

Short Communication

Determinants of minute ventilation–carbon dioxide production relationship in Chagas cardiomyopathy

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Abstract

Introduction: The minute ventilation–carbon dioxide production relationship (VE/VCO₂ slope) is among the main prognostic factors of Chagas cardiomyopathy whose determinants remain unknown. **Methods:** Seventy-eight patients with Chagas cardiomyopathy were evaluated using clinical assessment, cardiopulmonary exercise test, echocardiography, and International Physical Activity Questionnaire. **Results:** Age, functional class, International Physical Activity Questionnaire score, and dilated cardiomyopathy with systolic dysfunction were independent determinants of VE/VCO₂ slope, and these variables explained 63% of its variance. **Conclusions:** The VE/VCO₂ slope was related to age, functional class, physical activity level, and dilated cardiomyopathy with systolic dysfunction in patients with Chagas cardiomyopathy.

Keywords: Chagas cardiomyopathy. Chagas disease. Exercise test.

Chagas disease is defined as an acute or chronic infectious condition caused by the protozoan *Trypanosoma cruzi*. An estimated 6–7 million people are infected by the parasite worldwide, mostly in Latin America. Up to 30% of chronically infected people will develop cardiac abnormalities due to Chagas disease¹. The cardiac form, Chagas cardiomyopathy (ChC), is the most common and severe clinical manifestation of the disease in which patients usually develop thromboembolism, malignant arrhythmias, and heart failure². In ChC, even in the early stages of cardiopathy, intense fatigue, progressive dyspnea, and reduced functional capacity³ contribute to exercise intolerance.

The cardiopulmonary exercise test (CPET) is the gold standard for assessing functional capacity. In patients with heart

failure, peak oxygen uptake (VO_{2peak}) provides important clinical information. However, in recent decades, other CPET variables have demonstrated a strong prognostic value in these patients, such as the relationship between ventilation (VE) and carbon dioxide production (VCO₂) expressed as the VE/VCO₂ slope⁴. In a review, Arena, Myers, and Guazzi⁵ reported that an elevated VE/VCO₂ slope was linked to ventilation–perfusion abnormalities. The authors also demonstrated that the VE/VCO₂ slope and VO_{2peak} were the most well-established predictors of mortality in patients with heart failure.

In the setting of ChC, Ritt et al.⁶ reported that the VE/VCO₂ slope was the only independent predictor of a worse prognosis (cut-off value of 32.5) among the variables evaluated by the CPET. However, unlike heart failure, few studies have evaluated the VE/VCO₂ slope in patients with ChC⁷, and no study has demonstrated the determinants of the VE/VCO₂ slope in this population. Thus, the present study aimed to verify the clinical, echocardiographic, and functional determinants of the VE/VCO₂ slope in patients with ChC.

This cross-sectional study verified the determinants of VE/VCO₂ slope in patients with ChC recruited from an outpatient

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Received 28 January 2021

Accepted 3 September 2021

reference center for Chagas disease. The study was approved by the Institutional Ethics Committee (approval number: CAAE 03993912.6.0000.5149) and performed in accordance with the Declaration of Helsinki. All patients provided written informed consent before participating.

Inclusion criteria included positive serology for *Trypanosoma cruzi* and the presence of arrhythmias and intraventricular and atrioventricular conduction disorders with or without left ventricular dysfunction (compatible with ChC). Patients with cardiopathy of any other cause, with respiratory, neurological, or systemic comorbidities that affect the results of exercise testing, or those who were unable to perform the CPET were excluded.

All patients underwent clinical evaluation, echocardiography, physical activity level identification using the International Physical Activity Questionnaire (IPAQ), and CPET in the same week two days apart. The investigators were blinded to the experimental results.

All patients underwent a clinical evaluation by a cardiologist that included a structured anamnesis and physical examination protocol, with heart rate, blood pressure, and anthropometric data (weight, height, and body mass index). During the anamnesis, patients were also asked about their current medications and evaluated according to New York Heart Association (NYHA) functional class.

The CPET was performed on a treadmill using the metabolic analysis system MetaLyzer 3B (Cortex Medical, Leipzig, Germany). The VO_{2peak} and VE/VCO₂ slope were obtained according to current guidelines⁸, and the highest values achieved during the test for both variables were considered in the analysis. An impaired VE/VCO₂ slope was defined as values equal to or greater than 32.5⁶. The percentage of heart rate achieved during the test versus the maximal predicted value was also verified. The echocardiographic assessment was performed according to American Society of Echocardiography recommendations⁹. The target variables were the left ventricular ejection fraction (LVEF) and left ventricular end-diastolic diameter (LVDD). The LVEF was determined using Simpson's rule. Dilated cardiomyopathy with systolic dysfunction was defined as a dilated left ventricle (LVDD value higher than 55 mm) with impaired ventricular systolic function (LVEF value less than 54% and 52% for women and men, respectively). The physical activity level was verified by the IPAQ, which estimates the time spent weekly in physical activity and classifies the patient's physical level as sedentary (score 1), moderately active (score 2), or physically active (score 3)¹⁰.

The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software, version 17.0. Data distribution was verified using the Kolmogorov-Smirnov test. Continuous variables were expressed as means and standard deviations or medians and interquartile ranges, and categorical variables were expressed as absolute numbers and percentages. The determinants of the VE/VCO₂ slope were verified by univariate and multivariate linear regression analysis and were included in the multivariate analysis with a p value below 0.1 in the univariate model. To derive an equation to predict the VE/VCO₂ slope in cases

in which CPET findings were not available, the variables evaluated during the effort were not included in the univariate and multivariate models. The significance level was set at 5%.

A total of 78 patients were enrolled and evaluated in this study. The mean VE/VCO₂ slope was 26.5±9.0. Twenty-one patients (30%) showed an impaired VE/VCO₂ slope. The patients' demographic, clinical, echocardiographic, and functional features are presented in **Table 1**.

Table 2 shows that, in the univariate linear regression, age, sex, NYHA functional class, systolic and diastolic blood pressure, IPAQ score, and dilated cardiomyopathy with systolic dysfunction were associated with VE/VCO₂ slope. In the final multivariate model, age, NYHA functional class, IPAQ score, and dilated cardiomyopathy with systolic dysfunction remained independent determinants of VE/VCO₂ slope. Together, these variables explained 63% of the variance in the VE/VCO₂ slope, which can be predicted by the equation $VE/VCO_2 \text{ slope} = 47.69 + (0.41 \times \text{age}) + (2.38 \times \text{NYHA}) - (2.61 \times \text{IPAQ level}) + (7.30 \times \text{dilated cardiomyopathy with systolic dysfunction; coded 1 for its presence and 0 for its absence})$.

To the best of our knowledge, this is the first study to verify the determinants of the VE/VCO₂ slope in patients with ChC. The main finding of the present study was that dilated cardiomyopathy with systolic dysfunction, together with age, NYHA functional class, and physical activity level by IPAQ score were independent determinants of VE/VCO₂ slope in patients with Chagas disease, explaining 63% of the variance. We also derived a model to predict the VE/VCO₂ slope based on these parameters. The equation has potential value for estimating the VE/VCO₂ slope when CPET findings are not available.

In the present study, the presence of dilated cardiomyopathy with systolic dysfunction explained 30% of the variation in the VE/VCO₂ slope. We believe that the increase in the VE/VCO₂ slope in the presence of dilated cardiomyopathy with systolic dysfunction is due to the muscle hypothesis. One of the main findings of dilated cardiomyopathy is the reduction of cardiac output and, consequently, decreased peripheral blood flow. This reduction in peripheral blood flow is associated with skeletal and respiratory myopathies, leading to increased ergoreflex and chemoreflex sensitivity¹¹. The increased activity of the receptors induces ventilatory overactivation identified as the main factor responsible for the increase in the VE/VCO₂ slope during exercise¹². In addition, patients with cardiac chamber dilatation and chronic heart failure also presented with a restrictive lung pattern that could further compromise the ventilation and the VE/VCO₂ slope¹³.

Age, functional class, and physical inactivity were also determinants of the VE/VCO₂ slope. Aging is associated with the clinical worsening of heart disease as well as VO_{2peak} and VE/VCO₂ slope deterioration in healthy individuals¹⁴. Functional class and physical inactivity were associated with reduced peripheral muscle mass. Impaired NYHA functional class and physical inactivity reduce capillary density, the proportion of type I fibers, and oxidative activity and increase the production of carbon dioxide during exercise. These muscle abnormalities can also lead to overactivation of the peripheral ergoreflex and an increased VE/VCO₂ slope¹⁵.

TABLE 1: Characteristics of the sample (N=78).

| Variable | Value | |
|--|-------|-------------|
| | n | % |
| Age (years)* | 52.8 | 10.1 |
| Sex | | |
| Male | 35 | 44.9 |
| Female | 43 | 55.1 |
| NYHA functional class | | |
| I | 44 | 56.4 |
| II | 25 | 32.1 |
| III | 9 | 11.5 |
| BMI (kg/m ²)# | 26.6 | 22.7–29.3 |
| HR (bpm)# | 68.0 | 59.5–77.0 |
| SBP (mmHg)# | 106.0 | 100.0–130.0 |
| DBP (mmHg)# | 70.0 | 60.0–80.0 |
| Physical activity level | | |
| Sedentary | 12 | 15.4 |
| Insufficiently active | 37 | 47.4 |
| Moderately active | 29 | 37.2 |
| VO _{2peak} (mL.kg.min)* | 23.1 | 6.8 |
| VE/VCO ₂ slope* | 26.5 | 9.0 |
| % HR achieved* | 82.8 | 13.4 |
| LVEF (%) # | 58.0 | 40.5–64.0 |
| LVDd (mm) # | 52.3 | 46.3–61.0 |
| Systolic function | | |
| Dilated cardiomyopathy with systolic dysfunction | 28 | 35.9 |
| Preserved systolic function | 50 | 64.1 |

*Values shown as mean and standard deviation. #Values shown as median and interquartile range. **BMI:** body mass index; **DBP:** diastolic blood pressure; **HR:** heart rate; **LVDd:** left ventricular end-diastolic diameter; **LVEF:** left ventricular ejection fraction; **NYHA:** New York Heart Association; **SBP:** systolic blood pressure; **VE/VCO₂ slope,** minute ventilation–carbon dioxide production relationship; **VO_{2peak},** peak oxygen uptake.

TABLE 2: Univariate and multivariate analyses of the VE/VCO₂ slope determinants in patients with ChC.

| Variable | Univariate model | | | Multivariate model* | | |
|--|------------------|----------------|------------------|---------------------|----------------|------------------|
| | Beta coefficient | 95% CI | P value | Beta coefficient | 95% CI | P value |
| Constant | - | - | - | 47.69 | 40.12 to 55.25 | <0.001 |
| Age | 0.43 | 0.60 to 0.27 | <0.001 | 0.41 | 0.28 to 0.54 | <0.001 |
| Male sex | 6.88 | 3.17 to 10.52 | <0.001 | - | - | - |
| NYHA class | 4.78 | 2.12 to 7.43 | 0.001 | 2.38 | 0.34 to 4.42 | 0.023 |
| SBP | -0.32 | -0.39 to -0.26 | <0.001 | - | - | - |
| DBP | -0.51 | -0.67 to -0.34 | <0.001 | - | - | - |
| HR | -0.02 | -0.14 to 0.10 | 0.758 | - | - | - |
| BMI | -0.08 | -0.54 to 0.37 | 0.713 | - | - | - |
| Physical activity level | -5.77 | -8.32 to -3.21 | <0.001 | -2.61 | -4.59 to -0.64 | 0.010 |
| Dilated cardiomyopathy with systolic dysfunction | 10.06 | 6.47 to 13.65 | <0.001 | 7.30 | 4.20 to 10.40 | <0.001 |

Values highlighted in bold were included in the multivariate analysis ($p < 0.1$). *The adjusted r^2 value for the model was 0.63. **BMI:** body mass index; **ChC:** Chagas cardiomyopathy; **CI:** confidence interval; **DBP:** diastolic blood pressure; **HR:** heart rate; **SBP:** systolic blood pressure.

The present study provided an equation to predict the VE/VCO₂ slope based on its determinants. All variables were inexpensive and easy to determine except for the echocardiographic parameters. However, echocardiographic assessment is a part of the clinical routine of patients with ChC, and its features are often available. Because the VE/VCO₂ slope is a strong prognostic marker, the model can be used to estimate this parameter in the risk stratification of patients with ChC when CPET results are not available. Finally, as a limitation, the present study predominantly included patients with a preserved VE/VCO₂ slope; thus, further studies should be performed in patients with a severely impaired ventilatory efficiency. However, considering the setting of Chagas disease, the present study's findings can provide valuable assistance with establishing the patient's functional capacity.

In conclusion, ventilation efficiency assessed by VE/VCO₂ slope was related to age, NYHA functional class, physical activity level, and dilated cardiomyopathy with systolic dysfunction in patients with ChC. These parameters have potential value for predicting the VE/VCO₂ slope in these patients. To validate the model, a study using the proposed equation is desirable.

ACKNOWLEDGMENTS

None.

AUTHORS' CONTRIBUTION

LFFO: Conception and design of the study, acquisition of data, wrote the paper. JMA: Acquisition of data, wrote the paper. PHSF: Acquisition of data, wrote the paper. MRA: Analysis and interpretation of data, critical review of the manuscript. WTS: Analysis and interpretation of data, critical review of the manuscript. MVAV: Analysis and interpretation of data, critical review of the manuscript. RGTF: Analysis and interpretation of data. HSC: Conception and design of the study, critical review of the manuscript. MOCR: Conception and design of the study, wrote the paper. VPL: Conception and design of the study, critical review of the manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FINANCIAL SUPPORT

None.

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