



# CPET in heart failure

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Received 3 May 2004; accepted 24 May 2004

## KEYWORDS

Exercise testing (in) heart failure;  
Dyspnea;  
Prognosis;  
Symptoms

CPET has gained wide acceptance in CHF for evaluation and quantification of symptoms, for differential diagnosis of dyspnea, for judgement of prognosis, and as a guide to therapy. In this article technical as well as pathophysiological aspects are discussed and the clinical use of CPET in CHF is outlined. Aside from measurement of  $\text{VO}_2$  new parameters like  $\text{VE}/\text{VCO}_2$  and  $P_{\text{ETCO}_2}$  furnish the clinician with helpful information for diagnosis and treatment.

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## Exercise testing in heart failure

Exercise testing has been performed in clinical medicine for a very long period of time. Initially ventilation was studied, later on interpretation of exercise capacity and ECG alterations became the main interest. In the context of heart failure, the method to assess exercise capacity is primarily the evaluation of functional assessment by detailed patient history and the adjudication to a functional class according to the New York Heart Association (NYHA). Recently, the 6-min-walk-test has found considerable interest among investigators, however it does not correlate with other methods to assess exercise capacity like NYHA-class,  $\text{VO}_2\text{AT}$  and  $\text{VO}_2\text{max}^1$  and predicts survival less precise than NYHA-classification.<sup>2</sup> Cardiopulmonary exercise testing (CPET) was initially used to measure peak oxygen consumption, e.g., in sports medicine. Today, it is much more sophisticated and a variety of parameters is used to derive physiological or pathophysiological information beyond the measurement of oxygen uptake.

## Quantification of symptoms

In heart failure, the predominant symptoms are fatigue and dyspnea. Fatigue is largely caused by reduced exer-

cise cardiac output, which correlates very closely to oxygen uptake, and by muscular training condition, which again closely correlates with muscular aerobic capacity. CPET measures overall oxygen uptake, in which uptake in the lungs, transport in the blood and metabolism in the peripheral musculature is involved. Thus, several reasons for fatigue like oxygen uptake deficiencies, low cardiac output and low peripheral metabolic capacity contribute to CPET findings in patients with fatigue.

Dyspnea is mainly felt if there is inadequate high ventilatory requirement for the amount of external work caused, e.g., by early anaerobiosis or by malperfusion of ventilated parts of the lung (see below). In addition breathing rate and breathing pattern have major influence on dyspnea.

## Technical aspects

Measurement of gas exchange is done breath by breath and the result is almost simultaneously displayed on a computer screen by rapid computer processing and by correction for the time delay from expiration to measurement. Oxygen is usually measured either by the conium diode or paramagnetically and  $\text{CO}_2$  by infrared spectroscopy.

The most widely used exercise protocol is the modified Naughton-protocol.<sup>3</sup> This is an incremental exercise test on a treadmill with 2-min stages and increments in

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both gradient and velocity simulating increments of about one metabolic equivalent (approximately  $3.5 \text{ ml O}_2 \times \text{kg}^{-1} \times \text{min}^{-1}$ ). However in some relatively mild heart failure patients this protocol takes a long exercise time. An exercise test duration of 10–15 min is generally considered optimal and therefore in some cases a Bruce-protocol might be preferable. Moreover, instead of treadmill testing bicycle ergometry may be used, predominantly using a ramp protocol, with an exercise duration of 10–15 min. All tests are done as maximal exercise tests until exhaustion. However, submaximal parameters are at least as important. In addition percutaneous measurement of oxygen consumption is performed, usually via the ear-lobe.

Repeated daily calibrations and proof of tightness of face masks with no air leaking during maximal respiration as well as the familiarity of patients with the exercise situation are very important aspects of CPET.

## Pathophysiological aspects

The peak  $\text{VO}_2$ , which is achieved during maximal exercise is defined as  $\text{VO}_{2\text{max}}$ . Though usually no real plateau exists at the end of a maximal effort there is a flattening of the oxygen uptake while  $\text{VCO}_2$  continues to rise. The last 30 seconds' average is the best averaging method to avoid noise in this measurement. Though there is considerable sex and age dependence of oxygen uptake the normalisation of oxygen uptake to percent of predicted oxygen uptake is not clearly better than the maximal oxygen uptake itself. This might be explained by a critical value of oxygen uptake that is necessary at any age and for both gender.  $\text{VO}_{2\text{AT}}$  occurs at 55–75%<sup>4</sup> of maximal oxygen uptake and the more severe heart failure is the closer it comes to the maximal uptake.

The best way to determine the  $\text{VO}_{2\text{AT}}$  is the V-slope-method.<sup>5,6</sup> To improve the validity of  $\text{VO}_{2\text{AT}}$ -determination the sudden rise in  $\text{VE}/\text{VO}_2$  and in  $P_{\text{ETO}_2}$  at this point is used. It signals, that additional  $\text{CO}_2$  is produced from buffering of lactate by bicarbonate. The additional drive of ventilation by this  $\text{CO}_2$  production renders ventilation less efficient as to  $\text{O}_2$  uptake and as to alveolar  $\text{O}_2$  disappearance.

$\text{VE}/\text{VCO}_2$  nadir occurs around the anaerobic threshold, where the maximal ventilatory efficiency is reached.  $\text{VE}/\text{VCO}_2$  changes occur through uneven distribution of perfusion relative to ventilation (focal or areal alveolar hypoperfusion being the primary pathophysiology), by an increase in anatomical dead space through low tidal volumes, by a decreased  $P_{\text{aCO}_2}$  set point, e.g., in acidosis, by disturbances of diffusion, by the activation of putative muscle ergoreceptors (alveolar hypoperfusion being a secondary phenomenon, a theory not clearly proven so far).<sup>7</sup> The primary pathophysiology in CHF however is the uneven distribution of perfusion and ventilation.<sup>8,9</sup> If the  $\text{VE}/\text{VCO}_2$ -relationship is looked at as the steepness of the  $\text{VE}$  vs  $\text{VCO}_2$ -slope, the final part of exercise, when acidotic drive further

increases ventilation has to be excluded.<sup>9</sup> In this case, the strict linear relationship of  $\text{VE}$  and  $\text{VCO}_2$  leaves linearity in the final part of exercise.

$P_{\text{ETCO}_2}$  and  $P_{(\text{a-ET})\text{CO}_2}$  are additional parameters to judge ventilatory efficiency. The alveolar partial pressure of  $\text{CO}_2$  represented by the endtidal partial pressure of  $\text{CO}_2$  is being compared to arterial  $P_{\text{CO}_2}$ . Usually the difference between arterial and endtidal  $P_{\text{CO}_2}$  is very small. At rest, however, there might be a considerable difference of up to 7 mm caused by underperfusion of the apical parts of the lung due to the low pulmonary artery pressures. This is not the case in pulmonary arterial hypertension. In well-trained subjects and in patients with peripheral obstructive pulmonary disease  $P_{\text{ETCO}_2}$  might very well increase beyond  $P_{\text{aCO}_2}$ , in athletes by the high  $\text{CO}_2$ -inflow from venous blood, in chronic obstructive lung disease by trapping of air with large  $P_{\text{CO}_2}$  partial pressure.

## Normal values

We refer to the normal values that have been published in the European Journal of Applied Physiology by Habedank et al.<sup>10</sup> and normalise oxygen uptake for sex and age. In this paper, also the sex and age dependency of  $\text{VE}/\text{VCO}_2$  is described, as well as breathing reserve. While breathing reserve on average is 40% at the end of exercise (one standard deviation 10%), it is neither sex nor age dependent. Ventilatory efficiency is lower in women ( $\text{VE}$  vs.  $\text{VCO}_2$  is higher) and only to a small amount sex- and age-dependent.  $\text{VO}_2$  – as pointed out earlier – is very much sex and age dependent. For clinical use of cardiopulmonary exercise testing a normalization to sex and age adjusted values is not necessary, however, for determination whether heart failure is the reason of the patient's complaint it might be useful (as well as for giving expert opinions in answering legal or insurance questions).

## Parameters helpful for clinical assessment of heart failure

For clinical use, both  $\text{VO}_2$  max and  $\text{VO}_{2\text{AT}}$  are used to assess symptomatic and prognostic status. As outlined above sex and age normalization has been shown to be of advantage in some reports,<sup>11</sup> but this is not consistent in all publications.  $\text{VE}/\text{VCO}_2$  measures ventilatory efficiency while  $\text{VE}/\text{VO}_2$  measures ventilatory requirement in relation to oxygen uptake. Clinically, ventilatory efficiency as derived from  $\text{VE}/\text{VCO}_2$  is more important than  $\text{VE}/\text{VO}_2$ , since it provides important information on pulmonary function. The expression of ventilatory efficiency either as the nadir of  $\text{VE}/\text{VCO}_2$  ratio or as the slope of the  $\text{VE}$  vs  $\text{VCO}_2$  relationship gives a similar information. Clinically useful upper normal values are 30 for the  $\text{VE}/\text{VCO}_2$  ratio and 35 for the  $\text{VE}/\text{VCO}_2$  slope.

$P_{ETCO_2}$  and  $P_{aCO_2}$  have to be included in any CPET for comparison of entidal gas pressures in the alveolar air versus arterial blood. Arterial gas is usually substituted with hyperemic capillary earlobe blood.

MVV is measured as  $FEV_1 \times 41^{12}$  and is important to be compared with achieved maximal ventilation. If more than 42% of MVV at AT or more than 80% at maximal exercise is used pulmonary mechanical limitation is likely.<sup>13</sup>

$O_2$  pulse is calculated as  $VO_2/HR$  and is used to see an early levelling off of the increase in stroke volume which is seen mainly in pulmonary hypertension and in ischemic left ventricular dysfunction.

## Classification systems

Classification systems to categorize the patients have been proposed.<sup>3</sup> However, since all the mentioned parameters are continuous variables it is not useful to use cut off points or categorizations instead of reporting just the measured values. A cut off for  $VO_2$  max of 12, 14 or 16 is similar useful to judge the prognosis of patients.<sup>14</sup> On the bases of CPET results it is possible to compare the prognostic results of the proposed therapy (e.g., HTX with the natural history or other proposed therapeutic options).

## Measurement of symptoms

As outlined before fatigue closely correlates to oxygen uptake. Therefore  $VO_2AT$  and  $VO_2$  max represent in large the exercise capacity and the clinical symptom of fatigue in heart failure.

The measurement of dyspnea is more difficult, as dyspnea is a more complex sensation. Very important for

correct judgement of pathogenesis of dyspnea is to consider breathing reserve in order to rule out contributions of mechanical pulmonary limitation, to judge whether arterial hypoxia occurs and of course to measure the absolute amount of ventilation and to normalize it to gas exchange, especially to  $VCO_2$ . The almost unanimously found clinical symptom of dyspnea in pulmonary hypertension very closely correlates to the almost always reduced ventilatory efficiency.

## Judgement of prognosis

$VO_2$ max as prognostic parameter has been proposed by a large number of investigators, the database of Myers<sup>14</sup> being the largest one. The supplementation of  $VO_2$  max by hemodynamic parameters<sup>15</sup> or by systolic blood pressure<sup>16</sup> or simply by  $VO_2$  AT<sup>17</sup> or by VE vs  $VO_2$ slope<sup>18</sup> improves prognostic information considerably and should be done in all cases. Recently additional prognostic information is derived from BNP measurements<sup>19</sup> and the combination of BNP and  $VO_2$  (max or at AT) and VE/ $VCO_2$  (ratio or slope) is probably at least as good as any other prognostic multifactorial score to judge prognosis in heart failure.

## Information about concomitant diseases

In heart failure patients lung disease and pulmonary embolism are often accompanying heart disease and are contributing to symptoms. CPET offers simple and easy parameters to judge the contribution of these diseases in giving information on pulmonary mechanical limitation, on hypoxia under exercise and on pulmonary ventilation perfusion mismatch. Thus it has been shown by our group,<sup>20</sup> that similar increases in VE vs  $VCO_2$  slope in

**Table 1** Resting arterial and endtidal  $CO_2$  tensions, in patients with various diseases of the pulmonary vascular tree

|                           | $P_{aCO_2}$ mm Hg | $P_{ETCO_2}$ mm Hg | $P_{(a-ET)CO_2}$ mm Hg |
|---------------------------|-------------------|--------------------|------------------------|
| APE <sup>a</sup> (n = 54) | 37.5 ± 8.1        | 23.6 ± 9.7         | 13.7 ± 7.5             |
| CPE <sup>b</sup> (n = 23) | 33.6 ± 5.6        | 25.8 ± 5.7         | 7.7 ± 3.5              |
| PPH <sup>c</sup> (n = 14) | 30.6 ± 4.2        | 25.4 ± 4.3         | 3.9 ± 3.2              |

<sup>a</sup>Acute pulmonary embolism.

<sup>b</sup>Chronic pulmonary embolism.

<sup>c</sup>Primary pulmonary hypertension.

**Table 2** Changes of CHF parameters after CRT in 28 patients (2/2001–8/2003)

|                                       | EF <sup>a</sup> (%)<br>By echo | NYHA <sup>b</sup> | LVEDD<br>(mm) <sup>c</sup> | $VO_2$ AT<br>(ml/min/kg) | $VO_2$ max<br>(ml/min/kg) | Slope<br>(VE vs $VCO_2$ ) | Walking<br>distance (m) |
|---------------------------------------|--------------------------------|-------------------|----------------------------|--------------------------|---------------------------|---------------------------|-------------------------|
| Baseline before CRT                   | 20.9                           | 3.44              | 72.6                       | 9.5                      | 12.9                      | 38.5                      | 317                     |
| on CRT                                | 26.7                           | 2.65              | 67                         | 11.1                     | 16.0                      | 33.6                      | 459                     |
| P value (two-sided<br>Student t-test) | 0.06                           | <0.001            | 0.07                       | <0.05                    | <0.002                    | <0.02                     | 0.13                    |

<sup>a</sup>Ejection fraction.

<sup>b</sup>New York Heart Association's classification.

<sup>c</sup>Left ventricular enddiastolic diameter.

patients with acute and chronic pulmonary embolism and primary pulmonary hypertension have different pathophysiology with a large  $P_{(a-ET)CO_2}$  difference in acute pulmonary embolism and hyperventilation with low  $P_{aCO_2}$  and  $P_{ETCO_2}$  values in PPH, the patients with chronic pulmonary embolism showing findings in between these two (see Table 1). Thus not only the presence of pulmonary artery hypertension can be found in CPET, but also clues to the underlying pathophysiology are given.

## CPET as guide to therapy

Recently cardiac resynchronization therapy has been shown to be extremely useful for treatment of congestive heart failure. Its benefit is readily measured by CPET (see Table 2).

Many drug therapies have shown less benefits in CPET and some investigators have questioned the likelihood to show benefit of medical therapy with CPET parameters. However, institution of medical therapy in decompensated heart failure also leads to massive improvement of oxygen uptake and ventilatory efficiency.<sup>8,9</sup> Furthermore, in mild heart failure the improvement in exercise capacity is neither of great clinical importance nor is it as impressive as in severe heart failure.<sup>21</sup>

## Unsolved questions

Controversies in exercise testing in heart failure still exist as to the type of exercise test (walk test, bicycle), the type of exercise protocol (Naughton, Bruce etc.), the parameters to measure and the usefulness of cut off points, furthermore as to normalization for bodyweight and sex. The usefulness of serial tests to further judge survival after improvement through medical therapy is not studied sufficiently. New parameters as  $O_2$  response time,  $O_2$  recovery time, the importance of periodic breathing and sleep apnea and the estimation of  $VO_2$ max from submaximal parameters are fields that are being investigated currently.

## Conclusion

Well adapted and recognised applications for measuring exercise ventilation and gas exchange in heart failure include the evaluation of prognosis, the objective assessment of exercise capacity, the indication for heart and heart lung transplantation, the differential diagnosis of dyspnea, the assessment of resynchronization therapy, the monitoring of therapy in severe heart failure. Measurement of  $VE/VCO_2$  is superior to  $VO_2$ max measurement in patients limited by angina and motivation. Further useful fields include the diagnosis and differential diagnosis of heart failure and pulmonary hypertension, the judgement, which pathophysiology mostly contributes to dyspnea and/or to pulmonary hypertension and also the therapeutic monitoring in right heart failure.

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