Optimal use of cardio-pulmonary exercise testing (CPET) in clinical practice and chronic heart failure (CHF) requires appropriate data presentation and a flexible interpretative strategy. The greatest potential impact on the decision-making process may rest not on the value of any individual measurement, although some are obviously more important than others, but rather on their integrative use. Such an integrative approach relies on interrelationship, trending phenomena and patterns of key gas exchange variable responses. An multiparametric approach will be discussed in different clinical applications, for exercise prescription and monitoring, functional evaluation of drug therapy or cardiac resynchronisation therapy efficacy, and risk stratification. The role of CPET in the daily clinical decision-making process will be underscored. Future indications of CPET will be addressed, suggesting and promoting an extended candidacy either to all CHF patients, including those at high risk or most vulnerable, such as female, elderly patients, and patients with implantable cardioverter defibrillator or in every clinical setting where objective definition of exercise capacity provides implications for medical, surgical, and social decision making. Eur J Cardiovasc Prev Rehabil 13:485–494 © 2006 The European Society of Cardiology

Keywords: exercise, heart failure, physiology, training

Interpretation

Optimal use of cardio-pulmonary exercise testing (CPET) in clinical practice requires appropriate data presentation and a flexible interpretative strategy. The greatest potential impact on a decision-making process may rest, not on the utility of any individual measurement, although some are obviously more important than others, but rather on their integrative use. Such an integrative approach relies on interrelationship, trending phenomena, and patterns of key gas exchange variable responses.

Exercise tolerance evaluation

Since exercise intolerance is the cardinal clinical manifestation in chronic heart failure (CHF), an accurate estimation of functional capacity is imperative. A direct measurement of peak oxygen uptake (VO₂peak) provides reproducible and objective functional information.

Contrary to what is observed in athletes or fit subjects, what is measured at the end of exercise in a CHF patient is not a plateau of VO₂max. Therefore, one has to be sure, before interpreting the value of VO₂peak, that the test has been maximal or submaximal and can be considered valid. This is difficult a posteriori. Patients generally stop exercising early because of fatigue or dyspnoea. Tests stopped for other reasons (e.g. chest pain, ischaemia, decrease in blood pressure, arrhythmias) should not be
considered for the assessment of VO$_{2\text{peak}}$. It is important to stimulate the patient during the test. A high respiratory exchange ratio (RER; VCO$_2$/VO$_2$) value, greater than 1.15, confirms the validity of the test.

The combination of VO$_{2\text{peak}}$ and anaerobic threshold (AT) traditionally allowed a grading of the severity of functional impairment in CHF and assists in tracking the progression of disease objectively: according to Weber et al. [1], the exercise capacity of CHF patients can be divided into four classes (Table 1).

A study of 116 patients being considered for cardiac transplantation in a University of Pennsylvania programme found that in patients with VO$_{2\text{peak}}$ $\leq$ 14 ml/kg per min, the freedom from death or urgent cardiac transplantation was only 48% at 1 year [2]. Patients without significant co-morbidities and with VO$_{2\text{peak}}$ $\geq$ 14 ml/kg per min had a 1-year survival of 94%. This raised a consensus that an ejection fraction $< 20\%$ and VO$_{2\text{peak}}$ $\leq$ 14 ml/kg per min should be present to warrant referral for cardiac transplantation [3].

Although this classification has been widely used in daily clinical practice, it should be emphasized that a variety of factors may influence VO$_{2\text{peak}}$ and that assessment of effort of each individual patient is crucial, peculiarly when VO$_{2\text{peak}}$ is impaired.

VO$_{2\text{peak}}$ is traditionally normalized by body weight in kilograms, as this is the easiest way to calculate it: however, normalization for body weight may not be the most appropriate frame of reference for comparing the metabolic rate across patients of different sizes. Small patients have a higher VO$_{2\text{peak}}$ per kilogram than larger ones. Normalization by body weight may lead to misleadingly low VO$_{2\text{peak}}$ values in obese patients [4]. As body fat is a metabolically inactive mass, and the variability in body fat may contribute to the age-decline in VO$_{2\text{peak}}$ in CHF populations, a VO$_{2\text{peak}}$ corrected for lean body mass (LBM) would reflect a more accurate picture of cardiopulmonary function during exercise: VO$_{2\text{peak}}$ corrected for LBM is roughly half of VO$_{2\text{peak}}$ expressed as an absolute value [5]. Up to now, routine use of VO$_{2\text{peak}}$ corrected for LBM in clinical exercise laboratories is uncommon and difficult, due to measurement pitfalls, including cost, accessibility (dual-energy X-ray absorptiometry) and reproducibility (skinfold techniques).

VO$_{2\text{peak}}$ is strongly influenced by age and gender, and a proper description of exercise capacity should be integrated by the calculation of the percentage age and gender-predicted value VO$_{2\text{peak}}$%. Normal reference values provide the comparative basis for interpretation and can significantly impact the clinical decision-making process. For example, a VO$_{2\text{peak}}$% of $\leq$ 14 ml/kg per min may represent a fairly good exercise capacity for a 70-year-old female CHF patient, reaching almost 80% predicted VO$_{2\text{peak}}$% whereas it is a marker of a severely impaired functional capacity in a 20-year-old male patient, corresponding to less than 50% of the predicted value. Indeed, the selection of normal reference values is crucial to any interpretative scheme of CPET results, and each clinical exercise laboratory must select an appropriate set of reference values that best reflects the characteristics of the populations tested, and the equipment and methodology utilized.

Beside obvious physiological factors, including age, gender, muscle mass and conditioning status, VO$_{2\text{peak}}$ is also influenced by psychological and methodological factors [6]. Psychological factors include coaching by testing personnel, feedback and differences in patient’s motivation and ability to tolerate discomfort, whereas methodological factors embrace exercise protocol and data sampling. One effect of exercise mode and protocol on VO$_{2\text{peak}}$ is well known [7]. Treadmill testing compared to bicycle ergometry gives 8–12% higher VO$_{2\text{peak}}$, and a similar difference can be observed with an exercise protocol with brief increments of workload on the treadmill compared to a test carried out with gradual, prolonged increments. For selected CHF patients, these differences in VO$_{2\text{peak}}$ may be as much as 5–7 ml/kg per min.

Moreover, variation in data sampling can have a profound impact on the value chosen for VO$_{2\text{peak}}$ [6]. The current computerized systems permit the user to acquire, sample and express the data in innumerable ways. There is a great deal of variation in data expression and, although rarely reported in the methodology among articles, addressing the clinical implication of CPET in CHF, a given VO$_{2\text{peak}}$ can vary by approximately 20%, depending on the sampling interval chosen. In practice, a preferable method for calculating VO$_{2\text{peak}}$ would be to average the data for the last 30 s (as proposed here). Standardization among clinical exercise laboratories and metabolic systems is necessary to facilitate interpretation, and will improve the comparison of findings from one study to another.
Knowledge of patient effort and motivation are necessary for the interpretation of CPET: this is particularly important if exercise tolerance is greatly impaired. Currently, there is no gold standard for assessment of maximal effort. Most CHF patients may not be able to achieve a true VO$_2$ max, and VO$_2$peak is significantly related to a patient’s motivation. Some studies [8] have shown that VO$_2$peak is a reliable index of maximal effort, similar to VO$_2$ max, when at least one of the following requirements occurs: (1) predicted VO$_2$peak is achieved; (2) patient looks exhausted (Borg rating of 9–10 on a 0–10 scale); (3) heart rate or minute ventilation (VE) is close to predicted; (4) lactate is greater than 8 mEq/l; and/or (5) peak respiratory gas exchange ratio is greater than 1.1–1.15. Chest pain, ischaemic ECG changes, or a fall in heart rate and blood pressure may be an indication for stopping a CPET, and therefore these events prevent the assessment of maximal patient effort.

In summary, any VO$_2$peak value ascribed to a given patient carries inherent qualifications. VO$_2$peak normalization, exercise mode and protocol, and data sampling could all potentially and substantially affect a given VO$_2$peak value, causing a patient to fall into or out of the conventional cutoff level of Weber classification. All this information should be provided in the final report with data interpretation. These observations, coupled with the dramatic improvement in survival seen with beta-blockers (see ‘Effects of heart failure therapy on CPET parameters’ below), perhaps accompanied by a change in the natural history of the disease, have prompted some sources to question the prognostic significance of VO$_2$peak in the beta-blocker era.

**Pharmacological therapy: efficacy evaluation**

Increasing attention has been directed toward using exercise testing to measure the therapeutic response to a lifestyle, medical or surgical intervention in the CHF population. Serial assessment of exercise capacity poses greater challenges than the single determination, introducing both methodological and clinical issues.

Although no universal criteria exist for test reproducibility, VO$_2$peak is generally considered reproducible. The coefficient of variation is influenced by the severity of the condition and interval between tests: short-term coefficient of variation ranges between 4.1 and 6.0% [9,10]. To improve reproducibility, serial testing should be performed at the same time of the day: background therapy should be taken in the same doses and time intervals before each exercise testing. Every clinical exercise laboratory should provide short and long-term coefficients of variation of peak and submaximal gas exchange parameters, and changes over time of gas exchange measurements should be interpreted against inter-test coefficients of variation. A variation of peak gas exchange variables within the variability range should be considered potentially neutral (see below).

Of greatest concern is defining the magnitude of change in functional capacity that represents a significant change from baseline. Changes over time of gas-exchange parameters should be expressed as a percentage of baseline capacity, in order to avoid under and overestimation with absolute values. An increase of 2 ml/kg per min of VO$_2$peak may represent, on the one hand, a fairly modest gain for patients with VO$_2$peak of 20 ml/kg per min (+10%), but on the other hand, a consistent improvement for patients with VO$_2$peak of 10 ml/kg per min (+20%). Moreover, as stated before, time-related changes of gas-exchange parameters over time should be interpreted according to variability of measurement range: if coefficient of variation of VO$_2$peak is 4%, we may assume that change in VO$_2$peak between −4% and +4% may be related to measurement variability; above 4% it is more likely to be a real improvement; below 4%, a warning of decline. Examples are reported in Table 2.

The quantification and characterization of symptoms during exercise are useful for clinical decision-making: changes of symptoms over time are also valuable. Variations of VO$_2$peak do not necessarily reflect changes in symptomatic status, and several studies have shown a non-linear relation between VO$_2$peak symptoms and quality of life [11–13].

**Effects of heart failure therapy on CPET parameters**

Vasodilator drugs may improve VO$_2$peak through a combination of improvement of cardiac output and peripheral blood distribution; long-term reduction of right ventricular filling pressure and pulmonary pressure, and a more favourable ventricular chamber interaction and left ventricular preload reserve may also contribute to enhance VO$_2$peak. Nevertheless, the effects of vasodilator drugs on VO$_2$peak are not homogeneous. Due to a reactive neurohormonal activation, a negative inotropic effect and an impaired peripheral blood flow distribution, a lack of significant improvement of VO$_2$peak has been observed after prazosin administration [14], whereas, non-selective

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### Table 2: Exercise tolerance as a guide to clinical management of chronic heart failure: an individual approach

<table>
<thead>
<tr>
<th>Patient no. 1</th>
<th>Patient no. 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO$_2$ (ml/kg per min) at baseline evaluation 8</td>
<td>20</td>
</tr>
<tr>
<td>Laboratory peak VO$_2$ variability; coefficient of variation</td>
<td>4%</td>
</tr>
<tr>
<td>Changes in peak VO$_2$ (ml/kg per min) related to measurement variability</td>
<td>0.3</td>
</tr>
<tr>
<td>Within-peak VO$_2$ variability (ml/kg per min)</td>
<td>7.7–8.3</td>
</tr>
<tr>
<td>Therapeutic efficacy (ml/kg per min)</td>
<td>&gt;8.3</td>
</tr>
<tr>
<td>Warning decrease in peak VO$_2$ (ml/kg per min)</td>
<td>&lt;7.7</td>
</tr>
</tbody>
</table>

VO$_2$, oxygen uptake.
dihydropyridine Ca-blockade channel drugs have a controversial impact on VO2peak [15]. Angiotensin-converting enzyme (ACE) inhibitors are one of the most effective pharmacological remedies for improving exercise capacity in CHF [16]: functional therapeutic efficacy seems to be class dependent, with no significant differences due to phakkinetics, tissue ACE specificity or long and short-term acting agents. Angiotensin I (AT1) receptor blockers have similar haemodynamic effects to ACE inhibitors, and improvement of VO2peak is comparable [17].

Long-term beta-receptor blockade therapy improves functional and biological properties of the failing heart, slows the progression of disease and increases life expectancy. However, beta-blockers differ significantly in their pharmacological properties in ways that may affect their relative efficacy and tolerability. Metoprolol and bisoprolol selectively inhibit β1-receptors but increase the density of β2-receptors and tend to raise cardiac norepinephrine (noradrenaline) during long-term administration, whereas carvedilol blocks β1-, β1- and β2-receptors, decreases cardiac norepinephrine, tends to suppress β-receptor density, and has additional antioxidant and anti proliferative effects. Metoprolol compared to carvedilol provides a greater increase in left ventricular ejection fraction at rest and in left ventricular stroke volume and stroke work during exercise. In contrast, carvedilol produced greater decreases in mean pulmonary artery pressure and pulmonary wedge pressure, both at rest and during exercise. Instead, metoprolol is associated with greater increases in maximal exercise capacity than carvedilol, but the two drugs improve symptoms, submaximal exercise tolerance, and quality of life to a similar extent. In conclusion, also in the beta-blocking area, the value of CPET is maintained: VO2peak does not seem to be influenced by chronic treatment with beta-receptor blockade agents [18]. The use of β1-selective [19] and non-selective beta-blocking [18] agents in CHF is associated with some increase in exercise performance.

However, because of improved survival in CHF patients treated with beta-blockers, the traditional cut-off point of VO2peak ≤ 14 ml/kg per min for referral for cardiac transplantation in these patients requires re-evaluation, and a lower cut-off point value seems more appropriate [20].

The effects of AT1 receptor blockers, ACE inhibitors and beta-receptor blockade therapy on gas exchange parameters derived from symptom-limited CPET are summarized in Table 3.

**Non-pharmacological therapy: efficacy evaluation**

**Cardiac resynchronization therapy (CRT)**

CRT is an emerging therapy that improves symptoms and exercise tolerance in patients with advanced heart failure, left ventricular systolic dysfunction, and intraventricular conduction delay. By correcting the atioventricular (AV), interventricular and intraventricular dyssynchrony induced by conduction disorders, controlled studies have shown that CRT improved functional status, decreased heart failure hospitalization rate, and might have a positive effect on left ventricular remodelling.

The consistency among the largest of the published trials on CRT [21–25] suggests that a significant subset of patients with CHF will derive a clear clinical benefit by an improvement in functional capacity: increases in AT, peak VO2, VE/VCO2 (minute ventilation/carbon dioxide output) slope (Table 4).

The short-term encouragement of haemodynamic responses with CRT may only partially explain these improvements, and other factors have become of interest: a more efficient regulation of vascular beds, enhanced skeletal muscle metabolism, reverse remodelling of the left ventricle (LV) to reduce its size, and promotion of a more physiological chronotropic response to exercise.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Effects of cardiovascular agents on gas exchange variables derived by symptom-limited exercise testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT1 receptor blockers</td>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>VO2peak</td>
<td>↑</td>
</tr>
<tr>
<td>Peak VE</td>
<td>↑</td>
</tr>
<tr>
<td>VE/VCO2</td>
<td>↓</td>
</tr>
<tr>
<td>O2 pulse</td>
<td>↑</td>
</tr>
<tr>
<td>VO2/WR</td>
<td>↑</td>
</tr>
</tbody>
</table>

**Table 4 | Effects of cardiac resynchronization therapy on cardio-pulmonary exercise testing (CPET) parameters: major prospective randomized trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of patients</th>
<th>Inclusion</th>
<th>Effects on CPET parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUSTIC [21]</td>
<td>68</td>
<td>NYHA class 3; LVEF&lt;35%; QRS&gt;150 ms</td>
<td>↑ VO2peak, ↑ AT; ↓ VE/VCO2slope</td>
</tr>
<tr>
<td>MIRACLE [22]</td>
<td>453</td>
<td>NYHA class 3–4; LVEF&lt;35%; QRS&gt;130 ms</td>
<td>↑ VO2peak</td>
</tr>
<tr>
<td>PATH-CHF [23]</td>
<td>63</td>
<td>NYHA class 3–4; QRS&gt;120 ms; P–R&gt;150 ms; ‘severe cardiomyopathy’</td>
<td>↑ VO2peak, ↑ AT; ↓ VE/VCO2slope</td>
</tr>
<tr>
<td>CONTAK CD [24]</td>
<td>490</td>
<td>NYHA class 2–4; LVEF&lt;35%; QRS&gt;120 ms</td>
<td>↑ VO2peak</td>
</tr>
<tr>
<td>MIRACLE-ICD [25]</td>
<td>636</td>
<td>NYHA class 2–4; LVEF&lt;35%; QRS&gt;120 ms</td>
<td>↑ Exercise duration</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association functional classification; LVEF, left ventricular ejection fraction; QRS and P–R, electrocardiogram duration; VO2peak, peak oxygen uptake; AT, anaerobic threshold; VE/VCO2, minute ventilation/carbon dioxide output.
Exercise rehabilitation prescription and evaluation

The Working Group on Cardiac Rehabilitation and Exercise Physiology and the Working Group on Heart Failure on behalf of the European Society of Cardiology [26] and the American Heart Association Committee on Exercise, Rehabilitation, and Prevention [27] have confirmed that exercise training should be prescribed to all stable CHF patients, as a component of a multifactorial cardiac rehabilitation programme. Benefits of training have been reported in skeletal muscles, respiratory and cardiovascular systems, and in their physiological responses to exercise [28]: exercise training increases functional capacity, and improves symptoms without deterioration of left ventricular function [29]. Moreover, a systematic review of 81 published studies, including 2387 exercising CHF patients [30], and a meta-analysis of nine randomized, parallel-controlled trials, including 801 patients, have recently concluded that properly supervised training programmes are safe and associated with clear evidence of an overall reduction in mortality [31]. To sum up, in the past 25 years, the applicability and efficacy of exercise training and a long list of impressive physiological gains have been substantiated in thousands of selected stable CHF patients, overwhelmingly advocating that exercise training can be a highly cost-effective resource in CHF in an increasingly competitive healthcare climate.

The results of exercise training are related to screening and evaluation of CHF patients and selection of the appropriate exercise programme. Accurate evaluation of cardiovascular, respiratory and metabolic responses to exercise is crucial for CHF patients who are going to participate in a training programme. In this setting, symptom-limited CPET has the following uses: (1) definition of exercise tolerance; (2) selection of exercise training intensity; (3) assessment of improvement in functional capacity; and (4) prognostic evaluation.

Since VO2peak is a more accurate marker of exercise tolerance than heart rate, it is preferable to measure gas exchange during exercise and to prescribe the intensity of the exercise regimen at the heart rate corresponding to 50–70% of VO2peak. In CHF patients with severe functional impairment, a low-intensity exercise training programme, calculated as 40–50% of VO2peak measured at the initial CPET, has been shown to be safe, efficacious and well-tolerated [32].

The magnitude of improvement in VO2peak after various exercise programmes ranges between 10 and 26% of initial (pre-training) value. A post-training increase in VO2peak is generally associated with both a steeper VO2/W slope (VO2–work relationship slope) and a shallower VE/VCO2 slope, indicating a greater cardiovascular and gas exchange efficiency.

Prognostic evaluation

Identification of individuals at high risk in a general CHF population is a medical art of growing concern, and CPET has an important clinical tool to predict outcome. The value of VO2peak rests in the fact that it integrates

| Table 5 | Clinical studies documenting the relationship between peak VO2 ‘adjusted’ value and prognosis in chronic heart failure patients undergoing symptom-limited pulmonary exercise training (CPET) |
|---|---|---|---|---|
| Reference | No. of patients | Mean peak VO2 (ml/kg per min) | Event rate (%) | CPET variables related to outcome |
| Steiken et al. (1996) [33] | 181 | 16.3 ± 5.9 | 24 | Percent achieved of predicted peak VO2 |
| Cohen-Solal et al. (1997) [34] | 179 | 17.6 ± 5.6 | 19 | Peak SBP and percent achieved of predicted peak VO2 |
| Osada et al. (1998) [35] | 500 | 17.3 ± 5.7 | 26 | VE/VCO2 slope in patients with VO2peak < 10 and < 18 ml/kg per min |
| Osman et al. (2000) [36] | 225 | 16.0 ± 5.9 | 13 | Adjusted peak VO2 to lean body mass |

VO2, oxygen uptake; SBP, systolic blood pressure.

| Table 6 | Clinical studies documenting the relationship between ventilatory parameters and prognosis in chronic heart failure patients undergoing symptom-limited pulmonary exercise training (CPET) |
|---|---|---|---|---|
| Reference | No. of patients | Mean peak VO2 (ml/kg per min) | Event rate (%) | CPET variables related to outcome |
| MacGowan et al. (1997) [37] | 104 | NA | 19 | Peak VE/VCO2 in patients with peak ≤ 15 ml/kg per min |
| Chua et al. (1997) [38] | 155 | 18.5 ± 7.3 | 24 | VE/VCO2 slope |
| Robbins et al. (1999) [39] | 470 | 13.0 ± 7.0 | 15 | Peak VE/VCO2 and low HR response |
| Kleber et al. (2000) [40] | 142 | 15.2 ± 4.7 | 29 | VE/VCO2 slope |
| Francis et al. (2002) [41] | 303 | 17.8 ± 6.6 | 30 | VO2peak and VE/VCO2 slope |
| Ponikowski et al. (2001) [42] | 123 | 23.0 ± 5.0 | 19 | VO2peak in patients with peak VO2 > 18 ml/kg per min |
| Arena and Humphrey (2002) [43] | 37 | 13.3 ± 4.5 | 51 | VE/VCO2 slope |
| Mejhert et al. (2002) [44] | 67 | 11.7 ± 3.6 | 21 | Peak VE/VCO2 |
| Corrà et al. (2002) [45] | 323 | 14.0 ± 3.0 | 16 | Oscillatory exertional ventilation |
| Corrà et al. (2004) [46] | 600 | 14.8 ± 4.0 | 15 | VE/VCO2 slope in patients with VO2peak < 10 and < 18 ml/kg per min |
| Mezzani et al. (2003) [47] | 570 | 14.2 ± 4.0 | 12 | Peak RER in patients with VO2peak < 10 ml/kg per min |
| Leitte et al. (2003) [48] | 84 | 16.2 ± 5.2 | 30 | Oscillatory exertional ventilation |

NA, not available; VE/VCO2, minute ventilation/carbon dioxide output; HR, heart rate; VO2, oxygen uptake; RER, respiratory exchange ratio.
elements of cardiac adaptation, with skeletal muscle, pulmonary, and endothelial dysfunction more than other traditional measures of severity in CHF. There is overwhelming evidence of the important role played by VO2peak in stratifying risk in CHF patients, and a VO2peak < 14 ml/kg per min has been associated with higher risk of events and has been accepted as a functional criterion for heart transplantation candidacy. Also, the percentage achieved predicted VO2peak and adjustment of VO2peak to LBM have provided prognostic strength, in some cases greater than the traditionally reported standard VO2peak in ml/kg per min [5,33–36] (Table 5).

Over the past 5 years, research has revealed that ventilatory expired gas parameters obtained from symptom-limited CPET also carry accurate prognostic information in CHF [37–48] (Table 6): an abnormally high relationship between minute ventilation (VE) and carbon dioxide production (VCO2), expressed as the VE/VCO2 slope measured between the onset of loaded exercise and the end of the isocapnic buffering period, identified by the rise in the VE/VCO2 slope and the reduction of end-tidal expired CO2 pressure (PETCO2) (or mixed expired value of alveolar and dead space gas, PaCO2), is associated with a poor outcome, as is an oscillatory pattern of ventilation during exercise, defined as cyclic fluctuations in minute ventilation at rest that persist during effort [45].

Beside gas-exchange parameters, other exercise variables have been investigated to further stratify CHF patients undergoing CPET [35,39,49–51] (Table 7). Peak systolic pressure less than 120 mmHg and a percentage of VO2peak less than 50 were selected as significant additional and independent variables in patients with VO2peak < 14 ml/kg per min [52], and low chronotropic index (≤ 0.51), applying Wilkoff’s method based on the linear relation between heart rate (HR) and metabolic work, was selected as an independent predictor of death due to any cause [39].

Indeed, several respiratory gas-exchange and exercise variables obtained during symptom-limited CPET have been proposed to improve outcome prediction in CHF. Each single exercise parameter awards additional outcome discrimination, with the appeal of providing, for clinicians, a convenient ‘high/low risk’ categorization. In reality, such a dichotomizing approach which forces patients into one of two categories tends to oversimplify the issue and is of limited relevance in CHF, a complex, heterogeneous clinical condition. On the contrary, the integrative use of gas-exchange parameters complementary to VO2peak may provide additional prognostic information, particularly in CHF patients with intermediate exercise ability range or in those with severe exercise intolerance. In patients with VO2peak 10–18 ml/kg per min, the selection of a unique and optimal threshold has been unfruitful and discordant [53,54], and the limited prognostic and decisional value of peak VO2 is aggravated by the fact that the majority of patients referred for heart transplantation fall into this intermediate group. On the other hand, patients with VO2peak < 10 ml/kg per min are at high risk of events, and they need complex and costly therapy. The combination of VO2peak and VE/VCO2 slope for patients with intermediate exercise tolerance [55], and VO2peak and peak RER for those with severe functional impairment [47], may enhance the risk stratification process.

Recently, non-invasive surrogates of cardiac output have been investigated in CHF patients undergoing symptom-limited CPET. The ‘circulatory power’, calculated as the product of VO2 and peak systolic pressure, strengthens the prognostic value of CPET, especially in CHF patients with low VO2peak. Although the assessment of these new, easily available, and accurate parameters can improve risk stratification and avoid measurement of invasive haemodynamic variables, further studies are needed to confirm their potential risk prediction power (Table 7).

### Which cutoff value for VO2peak?

VO2peak remains the better parameter to assess, on condition that the exercise has been really conducted until exhaustion. The cut-off is not easy to determine. Following the pioneering work of Mancini [2] and other studies, it has appeared that:

1. VO2peak < 10 ml/kg per min is always associated with a very poor prognosis. If no other contraindications, these patients should be put on a transplant list.
2. VO2peak > 18 ml/kg per min is generally associated with a good outcome at 1 year. In these patients, survival without transplantation is better than after transplantation.

### Table 7 Clinical studies documenting relationship between non-invasive exercise variables and prognosis in chronic heart failure (CHF) patients undergoing symptom-limited cardio-pulmonary exercise testing (CPET)

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Mean VO2peak (ml/kg per min)</th>
<th>Event rate (%)</th>
<th>CPET variables related to outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osada et al. (1998) [39]</td>
<td>500</td>
<td>17.3 ± 5.7</td>
<td>28</td>
<td>Peak SBP and percent achieved of predicted VO2peak</td>
</tr>
<tr>
<td>Robbins et al. (1999) [38]</td>
<td>470</td>
<td>13.0 ± 7.0</td>
<td>15</td>
<td>Peak VE/VCO2 and low HR response</td>
</tr>
<tr>
<td>Williams et al. (2001) [49]</td>
<td>219</td>
<td>23.0 ± 9.2</td>
<td>12</td>
<td>Non-invasive peak cardiac power</td>
</tr>
<tr>
<td>Cohen-Solal et al. (2002) [50]</td>
<td>175</td>
<td>20.3 ± 5.6</td>
<td>16</td>
<td>Circulatory power; ‘surrogate of cardiac output’</td>
</tr>
<tr>
<td>Schraff et al. (2002) [51]</td>
<td>154</td>
<td>18.8 ± 0.4</td>
<td>21</td>
<td>Non-invasive exercise cardiac power</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; VO2, oxygen uptake; VE/VCO2, minute ventilation/carbon dioxide output; HR, heart rate.
(3) There is a grey zone around 14 ml/kg per min where other parameters, from CPET or from other techniques, should be taken into account. The VE/VCO₂ slope, the AT and RER can be used here [46]. In the beta-blocker era, this cut-off should be decreased by at least 2 ml/kg per min [56]. This means that the outcome of a patient with a peak VO₂ of 11–12 ml/kg per min on beta-blocker may not be worse than that of another one not on beta-blocker with a peak VO₂ of 14 ml/kg per min.

Clearly, further studies are necessary to more precisely define the cut-offs of peak VO₂ in patients on beta-blockers

**Particular applications**

Although CPET is a useful adjunctive tool in assessment of patients with cardiovascular and pulmonary disease, the reviewed 2002 ACC/AHA (American College of Cardiology/American Heart Association) guidelines for Exercise Testing [8] confirmed ‘only’ two class I indications for CPET: evaluation of exercise capacity and response to therapy in patients with heart failure who are being considered for heart transplantation, and assistance in the differentiation of cardiac versus pulmonary limitations as a cause of exercise-induced dyspnoea or impaired exercise capacity when the cause is uncertain. Due to the potential of CPET, we believe it is time to broaden its indications in the future, extending candidacy either to all CHF patients, including those at high risk or most vulnerable, such as female, elderly and patients with implantable cardioverter defibrillator (ICD), or to every clinical setting where objective definition of exercise capacity provides implications for medical, surgical and social decision making.

**Female**

Literature on CPET has been conducted for the most part on ‘stereotypic’ heart transplant candidates, namely selected middle-aged men with severe CHF. Although cardiovascular disease is one of the principal causes of death in women, females are largely under-represented in CHF cohorts undergoing CPET. Female CHF patients have a significantly lower VO₂peak compared to males, traditionally attributed to differences in body size and composition, muscle fibre distribution, capacity of the blood to carry oxygen, blood haemoglobin and physical attitude [57]. Percentage of predicted maximum oxygen consumption, age and gender-adjusted measurement of exercise capacity, describes the degree of functional impairment in women more accurately than VO₂peak [58] and this evidence must be considered when CPET metabolic parameters are used for prognostic stratification of women with CHF.

**Elderly population**

Patients older than 65 years are usually defined as ‘elderly’. Although the prevalence of CHF in the elderly is increasing, the feasibility and applicability of CPET to monitor functional capacity and assess prognosis has been poorly addressed. The performance of CPET poses several problems, but it is certainly not contraindicated. In elderly CHF patients, functional capacity is often compromised because of muscle weakness and deconditioning, and therefore the decision whether to send the patient for a CPET is more important than in younger patients. In some elderly patients with problems of gait and co-ordination, a bicycle exercise test may be more attractive than a treadmill exercise test, but in older patients, bicycle exercise is often limited by unfamiliarity. Nevertheless, available data are encouraging. More than half of elderly CHF patients (> 70 years) are able to perform a symptom-limited CPET [59], and VO₂peak provides strong and independent prognostic information [44].

**Valvular heart diseases**

In symptomatic patients with documented valvular stenosis or regurgitation, the course of treatment is usually clear, and CPET is not required. However, the development of Doppler echocardiography has increased the number of asymptomatic patients with defined valvular abnormalities. The primary value of CPET in valvular heart disease is to objectively assess atypical symptoms, exercise capacity, and extent of disability, which may have implications for medical, surgical and social decision making. As in other clinical conditions, CPET may help clarify objectively the functional capacity of the patient who is a poor historian.

**Aortic stenosis**

Severe aortic stenosis is classically considered a contraindication to exercise testing. Although in asymptomatic patients, aortic valve replacement is probably not justified [60], many patients are asymptomatic just because they are inactive, and it may be difficult to plan treatment on clinical grounds in these patients. The haemodynamic response to exercise (abnormal blood pressure increase), concomitant ECG abnormalities (ST segment depression), reduced aerobic capacity (low VO₂peak) may be of value in selecting a subpopulation of asymptomatic patients who are haemodynamically compromised by aortic stenosis, in whom more aggressive therapy might be considered.

**Aortic regurgitation**

Because volume overload is less demanding on the heart than pressure overload, and because the reduction of diastolic duration with exercise favours forward cardiac output, exercise capacity is maintained until late in the course of aortic regurgitation. The decision to proceed to
Mitral stenosis

Patients with severe mitral stenosis have a fixed stroke volume and are only able to augment cardiac output by increasing heart rate. Because the major indication for surgery in mitral stenosis is symptom status, CPET is of the most value when a patient is thought to be asymptomatic because of inactivity or when a discrepancy exists between the patient’s symptom status and the valve area. When exercise testing is performed to clarify these issues, excessive heart rate responses to a relatively low level of exercise, excessive exercise-induced pulmonary hypertension, reduction of cardiac output with exercise (evidenced by exercise-induced hypotension), and chest pain (caused by ischaemia secondary to low cardiac output or pulmonary hypertension) are indicators in favour of earlier surgery.

Mitral regurgitation

Mild and moderate mitral regurgitation are generally well compensated, although exercise testing in these situations for assessment of coronary artery disease is often compromised by false-positive ST-segment changes (such as in mitral valve prolapse). Patients with severe mitral regurgitation may demonstrate reduction of exercise capacity and exercise-induced hypotension. Because resting ejection fraction is a poor guide to ventricular function in patients with mitral regurgitation, combinations of CPET and assessment of left ventricular function may be of value in documenting occult dysfunction and provoking earlier surgery. The documentation of exercise-induced mitral regurgitation in patients with mitral valve prolapse but without regurgitation at rest has been associated with the subsequent development of progressive mitral regurgitation, congestive heart failure and syncope [62].

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a genetic disorder. Patients with HCM experience symptoms such as chest pain, exertional dyspnoea and syncope, and as a result are functionally limited. Determinants of functional impairment involve left ventricular hypertrophy, left ventricular outflow tract pressure gradient, diastolic dysfunction, chronotropic incompetence, and peripheral mechanisms, including musculoskeletal disorders and abnormal vascular responses [63]. CPET is useful in the management of HCM, in assessing functional capacity and prognosis and providing valuable information to identify determinants and unravel mechanisms for exercise limitation. Most HCM patients show a low ΔVO2/ΔWR and a high VE/VCO2 slope. A failure of systolic blood pressure to increase by 20 mmHg from rest to peak exercise or a progressive decrease in blood pressure during exercise is regarded as an abnormal response and a risk factor for sudden death. VO2peak > 50 ml/kg per min, or > 20% of the predicted peak value, fully discriminate athletes with left ventricular hypertrophy from athletes with genetically proved HCM [64].

Conclusions

Over the past 40 years, a considerable number of automated metabolic gas analysis systems have been developed, with over a dozen commercial manufacturers producing in excess of 20 different automated systems [65]. Manufacturers bear the responsibility for demonstrating that CPET systems are accurate and precise, but the user bears the responsibility for assuring that measurements remain accurate. Although an appropriate modus operandi adds cost and time to the test, it is a fundamental prerequisite for proficient and optimal clinical use. Both appropriateness and uniformity of performance and interpretation enhance the critical role of CPET as a risk estimation tool and gatekeeper of transplantation listing. Moreover, gas exchange measurements during exercise provide an accurate assessment of severity of CHF and, performing repeated studies, progression of disease and response to therapy.

In conclusion, the comprehensive evaluation of heart failure patients obtained by the CPET test plays a fundamental role and its indications are expanding.

The intrinsic mechanisms behind the response to exercise are still under active investigation: several novel aspects have been revealed recently, also leading to revolutionary therapy, such as exercise training. Future efforts should focus on the complex inter-relationship between derangements of the body systems, such as immune activation, neural–autonomic dysfunction, peripheral muscle, which all have important implications in CHF syndrome.

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Appendix

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