Evaluation of Prognostic Stratification of Patients with Chronic Heart Failure by Recovery Cardiopulmonary Indices Compared to Cardiopulmonary Exercise Indices

Klainman E, Sakhnovski S, Yarmolovsky A, Rosenberg I
Fink G

Homepage:

www.kup.at/jcbc

Online Data Base Search
for Authors and Keywords

Evaluation of Prognostic Stratification of Patients with Chronic Heart Failure by Recovery Cardiopulmonary Indices Compared to Cardiopulmonary Exercise Indices

E. Klainman[1,2], S. Sakhnovski[2], A. Yarmolovsky[2], I. Rosenberg[2], G. Fink[2]

Background: Cardiopulmonary exercise testing (CPET) with monitoring of gas exchange parameters provides useful information on exercise capacity and prognosis in congestive heart failure (CHF). Little is known about prognostic importance of recovery cardiopulmonary indices of CPET for all-cause mortality in CHF patients. *Objective:* The objective of this study is to evaluate the CPET-based recovery cardiopulmonary indices as predictive prognostic factors for death and readmissions. *Methods:* 104 patients with CHF, 81 males (77.9 %), mean age 50.3 years (SD = 13.9), were studied. 39 patients (37.5 %) had diabetes mellitus (DM), 26 (25.0 %) had COPD, 46 (44.2 %) had ischemic heart disease (IHD), and 74 (71.2 %) had hypertension. All patients underwent CPET, including recovery indices, and were followed between 2000 and 2005 for all-cause mortality and for admission (as end point events). Exercise indices were: HR, BP, O_2 consumption (VO_2), O_2 pulse (O_2-P), ventilation (Ve), respiratory exchange ratio (RER), and ventilatory anaerobic threshold (VAT), among others. Recovery indices were: ½ time recovery of VO_2 (½VO_2-t- Rec.), in sec; ½ time recovery of O_2-P (½O_2-P-t-Rec.), in sec; and full-time recovery of VO_2 (VO_2-T-Rec.), in minutes (min). *Results:* There were no factors which predicted readmissions. All-cause mortality rate was 24.0 % (n = 25). Significant correlations were demonstrated between all-cause mortality and: peak-Ve (p < 0.007); peak-VO_2 (% pred.; p < 0.001); peak-O_2-P (p < 0.000); VAT (p < 0.020); ½VO_2-t-Rec (p < 0.025); ½O_2-P-t-Rec (p < 0.019) ; ½VO_2-t-Rec/RER-peak (RER at peak exercise) (p < 0.002); ½O_2-P-t-Rec/RER-peak (p < 0.020); ½VO_2-t-Rec × RER-peak (p < 0.000); ½O_2-P-t-Rec × RER-peak (p < 0.021); ½VO_2-t-Rec/RER-max (maximal RER at exercise or recovery) (p < 0.000); ½O_2-P-t-Rec/RER-max (p < 0.013); ½VO_2-t-Rec × RER-max (p < 0.003), and ½O_2-P-t-Rec × RER-max (p < 0.044). By multivariate logistic regression analysis, peak-Ve (regression coefficient= –0.083), ½VO_2-t-Rec/RER-peak (regression coefficient = –0.216), ½VO_2-t-Rec/RER-max (regression coefficient = 0.272), and DM (regression coefficient = 0.705) were found as the independent predictors of all-cause mortality. *Conclusions:* Recovery cardiopulmonary parameters, as definded in the present study, were found to be significant prognostic predictors at least as exercise indices. Thus, it is suggested to complete the CPET with continuing monitoring during the whole recovery period for further evaluation of CHF patients. *J Clin Basic Cardiol 2012; 15 (online): 13–6.*

Key words: heart failure, cardiopulmonary exercise testing, VO_2 recovery kinetics, prognostic factors

Cardiopulmonary exercise testing (CPET), when properly performed, provides an objective measurement of peak functional capacity and as such has become an important clinical tool for disease severity estimation and for outcome prediction in patients (pts) with chronic heart failure (CHF) [1]. This very test is considered to be the gold standard for the prognostic evaluation of such pts, and low peak-VO_2 is widely recognized as a predictor of poor prognosis [2–4]. Other prognostic factors which have gained interest in recent years were VE/VCO$_2$ slope and heart rate recovery (HRR) for their prognostic power independent from peak-VO_2 [5–7]. The VE/VCO$_2$ slope was also found not to be affected by the exercise mode at least in pts with mild CHF [8]. Other studies have shown that oxygen uptake kinetics during recovery from exercise are delayed at more advanced stages of heart failure and that the kinetics of recovery oxygen uptake can be used to measure the functional capacity of CHF pts [9–14]. There is a lack of data regarding the prognostic significance of recovery cardiopulmonary indices in pts with CHF. In the present study, we try to define such a significance of variouse recovery parameters, taking in account the fact that many pts with CHF do not reach maximal predicted physiological effort during exercise.

Material and Methods

104 pts with CHF, 81 males (77.9 %), mean age 50.3 years (SD = 13.9), were included in the study. They were selected from a pool of 150 pts with CHF who underwent CPET according to the following criteria:

– Age 18–80
– Systolic CHF, with LVEF ≤ 35 %
– Satisfying data inquired for the study

39 patients (37.5 %) had diabetes mellitus (DM), 26 (25.0 %) had COPD, 46 (44.2 %) had ischemic heart disease (IHD), and 74 (71.2 %) had hypertension. All pts underwent CPET, including recovery indices, and were followed from 2000–2005 for all-cause mortality and for admission (as end point events).

Cardiopulmonary Exercise Test

An upright symptom-limited test was performed on an electronically braked cycle ergometer (Ergo-line 800). Exercise was initiated after a 3-minute rest and 2 minutes of free pedalling at a rate of 60 rpm. The effort was then progressively increased by 10–20 Watt/min until the predefined end-point was reached, namely, symptoms, volitional fatigue, or attainment of the target HR. Cardiopulmonary data were collected by an online metabolic unit (CPX Medical Graphics, MN, USA).

Patients breathed through a low-resistance, 2-way valve (Hans-Rudolph, MO, USA) connected to the expiratory limb. The breath-by-breath signals were integrated by a computer to yield 30-sec and averages of HR, minute ventilation, VO_2, VCO_2 and O_2-P (VO_2/HR). VAT was defined as the point at which the ventilatory equivalent of O_2 (Ve/VO_2) increased in the absence of a similar increase in the ventilatory equivalent of CO_2 (Ve/VCO_2), as described by Beaver et al [15]. Blood pressure was measured at rest, every 2 minutes, at peak exercise and during recovery.
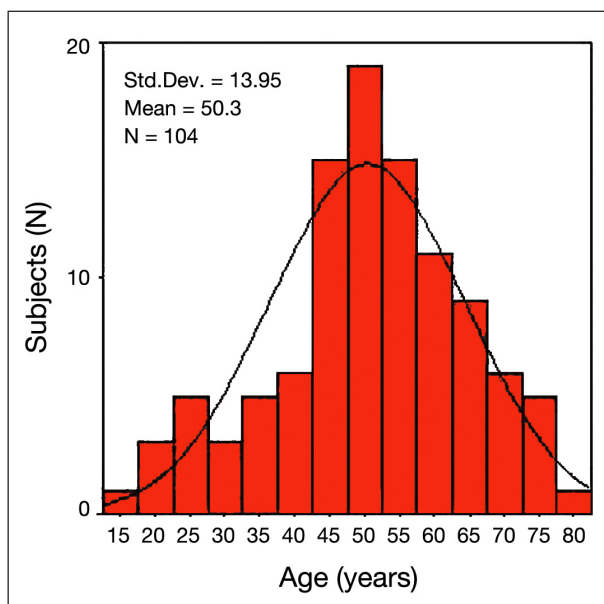
Figure 1. Age variability of the 104 patients participating in the study.

Blood pressure at rest, during exercise, and recovery was measured as for a standard.

Recovery indices were defined as: ½time recovery of VO_2 (½VO_2-t-Rec.), in sec; ½ time recovery of O_2-P (½O_2-P-t-Rec.), in sec; and full-time recovery of VO_2 (VO_2-T-Rec.), in min, until RER reached value of 1 or less.

Since the pts included in the study had various degrees of CHF, not all of them reached the expected peak exercise, namely, RER of at least 1.15. Therefore, we had to define new combined parameters, involving the RER index, which might minimize the effect of this limitation. These 12 parameters were defined as follows:

1. VO_2-T-Rec./RER-peak (parameter A)
2. ½VO_2-t-Rec./RER-peak (parameter B)
3. ½O_2-P-t-Rec./RER-peak (parameter C)
4. VO_2-T-Rec. × RER-peak (parameter D)
5. ½VO_2-t-Rec. × RER-peak (parameter E)
6. ½O_2-P-t-Rec. × RER-peak (parameter F)
7. VO_2-T-Rec./RER-max. (parameter G)
8. ½VO_2-t-Rec./RER-max. (parameter H)
9. ½O_2-P-t-Rec./RER-max. (parameter I)
10. VO_2-T-Rec. × RER-max. (parameter J)
11. ½VO_2-t-Rec. × RER-max. (parameter K)
12. ½O_2-P-t-Rec. × RER-max.(parameter L)

VO_2-T-Rec.: full-time recovery of oxygen consumption (in minutes); ½VO_2-t-Rec.: half-time recovery of oxygen consumption (in seconds); ½O_2-P-t-Rec.: half-time recovery of oxygen pulse (in seconds); RER-max.: maximal respiratory exchange ratio achieved in exercise or recovery; RER-peak: peak respiratory exchange ratio at exercise.

Follow-Up Period
All pts were followed from 2000–2005 for at least 2 years per patient, continuously or until death. Follow-up visits of the pts were at the hospital outpatient CHF clinic and/or by their general physician. Each significant event like hospitalization and all-cause mortality were taken from the patients' computerized files for statistical prognostic evaluation.

Statistical Analysis
T-test or Chi-square test were used to compare the parameters between the groups "deceased" vs "survived" and "hospi-

Table 1. Relationship between CPET indices and death (n = 104).

Parameter	Survivors (n = 79)		Deceased (n = 25)		p
	Mean	1 SD	Mean	1 SD	
Age	45.9	12.8	48.7	17.1	0.560
Male %	84.0	–	75.9	–	0.398
Female %	16.0	–	24.1	–	0.398
Peak-Ve*	45.1	13.6	38.7	8.3	0.007
Peak-VO$_2$, ml/kg/min	13.1	4.4	11.5	4.2	0.125
Peak-VO$_2$, %*	50.2	12.4	40.4	11.1	0.001
Peak-O$_2$-Pulse, %*	71.4	19.9	57.1	13.1	0.001
Peak-O$_2$-Pulse, ml/beat*	9.0	2.4	6.7	1.7	0.000
VAT, %*	32.6	8.7	27.6	7.2	0.020
peak-HR*	113.9	32.5	101.2	28.1	0.087
WATTS*	56.7	17.4	47.0	18.2	0.025
RER	1.13	0.1	1.14	0.1	0.694
METS*	50.2	12.3	40.0	11.3	0.001
VO$_2$-T-Rec, min	6.9	2.3	6.9	2.4	0.920
½VO$_2$-t-Rec, sec*	120	40.7	156	60.4	0.025
O$_2$-Pulse-t-Rec, sec*	206	70.7	250.4	89	0.019
A	6	1.7	5.9	1.9	0.819
B*	107.2	45.4	142.4	50	0.002
C*	183	64	220	75	0.020
D	8	3	7.9	3	0.957
E*	137	56.2	190.2	78.9	0.000
F*	231.6	99	288	100.3	0.021
RER-max	1.4	0.2	1.4	0.2	0.831
G	4.8	1.3	4.9	1.6	0.842
H*	84.3	37.4	119	47.1	0.000
I*	147.6	50.5	182.4	63.3	0.013
J	10.2	4.3	9.8	4	0.696
K*	172	70	228.4	80	0.003
L*	296.3	120	355.7	130	0.044
HRR	22.5	11.6	23.8	12.6	0.064

Ve: ventilation in l/min; VO$_2$: oxygen consumption; O$_2$-Pulse: oxygen pulse; VAT: ventilatory anaerobic threshold; HR: heart rate; RER: respiratory exchange ratio; METS: metabolic units; T,t: time; rec: recovery; A–L parameters: see Methods section; HRR: heart rate recovery

talized" vs "not hospitalized". Each parameter was presented as mean ± 1 SD. Multivariate logistic regression analysis models were used for identification of non-dependent prognostic parameters. $P < 0.05$ was considered statistically significant.

Results

Figure 1 shows the patients' age spread.

The all-cause mortality rate was 24.0 % (n = 25). Significant correlations were demonstrated between all-cause mortality and peak-Ve ($p < 0.007$); peak-VO$_2$ (% pred.; $p < 0.001$); peak O$_2$-P ($p < 0.000$); VAT ($p < 0.020$); ½VO$_2$-t-Rec ($p < 0.025$); ½O$_2$-P-t-Rec ($p < 0.019$); ½VO$_2$-Rec/RER-peak (RER at peak exercise) ($p < 0.002$); VO$_2$-T-Rec/RER-peak ($p < 0.020$); ½VO$_2$-t-Rec X RER-peak ($p < .0000$); VO$_2$-T-Rec X RER-peak ($p < 0.021$); ½VO$_2$-t-Rec/RER-max (maximal RER at exercise or recovery) ($p < 0.000$); VO$_2$-T-Rec/RER-max ($p < 0.013$); ½VO$_2$-t-Rec × RER-max ($p < 0.003$); VO$_2$-T-Rec × RER-max ($p < 0.044$; Table 1).

Table 2. Relationship between CPET indices and hospitalizations (n = 104).

Parameter	Hospitali-zations (n = 97)	1 SD	Not hospita-lized (n = 7)	1 SD	p
Age	50.7	14.0	49.5	13.8	0.669
Male, %	78.6		45.5		0.809
Female, %	21.4		54.5		0.809
Peak-Ve	42.5	13.2	71.3	11.9	0.276
Peak-VO$_2$, %	46.6	13.7	32.8	10.5	0.152
Peak-VO$_2$, ml/kg/min	12.7	4.8	12.7	4.2	0.968
Peak-O$_2$-Pulse, %	66.5	19.9	119.0	18.3	0.244
Peak-O$_2$-Pulse, ml/beat	8.7	2.6	8.5	2.4	0.647
VAT, %	30.6	9.0	55.9	7.6	0.290
Peak-HR	106.9	28.0	1.1	37.7	0.069
WATTS	53.9	19.8	51.0	13.9	0.603
Peak-RER	1.1	0.1	1.1	0.1	0.242
METS	46.1	13.5	51.0	10.6	0.071
VO$_2$-T-Rec, min	7.14	1.7	6.84	2.6	0.481
½VO$_2$-Rec, sec	126.8	55.7	129.3	56.4	0.831
½O$_2$-P-t-Rec, sec	217.8	75.6	216.4	73.5	0.938
A	6.2	1.2	6	1	0.587
B	11.9	52	116.6	46.6	0.650
C	192.5	65	191.9	66	0.965
D	8.3	2.4	7.9	3.4	0.504
E	141	62	151.6	67	0.449
F	241	101	246	106.4	0.825
RER-max	1.45	0.2	1.42	0.2	0.437
G	5	1.1	4.8	1.5	0.596
H	85.9	42.3	95	42.1	0.314
I	153.6	56.5	156.6	60.2	0.802
J	10.5	3.2	4.6	9.9	0.549
K	185	82.6	184	88	0.976
L	314.4	115.5	308.5	115.3	0.840
HRR	21.3	10.8	25.9	13.3	0.065

Ve: ventilation in l/min; VO$_2$: oxygen consumption; O$_2$-Pulse: oxygen pulse; VAT: ventilatory anaerobic threshold; HR: heart rate; RER: respiratory exchange ratio; METS: metabolic units; T,t: time; Rec: recovery; A–L parameters: see Methods section; HRR: heart rate recovery

Table 3. Independent relationship between CPET and disease parameters and death.

Parameter	Regression factor	Standard error	p
Peak-Ve	–0.083	0.041	0.043
O$_2$-Pulse	–0.025	0.020	0.212
½VO$_2$-t-Rec.	–0.105	0.098	0.283
O$_2$-Pulse-t-Rec.	0.004	0.215	0.983
B	–0.216	0.118	0.068
C	0.141	0.127	0.269
E	0.010	0.032	0.767
F	0.038	0.084	0.650
H	0.272	0.137	0.047
I	–0.157	0.118	0.184
K	0.067	0.046	0.139
L	–0.041	0.049	0.408
IHD	0.716	0.700	0.307
Male gender	1.265	0.946	0.181
DM	0.705	0.743	0.062

Ve: ventilation in l/min; VO$_2$: oxygen consumption; O$_2$-Pulse: oxygen pulse; T,t: time; Rec: recovery; A–L parameters: see Methods section; IHD: ischemic heart disease; DM: diabetes mellitus

Table 4. Relationship between background diseases and death (n = 104).

Parameter	Survivors	Deceased	p
DM*	31.6	56.0	0.028
COPD	24.1	28.0	0.691
IHD*	38.0	64.0	0.022
HTN	73.4	64.0	0.365

IHD: ischemic heart disease; DM: diabetes mellitus; HTN: hypertension; COPD: chronic obstructive pulmonary disease

The main results are summarized in Tables 1–4.

There were no factors which predicted hospitalisations. The main reason for this finding might be the fact that only 7 out of the 104 pts were not hospitalized during the follow-up period (Table 2).

By multivariate logistic regression analysis, peak-Ve (regression coefficient = –0.083; p = 0.043), and ½VO$_2$-t-Rec/RER-max (regression coefficient = 0.272; p = 0.047) were found as independent predictors of all-cause mortality. ½VO$_2$-t-Rec/RER-peak (regression coefficient = –0.216; p = 0.068) and DM (regression coefficient = 0.705; p = 0.062) were borderline independent predictors (Table 3).

Table 4 shows that background diseases of IHD or DM are prognostically significant for death while COPD or HTN are not.

Discussion

In daily practice, peak-VO$_2$ significantly influences decisions regarding the management of pts with CHF and is consid-ered to be an important mortality predictor in such pts [15–21]. However, this very index depends on the mode of exercise particularly in such CHF pts [8, 22–24]. The independent prediction power of other indices, like Ve/VCO$_2$ or heart rate recovery (HRR), are still to be proven. On the other hand, exercise intolerance in CHF pts is hard to quantify since the end point for the test is usually subjective, depending on motivation of the pt or the examiner. Even the VAT, which is independent of pt motivation, might be limited for prognostic evaluation especially in those with undetectable VAT [25, 26]. Therefore, it is necessary to identify new prognostic parameters which may strengthen the ability for such assessment of CHF pts. The present study demonstrates several recovery, as well as exercise, cardiopulmonary parameters as prognostic predictors in pts with CHF. All-cause mortality is significantly correlated with several exercise CPET indices but not less significantly with recovery indices as well (Table 1). According to regression analysis, Peak-Ve, ½VO$_2$-t-Rec/RER-peak and ½VO$_2$-t-Rec/RER-max are the most significant independent predictors of prognosis in CHF.

Exercise Indices

The study by Mancini et al [3] is still considered a cornerstone of the prognostic power of peak-VO$_2$ in the the evaluation of CHF pts. Nevertheless, it is important to prove that

exercise testing was truly maximal, a task which is quite hard to achieve in many CHF pts. In our study it was shown that this very parameter, especially when expressed by the percentage of maximal predicted values, has quite a strong predictive power for death. The O_2-pulse, which reflects the SV, has even more significant predictive power in such an evaluation, as can be seen in Table 1. The prognostic significance of the O_2-Pulse is barely discussed in the medical literature.

VAT is considered as a submaximal index of exercise capacity, independent of patient motivation. A failure to reach VAT suggests poor motivation or non-cardiac limitation of exercise tolerance. Such a failure may be observed in a large proportion of CHF pts [25].

VAT in the present study has been shown as a strong predictor of death in CHF pts (Table 1).

The only exercise index that was found to be significantly independent for all-cause mortality was peak-Ve (Table 3).

It is a lack of information about this factor by itself but its relationship to VCO_2 is demonstrated to be an important prognostic predictor, as Ve/VCO_2 slope > 34 was associated with worse prognosis in CHF [27].

CHF pts with severe exercise intolerance need more objective indices for evaluation of maximal effort since their motivation to reach such an effort is limited or lacking [28].

Recovery Indices

In our study, we tried to evaluate the contribution of recovery cardiopulmonary indices in the prognostic prediction of CHF pts. To add objective strength, we defined additional parameters in which the already defined recovery indices were multiplied by or divided in the peak-RER achieved during exercise or maximal RER which was achieved during the whole recording within exercise or recovey period as well. Since such RER values might be affected by subjective factors like patient motivation, where pts do not reach the peak, physiological expected, RER of ≥ 1.15, as shown in the Mezzani et al study [29], these new parameters might suggest a physiological correction to the bare recovery indices, which might be subjective as well.

Table 1 demonstrates that the recovery indices ½VO_2-t-recovery and ½O_2-P-t-recovery are significant death-predicting factors in CHF, strengthened by the high significance of these very factors multiplied by or divided in the RER values (parameters: B, C, E, F, H, I, K, and L in Table 1). Nevertheless, from all these parameters, only factor H (½VO_2-t-recovery/RER-max) was found to be a significantly independent one for death prediction, while factor B (½VO_2-t-recovery/RER-peak) was borderline, as well as DM (Table 3).

Limitations and Conclusions

The main limitations of the present study were its retrospective characteristics and the relatively small number of patients. Such a sample does not allow to calculate quantitatively the new recovery parameters checked in this study in relationship to prognostic significance. Nevertheless, these findings suggest that recovery indices should be recorded following the CPET for further prognostic evaluation in CHF patients. More studies, and with larger patient samples, are necessary for further quantitative assessment of recovery parameter values and their contribution to evaluate prognosis in CHF patients.

References:

1. Beniaminovitz A, Mancini DM. The role of exercise-based prognostification algorithms in the selection of patients for heart transplantation. Curr Opin Cardiol 1999; 4: 114–20.

2. Mudge GH, Goldstein S, Addonizo LJ, et al. 24th Bethesda Conference Taskforce 3: Heart transplantation: Recipient guidelines/prioritization. J Am Coll Cardiol 1993; 22: 21–31.

3. Mancini DM, Eisen H, Kussmaul W, et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991; 83: 778–86.

4. Fuster V, O'Rourke RA, Walsh R, et al (eds). Hurst's the Heart. 12th ed. McGraw-Hill Medical, New York, 2007.

5. Francis DP, Shamim W, Davies LC, et al. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO2 slope and peak VO2. Eur Heart J 2000; 21: 154–61.

6. Arena R, Guazzi M, Myers J, et al. Prognostic value of heart rate recovery in patients with heart failure. Am Heart J 2006; 151: 851.e7–851.e13.

7. Arena R, Myers J, Aslam SS, et al. Peak-VO2 and VE/VCO2 slope in patients with heart failure: a prognostic comparison. Am Heart J 2004; 147: 354–60.

8. Maeder MT, Wolber T, Ammann P, et al. Cardiopulmonary exercise testing in mild heart failure: impact of the mode of exercise on established prognostic predictors. Cadiology 2008; 110: 135–41.

9. Hayashida W, Kumada T, Kohno F, et al. Post-exercise oxygen uptake kinetics in patients with left ventricular dysfunction. Int J Cardiol 1993; 38: 63–72.

10. Riley M, Stanford CF, Nicholls DP. Ventilatory and heart rate responses after exercise in chronic cardiac failure. Clin Sci 1994; 87: 231–8.

11. Sietsema KE, Ben-Dov I, Zhang YY, et al. Dynamics of oxygen uptake for submaximal exercise and recovery in patients with chronic heart failure. Chest 1994; 105: 1693–700.

12. Cohen-Solal A, Laperche T, Morvan D, et al. Prolonged kinetics of recovery of oxygen consumption after maximal graded exercise in patients with chronic heart failure. Circulation 1995; 91: 2924–32.

13. Koike A, Yajima T, Adachi H, et al. Evaluation of exercise capacity using submaximal exercise at a constant work rate in patients with cardiovascular disease. Circulation 1995; 91: 1719–24.

14. de Groote P, Millaire A, Decoulx E, et al. Kinetics of oxygen consumption during and after exercise in patients with dilated cardiomyopathy. New markers of exercise intolerance with clinical implications. J Am Coll Cardiol 1996; 28: 168–75.

15. Lainchbury JG, Richards AM. Exercise testing in the assessment of chronic congestive heart failure. Heart 2002; 88: 538–43.

16. Davies LC, Francis DP, Piepoli M et al. Chronic heart failure in the elderly: value of cardiopulmonary exercise testing in risk stratification. Heart 2000; 83: 147–51.

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

18. 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: 577–82.

19. Wilson JR, Hanamanthu S, Chomsky DB, et al. Relationship between exertional symptoms and functional capacity in patients with heart failure. J Am Coll Cardiol 1999; 33: 1943–7.

20. Guazzi M, De Vita S, Cardano P, et al. Normalization for peak oxygen uptake increases the prognostic power of the ventilatory response to exercise in patients with chronic heart failure. Am Heart J 2003; 146: 542–8.

21. Roul G, Moulichon ME, Bareiss P, et al. Exercise peak VO2 determination in chronic heart failure: is it still of value? Eur Heart J 1994; 15: 495–502.

22. Page E, Cohen-Solal A, Jondeau G, et al. Comparison of treadmill and bicycle exercise in pts with CHF. Chest 1994; 106: 1002–6.

23. Strzelczyk TA, Cusick DA, Pfeifer PB, et al. Value of the Bruce protocol to determine peak exercise oxygen consumption in pts evaluated for cardiac transplantation. Am Heart J 2001; 142: 466–75.

24. Witte KKA, Clark AL. Cycle exercise causes a lower ventilatory response to exercise in CHF. Heart 2005; 91: 225–6.

25. Cohen-Solal A, Zannad F, Kayanakis JG, et al. Multicenter determination of the oxygen uptake and ventilatory threshold. Eur Heart J 1991; 12: 1055–63.

26. Opasich C, Pinna GD, Bobbio M, et al. Peak oxygen consumption in CHF: toward efficient use in the individual patient. J Am Coll Cardiology 1998; 31: 766–75.

27. Chua TP, Ponikowski P, Harrington D, et al. Clinical correlates and prognostic significance of the ventilatory response to exercise in CHF. J Am Coll Cardiol 1997; 29: 1585–90.

28. Clark AL, Pool-Wilson PA, Coats AJS. Effect of motivation of the patient on indices of exercise capacity in CHF. Br Heart J 1994; 71: 162–5.

29. Mezzani A, Corrà U, Bosimini E, et al. Contribution of peak respiratory exchange ratio to peak VO2 prognostic reliability in patients with chronic heart failure and severely reduced exercise capacity. Am Heart J 2003; 145: 1102–7.