Am J Cardiovasc Dis 2020;10(5):578-584
www.AJCD.us /ISSN:2160-200X/AJCD0122665

Original Article

Prognostic value of VE/VCO_2 slope in overweight heart failure patients

António Valentim Goncalves, Tiago Pereira-da-Silva, Rui Soares, Joana Feliciano, Ana Abreu, Pedro Rio, Rita Ilhao Moreira, Rui Cruz Ferreira

Department of Cardiology, Hospital de Santa Marta, Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal

Received September 18, 2020; Accepted November 14, 2020; Epub December 15, 2020; Published December 30, 2020

Abstract: Background: A decreased hypercapnic ventilatory response of the overweight patients would lower the ventilation equivalent of carbon dioxide (VE/VCO_2) slope but worsen prognosis. The aim of this study was to compare the prognostic ability of the VE/VCO_2 slope and peak oxygen consumption (pVO_2) between normal and overweight heart failure (HF) patients. Methods: Prospective evaluation of ambulatory patients with reduced left ventricular ejection fraction who underwent baseline assessment with a cardiopulmonary exercise test. The primary endpoint was cardiac death or urgent heart transplantation in the 5-year period of follow-up. The predictive power of VE/VCO_2 slope and pVO_2 were compared (area under the curve (AUC) analysis and Hanley & McNeil test), in the subgroups of patients with body mass index (BMI) of 18.5-24.9 kg/m^2 and ≥ 25 kg/m^2. Statistical differences with a *p* value < 0.05 were considered significant. Results: There were 270 enrolled patients, with a mean BMI of 27 ± 4 kg/m^2. No differences between normal and overweight patients (38.0% vs 29.8%, P=0.170) were found during the 5-year period for the primary endpoint. The VE/VCO_2 slope was non-inferior to pVO_2 in both groups at 1, 3 and 5 years of follow-up. The comparison of VE/VCO_2 slope between groups revealed a significant lower AUC at 3 (0.921 vs 0.787, P=0.022) and 5 years (0.898 vs 0.787, P=0.044) of follow-up for overweight patients. Conclusion: Despite VE/VCO_2 slope provides a discriminative power at least as good as pVO_2 for predicting adverse events in both normal and overweight HF patients, a significant lower predictive power was found in overweight patients.

Keywords: VE/VCO_2 slope, heart failure, overweight, peak O_2 consumption

Introduction

The cardiopulmonary exercise test (CPET) is a powerful predictor of mortality in heart failure (HF) patients and is used as the criterion standard for the need for heart transplantation [1-8], with peak O_2 consumption (pVO_2) and the relation between ventilation and CO_2 production (VE/VCO_2 slope) as the most used risk assessment tools [9]. The VE/VCO_2 slope prognostic value was demonstrated to add additional information or even to be superior to pVO_2 for the prediction of major HF events in previous trials [10, 11].

Overweight is associated with changes in pulmonary mechanics and function, leading to a decreased hypercapnic ventilatory response, which would lower the VE/VCO_2 slope [12]. Consequently, a smaller VE/VCO_2 slope value, which represents a sign of good prognosis, can be found in overweight HF patients [13]. However, this reduction can be due to an abnormal ventilation mechanics and pulmonary function which would only worsen the prognosis of HF patients.

Given the high prevalence of overweight in HF patients [14], it is important to know how body mass index (BMI) may affect CPET parameters prognostic power. Previous studies showed that VE/VCO_2 slope maintains prognostic value irrespective of BMI when compared to pVO_2, but did not study whether VE/VCO_2 slope prognostic power was different in overweight patients from normal BMI patients at long term [12, 13].

The aim of this study was to compare the prognostic ability of the VE/VCO_2 slope and pVO_2 between normal and overweight HF patients, as well as whether VE/VCO_2 slope prognostic power is kept in overweight patients in relation to normal BMI HF patients. To the best of our knowledge, this is the first study addressing this issue at long-term follow-up time.

Methods

The study follows the principles defined in the Declaration of Helsinki. Patients provided written informed consent and the conses committee approved the protocol.

Patient population and study protocol

Single centre analysis of 274 HF patient's consecutive sent to our institution with left ventricular ejection fraction (LVEF) ≤ 40% and New York Heart Association (NYHA) class II or III, from 2007-2013. All the patients were evaluated by our HF team for the indication for mechanical circulatory support or heart transplantation.

Patients were divided in two groups:

- Group A: BMI of 18.5-24.9 kg/m^2
- Group B: BMI ≥ 25 kg/m^2

The prospective follow-up of the patients involved an initial evaluation within a period of one month including:

- Clinical data: HF etiology, medication, comorbidities, NYHA class and Heart Failure Survival Score [15];
- Laboratorial data;
- Electrocardiographic data;
- Echocardiographic data;
- CPET data.

Exclusion criteria were the following:

- Age < 18 years;
- Exercise-limiting comorbidities (cerebrovascular disease, musculoskeletal impairment, or severe peripheral vascular disease);
- Planned percutaneous coronary revascularization or cardiac surgery;
- Previous heart transplantation;
- BMI < 18.5 kg/m^2.

Follow-up protocol and study endpoint

All patients were followed for 5 years after the baseline exams.

The primary endpoint was a composite of cardiac death or urgent heart transplantation (defined if it was associated with inotrope dependency). Elective heart transplantation patients during the follow-up were censored for the primary endpoint at that period.

Data was obtained from the medical charts review, outpatient clinic visits and standard telephone interview to all patients at 1, 3 and 5 years of follow-up.

Cardiopulmonary exercise testing

The CPET (GE Marquette Series 2000 treadmill) was performed using the modified Bruce protocol. Before the gas analysis the equipment was calibrated. Minute ventilation, oxygen uptake and carbon dioxide production were acquired breath-by-breath, using a SensorMedics Vmax 229 gas analyser. The VE/VCO_2 slope was calculated by least squares linear regression, using data acquired throughout the whole exercise. The pVO_2 was defined as the highest 30-second average achieved during exercise and was normalized for body mass [16]. Patients were motivated to achieve a respiratory exchange ratio (RER) higher than ≥ 1.10.

Statistical analysis

All analyses compare normal and overweight patients. Data was analysed using the version 24.0 of the Statistical Package for the Social Science for Windows software (SPSS Inc, Chicago IL).

Normal distribution of the variables were analysed by the Kolmogorov-Smirnov test. Baseline characteristics were represented as means and standard deviations for continuous variables and as frequencies (percentages) for categorical variables. The Student's t-test for independent samples was also used.

Univariable Cox proportional-hazards models were applied, with *P* values for time-to-event analyses being based on log-rank tests, and hazard ratios for treatment effects and 95% confidence intervals presented to study the

Table 1. Baseline characteristics

CHARACTERISTICS	BMI 18.5-24.9 kg/m²	BMI ≥ 25.0 kg/m²	P
Age (years)	50.6 ± 14.3	55.2 ± 10.4	0.006
Male (%)	71.7%	78.1%	0.247
Ischemic etiology (%)	38.0%	38.2%	0.980
NYHA ≥ III (%)	28.3%	19.7%	0.121
Diabetes mellitus	8.2%	28.9%	< 0.001
Arterial Hypertension	50.0%	61.4%	0.023
Ex/Current Smoker	41.9%	40.1%	0.793
Sinus rhythm (%)	80.4%	81.5%	0.838
Left ventricular ejection fraction (%)	25.6 ± 6.9%	28.3 ± 7.4%	0.004
Hemoglobin (mg/dL)	13.4 ± 1.6	13.4 ± 2.5	0.922
Creatinine (mg/dL)	1.03 ± 0.27	1.11 ± 0.37	0.063
Sodium (mEq/L)	136.4 ± 3.3	137.5 ± 3.2	0.009
BNP (pg/ml)	534.3 ± 365.3	520.7 ± 576.7	0.966
Duration of exercise (minutes)	10.5 ± 4.4	10.3 ± 4.0	0.746
Heart Failure Survival Score	8.43 ± 0.6	8.8 ± 0.9	0.004
pVO_2 (ml/kg/min)	19.7 ± 6.0	19.9 ± 5.4	0.834
VE/VCO_2 slope	33.6 ± 8.9	30.2 ± 6.1	0.001

Values are mean ± standard deviation (normal distribution in all characteristics) or frequencies (percentages).

combined endpoint considering the follow-up time of 1, 3 and 5 years. Multivariate Cox analysis was also performed including the following variables: pVO_2, VE/VCO_2 slope, age, LVEF, Heart Failure Survival Score (HFSS), Sodium and Creatinine values.

In addition to the Cox analysis, the discriminative power regarding the primary outcome in the 3 periods of the follow-up of these CPET parameters were analysed for the highest area under the curve (AUC) value [17]. Cut-off values for variables were determined from the receiver operating characteristics (ROC) curves so that the sum of sensitivity and specificity was maximized [18]. Hanley & McNeil test was used to compare two correlated ROC curves [19].

A *p* value < 0.05 was considered a significant statistical difference.

Results

Overview of normal and overweight patients

The 270 enrolled patients had a mean BMI of 27 ± 4 kg/m², with 61 (22%) of the patients with a BMI ≥ 30 kg/m². 92 (34%) patients had a BMI of 18.5-24.9 kg/m² (group A) and 178 (66%) a BMI ≥ 25 kg/m² (group B). No patient was lost during the follow-up.

The baseline characteristics of the two groups are presented and compared in **Table 1**.

Group B patients were older, but with higher LVEF, sodium plasmatic values and HFSS. VE/VCO_2 slope values were significantly lower in group B patients (33.6 vs 30.2; P=0.001) with no differences regarding pVO_2 values (19.7 vs 19.9 ml/kg/min; P= 0.834).

Primary endpoint

There were 88 events (70 deaths and 18 urgent heart transplantations) during the 5-years period of follow-up, with no significant differences between groups A and B (38 vs 30%; P=0.170), as well as no statistical differences at 3 years (32 vs 22%; P=0.085). However, overweight patients had significantly less events at 1 year (19% vs 8%; P=0.010) of followup. No patients required mechanical circulatory support.

Relationship between CPET parameters and primary outcome

Univariate Cox analysis showed that both pVO_2 and VE/VCO_2 slope were predictors of the primary outcome in both groups at 1, 3 and 5 years of follow-up (P < 0.001 for all). Multivariate Cox analysis results are presented in **Table 2**. VE/VCO_2 slope, LVEF, HFSS and Sodium were the multivariate outcome predictors in group A. In group B, pVO_2, age and Creatinine values were significant predictors, while VE/VCO_2 slope was only a multivariate predictor for the 5-years outcomes.

Regarding the discriminative power for the primary outcome in the 3 periods of follow-up, both VE/VCO_2 slope and pVO_2 had high AUC values (**Table 3**) irrespective of the time of the follow-up and the group of BMI. The comparison

Table 2. Multivariate Cox analysis of CPET[1] prognostic parameters

MULTIVARIATE COX ANALYSIS	BMI 18.5-24.9 kg/m^2			BMI ≥ 25.0 kg/m^2		
	HR[2]	95% CI[3]	p	HR[2]	95% CI[3]	P
OUTCOME AT 3 YEARS						
pVO_2[4]	0.874	0.762-1.002	0.053	0.863	0.749-0.994	0.041
VE/VCO_2 slope	1.109	1.037-1.187	0.003	1.075	0.994-1.162	0.069
Age	0.976	0.948-1.006	0.115	0.957	0.921-0.995	0.027
Sodium	0.851	0.750-0.965	0.012	0.926	0.832-1.029	0.153
LVEF[5]	0.891	0.823-0.964	0.004	0.992	0.940-1.047	0.764
Creatinine	4.473	0.900-22.239	0.067	2.800	1.449-5.409	0.002
HFSS	3.173	1.259-7.999	0.014	1.093	0.575-2.079	0.787
OUTCOME AT 5 YEARS						
pVO_2[4]	0.891	0.789-1.006	0.062	0.883	0.783-0.996	0.043
VE/VCO_2 slope	1.114	1.047-1.185	0.001	1.089	1.015-1.168	0.018
Age	0.989	0.962-1.017	0.434	0.965	0.934-0.997	0.033
Sodium	0.851	0.760-0.953	0.005	0.923	0.840-1.013	0.091
LVEF[5]	0.908	0.846-0.945	0.008	0.995	0.950-1.042	0.827
Creatinine	3.122	0.770-12.663	0.111	2.498	1.400-4.460	0.002
HFSS	2.885	1.293-6.428	0.010	1.026	0.596-1.766	0.926

1 - cardiopulmonary exercise test; 2 - hazard ratio; 3 - confidence interval; 4 - peak O_2 consumption; 5 - Left ventricular ejection fraction.

Table 3. Area under the curve (AUC) analysis

	AUC - Group A	AUC - Group B	Hanley & McNeil test - p
VE/VCO_2 slope			
Outcome at 1 year	0.848	0.921	0.357
Outcome at 3 years	0.921	0.787	0.022
Outcome at 5 years	0.898	0.787	0.044
pVO_2 (ml/kg/min)			
Outcome at 1 year	0.802	0.854	0.816
Outcome at 3 years	0.805	0.786	0.788
Outcome at 5 years	0.844	0.787	0.911

Group A - BMI 18.5-24.9 kg/m^2; Group B - BMI ≥ 25.0 kg/m^2; Hanley & McNeil test for differences in A and B AUC results.

Table 4. Differences[1] between VE/VCO_2 slope and pVO_2 prognostic value

Outcome time	BMI 18.5-24.9 kg/m^2	BMI ≥ 25.0 kg/m^2
Outcome at 1 year	0.963	0.415
Outcome at 3 years	0.072	0.988
Outcome at 5 years	0.125	1.000

1 - Hanley & McNeil test results for differences between VE/VCO_2 slope and pVO_2.

of VE/VCO_2 slope between groups A and B revealed a significant lower predictive power with VE/VCO_2 slope at 3 years (0.921 vs 0.787; P=0.022) and 5 years (0.898 vs 0.787; P= 0.044) for overweight patients, with no differences at 1 year (0.848 vs 0.921; P=0.357). No differences were found regarding pVO_2 prognostic power in overweight patients.

Despite VE/VCO_2 slope provides a lower predictive power in overweight patients at 3 and 5 years of follow-up, the VE/VCO_2 slope values were at least as good as the AUC values of pVO_2 in both A and B groups and no differences were found in the Hanley & McNeil test (**Table 4**) for the comparison with pVO_2 values.

Sensitivity and specificity results for VE/VCO_2 slope

Cut-off values for VE/VCO_2 slope were determined from the ROC curves so that the sum of sensitivity and specificity was maximized and are presented in **Table 5**.

A VE/VCO_2 slope > 32 had the highest discriminative power at 1 year of follow-up, with a sensitivity of 100% and a specificity of 73% in the overweight group.

At 3 and 5 years of follow-up, VE/VCO_2 slope > 31 was the best value for the prediction of the primary outcome. Specificity values were similar between the two groups (79 vs 74% and 81 vs 78%), but a loss of sensitivity was seen in

Table 5. Sensitivity and specificity results of VE/VCO_2 slope

BMI group	Best value	Sensitivity	Specificity
1 year			
18.5-24.9 kg/m^2	> 32	88%	69%
≥ 25 kg/m^2	> 32	100%	73%
3 years			
18.5-24.9 kg/m^2	> 31	93%	79%
≥ 25 kg/m^2	> 31	77%	74%
5 years			
18.5-24.9 kg/m^2	> 31	86%	81%
≥ 25 kg/m^2	> 31	72%	78%

the overweight group (93 vs 77% and 86 vs 72%).

Discussion

Lower values of VE/VCO_2 slope are associated with a lower risk of HF events [11]. However, overweight is associated with changes in pulmonary mechanics and function, leading to a decrease in hypercapnic ventilatory response and a higher prevalence of central hypoventilation syndrome, which would lower the VE/VCO_2 slope [12] but without a benefit in the HF prognosis. On the other hand, several trials have demonstrated that overweight and obese HF patients have a survival advantage in relation with normal or low BMI parameters, known as the obesity paradox [13, 14, 20], so we could also expect lower values of VE/VCO_2 slope in overweight patients to have relation with a better prognosis.

Given the high prevalence of overweight in HF patients [14], it is important to know how BMI may affect CPET parameters prognostic power. Previous studies, showed that VE/VCO_2 slope maintains prognostic value irrespective of BMI when compared to pVO_2, but did not study whether VE/VCO_2 slope prognostic power was different in overweight patients from normal BMI patients at long term prognosis [12, 13].

To the best of our knowledge, this was the first study addressing this issue at 3 and 5 years of follow-up, since one previous trial had a follow-up time of 2 years, not finding any differences between VE/VCO_2 slope prognosis power between three groups of BMI (18.5-24.9 kg/m^2; 25.0-29.9 kg/m^2; ≥ 30 kg/m^2) with an event rate of death, heart transplant or mechanical circulatory support of 8.2% at 2 years.

Our results showed a significantly lower VE/VCO_2 slope values in overweight patients with no differences regarding pVO_2 values. Since our study had a higher follow-up time, and therefore a higher event rate (25.2% at three years and 32.6% at five years), a lower predictive power with VE/VCO_2 slope was demonstrated at 3 years (0.921 vs 0.787; P=0.022) and 5 years (0.898 vs 0.787; P=0.044) for overweight patients, with no differences at 1 year (0.848 vs 0.921; P=0.357).

Similarly to the result of previous trials [12, 13], the AUC values of VE/VCO_2 slope were at least as good as pVO_2 for the primary endpoint irrespective both the follow-up time and the BMI group. Thereby, pVO_2 should not be the only parameter to have in count in the evaluation of CPET results, and consideration should be given for VE/VCO_2 slope result too [10, 11].

A VE/VCO_2 slope > 31 had the highest discriminative power at 3 and 5 years of follow-up regardless the BMI group. In overweight patients, specificity results were between 74-78% and sensitivity between 72-77%, while in normal BMI patients specificity results were between 79-81% and sensitivity between 86-93% for the primary outcome.

With regard to the better prognosis associated in previous studies with overweight HF patients, no significant differences between groups were found for the primary endpoint at 5 years of follow-up, which could be explained by a higher age in the overweight group (50.6 vs 55.2 years; P=0.006). However, overweight patients showed some signs of better prognosis, since they had slightly better baseline LVEF (26 vs 28%; P=0.004) and Heart Failure Survival Score (8.4 vs 8.8; P=0.004).

Study limitations

This was a single-centre prospective study and therefore the results can reflect local practice. BMI was only assessed baseline. Whether patients cross-over from the BMI groups in the time of follow-up could not be assessed in our study.

The analysed population included a seven-year follow-up of patients evaluated for heart transplantation in one advanced heart failure centre. However, these previous studies only showed that VE/VCO_2 slope has prognostic value irrespective of BMI when compared to pVO_2 but did not study whether VE/VCO_2 slope prognostic power was different in overweight patients from normal BMI patients at long term follow-up. To the best of our knowledge, this is the first study addressing this issue and our cohort of 270 patients were enough to reveal a significant statistical reduction in the prognostic power of VE/VCO_2 slope at 3 and 5 years of follow-up.

Previous studies had shown that increasing BMI has an inversely related to VE/VCO_2 slope so we could expect that in obese patients (BMI ≥ 30 kg/m^2) the loss of predictive power with VE/VCO_2 slope could be even higher than in overweight patients. However, our cohort of patients with a BMI ≥ 30 kg/m^2 included only 61 (22.3%) patients and 20 (22.7%) of the outcomes, making these group too small for reaching conclusions without adding them to the overweight patients.

Another limitation of the study was not to use the value of pVO_2 adjusted to lean body mass in the population with a BMI ≥ 30 kg/m^2, since it can improve the prognosis power of pVO_2 in obese patients [21]. However, even with some improvement in the prognosis power of pVO_2 in the 22% of the population with a BMI ≥ 30 kg/m^2, it would not be able to significantly overcome the predictive power of VE/VCO_2 slope.

Conclusions

A smaller VE/VCO_2 slope, which is a sign of good prognosis in HF, can be found in overweight HF patients, but this reduction can be due to an abnormal pulmonary function and ventilation mechanics which would only worsen the prognosis of HF patients.

Our study showed that VE/VCO_2 slope is at least as good as pVO_2 for predicting adverse events in both normal and overweight HF patients. However, a significant lower predictive power was found for VE/VCO_2 slope in overweight patients in long-term HF outcomes when compared to normal weight HF patients.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Antonio Valentim Goncalves, Department of Cardiology, Hospital de Santa Marta, Rua de Santa Marta, nº 50, Lisbon 1169-024, Portugal. Tel: +351-961156697; E-mail: antonio.a.goncalves.14@gmail.com

References

[1] Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, Danziger-Isakov L, Kirklin JK, Kirk R, Kushwaha SS, Lund LH, Potena L, Ross HJ, Taylor DO, Verschuuren EA and Zuckermann A; International Society for Heart Lung Transplantation (ISHLT) Infectious Diseases, Pediatric and Heart Failure and Transplantation Councils. The 2016 international society for heart lung transplantation listing criteria for heart transplantation: a 10-year update. J Heart Lung Transplant 2016; 35: 1-23.

[2] Corrà U, Agostoni PG, Anker SD, Coats AJS, Crespo Leiro MG, de Boer RA, Harjola VP, Hill L, Lainscak M, Lund LH, Metra M, Ponikowski P, Riley J, Seferović PM and Piepoli MF. Role of cardiopulmonary exercise testing in clinical stratification in heart failure. A position paper from the Committee on Exercise Physiology and Training of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2018; 20: 3-15.

[3] Goncalves AV, Pereira-da-Silva T, Soares R, Feliciano J, Moreira RI, Rio P, Abreu A and Ferreira RC. Prognostic prediction of cardiopulmonary exercise test parameters in heart failure patients with atrial fibrillation. Arq Bras Cardiol 2020; 114: 209-218.

[4] Arena R, Guazzi M, Cahalin LP and Myers J. Revisiting cardiopulmonary exercise testing applications in heart failure: aligning evidence with clinical practice. Exerc Sport Sci Rev 2014; 42: 153-160.

[5] Malhotra R, Bakken K, D'Elia E and Lewis GD. Cardiopulmonary exercise testing in heart failure. JACC Heart Fail 2016; 4: 607-616.

[6] Nadruz W Jr, West E, Sengelov M, Santos M, Groarke JD, Forman DE, Claggett B, Skali H and Shah AM. Prognostic value of cardiopulmonary exercise testing in heart failure with reduced, midrange, and preserved ejection fraction. J Am Heart Assoc 2017; 6: e006000.

[7] Santoro C, Sorrentino R, Esposito R, Lembo M, Capone V, Rozza F, Romano M, Trimarco B and Galderisi M. Cardiopulmonary exercise testing and echocardiographic exam: an useful interaction. Cardiovasc Ultrasound 2019; 17: 29.

[8] Pereira-da-Silva T, M Soares R, Papoila AL, Pinto I, Feliciano J, Almeida-Morais L, Abreu A and Cruz Ferreira R. Optimizing risk stratification in heart failure and the selection of candidates for heart transplantation. Rev Port Cardiol 2018; 37: 129-137.

[9] Butler J, Khadim G, Paul KM, Davis SF, Kronenberg MW, Chomsky DB, Pierson RN 3rd and Wilson JR. Selection of patients for heart transplantation in the current era of heart failure therapy. J Am Coll Cardiol 2004; 43: 787-793.

[10] Poggio R, Arazi HC, Giorgi M and Miriuka SG. Prediction of severe cardiovascular events by VE/VCO2 slope versus peak VO2 in systolic heart failure: a meta-analysis of the published literature. Am Heart J 2010; 160: 1004-1014.

[11] Arena R, Myers J, Aslam SS, Varughese EB and Peberdy MA. Peak VO2 and VE/VCO2 slope in patients with heart failure: a prognostic comparison. Am Heart J 2004; 147: 354-360.

[12] Chase P, Arena R, Myers J, Abella J, Peberdy MA, Guazzi M and Bensimhon D. Relation of the prognostic value of ventilatory efficiency to body mass index in patients with heart failure. Am J Cardiol 2008; 101: 348-352.

[13] Horwich TB, Leifer ES, Brawner CA, Fitz-Gerald MB and Fonarow GC; HF-ACTION Investigators. The relationship between body mass index and cardiopulmonary exercise testing in chronic systolic heart failure. Am Heart J 2009; 158: S31-36.

[14] Nagarajan V, Kohan L, Holland E, Keeley EC and Mazimba S. Obesity paradox in heart failure: a heavy matter. ESC Heart Fail 2016; 3: 227-234.

[15] Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE and 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.

[16] Guazzi M, Arena R, Halle M, Piepoli MF, Myers J and Lavie CJ. 2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Circulation 2016; 133: e694-711.

[17] Heagerty PJ, Lumley T and Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. Biometrics 2000; 56: 337-344.

[18] Bewick V, Cheek L and Ball J. Statistics review 13: receiver operating characteristic curves. Crit Care 2004; 8: 508-512.

[19] Hanley JA and McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982; 143: 29-36.

[20] Hainer V and Aldhoon-Hainerova I. Obesity paradox does exist. Diabetes Care 2013; 36 Suppl 2: S276-281.

[21] Osman AF, Mehra MR, Lavie CJ, Nunez E and Milani RV. The incremental prognostic importance of body fat adjusted peak oxygen consumption in chronic heart failure. J Am Coll Cardiol 2000; 36: 2126-2131.