

Global Longitudinal Strain Predicts Poor Functional Capacity in Patients with Systolic Heart Failure

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Abstract

Background: Left ventricular global longitudinal strain value (GLS) can predict functional capacity in patients with preserved left ventricular ejection fraction (LVEF) heart failure (HF) and to assess prognosis in reduced LVEF HF.

Objective: Correlate GLS with parameters of Cardiopulmonary Exercise Test (CPET) and to assess if they could predict systolic HF patients that are more appropriated to be referred to heart transplantation according to CPET criteria.

Methods: Systolic HF patients with LVEF < 45%, NYHA functional class II and III, underwent prospectively CPET and echocardiography with strain analysis. LVEF and GLS were correlated with the following CPET variables: maxVO₂, VE/VCO₂ slope, heart rate reduction during the first minute of recovery (HRR) and time needed to reduce maxVO₂ in 50% after physical exercise (T_{1/2}VO₂). ROC curve analysis of GLS to predict VO₂ < 14 mL/kg/min and VE/VCO₂ slope > 35 (heart transplantation's criteria) was performed.

Results: Twenty six patients were selected (age, 47 ± 12 years, 58% men, mean LVEF = 28 ± 8%). LVEF correlated only with maxVO₂ and T_{1/2}VO₂. GLS correlated to all CPET variables (maxVO₂: r = 0.671, p = 0.001; VE/VCO₂ slope: r = -0.513, p = 0.007; HRR: r = 0.466, p = 0.016, and T_{1/2}VO₂: r = -0.696, p = 0.001). GLS area under the ROC curve to predict heart transplantation's criteria was 0.88 (sensitivity 75%, specificity 83%) for a cut-off value of -5.7%, p = 0.03.

Conclusion: GLS was significantly associated with all functional CPET parameters. It could classify HF patients according to the functional capacity and may stratify which patients have a poor prognosis and therefore to deserve more differentiated treatment, such as heart transplantation. (Arq Bras Cardiol. 2019; 113(2):188-194)

Keywords: Heart Failure; Longitudinal Strain; Torsion, Mechanical; Torsion Abnormality; Ventricular Dysfunction, Left; Echocardiography, Doppler/methods.

Introduction

The cardiopulmonary exercise test (CPET) is the gold standard method for assessing functional capacity in patients with heart failure (HF). It is able to measure during exercise, maximum myocardial oxygen consumption (maxVO₂), CO₂ production, ratio minute ventilation/carbon dioxide production VE/VCO₂ slope, VO₂ recovery kinetics after physical exertion (T_{1/2}VO₂), stratify cardiovascular risk and predict mortality and hospitalization by these parameters, for example, VO₂ values < 14 mL/kg/min and VE/VCO₂ slope > 35 that are criteria for heart transplantation.¹⁻⁴

Furthermore, CPET evaluates the presence of dysautonomia, by measuring the reduction in heart rate within the first minute after exercise (HRR),^{5,6} which is directly related to cardiovascular outcome.⁷⁻⁹

However, in patients with systolic HF, the reduction of myocardial contractility, measured mainly by echocardiography through the left ventricular ejection fraction (LVEF), is the main parameter used to classify the myocardial damage degree,¹⁰ although its value is little associated with the clinical symptoms and functional capacity of these patients.^{1,10} The strain analysis is a newer echocardiography tool and has demonstrated more effective in assessing global derangement of the left ventricle (LV) than the LVEF measurement.¹⁰

Recent studies show that the left ventricular global longitudinal strain value (GLS) can predict functional capacity in patients with HF and preserved LVEF,¹¹ and assess prognosis in HF with reduced LVEF when compared with life expectancy scores.¹² Additionally, this technique evaluates the degree of myocardial deformation and it seems to predict the degree of regional and global LV fibrosis.¹³ However, there are no studies comparing the GLS with CPET parameters

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in patients with systolic HF. The aim of this study was to correlate GLS value with functional parameters of CPET and to assess if GLS could predict systolic HF patients that were more appropriated to be referred to heart transplantation according to CPET criteria.

Methods

This is an observational, prospective cross-sectional study, guided by the recommendations of the STROBE Statement.¹⁴ This study was approved by the Ethics and Research Committee of our Institution under number 1507992.

The study population consisted of adults (21-65 years), both sexes, diagnosed with HF in functional class II and III by the New York Heart Association (NYHA), sedentary, with systolic dysfunction (LVEF <45%) assessed by transthoracic echocardiography performed until one month before they had been referred for cardiopulmonary program and recruited for this study. Data were collected between January, 2015 and March, 2016.

Exclusion criteria were: deformity in the face to prevent the coupling of the CPET mask, orthopedic and neurological diseases that could preclude the execution of CPET, psychological problems restricting them to respond to the questionnaire, functional class IV HF or hospitalization due to cardiac decompensation in the last three months, unstable angina, myocardial infarction or cardiac surgery up to three months before the study; forced expiratory volume on the first one second/forced vital capacity <70% of predicted characterizing obstructive respiratory disorder.

To ensure standardization, a single examiner performed the exams. None of them had access to the patients' other evaluations results. The researchers responsible for data collection were not responsible for carrying out the examinations, thus ensuring the blinding of the study.

Cardiopulmonary exercise test

All patients in the study underwent CPET by the method ramp on a treadmill (*Centurium 300*, Micromed, Brazil) through ErgoPC Elite® software associated with the electrocardiogram (Micromed, Brazil) with 12 channels. Respiratory variables were evaluated by a gas analyzer (Cortex - Metalyzer II, Germany) and obtained in conditions of standard temperature, pressure and dry (STPD), breath-by-breath, with the patient breathing in a face mask without leaks during exercise. During the test, functional capacity, maxVO₂ measured in METs, the maximum VE/VCO₂, VE/VCO₂ slope, T_{1/2} VO₂ and HRR were evaluated.

Echocardiography

All echocardiograms were performed according to ASE.¹⁴ Patients underwent the two-dimensional echocardiography, using an ultrasound system Vivid I (GE Medical Systems, Horten, Norway) with a multifrequency transducer from 2.5 to 5 MHz.

After the echocardiogram, a strain analysis technique was performed using an echocardiogram analysis software (EchoPAC, GE Medical Systems, Horten, Norway, version

10.0). The images in the longitudinal sections were analyzed (4 chambers, 3 chambers and 2 chambers).¹⁵ A region of interest was applied automatically by the software and, if necessary, was adjusted manually. The strain analysis software performed the analysis. Patients were excluded when more than two segments were considered to have insufficient quality for monitoring by the analysis system.¹⁶

Statistical analysis

To calculate the sample, G*Power 3 software was used,¹⁷ in which we chose the post hoc option with $\alpha = 0.05$ and two-tailed hypothesis. Thus, the two most important ergospirometric variables were chosen for the study population: maxVO₂ and VE/VCO₂ slope. We found an effect size of 0.81 ($R^2 = 0.67$) for the maxVO₂ and 0.71 ($R^2 = 0.51$) for the VE/VCO₂ slope. We observed for both variables a power of 99% with a total sample of 25 patients.

Patients were later divided into two groups according to values of maxVO₂ and VE/VCO₂ slope found to CPET: Group 1 - maxVO₂ > 14 mL/kg/min and/or VE/VCO₂ slope < 35; and Group 2 - maxVO₂ < 14 mL/kg/min and VE/VCO₂ slope > 35 (IIa class indication criteria for heart transplantation).¹⁶

The data was presented by absolute and percentage frequencies for categorical variables; by the mean and standard deviation for parametric quantitative variables; and by median and interquartile range for non-parametric variables. Shapiro-Wilk test was applied to verify if the quantitative data were normals. For comparison of parametric variables, we used the Student t-test for independent samples and for non-parametric variables the Mann-Whitney test. To compare categorical variables, we used the chi-square non-parametric test.

In the second step, the correlation between the values of the GLS strain index with ergospirometric variables was performed by using the Pearson coefficient for parametric and Spearman variables for non-parametric variables. The Receiver Operating Characteristic (ROC) curve was performed to evaluate the GLS's ability to predict maxVO₂ < 14 mL/kg/min and VE/VCO₂ slope > 35.

P value inferior to 0.05 was considered statistically significant. Data were entered in an EXCEL spreadsheet and statistical software used for statistical calculations was the SPSS (Statistical Package for Social Sciences) version 23.

Results

During the study period, 39 patients with HF were referred to the cardiopulmonary rehabilitation program. Of these, 10 were not included because of a LVEF higher than 45%, one patient for presenting inadequate acoustic window for subsequent analysis of the GLS and two patients due to arrhythmia. Therefore, 26 patients (mean age, 47 ± 12 years, 58% men) participated in this study, Table 1.

Regarding the CPET results the average maxVO₂ was 19.09 ± 9.52 mL/kg/min and the VE/VCO₂ slope was 39.43 ± 9.91. The mean HRR and T_{1/2} VO₂ were respectively, 19.65 ± 17.42 bpm and 168.61 ± 43.90s. By echocardiography, the mean LVEF was 28.0 ± 8.6% and mean GLS index was -7.5 ± 3.92 % for all studied patients, Table 1.

Table 1 – Characteristics of the study population

Variable	(n = 26)
Age (years), mean ± DP	47.31 ± 12.71
Gender: n (%)	
Men	15 (57.7)
Women	11 (42.3)
BMI (Kg/m ²): Mean ± DP	29.31 ± 5.38
Comorbidities: n (%)	
SAH	20 (77)
DM	15 (61)
HF Etiology: n (%)	
Ischemic	6 (23)
Hypertensive	10 (39)
Myocarditis	4 (15)
Chagas' Disease	1 (4)
Idiopathic	5 (19)
Medication: n (%)	
ACEI/ARB	23 (88)
Beta blocker	26 (100)
Diuretics K-sparing	22 (84)
LVEF (%) (mean ± DP)	28.0 ± 8.62
Strain (%) (mean ± DP)	-7.5 ± 3.92
maxVO ₂ (mean ± DP)	19.09 ± 9.52
VE/VCO ₂ slope (mean ± DP)	39.43 ± 9.91
HRR (bpm) (mean ± DP)	19.65 ± 17.42
T _{1/2} VO ₂ (s) (mean ± DP)	168.61 ± 43.90

BMI: body mass index; SAH: systemic arterial hypertension; DM: diabetes mellitus; ACEI/ARB: converting the angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; LVEF: left ventricular ejection fraction; maxVO₂: maximal oxygen consumption; VE/VCO₂ slope: slope of the VE/VCO₂ curve; HRR: heart rate recovery; T_{1/2}VO₂: time to VO₂ halving recovery.

Correlation of CPET variables with LVEF and GLS measurements

When comparing the CPET with LVEF data (Table 2), a positive correlation was observed only with maxVO₂ (r = 0.585, p = 0.02) and negative with T_{1/2}VO₂ (r = -0.530; p = 0.005). For the other variables, LVEF showed no correlation, Table 2.

The GLS showed significant correlation with all analysed CPET variables. This parameter was positively correlated with maxVO₂ and HRR and inversely with VE/VCO₂ slope and T_{1/2}VO₂, Table 2 and Figure 1.

Regarding VO₂ group > 14 mL/kg/min and/or VE/VCO₂ slope < 35 and VO₂ group < 14 mL/kg/min and VE/VCO₂ slope > 35, there were no differences in clinical variables, comorbidities and medications used. However, echocardiographic variables showed differences, as shown in Table 3.

The area under the ROC curve (Figure 2) for the GLS index value as a predictor of poor functional capacity and worse prognosis was 0.88 (95% CI = 0.75 to 1.00), with a sensitivity of 75%, specificity of 83%, positive predictive value of 67%, and negative predictive value of 88%, for a cut-off GLS value of -5.7%, p = 0.03.

Discussion

In this study, in patients with systolic HF referred for a cardiopulmonary rehabilitation program, the GLS was significantly associated with all functional CPET parameters. It seems to be more accurate than LVEF in classifying patients with HF according to the functional capacity and thus may stratify which patients have a poor prognosis and therefore to deserve more differentiated treatment, such as heart transplantation.

Previous studies have demonstrated that LVEF has no correlation with functional capacity.^{1,10} However, there is limited data on the association between exercise tolerance and the results of analysis by cardiac strain. This study showed that LVEF was associated with maxVO₂ and T_{1/2}VO₂, however, showed no correlation with the other CPET variables. Whereas peak VO₂ values and VE/VCO₂ slope are parameters which help in end-stage HF decision making^{4,16} and that in this study, the GLS value was correlated with all these variables, we could suggest that the GLS may have a prognostic significance in this group of patients. In addition, GLS correlation with maxVO₂ and T_{1/2}VO₂ was better than LVEF, thus demonstrating that the GLS is a more accurate tool.

Hasselberg et al.,¹¹ in their study that evaluated HF patients, either with normal or reduced LVEF, were able to show the importance of GLS as a predictor of exercise capacity in patients with preserved LVEF HF.¹¹ However, these authors have failed to demonstrate this relationship in patients with reduced LVEF. In the present study, we observed this correlation between GLS and functional capacity. This may have occurred since our study evaluated patients in more advanced stages of cardiac dysfunction. The average GLS in our study was worse than the Hasselbach study.¹¹

The T_{1/2}VO₂ has also proven an important tool for predicting outcomes. The longer the VO₂ recovery time of HF patients after physical exercise, the worse the cardiovascular prognosis.¹⁸⁻²¹ Our study demonstrated that the GLS was able to determine patients that have delayed recovery of VO₂. The lower the value of GLS, the greater the time required for the post-physical effort VO₂ to be reduced to half, suggesting the hypothesis that the GLS could estimate the prognosis of the patient.

Another evidence that supports the prognostic importance of GLS was dysautonomia analysis. It is known that there is a relationship between HRR in the first minute after physical exercise with mortality. The cardiovascular prognosis appears to be independent of symptoms, the type of recovery protocol, LVEF, and severity of coronary lesions in coronary angiography.^{7-9,21,22} This study showed a direct relationship between the GLS value and HRR in the first minute after effort, with a less accentuated drop in heart rate in patients who had a lower GLS value.

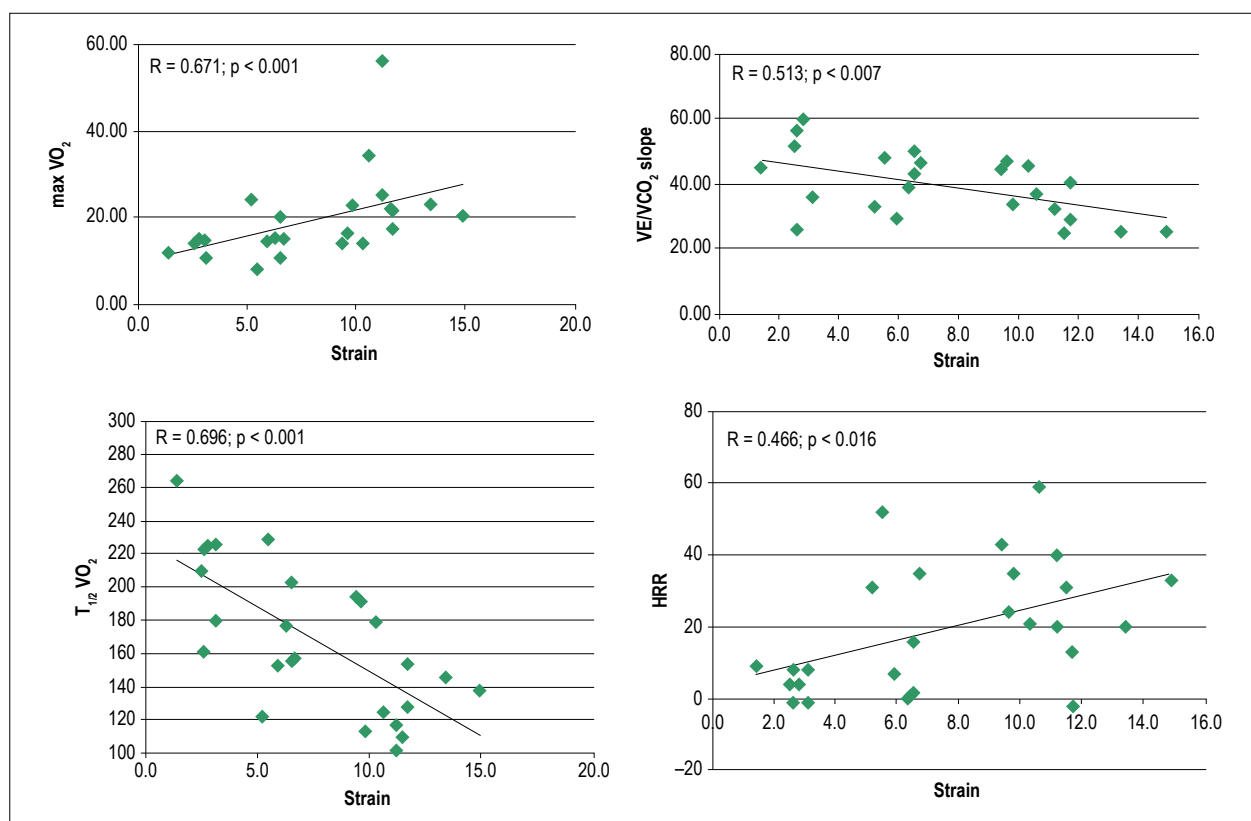


Figure 1 – Global longitudinal strain index (GLS) scatter plots compared to maxVO_2 , VE/CO_2 slope, HRR, and $T_{1/2}\text{VO}_2$. maxVO_2 : maximal oxygen consumption; VE/CO_2 slope: slope of the VE/CO_2 curve; HRR: heart rate recovery; $T_{1/2}\text{VO}_2$: time to VO_2 halving recovery.

Table 2 – Correlation of numerical variables of Cardiopulmonary Exercise Test with left ventricular ejection fraction (LVEF) and global longitudinal strain index (GLS)

Variables	LVEF (p value)	GLS (p value)
HRR-bpm	0.288 (0.154) ⁽¹⁾	0.466 (0.016) ^{*(1)}
maxVO_2	0.585 (0.002) ^{*(2)}	0.671 (< 0.001) ^{*(2)}
VE/CO_2 slope	-0.330 (0.100) ⁽¹⁾	-0.513 (0.007) ^{*(1)}
$T_{1/2}\text{VO}_2$	-0.530 (0.005) ^{*(1)}	-0.696 (< 0.001) ^{*(1)}

HRR: heart rate recovery; $T_{1/2}\text{VO}_2$: time to VO_2 halving recovery; VE/CO_2 slope: slope of the VE/CO_2 curve; maxVO_2 : maximal oxygen consumption. * $p < 0,05$; (1) – Pearson coefficient; (2) – Spearman coefficient.

Cameli et al.,¹³ evaluated patients with severe HF, with cardiac transplant indication, and, by histopathology of the heart after heart transplantation, found that no echocardiographic parameter, performed before heart transplant, was able to correlate with the presence of fibrosis except the GLS value. Therefore, a lower GLS value indicates that there is presence of more cardiac fibrosis, and consequently, there is less deformation and myocardium thickening, and relaxation and contractility is more defective. These changes entail low functional capacity and are responsible for worse prognosis.¹³ However, in that study, functional capacity was not assessed through an objective test, such as CPET.

Rangel et al.¹² evaluated patients with LVEF less than 45% and demonstrated that the GLS value correlates with more advanced stages of the disease and is an independent predictor of life expectancy.¹² That is, in patients with severe HF and similar LVEF, GLS was able to show which patients would present an unfavourable outcome. Our study showed that in patients with reduced LVEF, the lowest GLS value was correlated with CPET parameters that assess exercise tolerance and prognosis disease.

When rating the GLS cut-off in predicting poor prognosis, Rangel et al.¹² used the Seattle HF model to assess the long-term survival, and it was shown that the best GLS cut-off point

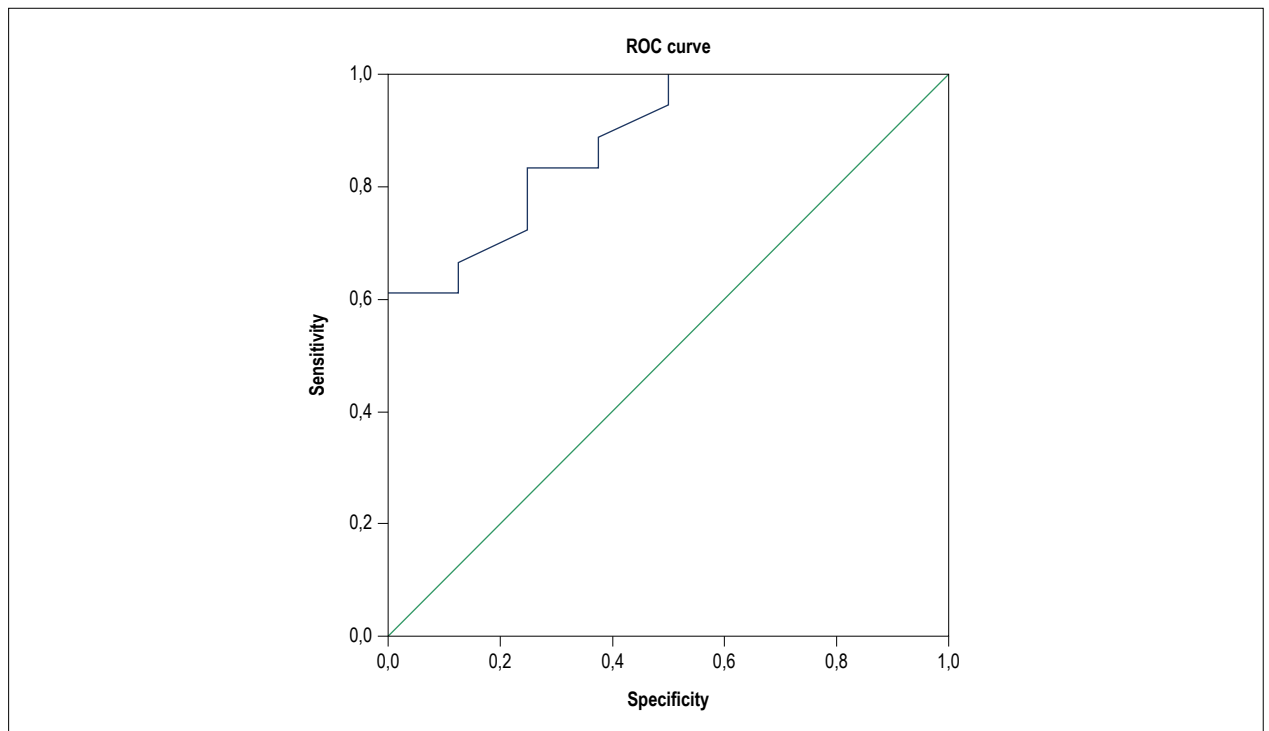


Figure 2 – ROC curve for evaluating the ability of the global longitudinal strain index (GLS) in predicting $VO_2 < 14$ mL/kg/min and VE/VO_2 slope > 35 . Sensitivity of 75% and specificity of 83% for a GLS cut-off of -5.7% , $p = 0.03$.

was -9.5% . Our study correlated the GLS value with CPET parameters and suggested a cut-off point of -5.7% for GLS value, with sensitivity of 75% and specificity of 83% in predicting CPET heart transplantation's criteria.

Study limitations

Considering the small number of patients included in this study, our findings that the GLS showed a strong correlation with the CPET data and have been able to identify the patients who had ergospirometric criteria of worse prognosis, need to be proven through a study with a larger number of patients and of long-term monitoring, and thus determine the real power of GLS in the prognostic assessment and therapeutic setting in systolic HF.

Conclusion

In systolic HF patients, the GLS showed significant association with the main parameters of CPET and was able to classify patients with low functional capacity. Thus, GLS may be a more accurate parameter than LVEF in stratifying systolic HF patients. Moreover, it may play a role in helping to evaluate patients in the end stage of HF.

Author contributions

Conception and design of the research: Brandão SCS, Brandão DC, Leite J, Martins SM, Andrade AD; Acquisition of data: Maia RJC, Brandão DC, Leite J, Pinheiro F, Araújo BTS, Aguiar MIR, Martins SM; Analysis and interpretation of the data: Brandão SCS, Brandão DC, Leite J, Parente GB,

Pinheiro F, Araújo BTS, Aguiar MIR, Andrade AD; Statistical analysis: Brandão SCS, Parente GB; Writing of the manuscript: Maia RJC, Brandão SCS, Leite J; Critical revision of the manuscript for intellectual content: Brandão SCS, Brandão DC, Andrade AD.

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of master submitted by Rafael José Coelho Maia, from Universidade Federal de Pernambuco.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de Pernambuco under the protocol number 38572614.1.000.5208. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Table 3 – Comparison between Group 1 - VO_2 max > 14 mL/kg/min and/or VE/VCO_2 slope < 35 and Group 2 - $maxVO_2$ < 14 mL/kg/ min and VE/VCO_2 slope > 35

Variables	VO_2 > 14 mL/kg/min and/or VE/VCO_2 slope < 35 (n = 18)	VO_2 < 14 mL/kg/min and VE/VCO_2 slope > 35 (n = 8)	p value
Age (years): Mean ± DP	45.7 ± 13.7	51.0 ± 10.0	0.334 ⁽¹⁾
Gender: n (%)			
Men	11 (61.1)	4 (50.0)	0.683 ⁽²⁾
Women	7 (38.9)	4 (50.0)	
BMI (Kg/m ²): Mean ± DP	29.4 ± 6.1	29.0 ± 3.7	0.849 ⁽³⁾
Comorbidities: n (%)			
SAH	13 (72.2)	7 (87.5)	0.628 ⁽²⁾
DM	10 (55.6)	6 (75.0)	0.420 ⁽²⁾
HF Etiology: n (%)			
Ischemic	5 (27.8)	1 (12.5)	0.628 ⁽²⁾
Hypertensive	7 (38.9)	3 (37.5)	1.000 ⁽²⁾
Myocarditis	3 (16.7)	1 (12.5)	1.000 ⁽²⁾
Chagas' disease	1 (5.6)	0 (0.0)	1.000 ⁽²⁾
Idiopathic	2 (11.1)	3 (37.5)	0.281 ⁽²⁾
Medication: n(%)			
ACEI/ARB	16 (88.9)	7 (87.5)	1.000 ⁽²⁾
Beta blocker	18 (100.0)	8 (100.0)	1.000 ⁽²⁾
Diuretics K-sparing	15 (83.3)	7 (87.5)	1.000 ⁽²⁾
LVEF (%) (mean ± DP)	30.6 ± 8.5	22.4 ± 6.0	0.021 ⁽¹⁾
Strain (%) (mean ± DP)	8.6 ± 3.8	5.2 ± 3.3	0.037 ⁽³⁾
$maxVO_2$ (mean ± DP)	22.1 ± 10.0	12.4 ± 3.3	0.014 ⁽³⁾
VE/VCO_2 slope (mean ± DP)	35.8 ± 9.3	47.5 ± 5.8	0.003 ⁽¹⁾
HRR (bpm) (mean ± DP)	20.2 ± 17.2	18.4 ± 19.0	0.004 ⁽³⁾
$T_{1/2}VO_2$ (s) (mean ± DP)	147.5 ± 32.1	216.1 ± 25.7	< 0.001 ⁽¹⁾

BMI: body mass index; SAH: hypertension; DM: diabetes mellitus; ACEI/ARB: converting the angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; LVEF: left ventricular ejection fraction; $maxVO_2$: maximal oxygen consumption; VE/VCO_2 slope: slope of the VE/VCO_2 curve; HRR: heart rate recovery; $T_{1/2}VO_2$: time to VO_2 halving recovery. (1) – Student t test; (2) – Mann-Whitney test; (3) – chi-square test.

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