

# The prognostic value of stress tests in chronic heart failure

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## Abstract

*Chronic heart failure is a debilitating condition with a poor prognosis despite advances in medical and invasive treatment modalities. Attempts have been made to improve risk stratification in order to single out very-high-risk patients who could benefit from invasive and costly therapies. Unfortunately clinical, echocardiographic, radiological or biochemical measurements performed at rest provide significant diagnostic information but fail to stratify the risk sufficiently. Cardiopulmonary exercise testing alone or in combination with stress echocardiography and biomarkers may offer a more profound insight into the progress of the disease and patient prognosis and aid in the choice of the most appropriate therapy. Peak oxygen consumption ( $\dot{V}O_2$ ) is the most powerful prognostic parameter obtained during cardiopulmonary exercise testing. Ventilation slopes, especially the slope of ventilation to  $CO_2$  production ( $VE/VCO_2$ ), can have additional prognostic value or be used as a surrogate risk predictor where exercise is sub-maximal. Other cardiopulmonary parameters seem to have, at best, an auxiliary role in risk assessment. In patients with grey zone  $\dot{V}O_2$  values the presence of contractile reserve on stress or dobutamine echocardiography can be prognostically favourable. Other echocardiographic findings, such as functional mitral regurgitation, pulmonary hypertension and right ventricle dysfunction, also yield prognostic information. Combining biomarker measurements with  $\dot{V}O_2$  obtained during the cardiopulmonary exercise test may further improve risk assessment in heart failure patients. Two markers, B type natriuretic peptides and high sensitivity C-reactive protein (hsCRP), both with established prognostic value in heart failure and cardiovascular diseases in general, are the best candidates for combined assessment with cardiopulmonary test results. Further studies are needed to confirm this notion. (Cardiol J 2007; 14: 340–346)*

**Key words:** heart failure, prognosis, cardiopulmonary exercise testing, stress echocardiography, biomarkers

## Introduction

In spite of advances in the therapy of chronic heart failure, the prognosis with regard to this disease remains dismal. Routine clinical, echocardiographic and radiological examinations performed

at rest suffice for the right diagnosis but have limited prognostic value. This may result from the complexity of the pathophysiological mechanisms involved in heart failure and the fact that heart dysfunction leads to multiple circulatory and extracirculatory consequences. These include compromised peripheral circulation, skeletal muscle hypoperfusion and abnormal pulmonary ventilation. Hypoperfusion of the skeletal muscles is a result of peripheral vasoconstriction, which leads to muscular atrophy and increases the number of glycolic fibres at the expense of oxygen-dependent myocytes. Pulmonary

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congestion results in increased dead space and reduced vital capacity or even bronchial obstruction due to overload of the bronchial veins. These processes are mediated by hemodynamic, humoral and inflammatory mechanisms. Their intensity reflects the stage of heart failure and influences the prognosis. This is a pathophysiological basis for the use of stress tests, especially cardiopulmonary exercise testing, aided by stress echocardiography in some cases, in determining the prognosis in patients with heart failure.

Cardiopulmonary exercise testing enables a complex and objective evaluation to be made of physical capacity and the factors influencing it, such as ventilatory and circulatory capacity and muscular endurance, all of which reflect the severity (thus the stage) of heart failure and determine the prognosis [1]. In the event of an equivocal cardiopulmonary exercise test result further prognostic information can be derived from stress echocardiography or biomarker levels, especially concentration of B-type natriuretic peptides (BNP). All these prognostic factors taken together may improve prognostication in heart failure and contribute to its more effective therapy.

### Peak oxygen consumption

The basic and most widely measured parameter during cardiopulmonary exercise testing is peak oxygen consumption ( $pVO_2$ ), which reflects the peak aerobic capacity of the patient.  $pVO_2$  correlates weakly with hemodynamic measurements performed at rest but relates much better to maximum cardiac output determined during stress tests [2].  $pVO_2$  is a measure of cardiovascular functional reserve in patients with heart dysfunction, as was demonstrated for the first time by Weber et al. [3] over 20 years ago. Several years later it was reported for the first time that  $pVO_2$  has a prognostic value in patients with heart failure. The study included 27 heart failure patients.  $pVO_2 < 10$  ml/kg/min translated into a 77% annual death rate, whereas  $pVO_2$  10–18 ml/kg/min meant a significantly lower 22% risk of death in one year [4]. Further studies confirmed the ability of  $pVO_2$  to predict overall mortality [5].  $pVO_2$  remained a statistically significant predictor, even when other variables with strong independent prognostic power such as age, natriuretic peptide levels and left ventricle systolic function were included [6]. This strongly supports the independent prognostic value of  $pVO_2$  in heart failure.

A parameter with prognostic value which does not influence therapeutic decisions is of limited

clinical use.  $pVO_2$  seem to be able to provide clinically useful information beyond pure prognostication in patients with heart failure. This was demonstrated in a pivotal study by Mancini et al. [7]. Of patients qualified for heart transplantation ( $n = 116$ )  $pVO_2 < 14$  ml/kg/min identified individuals who would benefit from this procedure, while values above 14 ml/kg/min implied that transplantation could safely be deferred. In the latter group annual survival rate was 94% ( $n = 52$ ), whereas among patients with  $pVO_2 < 14$  ml/kg/min who were not qualified for transplantation because of co-morbidities the annual survival rate was only 47% ( $n = 27$ ). On the other hand in patients with low preoperative  $pVO_2 (< 14$  ml/kg/min) who subsequently underwent heart transplantation the annual survival rate was 83% ( $n = 24$ ). In short, the one-year survival prognosis was comparable in patients with  $pVO_2 > 14$  ml/kg/min treated conservatively and in patients with  $pVO_2 < 14$  ml/kg/min subjected to heart transplantation and significantly better than in patients with  $pVO_2 < 14$  ml/kg/min treated conservatively. The results of Mancini et al. [7] resulted in the inclusion of  $pVO_2$  and cardiopulmonary exercise testing in routine patient evaluation preceding heart transplantation.

As shown above, in heart failure patients with a very poor prognosis  $pVO_2$  does not reach 10 ml/kg/min. On the other hand patients with a very good prognosis achieve  $pVO_2 > 18$  ml/kg/min. Thus there remains a grey zone of  $pVO_2$  values between 10 and 18 ml/kg/min, which can further be stratified into two ranges: the first, of 10–14 ml/kg/min, is characteristic of patients with a poor prognosis, and the other, at 14–18 ml/kg/min, is typical of patients with a moderate prognosis [8]. These ranges are not very different from the  $pVO_2$  cut-offs recommended for heart failure staging according to Weber et al. [3] (Table 1). The question which arises is whether patients with intermediate  $pVO_2$  values can be more accurately assessed in terms of prognosis and possible optimisation of therapy. Another important issue is risk assessment in patients who cannot perform maximum effort for reasons other than exhaustion of cardiovascular capacity. To answer these questions researchers have so far carried out numerous studies which have evaluated the prognostic value of parameters other than  $pVO_2$ .

### Other cardiopulmonary parameters

Percentage maximum predicted oxygen consumption ( $\%VO_2$  max) is, in theory, superior to  $pVO_2$ , because it is a measure of achieved aerobic

**Table 1.** Heart failure staging based on pVO<sub>2</sub> according to Weber and Janicki compared with pVO<sub>2</sub> ranges recommended for prognostic purposes.

Heart failure stage	pVO <sub>2</sub> ranges according to Weber et al. [ml/kg/min]	Prognosis	pVO <sub>2</sub> ranges according to Lainchbury and Richards [ml/kg/min]
A	> 20	Good	> 18
B	16–20	Moderate	14–18
C	10–16	Poor	10–14*
D	6–10	Very poor	< 10*
E	< 6		

\*Heart transplantation should be considered [7]

capacity adjusted for sex, age and body mass. Of two well documented studies comparing the prognostic value of both parameters neither is fully conclusive as to the superiority of one or the other. One showed the prognostic equivalence of pVO<sub>2</sub> and %VO<sub>2</sub> max in patients with heart failure [9], whereas in the other %VO<sub>2</sub> max predicted mortality better than the absolute value of pVO<sub>2</sub> [10]. In this study %VO<sub>2</sub> max < 50% was related to a significantly poorer prognosis. In another study, which included 500 patients with heart failure, three-year survival was comparable in groups with pVO<sub>2</sub> < 14, and pVO<sub>2</sub> > 14 ml/kg/min indicated that the decreased pVO<sub>2</sub> in the former group exceeded 50% of %VO<sub>2</sub> max [11]. The task of proving the superiority of either parameter can thus be difficult. It cannot be ruled out that %VO<sub>2</sub> max has a greater prognostic value in patients at the extremes of age and in women. This question cannot be answered unequivocally at present.

Some authors postulate that pVO<sub>2</sub> should be expressed in ml/kg/min, with adjustment for lean body mass calculated on the basis of fatty tissue layer measured in a standard place. Such an approach can be justified in cases of obesity, since fatty tissue is metabolically inert and constitutes a significant portion of body weight in the obese. It has been shown that pVO<sub>2</sub> = 19 ml/kg (lean body mass)/min is a more powerful prognosticator than pVO<sub>2</sub> = 14 ml/kg (total body weight)/min [12].

Use of the anaerobic threshold (AT), which is oxygen consumption measured at the moment of anaerobic metabolism onset, is an interesting concept, because it decreases along with pVO<sub>2</sub> in heart failure. In theory AT should be a good surrogate for pVO<sub>2</sub> where there is sub-maximal effort limited by factors other than exhaustion of cardiovascular reserve and including lack of patient motivation. Unfortunately AT is in no way prognostically superior to pVO<sub>2</sub>. Moreover its precise determination requires invasive procedures (arterial line) and non-invasive methods may yield inaccurate results [13].

Another cardiopulmonary parameter of potential prognostic value in heart failure is the slope of the curve of ventilation to carbon dioxide production (VE/VCO<sub>2</sub>) expressed as a regression coefficient of this curve. Excess of minute ventilation in relation to CO<sub>2</sub> production is characteristic of patients with heart failure and causes the VE/VCO<sub>2</sub> slope to run more steeply (VE/VCO<sub>2</sub> > 32–35). This phenomenon is called an “enhanced ventilatory response” (EVR). Its degree appears to correspond to the severity of heart failure. The prognostic value of the VE/VCO<sub>2</sub> slope has been evaluated in several studies. In a well designed and conducted study Chua et al. [14] showed that, in 173 patients with heart failure, EVR defined as a VE/VCO<sub>2</sub> slope > 34 produced a worse prognosis. In fact 18-month survival in patients without EVR was 95% and only 69% in patients presenting this abnormality (p = 0.0001). Furthermore in a multivariate analysis the VE/VCO<sub>2</sub> slope was an independent prognostic factor which contributed additional predictive information to that obtained from pVO<sub>2</sub>. In the study by Pardaens et al. [15] ventilatory slopes including VE/VCO<sub>2</sub> (after logarithmic transformation) did not add any prognostic information beyond that provided by pVO<sub>2</sub>. Ventilation slopes acquired prognostic value only after pVO<sub>2</sub> was eliminated from multivariate analysis, whereas pVO<sub>2</sub> retained its ability to predict cardiovascular events and death regardless of the presence of ventilatory data in the analysis. In this study ventilation slopes were determined for sub-maximal effort where the respiratory exchange ratio (RER) was below or equalled 1.0 (RER ≤ 1.0). On the other hand Chua et al. [14] determined the VE/VCO<sub>2</sub> slope for maximal effort. Thus one can assume that the VE/VCO<sub>2</sub> slope retains its full prognostic value additive to that offered by pVO<sub>2</sub> in the case of maximal effort and should be treated as a surrogate prognostic parameter in sub-maximal efforts (with RER ≤ 1.0). More recent studies confirm the role of ventilation slopes in risk

assessment in heart failure patients [16]. Other cardiopulmonary parameters were also evaluated. These include an oxygen pulse which is a ratio of  $\text{VO}_2$  and a heart rate dependent on stroke volume and arteriovenous oxygen concentration difference. A flat oxygen pulse curve during exercise implies a lack of inotropic reserve, leading to an inadequate increase in myocardial contractility at exertion. Such a pattern is typically observed in heart failure with severe left ventricle dysfunction or in multi-vessel coronary artery disease, where exertion may cause extensive myocardial stunning. Unfortunately in a study by Cohen-Solal et al. [17] oxygen pulse had no prognostic value. Moreover its mean values were the same in a group of patients whether they survived or died during follow up. In a subsequent study by the same main investigator the product of oxygen pulse and systolic blood pressure (SBP) did not have any prognostic value either, as opposed to the product of  $\text{VO}_2$  and SBP (referred to as circulatory or cardiac power), which turned out to be an independent predictor in multivariate analysis [18].

Failure to find cardiopulmonary parameters equivalent to or better than  $\text{pVO}_2$  in determining a prognosis has resulted in attempts to combine  $\text{pVO}_2$  with other parameters that can be obtained during any type of exercise stress, for example maximum mean or maximum SBP and exercise duration. The product of maximum SBP and  $\text{pVO}_2$  (peak circulatory power) turned out to have prognostic value in the previously quoted study by Cohen-Solal et al. [17]. In another study, which has also been already quoted, with 500 heart failure patients followed up for three years, the authors analysed maximum heart rate, maximum SBP, RER, minute ventilation and AT in addition to standard  $\text{pVO}_2$  expressed as  $\% \text{VO}_2$  max. Of all these parameters only  $\% \text{VO}_2$  max and maximum systolic blood pressure showed independent prognostic value. Three-year survival was 55% in the group with maximum SBP < 120 mm Hg and 83% with SBP > 120 mm Hg ( $p = 0.004$ ) [11]. It should be of no surprise that a larger inotropic reserve of the heart and its ability to generate higher blood pressure is associated with a better prognosis. This has also been confirmed by the study of Williams et al. [19], in which of many parameters with confirmed prognostic value in univariate analysis, such as  $\text{pVO}_2$ , duration of exercise, peak circulatory power, maximum systolic and mean blood pressure, NYHA class and NT-proBNP concentration, only the duration of exercise and maximum systolic blood pressure independently predicted the risk of death in 85 patients with heart failure. In this study the relative risk of

death was 1.28 ( $p = 0.007$ ) and 1.27 ( $p = 0.01$ ) for a shorter exercise time and lower maximum systolic blood pressure, respectively.

### **Stress and dobutamine echocardiography**

If the issue of prognosis determination on the basis of sub-maximal effort can be considered at least partially solved as a result of ventilation slope analyses, there remains a problem of further and more detailed risk assessment in the grey zone patients with moderate and poor prognoses corresponding to  $\text{pVO}_2$  values between 10 and 18 ml/kg/min (Table 1). Thus attempts have been made to stratify risk more precisely in these groups of patients by using alternative stress tests such as dobutamine echocardiography. Paraskevidis et al. [20] showed that in patients with dilated cardiomyopathy ( $n = 27$ ) and intermediate  $\text{pVO}_2$  (10–14 ml/kg/min) response to low-dose dobutamine (10  $\mu\text{g}/\text{kg}/\text{min}$ ) had a prognostic value over 18 months of follow up. In patients who died ( $n = 19$ ) the authors found a significant increase in left ventricle end-systolic strain and end-diastolic dimension. In patients who survived ( $n = 18$ ) these parameters did not change during dobutamine infusion. Other important prognostic parameters derived from dobutamine or stress echocardiography include contractile reserve (ejection fraction increase), the dynamics of functional mitral regurgitation, the presence of pulmonary hypertension and right ventricle dysfunction [21]. These parameters appear to have an additional prognostic value in heart failure patients with  $\text{pVO}_2$  between 10 and 14 ml/kg/min (Table 2). More detailed prognostication on the basis of stress/dobutamine echocardiography in the case of intermediate  $\text{pVO}_2$  is mainly reserved for dilated cardiomyopathy, although the presence of a significant contractile reserve in patients with ischemic heart disease is also predictive of a better prognosis, provided that revascularisation is attempted.

### **Cardiopulmonary exercise testing in conjunction with biomarkers and clinical assessment**

Interesting results have been presented by trialists who compared the prognostic value of  $\text{pVO}_2$  with that of natriuretic peptides, biomarkers whose role in risk stratification have long been established, and clinical risk assessment scales, especially the heart failure survival score (HFSS), which was developed to predict the necessity of heart transplantation in patients with advanced heart failure [22].

**Table 2.** Prognostic value of stress and dobutamine echocardiography in patients with heart failure and intermediate pVO<sub>2</sub> values (10–14 ml/kg/min).

	Low risk (5–10%/year)	High risk (> 25–30%/year)
Contractile reserve of the left ventricle	Present	Absent
Mitral regurgitation	Not changing or decreasing during stress/dobutamine infusion	Increasing during stress/dobutamine infusion
Pulmonary hypertension	< 45 mm Hg	> 45 mm Hg
Right ventricle dysfunction	Absent	Present
Exercise duration (during stress echocardiography)	≥ 8 min	< 8 min

This scale comprises seven variables which independently predicted the risk of death in a multivariate model derived from 289 patients and prospectively verified in 199 patients with advanced heart failure qualified for heart transplantation. They include the presence of ischemic heart disease, intraventricular conduction delay (both are categorical variables), left ventricle ejection fraction, pVO<sub>2</sub>, serum sodium concentration, mean blood pressure and heart rate (continuous variables). In the study by Gardner et al. [23] with 142 severe heart failure patients qualified for transplantation a single NT-proBNP measurement was more predictive of death (the primary end-point) and death or urgent transplantation (secondary combined end-point) than pVO<sub>2</sub> and HFSS. During a one-year follow up 16 out of 20 deaths occurred in the group with NT-proBNP above the median (> 1490 pg/ml) and only four in the group with NT-proBNP below this value, which translates into a relative risk of death of 5.0 in patients with elevated NT-proBNP. On the other hand de Groote et al. [24] showed that BNP concentration did not limit the prognostic value of pVO<sub>2</sub> in a group of heart failure patients with ejection fraction below 45%. In this study the value of pVO<sub>2</sub> (expressed as %VO<sub>2</sub> max) in predicting the risk of death was independent of and additional to information offered by BNP. In follow up of over two years the relative risk of death was 3.17 in the group with BNP over the median. In the same study aldosterone concentration was also an independent prognosticator. Inconsistency in the findings by Gardner et al. [23] and de Groote et al. [24] may be apparent. In the former trial to compare pVO<sub>2</sub> and NT-proBNP the patients were more severely ill (they were qualified for heart transplantation) and were quite homogenous in this respect, with narrow ranges of values of the potential predictors (EF = 14.9 ± 7.1%; pVO<sub>2</sub> = 11.8 ± 3.6 ml/kg/min). At the same time the range of NT-proBNP concentrations was, remarkably, 1490 (511–3887) pg/ml

(median and interquartile range). Therefore it should not be surprising that the ability of NT-proBNP to stratify the risk was preserved and the prognostic value of other parameters (especially ejection fraction and pVO<sub>2</sub>) was lost. In the latter study the patients' conditions varied to a greater extent and most of the participants did not have end-stage heart failure; the maximum ejection fraction was 45% and BNP median concentration was 109 pg/ml. The narrower dynamic range of BNP compared to NT-proBNP could also account for the difference observed between the two studies.

An interesting combination of cardiopulmonary exercise testing and biomarker measurement was proposed by Lainchbury et al. [25]. This team performed an cardiopulmonary exercise test on 68 heart failure patients in NYHA classes III/IV, measuring BNP before the test and at peak exercise. In multivariate analysis an increase in BNP during exercise was a good predictor, whereas its decrease implied a poor prognosis; two-year mortality was 15% in the group with a BNP increase and 45% in the group with a BNP decrease during exercise (p < 0.01).

In a study by French investigators BNP and high-sensitivity C-reactive protein (hsCRP) were measured along with pVO<sub>2</sub> in 545 patients with heart failure of mixed etiology (dilated and ischemic cardiomyopathy) undergoing cardiopulmonary exercise testing. The patients were followed for 2.5 years (median time) [6]. In a multivariate analysis concentrations of BNP and hsCRP independently predicted cardiovascular death. After the use of pVO<sub>2</sub> in the prognostic model it turned out to be the strongest predictor of death (RR = 4.30); however both biomarkers retained their independent and additive predictive value (RR = 1.98 for BNP and RR = 1.55 for hsCRP). It is interesting that hsCRP was a significant predictor only in the group of patients with ischemic cardiomyopathy, and the prognostic cut-off was 3.0 mg/L, which is identical to the cut-off

proposed by Ridker [26] for risk stratification in primary and secondary prevention of coronary artery disease.

### Summary

Stress tests provide additional prognostic information in patients with heart failure. They help to improve traditional risk stratification based on clinical, resting echocardiographic and radiological assessment. Of the many parameters obtained during cardiopulmonary exercise testing  $pVO_2$  is still the most powerful predictor of adverse events, including death.  $pVO_2$  can be expressed as  $\%VO_2$  max, which is potentially better adjusted for age, sex and body mass. In spite of this the absolute value of  $pVO_2$  of less than 14 ml/kg/min is still considered a decision cut-off in the process of qualifying patients for heart transplantation. Possibly heart transplantation can be safely deferred if  $\%VO_2$  max exceeds 50, even in cases of absolute measured  $pVO_2$  below 14 ml/kg/min.

It has to be stressed that for risk stratification in the general heart failure population, significantly broader than the group of heart transplantation candidates,  $pVO_2 = 14$  ml/kg/min alone has a limited prognostic value. It appears that there is no single threshold  $pVO_2$  value corresponding to a particular risk, but that  $pVO_2$  should rather be viewed as a continuous variable determining the risk in a gradual fashion. The slope of ventilation to carbon dioxide production ( $VE/VCO_2$  slope) can have an additive and independent prognostic value in the case of maximal effort ( $RER > 1.0$ ). Where there is sub-maximal effort (symptom-limited or prematurely terminated owing to inadequate patient motivation), it is acceptable to use the  $VE/VCO_2$  slope as a surrogate prognostic marker. In the risk assessment of heart failure patients undergoing cardiopulmonary exercise testing easily obtainable parameters such as maximum systolic blood pressure and exercise duration should also be considered, although their actual prognostic importance remains to be confirmed in further studies.

Peak oxygen consumption remains the primary cardiopulmonary parameter determining the risk of adverse events, mostly death, in heart failure patients. Other parameters, especially ventilation slopes can have additional value. This also includes cases where  $VO_2$  is of limited use (effort is sub-maximal or  $pVO_2$  is not reached). In the case of  $pVO_2$  in the grey zone, especially in the range of 10–14 ml/kg/min, stress or dobutamine echocardiography may contribute additional prognostic information.

Attempts at combining biomarker measurement, especially natriuretic peptides and hsCRP, with cardiopulmonary exercise testing yield promising results.

This article does not summarise all the parameters that can be of prognostic value in heart failure patients. The authors' intention was to discuss risk assessment methods of proven clinical and prognostic importance. Available data indicate that combined assessment of the hemodynamic and neurohormonal responses to exercise allows a better risk stratification and helps to identify high-risk patients who will benefit from invasive and costly therapies and low-risk patients who can safely be treated medically.

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