

# Predictive Value of Ventilatory and Metabolic Variables for Risk of Death in Patients with Cardiac Failure

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## OBJECTIVE

To analyze the predictive value of respiratory, metabolic, and hemodynamic variables obtained during the cardiopulmonary stress test for the risk of death in patients with heart failure.

## METHODS

Eighty-seven NYHA Functional Class II and III patients were analyzed, ages  $51 \pm 0.5$  years, 26 of them with Chagas' disease, 30 with coronary ischemia, and 31 with idiopathic etiology. The cardiopulmonary stress test consisted of a ramp-protocol with 5 to 15 W/min workload increments performed on a bicycle-ergometer until exhaustion.

## RESULTS

In this study, the multiple Cox regression analysis of age, height, weight, body surface, and gender showed that these parameters were not statistically significant control factors. Oxygen uptake, ventilatory equivalent of oxygen, ventilatory equivalent of carbon dioxide production, oxygen pulse, and end-tidal partial pressure of carbon dioxide at the anaerobic threshold, respiratory compensation point, and peak exercise proved to be important death predictors in heart failure patients. The relationship between the increase in carbon dioxide output as a function of the increase in minute ventilation, and the association between the oxygen uptake increase and the elevation of the workload from the beginning of exercise to the anaerobic threshold were statistically significant predictors of death in heart failure patients ( $p < 0.05$ ).

## CONCLUSION

The cardiopulmonary stress test makes it possible to evaluate ventilatory, metabolic, and hemodynamic variables that may be utilized as important markers of life prognosis in these patients.

## KEY WORDS

Cardiopulmonary stress test, prognosis, heart failure.

Heart failure is a syndrome characterized by exertional dyspnea and intolerance to exercise. The cardiopulmonary stress test is a method frequently used to evaluate the degree of exercise intolerance and functional capacity of heart failure patients. Based on this information it has been possible to identify the seriousness and even prognosis of patients with this syndrome that is responsible for innumerable deaths, including in Brazil<sup>1-2</sup>.

Among the variables obtained with the cardiopulmonary exercise test, oxygen uptake, measured at the peak of exercise (peak  $\text{VO}_2$ ) is the most employed variable since it allows the determination of the functional capacity of patients with several degrees of heart failure. This is vital in important decisions such as heart transplant indications<sup>3-5</sup>, or evaluations of the prognostic value of mortality<sup>3, 6-17</sup>, stratification of the degree of heart failure severity<sup>3, 18-21</sup>, differential diagnosis between dyspnea of cardiac origin or dyspnea of pulmonary origin,<sup>21-24</sup>, or an appraisal of an intervention with a cardiac pacemaker<sup>22, 25</sup>. It is also a useful means for assessment of drug therapy results relative to physical capacity<sup>21, 26-28</sup>, or even the prescription of physical exercise<sup>29</sup>. The maximum oxygen uptake ( $\text{VO}_2$  max.) estimated by linear regression equations is only precise in its application for submaximal exercise<sup>30</sup>.

Nevertheless, the evaluation of the  $\text{VO}_2$  peak in patients with cardiac failure may have limitations. Early interruption of the test on the part of the patient because of lack of motivation or fear of continuing the exercise, or an early interruption by the examiner may underestimate the peak  $\text{VO}_2$  value and hinder an adequate diagnostic evaluation<sup>11, 31</sup>. Moreover, a study by Chomsky et al<sup>32</sup> showed that cardiac output seems to be a better predictor of mortality in patients with heart failure than the peak  $\text{VO}_2$ . These authors observed that patients with a low cardiac output during exertion had a shorter survival, regardless of the peak  $\text{VO}_2$  value, compared to those patients with a normal cardiac output. More recently, Corrà et al<sup>6</sup>, demonstrated that patients with intermediate physical capacity, i.e., peak  $\text{VO}_2$  between 10 and 18  $\text{ml.kg}^{-1}.\text{min}^{-1}$  but with a ratio of increased carbon dioxide as a function of an increased minute ventilation ( $\text{VE}/\text{VCO}_2$  slope) greater than or equal to 35, showed a similar mortality rate as those patients with a peak  $\text{VO}_2$  smaller than or equal to 10  $\text{ml.kg}^{-1}.\text{min}^{-1}$ , but a  $\text{VE}/\text{VCO}_2$  slope of less than 35. Therefore, these results suggest the need for further information obtained during cardiopulmonary stress tests that may identify functional and metabolic limitations in these patients.

For this reason, some authors have sought to evaluate the prognostic value of other metabolic and respiratory variables, such as the ventilatory equivalent for oxygen ( $\text{VE}/\text{VO}_2$ )<sup>10, 33</sup>, the ventilatory equivalent for carbon dioxide ( $\text{VE}/\text{VCO}_2$ )<sup>10, 33, 34</sup>, oxygen pulse ( $\text{VO}_2/\text{HR}$ )<sup>7, 10</sup>, heart rate ( $\text{HR}$ )<sup>34-37</sup>,  $\text{VE}/\text{VCO}_2$  slope<sup>6, 11, 38-39</sup>, and the relationship between the increase in oxygen uptake and the increase

of work load ( $\Delta\text{VO}_2/\Delta\text{W}$  slope)<sup>6, 8-11</sup>.

Despite the many studies already conducted in this area, especially relating the prognostic value of  $\text{VO}_2$  and the  $\text{VE}/\text{VCO}_2$  slope, most of these authors assessed the prognostic value of the metabolic and respiratory variables at the peak of exercise<sup>3, 38</sup>.

However, since many times the patient with cardiac failure has difficulties in performing at maximal exercise, the analysis of the prognostic value of mortality as to the risk of death during the submaximal phase of exercise in the cardiopulmonary stress test is extremely appealing. In fact, many patients with heart failure cannot perform a maximal test, and must interrupt their exercise because of muscular-skeletal limitations<sup>40, 42</sup> or because they experience potentially lethal cardiac arrhythmias<sup>43-45</sup>. Additionally, the comparison of metabolic variables at distinct time points, such as at the anaerobic threshold and the point of respiratory compensation, assure us that the metabolic stress during exercise is proving to be the same in all of the patients. When the different metabolic variables are compared by absolute loads, the percentage of exertion put forth is not necessarily the same and therefore the metabolic stress and the hemodynamic impact will be different for each patient. Actually, in a study carried out by Gitt et al<sup>11</sup> a greater prognostic value was noted for risk of death in patients with heart failure with the association of  $\text{VO}_2$  at the anaerobic threshold and the  $\text{VE}/\text{VCO}_2$  slope. Nevertheless, in spite of this important finding, the study of the prognostic value for the risk of death of the metabolic variables at the transition from predominantly aerobic metabolism to predominantly anaerobic metabolism exercise timepoint and the establishment of metabolic acidosis (respiratory compensation point)<sup>46</sup> in patients with heart failure has not been amply divulged.

Another interesting aspect to be considered is that the prognostic value for risk of death of the metabolic variables analyzed at ventilatory thresholds has not been adequately studied in populations that include patients with cardiac failure of Chagasic etiology. This peculiar and unfortunate characteristic of our population has been considered a significant public health problem not only in Brazil, but in other countries of South America as well<sup>47</sup>.

Thus, the objective of this study was to test the hypothesis that the level of respiratory, metabolic, and hemodynamic responses during progressive physical exercise, at the anaerobic threshold, the point of respiratory compensation, and peak exercise can predict mortality in patients with heart failure.

## METHODS

A sample of 87 subjects was selected from 400 patients who were assessed by the cardiopulmonary stress test on a bicycle ergometer at the Heart

Institute of the *Faculdade de Medicina da Universidade de São Paulo* between 1990 and 1997. These were individuals with heart failure according to Weber's functional classification<sup>18</sup> and the group consisted of 74 men and 13 women, average age  $51 \pm 0.5$  years and ejection fraction of  $<50\%$ . Among the patients, 62% received digitalis drugs, 75% received furosemide, and 70% received angiotensin converting enzyme inhibitors (captopril or enalapril), and all were submitted to an echodopplercardiographic study.

Patients with physical exertion limitations because of muscular-skeletal disease, peripheral arteriopathy, cachexia, chronic obstructive pulmonary disease, or any reason other than dyspnea or fatigue of cardiac origin were excluded from the study. Also excluded were those patients with acute myocardial infarct with less than 2 months of disease progression, those with atrial fibrillation or flutter, congenital cardiopathy, valvulopathy as baseline illness such as mitral stenosis, aortic stenosis, mitral insufficiency, and aortic insufficiency.

All patients were submitted to the ramp-protocol cardiopulmonary stress test, characterized by a continuous load increment on a bicycle-ergometer with electromagnetic brakes (Medifit 400 I, Medical Fitness Equipment Maarn, Holland). The respiratory flow and the fractions of expired oxygen and carbon dioxide were collected at each respiratory cycle using the sixty-second average in the posterior analysis. This evaluation was made on a computed system (CAD/NET 2001 model, Medical Graphics Corporation, United States).

Corrections of gas volumes of the variables analyzed under BTPS conditions (body temperature, ambient pressure, saturated with water vapor), were made at a 37° C body temperature and pressure that corresponds to the barometric pressure. These corrections are made when we need to know the volume of air ventilated by the lungs. For this reason, ventilation, the product of the breathing rate by tidal volume, is analyzed under BTPS conditions. On the other hand, the corrections of gas volumes analyzed under STPD conditions (standard temperature and pressure, dry), were made at a standardized temperature of 0° C, barometric pressure of 760 mmHg at sea level, with the volume occupied by water vapor molecules corrected, i.e., dry. These corrections are made when we need to know the quantity of oxygen uptake and carbon dioxide output<sup>48</sup>.

After the patients were adapted to the surroundings and equipment, resting assessments were made for 2 minutes, followed by 3 minutes of warm-up with no load at a speed of 60 rotations per minute (rpm). From the fifth minute on, the load was progressively and constantly increased, and the increment was individualized for each patient. The choice of load increment was based on the predicted maximal load for normal adults according to established formulas for each gender that take into account age and anthropometric characteristics<sup>49-50</sup>.

In patients with heart failure, 80% of the predicted maximal potency was calculated for normal individuals; to determine the load variation, this predicted value was divided by 10. The load increment in the ramp-protocol utilized in patients with heart failure varied between 5 and 15 W/min. All patients were encouraged to exert progressive effort until symptoms such as dyspnea, fatigue, or that represented a risk made them incapable of continuing. Recovery period lasted 4 minutes; during the first minute, the load maintained was equivalent to 50% and during the second minute, equivalent to 25% of the maximal load attained in the test. During the third minute, the load was removed, but the 60 rpm speed was maintained, and during the fourth minute, the individual remained seated and still on the bicycle-ergometer. The anaerobic threshold was determined by the V-slope method that consists of the inflexion point at which the carbon dioxide gas production raises faster than the oxygen uptake<sup>51</sup>, or at the point where the lowest values and posterior elevation of the ventilatory equivalent curves for oxygen and partial pressure of oxygen are observed<sup>52</sup>. The respiratory compensation point was determined through the lowest point of the ventilatory equivalent for carbon dioxide before its continuous increase, and by the greatest value of the partial pressure of carbon dioxide preceding its abrupt fall<sup>46</sup>. Both the anaerobic threshold and the respiratory compensation point were determined by two experienced observers. When there was divergence between the two, a third observer was consulted in order to reach a consensus.

The arterial blood pressure (BP) was checked by auscultation using a mercury column while at rest, at every two minutes of exercise, and at the first, second, and fourth minutes of the recovery period. The heart rate (HR) was continually monitored by electrocardiographic signal (Tecnologia Eletrônica do Brasil, SM, or Apex 2000) and recorded at the end of each minute during the entire cardiopulmonary stress test. Patients refrained from ingesting caffeinated beverages and smoking on the day of the test.

*Statistical Analysis* - For comparison of the sample characteristics, age, stature, weight, body mass index, body surface, and ejection fraction the 1 path variance analysis was used. In case of significance, the Scheffé *post-hoc* test was used. A  $p < 0.05$  significance level was considered.

The inclusion of prognostic factors for the time between the cardiopulmonary stress test and the event of interest, considered death, during the period of  $1,060 \pm 90$  days, was made through multivariate Cox proportional risk models<sup>53</sup> considering the sample stratified by etiology. We observed the need to use possible control factors such as age, stature, weight, body mass index, body surface, and gender. Next, each one of the possible prognostic factors was evaluated separately, with the inclusion of the control factors that proved to be important in the previous

analysis. The prognostic factors considered were:  $VO_2$ , in  $ml.kg^{-1}.min^{-1}$ ,  $VE/VO_2$ ,  $VE/VCO_2$ ,  $VO_2/HR$  in  $ml.bt^{-1}$ , end-tidal partial pressure of carbon dioxide ( $PetCO_2$ ) in mmHg, HR in beats per minute (bpm), and the systolic arterial pressure (SAP) in millimeters of mercury (mmHg). All these variables were analyzed at the anaerobic threshold, respiratory compensation point, and peak exercise.

The percentage of maximal HR attained on the test was analyzed at the anaerobic threshold and respiratory compensation point. The anaerobic threshold percentage was calculated from the HR obtained at the anaerobic threshold and divided by the maximal HR attained on the test. The respiratory compensation point percentage was calculated from the HR obtained at the respiratory compensation point divided by the maximal HR obtained on the test.

The  $VE/VCO_2$  slope was calculated by means of a linear regression equation, from the start of the test to the anaerobic threshold, using the values of the minute ventilation elevation relative to the output of carbon dioxide. The  $\Delta VO_2/\Delta W$  ratio slope was calculated by means of the linear regression equation, from the beginning of the test to the anaerobic threshold, using the oxygen uptake ( $\Delta VO_2$ ) values increase relative to the workload ( $\Delta W$ ) elevation.

A significance level of  $p < 0.05$  was considered.

## RESULTS

The characteristics of the sample analyzed are shown on Table 1. In the survival analysis by the Cox multivariate model, age ( $p=0.4$ ), height ( $p=0.9$ ), weight ( $p=0.1$ ), body surface ( $p=0.3$ ) and gender ( $p=0.6$ ), were not variables that influenced the time to death. Nevertheless, the body mass index ( $p=0.05$ ) showed a significant prognostic value as to time to death. This variable was

considered the only control factor in the multivariate analysis performed for the prognostic factors.

The ejection fraction was significantly smaller in patients with idiopathic etiology as compared to those of Chagasic etiology ( $p < 0.05$ ).

Tables 2, 3 and 4 show the metabolic, respiratory, and hemodynamic variables with their predictive risk values for death, at the anaerobic threshold, respiratory compensation point, and peak exercise, respectively.

The  $VO_2$ ,  $VE/VO_2$ ,  $VE/VCO_2$ ,  $PetCO_2$ , and  $VO_2/HR$  held a statistically significant correlation with the risk of death at the anaerobic threshold, respiratory compensation point, and peak exercise.

The HR did not show a statistically significant prognostic value at any phase of exercise. However, the maximal HR percentage showed a statistically significant correlation with the risk of death at the anaerobic threshold and the respiratory compensation point. In addition, the SAP had a prognostic value for death at peak exercise.

The angular coefficients of the metabolic variables during the cardiopulmonary stress test were analyzed up to the anaerobic threshold, and both the  $VE/VCO_2$  slope and the  $\Delta VO_2/\Delta W$  slope showed a statistically significant correlation to risk of death.

## DISCUSSION

The principal results of this study are: 1) metabolic and respiratory variables  $VO_2$ ,  $VE/VO_2$ ,  $VE/VCO_2$ ,  $PetCO_2$  and  $VO_2/HR$  at the anaerobic threshold, respiratory compensation point, and peak exercise obtained during the cardiopulmonary stress test may predict the relative mortality risk in patients with cardiac failure; 2) the degree of inclination of the  $VE/VCO_2$  and  $\Delta VO_2/\Delta W$  slopes up to the anaerobic threshold during a

**Table 1 – Sample Characteristics**

	Chagasic (n=26)	Ischemic (n=30)	Idiopathic (n=31)
Age (years)	47±2	59±2*†	46±2
Height (cm)	164±1.6	164±1.3	168±1.4
Weight (kg)	66±2	73±2.4	73±2.3
Body surface (m <sup>2</sup> )	1.7±0.03	1.8±0.03	1.8±0.04
Body mass index (Kg/m <sup>2</sup> )	25±0.8	27±0.7	26±0.9
Gender (M/F)	25/1	24/6	25/6
Peak $VO_2$ ( $ml.kg^{-1}.min^{-1}$ )	18.1±1.0	14.4±1.0*	15.3±1.0
Peak HR (bpm)	139±4	131±4†	149±4
EF (%)	42±0.8	41±1.5	36±1.4*
<b>Medications</b>			
ACE Inhibitors	19	20	22
Furosemide	20	21	20
Digoxin	20	18	16
<i>Numerical variables mean ± standard error; Peak <math>VO_2</math> – oxygen consumption at peak exercise; Peak HR – heart rate at peak exercise; EF – ejection fraction of left ventricle; ACE inhibitors – angiotensin converting enzyme inhibitors. * - significant difference relative to Chagasic etiology (<math>p &lt; 0.05</math>). † - significant difference relative to idiopathic etiology (<math>p &lt; 0.05</math>).</i>			

**Table 2 – Descriptive levels and relative risks of metabolic, respiratory, and hemodynamic variables associated to time to death at the anaerobic threshold in heart failure patients**

	RR	CI 95%	p
VO <sub>2 AT</sub> (ml.kg <sup>-1</sup> .min <sup>-1</sup> )	0.78	0.67-0.93	0.007
VE/VO <sub>2 AT</sub>	1.07	1.03-1.10	0.001
VE/VCO <sub>2 AT</sub>	1.06	1.02-1.10	0.001
VO <sub>2</sub> /HR <sub>AT</sub> (ml.bt <sup>-1</sup> )	0.75	0.64-0.89	0.001
FC <sub>LA</sub> (bpm)	1.00	0.99-1.02	0.19
%HR <sub>max</sub> at AT	1.04	1.01-1.08	0.02
PetCO <sub>2 AT</sub> (mm Hg)	0.89	0.84-0.95	0.001
Slope of VE/VCO <sub>2</sub> ratio	1.04	1.01-1.07	0.01
Slope of ΔVO <sub>2</sub> /ΔW (ml/W) ratio	0.77	0.62-0.94	0.01

RR – relative risk; CI 95% - 95% confidence interval; p – value of p; VO<sub>2 AT</sub> – oxygen uptake at anaerobic threshold; VE/VO<sub>2 AT</sub> – ventilatory equivalent for oxygen uptake at anaerobic threshold; VE/VCO<sub>2 AT</sub> – respiratory equivalent for the production of carbon dioxide at anaerobic threshold; VO<sub>2</sub>/HR<sub>AT</sub> – oxygen pulse at anaerobic threshold; HR<sub>AT</sub> – heart rate at anaerobic threshold; % HR<sub>max</sub> at AT – percentage of maximal heart rate at which the anaerobic threshold occurred; PetCO<sub>2 AT</sub> – end-tidal partial pressure of carbon dioxide at anaerobic threshold; Inclination of the VE/VCO<sub>2</sub> ratio slope – inclination of the ventilation and carbon dioxide production slope at anaerobic threshold; Inclination of the ΔVO<sub>2</sub>/ΔW ratio – inclination of the oxygen uptake increase to workload increase ratio at anaerobic threshold.

**Table 3 – Descriptive levels and relative risks of metabolic, respiratory, and hemodynamic variables associated to time to death at the respiratory compensation point in patients with heart failure**

	RR	CI 95%	p
VO <sub>2 RCP</sub> (ml.kg <sup>-1</sup> .min <sup>-1</sup> )	0.86	0.72-0.95	0.002
VE/VO <sub>2 RCP</sub>	1.04	1.02-1.07	0.0004
VE/VCO <sub>2 RCP</sub>	1.05	1.01-1.09	0.003
VO <sub>2</sub> /HR <sub>RCP</sub> (ml.bt <sup>-1</sup> )	0.81	0.70-0.94	0.005
HR <sub>RCP</sub> (bpm)	1.00	0.99-1.02	0.37
%HR <sub>max</sub> at RCP	1.08	1.01-1.15	0.02
PetCO <sub>2 RCP</sub>	0.91	0.86-0.97	0.002

RR – relative risk; CI 95% - 95% confidence interval; p – value of p; VO<sub>2 RCP</sub> – oxygen uptake at respiratory compensation point; VE/VO<sub>2 RCP</sub> – ventilatory equivalent for the oxygen uptake at the respiratory compensation point; VE/VCO<sub>2 RCP</sub> – respiratory equivalent for the production of carbon dioxide at the respiratory compensation point; VO<sub>2</sub>/HR<sub>RCP</sub> – oxygen pulse at the respiratory compensation point; HR<sub>RCP</sub> - heart rate at the respiratory compensation point; %HR<sub>max</sub> at RCP – percentage of maximal heart rate at which the respiratory compensation point occurred; PetCO<sub>2 RCP</sub> – end-tidal partial pressure of carbon dioxide at the respiratory compensation point.

**Table 4 – Descriptive levels and relative risks of metabolic, respiratory, and hemodynamic variables associated to time to death at peak exercise in patients with heart failure.**

	RR	CI 95%	p
VO <sub>2 peak</sub> (ml. kg <sup>-1</sup> .min <sup>-1</sup> )	0.86	0.78-0.95	0.002
VE/VO <sub>2 peak</sub>	1.05	1.02-1.08	0.0007
VE/VCO <sub>2 peak</sub>	1.07	1.03-1.11	0.001
VO <sub>2</sub> /HR peak (ml.bt <sup>-1</sup> )	0.84	0.71-0.98	0.02
HR peak (bpm)	0.99	0.98-1.00	0.42
PetCO <sub>2 peak</sub> (mm Hg)	0.90	0.83-0.97	0.005
SAP peak (mm Hg)	0.97	0.96-0.98	0.001

RR – relative risk; CI 95% - 95% confidence interval; p – value of p; VO<sub>2 peak</sub> – oxygen uptake at peak exercise; VE/VO<sub>2 peak</sub> – ventilatory equivalent for the oxygen uptake at peak exercise; VE/VCO<sub>2 peak</sub> - respiratory equivalent for the production of carbon dioxide at peak exercise; VO<sub>2</sub>/HR peak - oxygen pulse at peak exercise; HR peak – heart rate at peak exercise; PetCO<sub>2</sub> - end-tidal partial pressure of carbon dioxide at peak exercise; SAP peak – systolic arterial blood pressure at peak exercise.

progressive cardiopulmonary stress test may predict the relative mortality risk in patients with cardiac failure; 3) the percentages of maximal heart rate obtained at the anaerobic threshold and the respiratory compensation point were predictors of mortality during a progressive cardiopulmonary stress test in patients with cardiac failure; and 4) the systolic arterial blood pressure at peak exercise may predict the relative mortality risk in patients with cardiac failure.

The results of this study broaden our knowledge as they show that other respiratory and metabolic variables obtained during the cardiopulmonary stress test evaluation may estimate the mortality risk in patients with cardiac failure, not only at peak exercise, but also during submaximal physical exercise at the anaerobic threshold and at the respiratory compensation point, which are important moments of exercise. Besides clinical implications, these results have a practical importance as they point out the possibility of obtaining information on mortality risks, both at the peak exercise and during submaximal exercise, without necessarily exposing the patient to a very intense exertion. Currently, many heart failure patients may discontinue the procedure because of ischemia and/or arrhythmias<sup>10</sup> or even because of an important functional limitation, hindering a maximal evaluation.

Additionally, the evaluation of PetCO<sub>2</sub> has been the focus of interest during the cardiopulmonary stress test evaluation in patients with cardiac failure<sup>54-55</sup>. However, as far as we know, this is the first time the prognostic value of this variable at the anaerobic threshold, respiratory compensation point, and peak exercise is demonstrated. This fact is extremely important since PetCO<sub>2</sub> has been recently correlated with cardiac output during exercise in patients with heart failure<sup>54-55</sup>. That is, in patients with cardiac failure in whom a low cardiac output response is seen during exercise, the PetCO<sub>2</sub> has lower values as well.

The level of metabolic and respiratory responses and even the altered ratio between them that leads to a predictive prognostic value of mortality in these patients raises the question as to which mechanisms direct the exaggerated ventilatory response during exercise in the presence of heart failure. Diminished perfusion in skeletal muscles because of a low cardiac output associated with a decrease in muscular oxidative capacity and even cachexia, leads to early metabolic acidosis. In patients with cardiac failure in whom muscular chemoreceptors are already hypersensitive<sup>56-58</sup>, a premature worsening of metabolic acidosis may enormously potentiate the ventilatory drive during exercise. Our results clearly show this ventilatory behavior in heart failure. While in normal individuals the ventilatory equivalent for carbon dioxide at peak exercise is approximately  $37 \pm 0.2$ , in patients with cardiac failure it is  $47 \pm 0.2$ .

Another interesting finding in our study is that we did not detect that heart rate has a predictive value for

mortality in these patients. However, when a correlation is made of the percentage of maximal HR attained at peak exercise, we observe a significant prognostic value both at the anaerobic threshold and at the respiratory compensation point. The fact that the heart rate at the peak exercise did not show a predictive value for mortality might be explained by the chronotropic incompetence observed in heart failure<sup>37,59</sup>. It is known that patients with heart failure have a greater sympathetic activity as a result of elevated levels of circulating catecholamines<sup>60</sup> that seems to be associated with desensitization, reduction of  $\beta$ -adrenergic receptors and down regulation of cardiac receptors<sup>61</sup>, and depressed inotropic and chronotropic responses<sup>35, 37, 62</sup>.

In normal individuals, systolic arterial blood pressure increases progressively with progressive physical exercise, indirectly furnishing the evaluation of the inotropic response of the heart. In our results, it is clear that an inadequate increase of SAP is considered a risk factor for death in patients with cardiac failure.

Finally, we highlight a significant aspect related to the sample analyzed. Contrary to other studies that also evaluated the prognostic value for mortality of the metabolic variables obtained during the ergospirometry test, racial miscegenation, a characteristic of our population, has been suggested as a factor that may influence the VO<sub>2</sub> during exercise<sup>63</sup>.

*Limitations* - We recognize several limitations in this study. The cardiopulmonary stress test was carried out on a bicycle-ergometer and we do not know if these results are reproducible on a treadmill. However, the test done on the bicycle-ergometer with the ramp-protocol has proved to be very applicable in patients with cardiac failure, including for follow-up purposes of drug and non-drug treatments<sup>64-65</sup>. During the period in which this study was conducted, the indication of beta-blockers in the treatment of patients with heart failure was not yet a decisive procedure. Today, treatment with beta-blockers is mandatory. Therefore, we do not know the importance of these metabolic and respiratory variables as predictors of a relative mortality risk while using beta-blockers.

*Perspectives* - A natural continuation of this study would be the analysis of the predictive value of respiratory, metabolic, and hemodynamic variables of exercise for the relative risk of mortality with the use of beta-blockers. Added to this, it would be interesting to verify if the type of ergometer can influence the results attained in this study.

In closing, besides being safe and enabling an evaluation of functional capacity, the cardiopulmonary stress test, based on respiratory, metabolic, and hemodynamic responses, can provide important information as to the relative mortality risk in patients with heart failure.

#### Potencial Conflict of Interest

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

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