean [$\pm$ 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
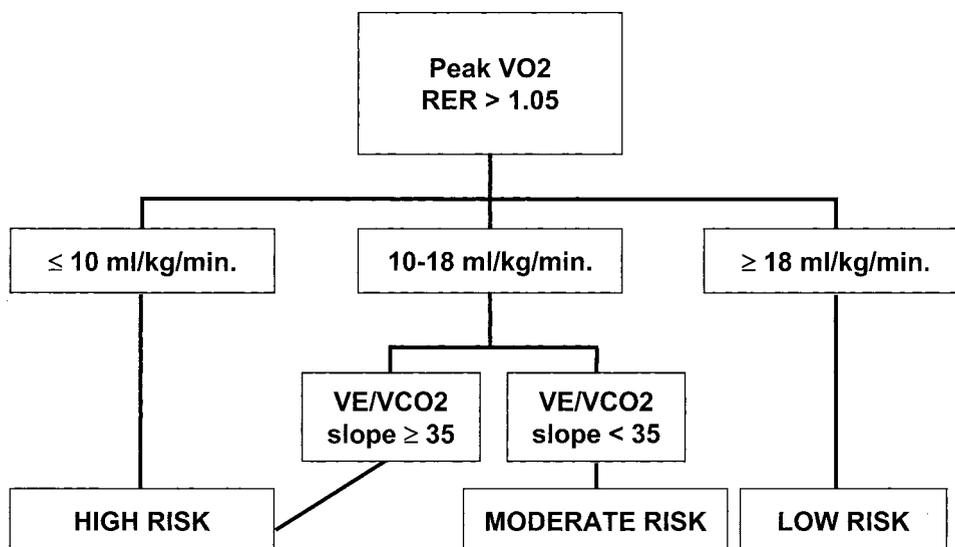

FIGURE 2. The prognostic and decisional impact of peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope in chronic HF patients with intermediate functional capacity.

used to accomplishing strenuous daily activities with clinical progression of the disease,[37] and their motivation to reach maximal effort and to experience symptoms during an exercise test may be lacking.[38] Indeed, objective indexes of maximal effort are needed in order to ensure a peak $\dot{V}O_2$ reliability and to avoid inappropriate prognostic stratification due to poor motivation.

Mezzani et al[39] evaluated 570 chronic HF patients, 273 of whom had a peak $\dot{V}O_2$ of ≤ 14 mL/kg/min (peak $\dot{V}O_2 > 10$ to ≤ 14 mL/kg/min, 193 patients; peak $\dot{V}O_2 \leq 10$ 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 $\dot{V}O_2$ values of > 14, > 10 to ≤ 14, and ≤ 10 mL/kg/min (p < 0.0001). In the group with a peak $\dot{V}O_2$ 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 $\dot{V}O_2$ 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 $\dot{V}O_2$ 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 $\dot{V}O_2$ prognostic reliability. In the case of peak RER values of < 1.15, a cautious use of peak $\dot{V}O_2$ 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 $\dot{V}O_2$ 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 $\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$ slope, and peak RER. Indeed, commencing with peak $\dot{V}O_2$, a threshold of peak $\dot{V}O_2$ 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 $\dot{V}O_2$
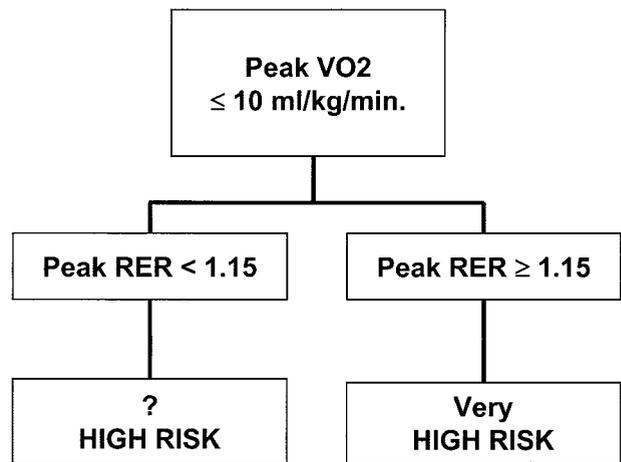

FIGURE 3. Decision making in chronic HF patients with some exercise intolerable and peak RER values of < 1.15.

between 10 and 18 mL/kg/min indicates a moderate risk of cardiac events. In this latter subset of patients, a $\dot{V}E/\dot{V}CO_2$ slope of ≥ 35 allows for the identification of those patients with worse outcomes. In chronic HF patients with a peak $\dot{V}O_2$ 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 $\dot{V}E/\dot{V}CO_2$ 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.[40–42] A number of noninvasive surrogates of cardiac output have been investigated in chronic HF patients undergoing symptom-limited CPX.[43–45] Cohen-Solal et al[44] stated that "circulatory power," calculated as the product of $\dot{V}O_2$ and peak systolic BP, strengthens the prognostic value of CPX, especially in patients with a low peak $\dot{V}O_2$ and a low BP, whereas Scharf et al[45] documented that exercise cardiac power, defined as the product of the achieved percent predicted peak
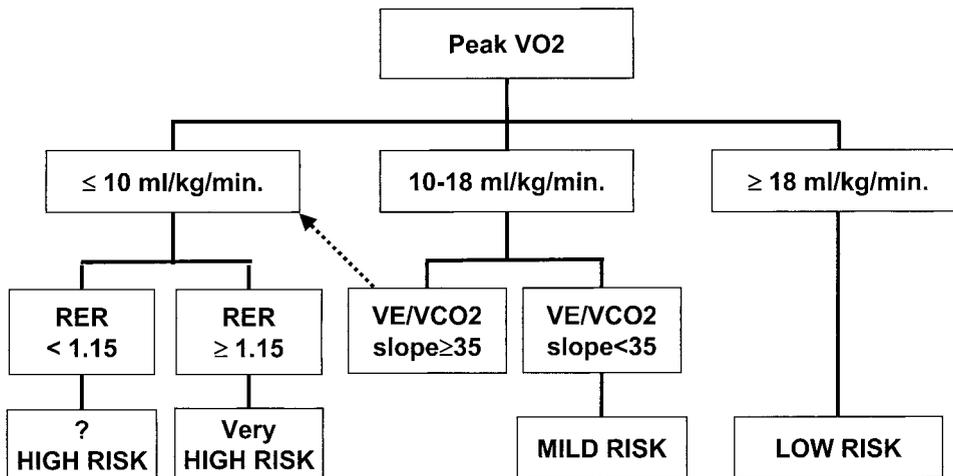
FIGURE 4. A new prognosticating algorithm that is structured on a multiparametric decoding scrutiny employing the stepwise introduction of peak $\dot{V}o_2$, $\dot{V}e/\dot{V}co_2$ slope, and peak RER. The dotted line indicates that patients with intermediate exercise capacity (ie, peak $\dot{V}o_2$ of > 10 and < 18 mL/kg/min) and excessive ventilatory response (ie, $\dot{V}e/\dot{V}co_2$ slope of ≥ 35) have a total mortality rate that is comparable to that detected with a peak $\dot{V}o_2$ of ≤ 10 mL/kg/min (whole population).

$\dot{V}o_2$ 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 (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 $\dot{V}o_2$, 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 β-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 (ie, high $\dot{V}e/\dot{V}co_2$ 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 results 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 ≤ 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 $\dot{V}o_2$ 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 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

lack of an accepted standard for the assessment of $\dot{V}O_2$ 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 $\dot{V}O_2$ 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 $\dot{V}O_2$ 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

1 McMurray J, Pfeffer MA. New therapeutic options in congestive heart failure: part I. Circulation 2002; 105:2099–2106

2 McMurray J, Pfeffer MA. New therapeutic options in congestive heart failure: part II. Circulation 2002; 105:2223–2228

3 Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term mechanical left ventricular assistance for end-stage heart failure. N Engl J Med 2001; 345:1435–1443

4 Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002; 346:1845–1853

5 Beniaminovitz A, Mancini DM. The role of exercise-based prognasticating algorithms in the selection of patients for heart transplantation. Curr Opin Cardiol 1999; 4:114–120

6 Mancini DM, LeJemetel T, Aaronson K. Peak $\dot{V}O_2$: a simple yet enduring standard. Circulation 2000; 101:1080–1082

7 Szlachcic J, Massie B, Kramer B, et al. Correlates and prognostic implication of exercise capacity in chronic congestive heart failure. Am J Cardiol 1985; 55:1037–1042

8 Likoff MJ, Chandler SF, Kay HR. Clinical determinants of mortality in chronic congestive heart failure secondary to idiopathic dilated or ischemic cardiomyopathy. Am J Cardiol 1987; 59:634–638

9 Cohn JN, Johnson G, Shabetai R, et al. Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias, and plasma norepinephrine as determinants of prognosis in heart failure. Circulation 1993; 87:VI5–VI16

10 Mancini DM, Eisen H, Kussmaul W, et al. Value of peak oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991; 83:778–786

11 Costanzo MR, Augustine S, Bourge R, et al. Selection and treatment of candidates for heart transplantation. Circulation 1995; 92:3595–3612

12 Brooks GA. Anaerobic threshold: review of the concept and directions for future research. Med Sci Sports Exerc 1985; 17:22–31

13 Cohen-Solal A, Zannad F, Kayanakis JG, et al. Multicenter determination of the oxygen uptake and ventilatory threshold. Eur Heart J 1991; 12:1055–1063

14 Opasich C, Pinna GD, Bobbio M, et al. Peak oxygen consumption in chronic heart failure: toward efficient use in the individual patient. J Am Coll Cardiol 1998; 31:766–775

15 Stelken AM, Younis LT, Jennison SH, et al. Prognostic value of cardiopulmonary exercise testing using percent achieved of predicted peak oxygen uptake for patients with ischemic and dilated cardiomyopathy. J Am Coll Cardiol 1996; 27:345–352

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

17 Wasserman K, Hansen JE, Sue DY, et al. Principles of exercise testing and interpretation. Philadelphia, PA: Lea & Febiger, 1986

18 Astrand P. Human physical fitness with special reference to sex and age. Physiol Rev 1956; 36(suppl):307–335

19 Osman AF, Mehra MR, Lavie CJ, et al. The incremental prognostic importance of body fat adjusted peak oxygen consumption in chronic heart failure. J Am Coll Cardiol 2000; 36:2126–2131

20 Chua TP, Ponikowski P, Harrington D, et al. Clinical correlates and prognostic significance of the ventilatory response to exercise in CHF. J Am Coll Cardiol 1997; 29:1585–1590

21 Kleber FX, Vietzke G, Wernecke KD, et al. Impairment of ventilatory efficiency in heart failure: prognostic impact. Circulation 2000; 101:2803–2809

22 Francis DP, Shamin W, Ceri Davies L, et al. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from $\dot{V}E/\dot{V}CO_2$ slope and peak $\dot{V}O_2$. Eur Heart J 2000; 21:154–161

23 MacGowan GA, Janosko K, Cecchetti A, et al. Exercise-related ventilatory abnormalities and survival in congestive heart failure. Am J Cardiol 1997; 79:1264–1266

24 Robbins M, Francis G, Pashkow FJ, et al. Ventilatory and heart rate response to exercise: better predictors of heart failure mortality than peak oxygen consumption. Circulation 1999; 100:2411–2417

25 Arena R, Humphrey R. Comparison of ventilatory expired gas parameters used to predict hospitalization in patients with heart failure. Am Heart J 2002; 143:427–432

26 Cicoria M, Davos CH, Florea V, et al. Chronic heart failure in the very elderly: clinical status, survival, and prognosis factors in 188 patients more than 70 years old. Am Heart J 2001; 142:147–180

27 Mejhert M, Linder-Klingsell E, Edner M, et al. Ventilatory variables are strong prognostic markers in elderly patients with heart failure. Heart 2002; 88:239–243

28 Corrà U, Giordano A, Bosimini E, et al. Oscillatory ventilation during exercise in patients with chronic heart failure: clinical correlates and prognostic implications. Chest 2002; 121:1572–1580

29 Osada N, Chiatman BR, Miller LW, et al. Cardiopulmonary 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

30 Wilkoff BL, Miller RE. Exercise testing for chronotropic assessment. Cardiol Clin 1992; 10:705–717

31 Van den Broek S, Van Veldhuisen D, De Greaff P, et al. Comparison between New York Heart Association classification and peak oxygen consumption in the assessment of functional status and prognosis in patients with mild to moderate chronic congestive heart failure secondary either to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1992; 70:359–363

32 Cohen-Solal A, Barnier P, Pessione F, et al. Comparison of the long-term prognostic value of peak exercise oxygen pulse and peak exercise oxygen uptake in patients with chronic heart failure. Heart 1997; 78:572–576

33 Kao W, Winkle EM, Johnson MR, et al. Role of maximal oxygen consumption in establishment of heart transplantation candidacy for heart failure patients with intermediate exercise tolerance. Am J Cardiol 1997; 79:1124–1127

34 Myers J, Gullestad L, Vagelos R, et al. Clinical, hemodynamic, and cardiopulmonary exercise test determinants of survival in patients referred for evaluation of heart failure. Ann Intern Med 1998; 129:286–293

35 Myers J, Gullestad L, Vagelos R, et al. Cardiopulmonary exercise testing and prognosis in severe heart failure: 14 ml/kg/min revisited. Am Heart J 2000; 139:78–84

36 Corrà U, Mezzani A, Bosimini E, et al. Ventilatory response to exercise improves risk stratification in chronic heart failure patients with intermediate functional capacity. Am Heart J 2002; 143:418–426

37 Mezzani A, Corrà U, Baroffio C, et al. Habitual activities and peak aerobic capacity in patients with asymptomatic and symptomatic left ventricular dysfunction: use of a new physical activity scoring system. Chest 2000; 117:1291–1299

38 Clark AL, Poole-Wilson PA, Coats AJS. Effects of motivation of the patient on indices of exercise capacity in chronic heart failure. Br Heart J 1994; 71:162–165

39 Mezzani A, Corrà U, Bosimini E, et al. Contribution of peak respiratory exchange ratio to peak VO2 prognostic reliability in patients with chronic heart failure and severely reduced exercise capacity. Am Heart J 2003; 145:1102–1107

40 Roul G, Moulichon ME, Bareiss P, et al. Prognostic factors of chronic heart failure in NYHA class II or III: value of invasive hemodynamic data. Eur Heart J 1995; 16:1387–1398

41 Chomsky DB, Lang CC, Rayos GH, et al. Hemodynamic exercise testing: a valuable tool in selection of cardiac transplantation candidates. Circulation 1996; 94:3176–3183

42 Metra M, Faggiano P, D'Aloia A, et al. Use of cardiopulmonary exercise testing with hemodynamic monitoring in the prognostic assessment of ambulatory patients with chronic heart failure. J Am Coll Cardiol 1999; 33:943–950

43 Williams SG, Cooke GA, Wright DJ, et al. Peak exercise cardiac power output: a direct indicator of cardiac function strongly predictive of prognosis in chronic heart failure. Eur Heart J 2001; 22:1496–1503

44 Cohen-Solal A, Tabet JY, Logeart D, et al. A non-invasively determined surrogate of cardiac power ("circulatory") at peak exercise is a powerful prognostic factor in chronic heart failure. Eur Heart J 2002; 23:806–814

45 Scharf C, Merz T, Kiowski W, et al. Noninvasive assessment of cardiac pumping capacity during exercise predicts prognosis in patients with congestive heart failure. Chest 2002; 122:1333–1339

46 Zugck C, Haunnstetter A, Krüger C, et al. Impact of beta-blocker treatment on the prognostic value of currently used risk predictors in congestive heart failure. J Am Coll Cardiol 2002; 39:1615–1622

47 Corrà U, Mezzani A, Bosimini E, et al. Limited predictive value of cardiopulmonary exercise indexes in patients with chronic heart failure treated with carvedilol [abstract]. Eur Heart J 2002; 23:705

48 Peterson LR, Schechtman KB, Ewald GA, et al. The effect of β-adrenergic blockers on the prognostic value of peak exercise oxygen uptake in patients with heart failure. J Heart Lung Transplant 2003; 22:70–77

49 Pohwani AL, Murali S, Matheir MM, et al. Impact of β-blocker therapy on functional capacity criteria for heart transplant listing. J Heart Lung Transplant 2003; 22:78–86

50 Metra M, Giubbini R, Nodari S, et al. Differentials effects of β-blockers in patients with heart failure: a prospective, randomized, double-blind comparison of the long-term effects of metoprolol versus carvedilol. Circulation 2000; 102: 546–551

51 Pardaens K, Van Cleemput J, Vanhaecke J, et al. Peak oxygen uptake better predicts outcome than submaximal respiratory data in heart transplant candidates. Circulation, 2000; 101: 1152–1157

52 Schalcher C, Rickli H, Brehm M, et al. Prolonged oxygen uptake kinetics during low-intensity exercise are related to poor prognosis in patients with mild-to-moderate congestive heart failure. Chest 2003; 124:580–586

53 Rickli H, Kiowski W, Brehm M, et al. Combining low-intensity and maximal exercise test results improves prognostic prediction in chronic heart failure. J Am Coll Cardiol 2003; 42:116–122