Peak VO_2 and VE/VCO_2 Slope in Betablockers Era in Patients with Heart Failure: a Brazilian Experience

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Summary

Background: Studies have demonstrated that peak oxygen consumption (peak VO_2) and the VE/VCO_2 slope are predictors of survival in patients with heart failure (HF). However, with the advent of betablockers in the treatment of HF, the prognostic values of peak VO_2 and VE/VCO_2 slope have not been fully established.

Objective: To evaluate the effect of betablocker use on the prognostic value of peak VO_2 and VE/VCO_2 slope in patients with HF.

Methods: We studied 391 patients with heart failure, aged 49 ± 14 years and presenting a left ventricular ejection fraction of 38 ± 10%. The total number of patients that used (Group I - GI) or did not use (Group II - GII) betablockers was 229 and 162, respectively. All patients were submitted to a cardiopulmonary stress test on a treadmill, using the Naughton protocol.

Results: A peak $VO_2 \leq 10$ ml.kg^{-1}.min^{-1} identified high-risk patients, whereas values > 16 ml.kg^{-1}.min^{-1} categorizes patients with a better mid-term prognosis. Peak VO_2 values between > 10 and ≤ 16 ml.kg^{-1}.min^{-1} indicated moderate risk for cardiac event in four years of follow up. The betablocker use significantly reduced the VE/VCO_2 slope in patients with HF. The prognostic value of the VE/VCO_2 slope ≤ 34 in the group using betablocker can reflect the impact of the drug on this cardiorespiratory variable.

Conclusion: A low peak VO_2 and an elevated VE/VCO_2 slope are strong and independent predictors of cardiac events in HF. Thus, both variables remain important survival predictors in patients with HF, especially at the age of betablockers. (Arq Bras Cardiol 2008;91(1):39-45)

Key words: Betablockers; heart failure, low; prognosis.

Introduction

The use of betablockers (BB) in the treatment of patients with heart failure (HF) started a new era in the management of this cardiomyopathy. Betablockers are capable of partially antagonizing the sympathetic and the inflammatory activity, with effects on the apoptosis and hypertrophy of cardiomyocytes, leading to an increase in the ejection fraction and attenuation of the ventricular remodeling progression[1-4]. Additionally, these drugs increase survival and reduce hospitalization in this group of patients[5], although, in parallel, they do not improve tolerance to exercise[6].

The cardiopulmonary stress (CPX) test is a well-established technique for the diagnosis of patients with HF. The peak oxygen consumption (peak VO_2) measured during the CPX is a predictor of mortality in patients with HF and an important criterion in the selection of heart transplant candidates[7]. However, other CPX variables have also demonstrated a prognostic value in HF, such as the ratio between ventilation (VE) and the carbon dioxide production (VCO_2) expressed as the VE/VCO_2 slope[8]. Nevertheless, investigations in our country about the effects of betablockers on the prognostic value of peak VO_2 and VE/VCO_2 slope are limited in this group of patients.

The aim of this study was to assess the effect of betablockers on the prognostic value of peak VO_2 and the VE/VCO_2 slope in patients with heart failure, treated at a cardiology outpatient clinic specialized in this cardiopathy.

Methods

Sample

A total of 391 consecutive patients with HF were studied at the Heart Failure Clinical Unit of *Instituto do Coração* of *Hospital das Clínicas* of the University of Sao Paulo School of Medicine, from January 1999 to May 2004. Of these, 162 patients did not use BB agents before the CPX test and during the follow-up due to low tolerance to the drug, as well as due to the fact that it is not a fully established conduct for Chagas'

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disease. All 229 patients undergoing treatment with BB had received a stable dose for more than 3 months before the CPX test. The patients' clinical characteristics are described in Table 1.

Exclusion criteria

Patients who did not have the drug therapy optimized for more than three months or those with chronic atrial fibrillation, interrupted test due to hemodynamic and electrocardiographic complications, respiratory quotient RQ ≤ 1.0[9], neuromuscular disease, peripheral vascular disease, pulmonary diseases, myocardial infarction ≤ 6 months before or orthopedic limitations, were excluded.

Table 1 - Clinical characteristics of patients with heart failure

	With betablocker	Without betablocker	p
n	229	162	
Age	49 ± 14	46 ± 18	ns
Sex (M/F)	174/55	112/50	---
Weight (kg)	71 ± 16	67 ± 19	0,02
RVEF (%)	35,4 ± 11,2	36,4 ± 11	ns
LVEF (%)	30 ± 12	34 ± 13	0,02
Hb (g/dl)	14.1 ± 1.8	14.2 ± 2.7	ns
Catecholamine (pg/ml)	446 ± 300	546± 265	< 0.001
Etiology			
Idiopathic	102	67	
Hypertensive	47	32	
Ischemic	73	53	
Chagas' disease	7	10	
Medication (%)			
Diuretics	76	82	
Digitalis	61	68	
ACEI	83	78	
Aldosterone	46	52	
Hydralazine	1.7	0.6	
Nitrate	4.8	5.5	
Amrinone	7	13	
Amlodipine	1.3	1.2	
Anticoagulant	5.8	5.5	
ARBII	4.4	5.5	
Others	22	20	
Carvedilol (dose)	83.4 (25±18)	---	
Metoprolol	7,86 (108±60)	---	
Bisoprolol	3.94 (1.5±0.7)	---	
Others	4.8 (65±51)	---	

RVEF - right ventricle ejection fraction; LVEF - left ventricle ejection fraction; Hb - hemoglobin; ACEI - angiotensin-converting enzyme inhibitor; ARBII - angiotensin II receptor blocker.

Cardiopulmonary stress test

Initially, all patients were submitted to a 12-derivation electrocardiogram at rest and stress test with continuous monitoring of the electrocardiogram (Max 1; Marquette Electronics; Milwaukee, WI, USA), of blood pressure through auscultation and gas exchanges during the stress test. The stress test was performed on a programmable treadmill (Series 2000; Marquette Electronics; Milwaukee, WI, USA) according to the modified Naughton protocol[10]. After 2 minutes in the standing position at rest, all patients were encouraged to perform the exercise until the symptoms (fatigue or dyspnea) made them unable to continue the test. The ventilatory data as well as the oxygen consumption and carbon dioxide production data were obtained at each respiratory cycle, using a computerized system (Vmax 229 model, SensorMedics, Yorba Linda, CA, USA) and the analysis of the collected data was made through the arithmetic mean of intervals obtained every sixty seconds. Peak oxygen consumption (peak VO_2) was considered as the highest VO_2 attained during the exercise[11], which was used as the index of maximum physical capacity for each individual. The ventilation slope (VE, ml/min) *versus* carbon dioxide production (VCO_2, ml/min) was calculated based on the inclination of the straight line between the VE and VCO_2 at rest, at the end of the exercise.

Study design

All assessments performed were part of the clinical procedures and all patients gave their informed consent prior to the scientific publication of the data. The present study is a retrospective and descriptive study, as the phenomena were analyzed and correlated without being manipulated[12]. The patients were divided in two groups according to treatment – with or without betablockers. Regarding the prognostic value of peak VO_2, patients were classified as class A (>20 $ml.kg^{-1}.min^{-1}$), B (>16 $ml.kg^{-1}.min^{-1}$ to ≤20 $ml.kg^{-1}.min^{-1}$), C (>10 $ml.kg^{-1}.min^{-1}$ to ≤16 ml.kg-1.min^{-1}) or D (≤10 $ml.kg^{-1}.min^{-1}$)[13,14]. Regarding the prognostic value of VE/VCO_2 slope, the patients were classified as ≤ 34 or > 34[8].

Follow-up and analysis of survival

The follow-up of patients was carried out by phone interviews with the patient and/or family members. The study cutoff was death due to cardiovascular causes (sudden death, heart failure progression, myocardial acute infarction or pulmonary embolism) or the need for transplant (status 1)[7]. The patients that died due to non-cardiac causes in the follow-up period were excluded from the study.

Statistical analysis

The continuous data were expressed as means and standard deviations. The Mann-Whitney test was used for the variables that did not have a normal distribution. Univariate as well as multivariate Cox regression analysis was used to evaluate the prognostic value of peak VO_2 and the VE/VCO_2 slope. The primitive variable value was generated with "receiver-operating characteristic" (ROC) curves at regular intervals, and the best threshold was automatically identified, minimizing the value of the expression $[(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2]$. The area

under the curve was obtained in accordance to Hanley and McNeil[15]. The Kaplan Meier test was used to analyze survival regarding peak VO_2 and the VE/VCO_2 slope. The statistical analysis of the differences between the survival curves were carried out by the long-rank test. Statistical differences with a p value < 0.05 were considered significant. The statistical analyses were carried out with the SPSS™ software package, version 11.5.

Results

The analysis of the cardiorespiratory response to heart rate (HR) at rest and the VE/VCO_2 slope were significantly lower in the group of patients with BB. The maximum HR, maximum systolic (SAP) and diastolic arterial pressure (DAP), as well as SAP and DAP at rest, peak VO_2 and time of exercise did not show any statistical difference between the groups (Table 2).

The mean follow-up period was 853 ± 442 days. In the group of patients with betablocker, 6 were class D, 88 were class C and 52 were class A. Of the patients without betablocker, 8 were class D, 63 were class C, 57 were class B and 34 were class A. In the group of patients with betablocker, 177 of them presented the VE/VCO_2 slope ≤ 34 and 52 of them > 34; in the group without betablocker, 100 and 62 patients presented the VE/VCO_2 slope ≤ 34 and > 34, respectively.

Prognostic analysis

The analysis of the survival curve of the peak VO_2 showed that the group with betablocker presented a significant difference regarding class D when compared with the other classes ($p<0.05$). There was also a significant difference regarding class C when compared to classes B and A ($p=0.00$). However, there was no difference between classes A and B. During the follow-up period, 2, 2.4, 16 and 33.3% of the patients died in classes A, B, C and D, respectively (Figure 1).

Table 2 - Cardiorespiratory variables of patients with heart failure

	With betablocker	Without betablocker	p
Heart rate (bpm)			
rest	78.5 ± 15	82 ± 17	0.03
maximum	125 ± 24	126 ± 27	ns
Systolic arterial pressure (mmHg)			
rest	118 ± 22	119 ± 22	ns
maximum	137 ± 28	134 ± 28	ns
Diastolic arterial pressure (mmHg)			
rest	67 ± 14	68 ± 14	ns
maximum	72 ± 17	72 ± 15	ns
Peak VO_2 ($ml.kg^{-1}.min^{-1}$)	16.3 ± 4	16.2 ± 4	ns
VE/VCO_2 slope	30.6 ± 7	33.1 ± 8	0.001
Duration of exercise (min)	11 ± 5	11 ± 5	ns

Peak VO_2 - peak oxygen consumption.

In the group without betablocker, the analysis of the survival curve of the peak VO_2 showed a statistical difference only in class D, when compared to the other classes. A total of 11.8, 12, 12.7 and 50% of the patients died in classes A, B, C and D, respectively (Figure 2).

The analysis of the survival curve of patients with betablocker showed that the VE/VCO_2 slope presented a significant difference ($p< 0.001$) between the patients with values ≤ 34 or > 34 and 7 and 13 of the patients died, respectively, during the study period (Figure 3). In the group without betablocker, no statistical difference was observed at the analysis of the survival curve of the VE/VCO_2 slope ≤ 34 with 10% and > 34 with 19% of deaths (Figure 4).

The result of the ROC curve analysis is shown in Table 3 and in Figures 1, 2, 3 and 4. The prognostic classification for the peak VO_2 and VE/VCO_2 slope was statistically significant for both in the group with betablocker; however, only the VE/VCO_2 slope curve presented statistical significance in the group without betablocker. The area under the ROC curve was 0.80 for the peak VO_2 as well as for the VE/VCO_2 slope of the patients under betablocker use, whereas in the group without betablocker, the area under the ROC curve was 0.60 and 0.65, respectively.

Discussion

Our results showed that the cardiopulmonary stress test maintained the prognostic value in individuals with HF at the age of betablockers. Peak VO_2 and the VE/VCO_2 slope were predictors of survival in patients with HF and betablocker use, showing high sensitivity and specificity in this group of patients treated with betablockers.

The reference value of peak VO_2 used in the present study was the one based on the classification of Weber-Janicki[14]. Our patients with peak $VO_2 \leq 16$ $ml.kg^{-1}.min^{-1}$ had a worse prognosis when compared to patients with peak $VO_2 > 16$ $ml.kg^{-1}.min^{-1}$, regardless of the etiology and cardiac function.

Several authors have demonstrated that peak VO_2 is an important prognostic variable in patients with HF with betablocker use, which supports our findings, regardless of the cutoff used in the study[14,16-19]. These studies have demonstrated that the peak VO_2 assessed on a treadmill remains a useful tool to determine prognosis in patients with HF with betablocker use. The peak VO_2 was considered a univariate predictor and independent from event-free survival and the betablocker therapy did not influence the status of absolute prediction of peak VO2 in relation to survival[14-21].

Nevertheless, studies where the evaluation of the physical capacity was carried out in a cycle ergometer showed that peak VO_2 is a variable with low prognostic value[8,22]. This may be due to the lower muscle mass involved in this type or ergometer, providing limited predictive information[23,24].

In healthy people, peak VO_2 obtained at the cycle ergometer was 10 to 15% lower than that obtained at the treadmill stress test[21,24].

Other potential limitations of peak VO_2 at the assessment of prognosis is its dependence on the intensity of the patient's

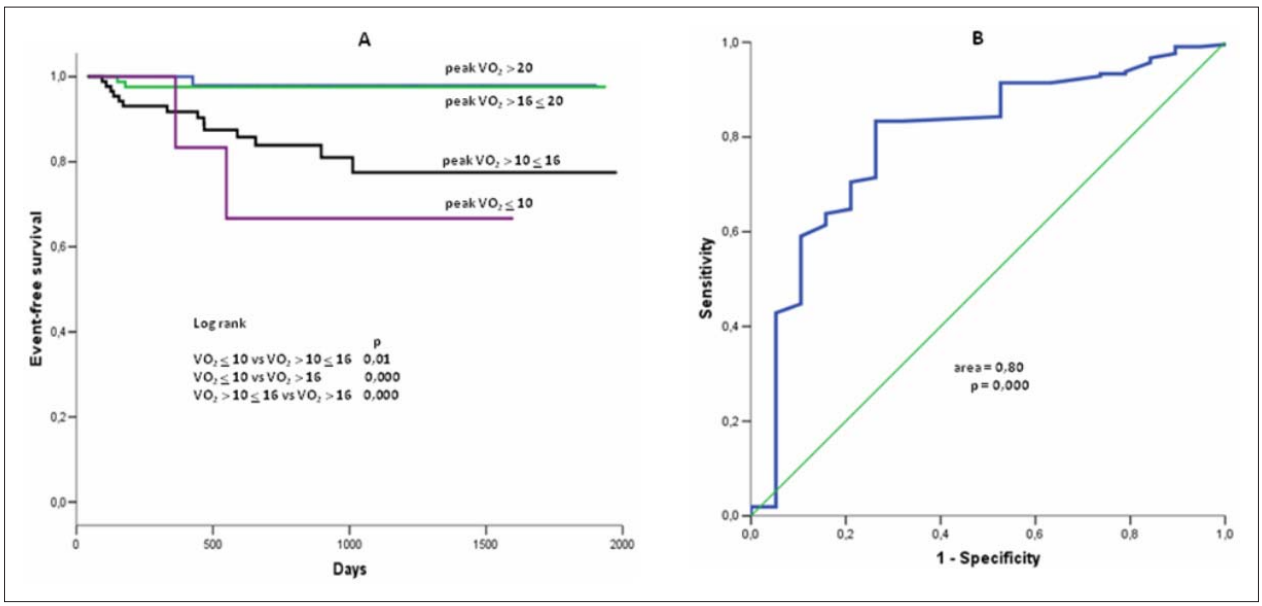

Figure 1 - Patients with HF undergoing treatment with betablocker. A - Kaplan-Meier survival curve of the VO_2 peak classification (ml.kg^{-1}.min^{-1}); B - Analysis of the ROC curve for the peak VO_2.

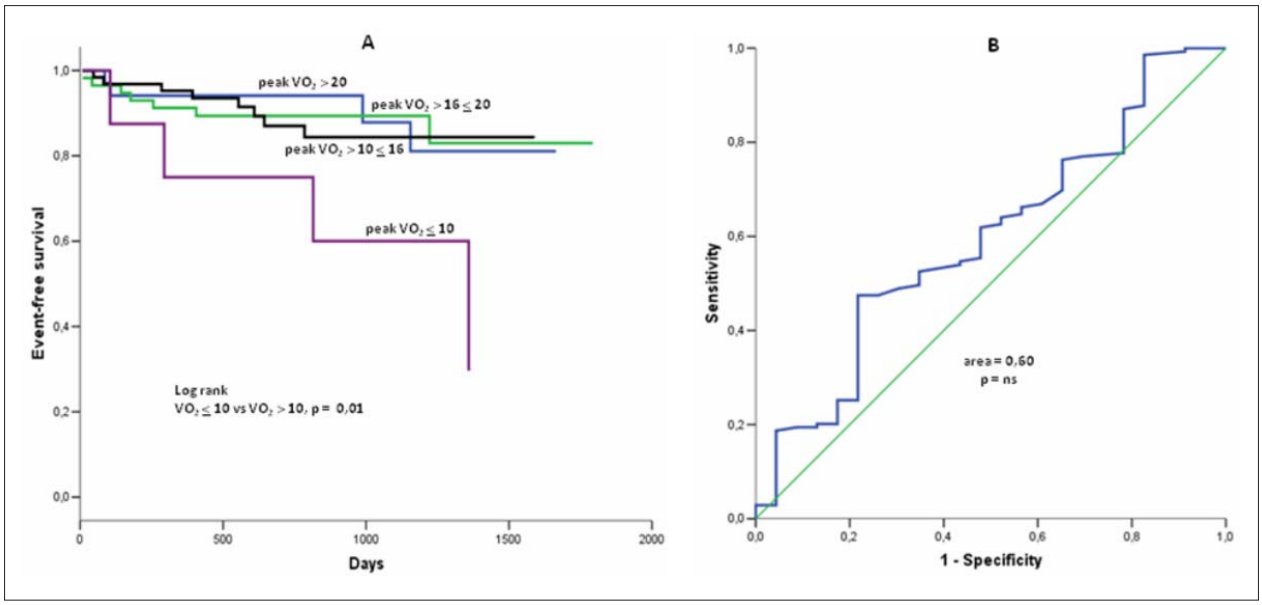

Figure 2 - Patients with HF without use of betablocker. A - Kaplan-Meier survival curve of the VO_2 peak classification (ml.kg^{-1}.min^{-1}); B - Analysis of the ROC curve for the peak VO_2.

stress, which is directly related to the examiner and the emotional state[25], as well as the metabolic capacity of the skeletal muscle, which can define, in parallel, values that are higher than peak VO_2[21-24], being associated with the sedentary or physically active lifestyle of the patients with HF[13].

The increased VE/VCO_2 slope is related to the decrease in the pulmonary perfusion capacity and cardiac output, contributing with the prognostic value in HF[26]. Additionally, it is usually stress-independent and represents the reflex conditions of the patients with HF[22,27].

Studies have adopted threshold values to define patterns of better and worse prognosis of patients with HF for the VE/VCO_2 slope[16,22,28]; in the present study, we used ≤ 34 and > 34, respectively. Our results were similar to those observed in the previous studies regarding prognosis in HF.

The prognostic value of the VE/VCO_2 slope in patients with betablockers when compared to those without BB might be due to the clinical condition, generally not associated with neuroautonomic instability, but to the signs of imbalance in the ventilatory control system[17,22].

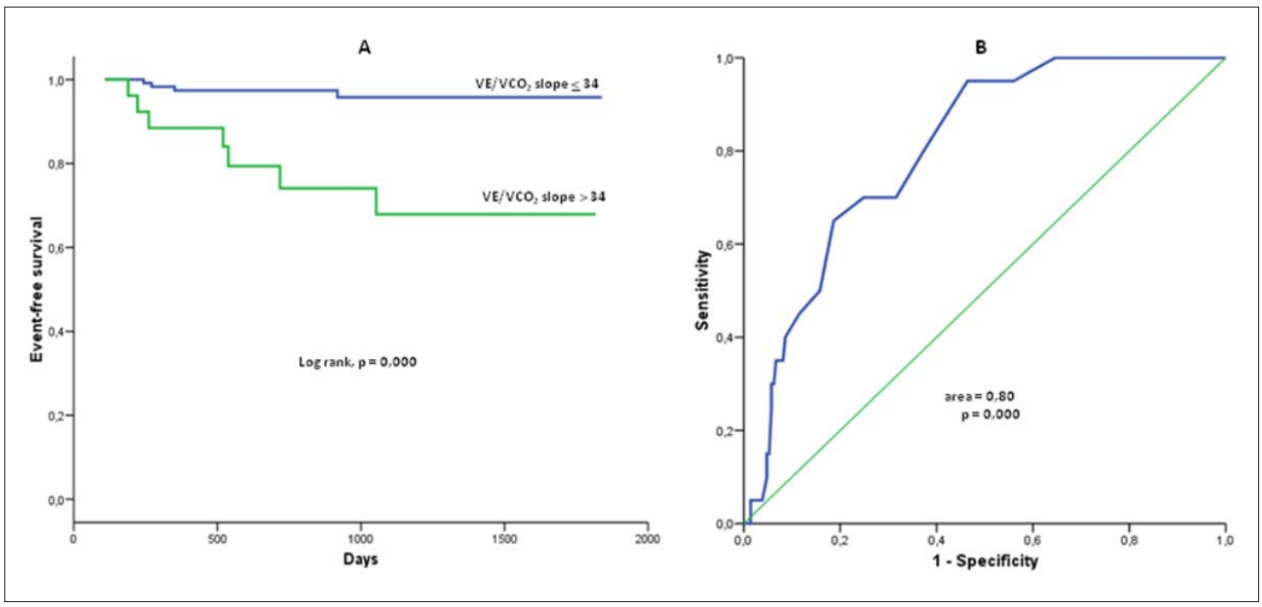

Figure 3 - Patients with HF undergoing treatment with betablocker. A - Kaplan-Meier survival curve for the VE/VCO_2 slope ≤ and > 34; B - Analysis of the ROC curve for the VE/VCO_2.

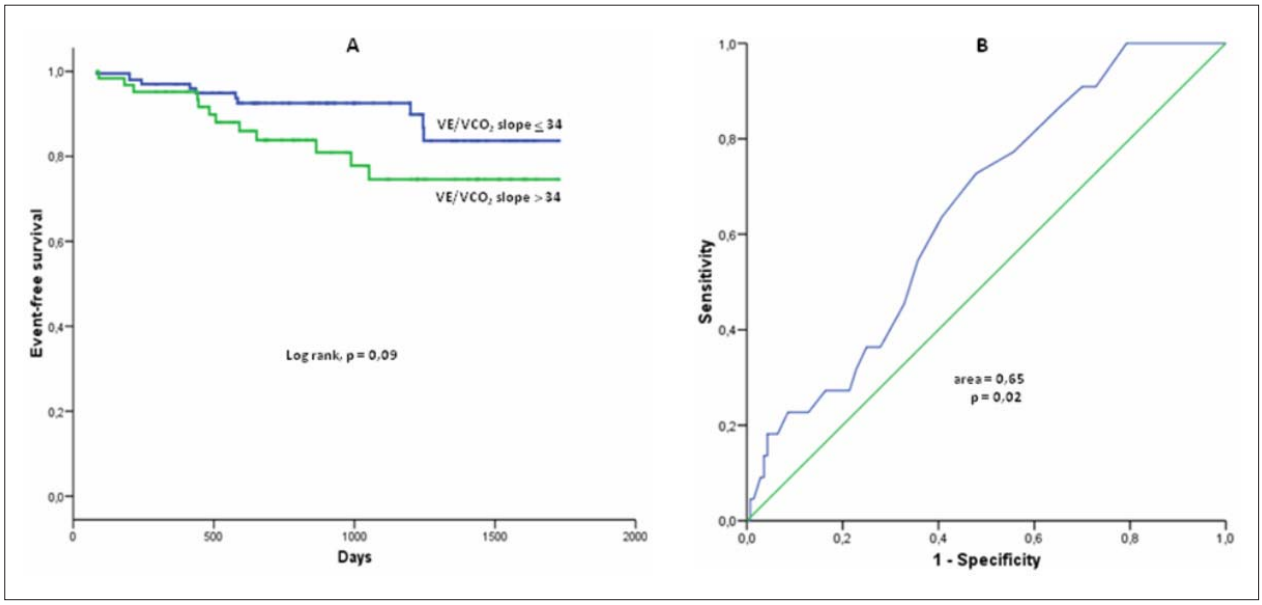

Figure 4 - Patients with HF without use of betablocker. A - Kaplan-Meier survival curve for the VE/VCO_2 slope ≤ and > 34; B - Analysis of the ROC curve for the VE/VCO_2 peak slope.

Table 3 - ROC curve analysis

Group	Area	p	95%CI
With betablocker			
VO_2 peak	0.80	< 0.00	0.69 – 0.90
VE/VCO_2 slope	0.80	< 0.00	0.72 – 0.88
Without betablocker			
Peak VO_2	0.60	Ns	0.47 – 0.72
VE/VCO_2 slope	0.65	0.02	0.54 – 0.76

Some hypotheses have been described to explain such response during exercise, such as the excess activation of muscular ergoreceptors as well as central and peripheral chemoreceptors[29,30].

The central chemoreceptors are associated with the ventilatory control in patients with HF, who have intact physical capacity, whereas the peripheral chemoreceptors and ergoreceptors are more important in those with decreased tolerance to exercise[15,20,27]. The potential benefit of the betablocker in the excessive ventilation response during exercise in patients with HF can be due to the re-establishment

of the hemodynamic profile and sympathetic drive[20]. In the present study, we observed direct evidence of the effect of the betablocker on the ventilatory response during the exercise. The association between the VE/VCO_2 slope and prognosis was indeed significant in patients treated with betablockers.

Study limitations

The management of patients with heart failure at our institution favors the use of Carvedilol, in relation to other betablockers. However, we have not evaluated the reasons for the specific prescription of the betablocker type. Our results can be applied to patients with HF treated with different betablocker agents, despite their pharmacological dissimilarity. We did not include in the present study the clinical and hemodynamic variables as well as the neurohormonal measurements that could help with the risk stratification in patients with intermediate functional capacity. Additionally, this study was a retrospective one. Although our findings are in accordance with previous studies, prospective studies are necessary.

Clinical implications

The use of betablockers in HF has shown a significant improvement in survival and quality of life in this group of patients, although it has little effect on peak VO_2. The peak VO_2 cutoff $\leq$ 10 $ml.kg^{-1}.min^{-1}$ identifies patients at high risk, whereas values > 16 $ml.kg^{-1}.min^{-1}$ categorizes patients with a better midterm prognosis. The peak VO_2 range between > 10 and $\leq$ 16 $ml.kg^{-1}.min^{-1}$ indicates moderate risk for cardiac event within four years of follow-up.

Previous studies demonstrated that the betablocker significantly reduces the VE/VCO_2 slope in patients with HF. The prognostic value of the VE/VCO_2 slope $\leq$ 34 in the group with betablocker may reflect the impact of this drug on this cardiorespiratory variable.

Conclusion

The cardiopulmonary stress test seems to maintain the prognostic value in patients with heart failure at the age of betablockers. A low VO_2 peak and an elevated VE/VCO_2 slope are strong and independent predictors of cardiac events in HF. The peak VO_2 and the VE/VCO_2 slope are easily measurable, with high sensitivity and specificity obtained through the cardiorespiratory test and the prognostic value has clinical relevance in a subgroup of patients presenting symptoms that are not compatible with the functional capacity.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

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Study Association

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References

1. Issa VS, Guimarães GV, Rezende MVC, Cruz F, Ferreira SA, Bacal F, et al. Efeitos do bisoprolol sobre a função cardíaca e o exercício em pacientes com insuficiência cardíaca. Arq Bras Cardiol. 2007; 88: 340-5.
2. Silva CP, Bacal F, Pires P, Mangini S, Issa V, Moreira AS, et al. Perfil do tratamento da insuficiência cardíaca na era dos betabloqueadores. Arq Bras Cardiol. 2007; 88: 475-9.
3. Tatli E, Kurum T. A controlled study of the effects of carvedilol on clinical events, left ventricular function and proinflammatory cytokines levels in patients with dilated cardiomyopathy. Can J Cardiol. 2005; 21: 344-8.
4. Nagatomo Y, Yoshikawa T, Kohno T, Yoshizawa A, Anzai T, Meguro T, et al. Effects of beta-blocker therapy on high sensitivity c-reactive protein, oxidative stress, and cardiac function in patients with congestive heart failure. J Card Fail. 2007; 13: 365-71.
5. Lechat P, Packer M, Chalon S, Cucherat M, Arab T, Boissel JP. Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. Circulation. 1998; 98: 1184-91.
6. Witte KK, Thackray S, Nikitin NP, Cleland JG, Clark AL. The effects of long-term beta-blockade on the ventilatory responses to exercise in chronic heart failure. Eur J Heart Fail. 2005; 7: 612-7.
7. Mehra MR, Kobashigawa J, Starling R, Russell S, Uber PA, Parameshwar J, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates-2006. J Heart Lung Transplant. 2006; 25: 1024-42.
8. Arena R, Myers J, Aslam SS, Varughese EB, Peberdy MA. Peak VO2 and VE/VCO2 slope in patients with heart failure: a prognostic comparison. Am Heart J. 2004; 147: 354-60.
9. Katz SD, Berkowitz R, LeJemtel TH. Anaerobic threshold detection in patients with congestive heart failure. Am J Cardiol. 1992; 15: 1565-9.
10. Patterson J, Naughton J, Pietras RJ. Treadmill exercise in assessment of functional capacity of patients with severe left ventricular disease. Am J Cardiol. 1972; 30: 757-62.
11. Wasserman K, Hausen JE, Sue DY, Whipp BJ, Casaburi R. Principes of exercise testing and interpretation. 2nd ed. Phyladelphia: Lea & Febiger, 1994.
12. Cervo AL, Bervian PA. Metodologia científica. 5ª ed. São Paulo: Pearson Prentice Hall, 2002
13. Milani RV, Lavie CJ, Mehra MR. Cardiopulmonary exercise testing: how do we differentiate the cause of dyspnea? Circulation. 2004; 110; e27-e31.
14. Weber KT, Kinasewitz GT, Janicki JS, Fishman AP. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. Circulation. 1982; 65: 1213-23.
15. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology. 1982; 143: 29-36.
16. Francis DP, Shamim W, Davies LC, Piepoli MF, Ponikowski P, Anker SD, et al. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuos and independent prognostic value from VE/VCO_2 slope and peak VO_2. Eur Heart J. 2000; 21: 154-61.

17. Guazzi M, De Vita S, Cardano P, Barlera S, Guazzi MD. 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.

18. Daida H, Allison TG, Johnson BD, Squires RW, Gau GT. Comparison of peak exercise oxygen uptake in men versus women in chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol. 1997; 80; 85-8.

19. Shakar SF, Lowes BD, Lindenfeld J, Zolty R, Simon M, Robertson AD, et al. Peak oxygen consumption and outcome in heart failure patients chronically treat with β-blockers. J Cardiac Fail. 2004; 10: 15-20.

20. O'Neill JO, Young JB, Pothier CE, Lauer MS. Peak oxygen consumption as a predictor of death in patients with heart failure receiving beta-blockers. Circulation. 2005; 111: 2313-8.

21. Lund LH, Aaronson KD, Mancini DM. Validation of peak exercise oxygen consumption and the Heart Failure Survival Score for serial risk stratification in advanced heart failure. Am J Cardiol. 2005; 95 (6): 734-41.

22. Corra U, Mezzani A, Bosimini E, Scapellato F, Temporelli PL, Eleuteri E, et al. Limited predictive value of cardiopulmonary exercise indices in patients with moderate chronic heart failure treated with carvedilol. Am Heart J. 2004; 147 (3): 553-60.

23. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines).Circulation. 2002;106: 1883-92.

24. Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, et al. Exercise standards: a statment for healthcare professionals from the American Heart Association. Circulation. 1995; 91: 580-615.

25. Guimaraes GV, Bellotti G, Bacal F, Mocelin A, Bocchi EA. Can the cardiopulmonary 6-minute walk test reproduce the usual activities of patients with heart failure? Arq Bras Cardiol. 2002; 78: 553-60.

26. Arena RA, Guazzi M, Myers J, Abella J. The prognostic value of ventilatory efficiency with beta-blocker therapy in heart failure. Med Sci Sports Exerc. 2007; 39: 213-9.

27. Arena R, Humphrey R. Comparison of ventilatory expired gas parameters used to predict hospitalization in patients with heart failure. Am Heart J. 2002; 143: 427-32.

28. Kleber FX, Vietzke G, Wernecke KD, Bauer U, Opitz C, Wensel R, et al. Impairment of ventilatory efficiency in heart failure: prognostic impact. Circulation. 2000; 101: 2803-9.

29. Chua TP, Harrington D, Ponikowski P, Webb-Peploe K, Poole-Wilson PA, Coats AJ. Effects of dihydrocodeine on chemosensitivity and exercise tolerance in patients with chronic heart failure. J Am Coll Cardiol. 1997; 29: 147-52.

30. Ponikowski PP, Chua TP, Francis DP, Capucci A, Coats AJ, Piepoli MF. Muscle ergoreceptor overactivity reflects deterioration in clinical status and cardiorespiratory reflex control in chronic heart failure. Circulation. 2001; 104: 2324-30.