

The prognostic value of stress tests in chronic heart failure

Wiktor Piechota and Grzegorz Gielera

Department of Internal Diseases and Cardiology, Military Medical Institute, Warsaw

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

Address for correspondence: Dr. Wiktor Piechota
 Kwiatowa 3, 05–400 Otwock, Poland
 e-mail: wiktoriechota@yahoo.pl
 Received: 14.11.2006 Accepted: 28.05.2007

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_2 according to Weber and Janicki compared with pVO_2 ranges recommended for prognostic purposes.

Heart failure stage	pVO_2 ranges according to Weber et al. [ml/kg/min]	Prognosis	pVO_2 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_2 and $\%VO_2$ max in patients with heart failure [9], whereas in the other $\%VO_2$ max predicted mortality better than the absolute value of pVO_2 [10]. In this study $\%VO_2$ 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_2 < 14, and pVO_2 > 14 ml/kg/min indicated that the decreased pVO_2 in the former group exceeded 50% of $\%VO_2$ max [11]. The task of proving the superiority of either parameter can thus be difficult. It cannot be ruled out that $\%VO_2$ 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_2 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 $pVO_2 = 19$ ml/kg (lean body mass)/min is a more powerful prognosticator than $pVO_2 = 14$ 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_2 in heart failure. In theory AT should be a good surrogate for pVO_2 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_2 . 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_2) expressed as a regression coefficient of this curve. Excess of minute ventilation in relation to CO_2 production is characteristic of patients with heart failure and causes the VE/VCO_2 slope to run more steeply ($VE/VCO_2 > 32$ – 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_2 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_2 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_2 slope was an independent prognostic factor which contributed additional predictive information to that obtained from pVO_2 . In the study by Pardaens et al. [15] ventilatory slopes including VE/VCO_2 (after logarithmic transformation) did not add any prognostic information beyond that provided by pVO_2 . Ventilation slopes acquired prognostic value only after pVO_2 was eliminated from multivariate analysis, whereas pVO_2 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 ($RER \leq 1.0$). On the other hand Chua et al. [14] determined the VE/VCO_2 slope for maximal effort. Thus one can assume that the VE/VCO_2 slope retains its full prognostic value additive to that offered by pVO_2 in the case of maximal effort and should be treated as a surrogate prognostic parameter in sub-maximal efforts (with $RER \leq 1.0$). 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 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 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 pVO_2 in determining a prognosis has resulted in attempts to combine 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 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 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 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 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. Paraskevaidis et al. [20] showed that in patients with dilated cardiomyopathy ($n = 27$) and intermediate 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 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 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 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 pVO₂ 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, pVO₂, serum natrium 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 pVO₂ 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 pVO₂ in a group of heart failure patients with ejection fraction below 45%. In this study the value of pVO₂ (expressed as %VO₂ 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 pVO₂ 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%; pVO₂ = 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 pVO₂) 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 pVO₂ 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 pVO₂ 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.

References

1. Straburzyńska-Migaj E, Szyszka A, Cieśliński A. Exercise testing in heart failure; utility and limitations. *Kardiol Pol*, 2003; 58: 77–79.
2. Clark AL, Poole-Wilson PA, Coats A. Exercise limitation in chronic heart failure: central role of the periphery. *J Am Coll Cardiol*, 1996; 28: 1092–1102.
3. Weber K, Kinasewitz G, Janicki J, Fishman AP. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. *Circulation*, 1982; 65: 1213–1223.
4. Szałchic J, Massie BM, Kramer BL, Topic N, Tubau J. Correlates and prognostic implication of exercise capacity in chronic congestive heart failure. *Am J Cardiol*, 1985; 55: 1037–1042.
5. Likoff MJ, Chandler SL, Kay HR. Clinical determinants of mortality in chronic congestive heart failure secondary to idiopathic or dilated cardiomyopathy. *Am J Cardiol*, 1987; 56: 634–638.
6. Lambdin N, Mouquet F, Hennache B et al. High-sensitivity C-reactive protein: potential adjunct for risk stratification in patients with stable congestive heart failure. *Eur Heart J*, 2005; 26: 2245–2250.
7. Mancini DM, Eisen H, Kusmaul W, Mull R, Edmunds LH Jr., Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation*, 1991; 83: 778–786.
8. Working Group on Cardiac Rehabilitation and Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology. Recommendations for exercise testing in CHF patients. *Eur Heart J*, 2001; 22: 37–45.
9. Lainchbury JG, Richards AM. Exercise testing in the assessment of chronic congestive heart failure. *Heart*, 2002; 88: 538–543.

10. 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.
11. 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.
12. Osada N, Chaitman 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.
13. Milani RV, Lavie CJ, Mehra MR. Cardiopulmonary exercise testing: how do we differentiate the cause of dyspnea? *Circulation*, 2004; 110: e27–e31.
14. Chua T, Ponikowski P, Harrington D et al. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol*, 1997; 29: 1585–1590.
15. Pardaens K, Van Cleemput J, Vanhaecke J, Fagard RH. Peak oxygen uptake better predicts outcome than submaximal respiratory data in heart transplant candidates. *Circulation*, 2000; 101: 1152–1157.
16. Jankowska EA, Pietruk-Kowalczyk J, Zymlński R et al. The role of exercise ventilation in clinical evaluation and risk stratification in patients with chronic heart failure. *Kardiol Pol*, 2003; 59: 115–127.
17. Cohen-Solal A, Barnier P, Pessione F et al. Comparison of the long-term prognostic value of peak exercise oxygen pulse and peak oxygen uptake in patients with chronic heart failure. *Heart*, 1997; 78: 572–576.
18. Cohen-Solal A, Tabet JY, Logeart D, Bourgoin P, Tokmakova M, Dahan M. A non-invasively determined surrogate of cardiac power ('circulatory power') at peak exercise is a powerful prognostic factor in chronic heart failure. *Eur Heart J*, 2002; 23: 806–814.
19. Williams S, Jackson M, Ng LL, Barker D, Patwala A, Tan L-B. Exercise duration and peak systolic blood pressure are predictive of mortality in ambulatory patients with mild-moderate chronic heart failure. *Cardiology* 2005; 104: 221–226.
20. Paraskevaidis IA, Adamopoulos S, Kremastinos DT. Dobutamine echocardiographic study in patients with nonischemic dilated cardiomyopathy and prognostically borderline values of peak exercise oxygen consumption: 18-month follow-up study. *J Am Coll Cardiol*, 2001; 37: 1685–1691.
21. Agricola E, Oppizzi M, Pisani M, Margonato A. Stress echocardiography in heart failure. *Cardiovasc Ultrasound*, 2004; 2: 11.
22. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation*, 1997; 95: 2660–2667.
23. Gardner RS, Ozalp F, Murday AJ, Robb SD, McDonagh TA. N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. *Eur Heart J*, 2003; 24: 1735–1743.
24. de Groote P, Dagorn J, Soudan B, Lamblin N, McFadden E, Bauters C. B-type natriuretic peptide and peak exercise oxygen consumption provide independent information for risk stratification in patients with stable congestive heart failure. *J Am Coll Cardiol*, 2004, 43: 1584–1589.
25. Lainchbury JG, Swanney MP, Beckert L. Change in plasma brain natriuretic peptide during exercise is an important predictor in systolic heart failure. *Eur Heart J*, 2001; 22 (suppl.): 377.
26. Ridker PM. High-sensitivity C-reactive protein, inflammation, and cardiovascular risk: from concept to clinical practice to clinical benefit. *Am Heart J*, 2004; 148 (1 suppl.): S19–S26.