

## ORIGINAL ARTICLE

## Dysautonomia Evaluation by Holter in Chagas Heart Disease

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### Abstract

**Background:** Sudden cardiac death is the main lethal mechanism associated with Chagas cardiomyopathy. Studies suggest that dysautonomia may represent a relevant, intense, independent, and early phenomenon in the natural history of the disease, even when ventricular systolic function is preserved, and may also be the mechanism that triggers malignant ventricular arrhythmias.

**Objective:** To evaluate the degree of dysautonomia and its possible association with ventricular arrhythmias in patients with Chagas cardiomyopathy, according to different categories of mortality risk, as defined by the score proposed by Rassi, used as a surrogate outcome for death.

**Methods:** A cross-sectional study involving 43 patients with Chagas cardiomyopathy stratified into risk categories based on the Rassi score, with 23 being classified as low risk and 20 as intermediate-to-high risk. Heart rate variability (HRV) was assessed using Holter monitoring for long-term recordings of 24 hours (time domain) and for short-term recordings of 5 minutes (frequency domain) at rest and after autonomic tests: deep breathing and Valsalva maneuver. The HRV variables were compared between the groups using the Student's t-test and  $\alpha=0.05$ .

**Results:** Comparison of the results between the risk stratification groups showed no differences in HRV indexes, either in the time or frequency domain. However, results showed a significant increase in the number of arrhythmias as a function of increased risk ( $p=0.02$ ).

**Conclusion:** There was no association between the degree of dysautonomia, evaluated by Holter monitoring, and the categories of mortality risk, despite a direct association between the rate of arrhythmias and the higher risk group.

**Keywords:** Chagas Cardiomyopathy/physiopathology; Chagas Disease; Death, Sudden, Cardiac; Prognosis; Primary Dysautonomias; Heart Rate; Sympathetic Nervous System/physiopathology.

### Introduction

Chagas disease is a tropical disease that is neglected worldwide, contributing substantially to the burden of morbidity and mortality in populations and exerting a considerable socioeconomic effect when cardiac alterations develop (20-30% of infected individuals).<sup>1-6</sup> Sudden cardiac death is the most common cause of death (55-65% of patients with Chagas disease). In general, the final stage consists of malignant ventricular arrhythmia, resulting from an interaction between the anatomical

substrate (fibrosis) and a functional trigger that creates areas of heterogeneous electrophysiological conduction and, consequently, cardiac electrical instability<sup>7-11</sup> In parallel, some evidence suggests that cardiac autonomic dysfunction is a relevant, intense, independent, and early phenomenon in the natural history of the disease, acting as a trigger for malignant arrhythmias and thus representing a potential marker of risk.<sup>12-20</sup>

Although important prognostic factors have already been described, the stratification of risk remains a challenge. Rassi et al. proposed a simple risk score

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consisting of six independent prognostic variables used to predict death. While this is the tool with the best clinical applicability, many patients who die from sudden cardiac death were not initially classified as high risk with the use of traditional markers alone, nor did they qualify for primary prevention with defibrillators according to current scientific guidelines. Furthermore, this model does not reserve a role for dysautonomia, as shown in some studies.<sup>7-11</sup>

Data on autonomic dysfunction may possibly improve the assessment of risk. Different methods could be used to perform this evaluation, including the investigation of heart rate variability (HRV). The prognostic application of HRV has already been established following acute myocardial infarction and heart failure.<sup>21-27</sup> However, much less information is available with respect to chronic cardiomyopathy in Chagas disease, and further studies are required. Therefore, the present study aimed to evaluate the degree of dysautonomia and its possible association with ventricular arrhythmias in different groups of patients stratified for the risk of death according to the Rassi score.

## Methods

**Study design:** This was a cross-sectional analytical study involving patients with chronic Chagas cardiomyopathy and different degrees of cardiac involvement, who were attending the cardiology outpatient department of a referral hospital between August 2018 and November 2019.

**Population:** Patients were selected by applying the same eligibility criteria used in the study conducted by Rassi. The inclusion criteria were: 1) A diagnosis of Chagas disease based on the results of two different positive serologic tests (indirect hemagglutination, indirect immunofluorescence, or enzyme-linked immunosorbent assay [ELISA]) and 2) Abnormalities detected on the electrocardiogram (right bundle branch block, left anterior fascicular block, premature ventricular contraction [PVC], ST-segment changes, pathologic Q waves, and low QRS voltage) or on the echocardiography (segmental or global wall motion abnormality, apical aneurysm, and intracavitary thrombus), which are typical of chronic Chagas cardiomyopathy. The following exclusion criteria were selected to remove other potential confounders of a risk of death: 1) Age over 70 years; 2) A history of sustained ventricular tachycardia or ventricular fibrillation; 3) Use of an implanted cardiac pacemaker; 4) Other associated cardiomyopathies (valvular, ischemic,

or hypertensive); 5) Any diseases that could potentially interfere in sympathetic innervation: diabetes mellitus (DM) and obstructive coronary artery disease; and 6) Non-sinus rhythm of the heart.<sup>9</sup>

**Sample type and size:** This was a systematic (non-randomized) sample. Sample size was calculated based on a power of 80%, with a 95% confidence interval (CI) ( $\alpha = 5\%$ ) and 10-year mortality rates estimated for each Rassi risk group (low risk = 10%; intermediate risk = 44%; high risk = 84%). According to these calculations, 40 individuals would be required in the final analysis, 20 in each group (low risk and intermediate-to-high risk).

**Procedures:** The study was divided into two steps. In the first step, data on the patient's clinical history and on any supplementary evaluation methods were collected for a period of up to six months to enable the participants to be classified into the risk groups. In the second step, HRV was analyzed.

**Stratification of risk:** All the patients underwent a 12-lead electrocardiogram, chest radiography, echocardiography, and 24-hour Holter monitoring. The electrocardiogram abnormalities typical of chronic Chagas cardiomyopathy were determined according to the modified Minnesota code adapted for Chagas disease.<sup>28</sup> Increased cardiothoracic ratio, used to diagnose cardiomegaly on a chest radiography, was defined as more than 0.5. Analysis of left ventricular function by echocardiography was performed visually and by calculating the left ventricular ejection fraction (LVEF), using the methods established by Teicholz or Simpson, according to guidelines.<sup>29</sup> Ventricular dysfunction was defined as LVEF less than 50%. PVCs identified by Holter monitoring were defined as frequent when over 1,000/24 hours. Non-sustained ventricular tachycardia (NSVT) was defined as three or more consecutive PVCs with a heart rate over 100 beats per minute for less than 30 seconds. Exercise testing was performed in selected cases to rule out suspected obstructive coronary artery disease and myocardial ischemia in individuals with complaints of chest pain in the presence of two or more risk factors for coronary artery disease. DM was investigated by measuring fasting glucose twice, with repeat levels  $\geq 126$  mg/dL detected at two different evaluation moments, confirming a diagnosis of DM.<sup>30</sup>

The Rassi risk categories were determined by calculating the score resulting from adding all the following points: New York Heart Association (NYHA) functional class III or IV = 5 points; cardiomegaly on chest

radiography = 5 points; segmental or global wall motion abnormality on echocardiography = 3 points; NSVT on 24-hour Holter monitoring = 3 points; low QRS voltage on electrocardiogram = 2 points; and male gender = 2 points. Three risk groups were thus defined: low risk (0-6 points), intermediate risk (7-11 points), and high risk (12-20 points).

**HRV analysis by Holter monitoring:** In the period of 48 hours preceding placement of the Holter monitor, the participants were to avoid beverages that would increase autonomic nervous system activity, suspend use of any drugs that could potentially interfere, and avoid smoking and the practice of any physical activity. In all cases, placement of the device and the commencement of monitoring were performed in the afternoon after a light meal in a quiet environment at a controlled temperature of 20-22°C. The individuals were monitored through disposable electrodes placed according to the Frank orthogonal lead system, with three leads being recorded simultaneously. With the patient seated in a chair, two steps were performed. First, the resting state (representing baseline autonomic conditions) was recorded over a 5-minute period. Secondly, separate interventions were performed through two autonomic tests (deep breathing and the Valsalva maneuver), with a 5-minute interval between them (Figure 1). Next, the patient was allowed to leave the clinic, wearing the Holter monitor, and was instructed to maintain normal routine activities during the 24-hour monitoring period.

HRV was evaluated in two domains (time and frequency) based on at least 18 hours of good quality tracings and 90% of sinus rhythm available. The entire recording was carefully reviewed and the QRS complexes were classified as normal heartbeats, artefacts, and ectopic beats to create a time series of normal RR intervals. An arrhythmia specialist, who was blinded with respect to the patients' identity and their risk categories, performed the data processing and analysis of HRV indexes. The CardioScan® software program, version 12.0, and the DMS® software program were used in the analysis in accordance with the current

scientific guidelines on the method (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).<sup>24</sup>

**Study variables associated with dysautonomia:** The variables of interest in the time domain, extracted from the 24-hour Holter monitor, were: 1) SDNN (standard deviation of the NN intervals) to represent long-term HRV; and 2) rMSSD (the square root of the mean squared differences of successive NN intervals) and pNN50 (the percentage of successive NN interval pairs with differences in duration >50 milliseconds) to represent short-term HRV. The variables of interest in the frequency domain extracted from the Holter monitor (5 minutes) at rest and following the autonomic tests were: 1) LF (low frequency spectral component) for the evaluation of sympathetic activity; 2) HF (high frequency spectral component) for the evaluation of vagal reserve; and 3) the LF/HF ratio (ratio between the low frequency and high frequency spectral components) for the evaluation of sympathetic/parasympathetic balance. In agreement with other studies, no cut-off points were used for a diagnosis of dysautonomia using these variables; rather, the absolute values of each one were used to establish a comparative analysis between the groups of risk.

**Ethical considerations:** In compliance with ethical standards, the study was initiated only after the internal review board of the Santa Isabel Hospital had approved the study protocol. All the participants signed an informed consent form in accordance with the Brazilian Ministry of Health's National Research Ethics Committee, CONEP, Resolution 466 of 2012.

## Statistical analysis

The study variables were presented as follows: categorical, through absolute values and %; continuous with normal distribution, through mean absolute values with their standard deviations; and continuous with abnormal distribution, across medians with their interquartile ranges. The chi-square test was used to compare the categorical variables between

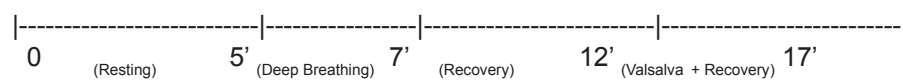


Figure 1 – Time schedule for autonomic testing.

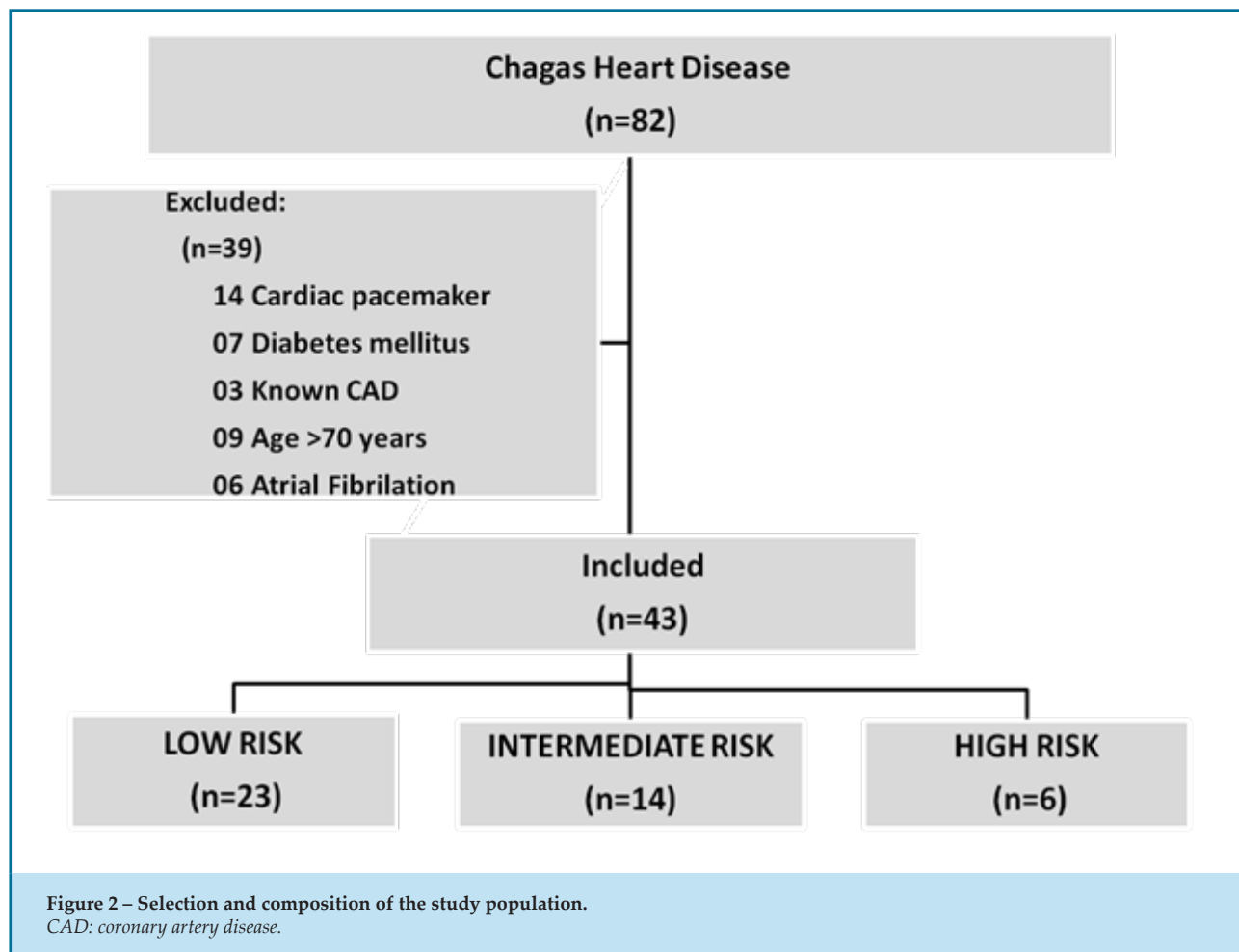
the groups, while unpaired Student's t-test was used for the continuous variables. For the evaluation of normality, Kolmogorov-Smirnov test was adopted. For the variables with non-normal distribution, log transformation was performed to normalize the data and the aforementioned parametric tests were used. To analyze the effects of the autonomic tests on individual baseline status, the deltas were used (obtained from the difference in the values of each index following maneuvers in relation to their baseline values in a resting state). Statistical tests with p-values <0.05 were considered significant throughout the analysis. The Statistical Package for the Social Sciences (SPSS Statistics for Windows), version 14.0 (SPSS Inc., Chicago, IL, USA), was used to perform statistical analysis.

## Results

Forty-three eligible patients were stratified into risk categories, following the application of the Rassi

score system, with 23 classified as low-risk and 20 as intermediate-to-high risk (Figure 2).

The general characteristics of the study population are shown in Table 2 according to the group. The mean age of the participants was  $58 \pm 18$  years and most were female (n=24; 56%), with no statistically significant differences in age or sex between the groups. The risk groups were different with respect to: NYHA functional class and the degree of cardiac involvement (as shown by cardiomegaly on chest radiography, low QRS voltage on electrocardiogram, the number of PVCs identified by 24-hour Holter monitoring, and enlargement of the left ventricle, systolic dysfunction and segmental or global wall motion abnormality on echocardiography). In relation to treatment, most of the individuals were using angiotensin receptor blockers (70%), diuretics (67%), and beta-blockers (67%). A statistically significant difference was found between the two groups only with respect to the use of beta-blockers and digoxin.



**Table 1 – General characteristics of the population**

Characteristic	All patients (n = 43)	Low risk (n = 23)	Intermediate-to- high risk (n = 20)	p-value*
Age ± SD (years)	58 ± 8	60 ± 8	57 ± 9	0.21
Male sex - n (%)	19 (44)	9 (39)	10 (50)	0.47
<b>NYHA Functional Class - n (%)</b>				
I	28 (65)	19 (83)	9 (45)	0.009
II	9 (21)	4 (17)	5 (25)	
III	6 (14)	0	6 (30)	
IV	0	0	0	
<b>Chest Radiography</b>				
Cardiomegaly - n (%)	20 (47)	2 (9)	18 (90)	<0.001
<b>Electrocardiogram</b>				
Low QRS voltage - n (%)	7 (16)	0	7 (35)	0.002
<b>24-hour Holter monitor</b>				
Frequent PVCs - n (%)	14 (33)	3 (13)	11 (55)	0.003
PVCs / 24h - n	1475	653	2420	0.02
NSVT - n (%)	9 (21)	3 (13)	6 (30)	0.17
<b>Echocardiography</b>				
Increased LVEDD - n (%)	17 (40)	2 (9)	15 (75)	<0.001
Segmental or global WMA - n (%)	23 (54)	4 (17)	19 (95)	<0.001
LVEF mean (%)	49	59	36	<0.001
Systolic dysfunction - n (%)	23 (54)	4 (17)	19 (95)	<0.001
<b>Medical Treatment</b>				
ACEI - n (%)	8 (19)	3 (13)	5 (25)	0.31
ARB - n (%)	30 (70)	17 (74)	13 (65)	0.53
Beta-blocker - n (%)	29 (67)	11 (48)	18 (90)	0.003
Hydralazine/Nitrate - n (%)	5 (12)	2 (9)	3 (15)	0.52
Diuretic - n (%)	29 (67)	14 (61)	15 (75)	0.32
Digoxin - n (%)	4 (9)	0	4 (20)	0.02
Amiodarone - n <sup>o</sup> (%)	6 (14)	2 (9)	4 (20)	0.29

\* Chi-square or Student's t-test. NYHA: New York Heart Association; PVCs: premature ventricular contractions; NSVT: sustained ventricular tachycardia; LVEDD: left ventricle diastolic diameter; WMA: wall motion abnormality; LVEF: left ventricular ejection fraction; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blockers.



Table 2 – Analysis of HRV in the time and frequency domains

Indexes (mean ± SD or median, IQR)	Low risk (n = 23)	Intermediate-to-high risk (n = 20)	p-value*
SDNN	140 ± 26	135 ± 58	0.72
rMSSD	30 (24 – 49)	39 (19 – 71)	0.10
pNN50	9.6 ± 9.8	15 ± 16	0.17
DELTA HF – DEEP BREATHING	38 (0 – 139)	49 (0 – 306)	0.37
DELTA LF – DEEP BREATHING	353 (48 – 814)	55 (0 – 601)	0.59
DELTA LF/HF – DEEP BREATHING	2 (0 – 5)	0.8 (0 – 2.5)	0.15
DELTA HF – VALSALVA MANEUVER	57 (17 – 185)	58 (16 – 506)	0.98
DELTA LF – VALSALVA MANEUVER	260 (-41 – 620)	96 (34 – 1098)	0.28
DELTA LF/HF – VALSALVA MANEUVER	2 (0.1 – 4.1)	1.1 (0.1 – 3.9)	0.47

\* Student's t-test. SDNN: standard deviation of the NN intervals; RMSSD: square root of the mean squared differences of successive NN intervals; pNN50: percentage of successive NN interval pairs with differences in duration >50 milliseconds; HF: high frequency; LF: low frequency; LF/HF: low/high frequency ratio.

Analysis of the HRV indexes in the time domain (SDNN, rMSSD and pNN50) and of the delta indexes in the frequency domain (delta values of HF, LF, and LF/HF for deep breathing and the Valsalva maneuver) between the groups (low risk versus intermediate-to-high risk) is shown in Table 2. HRV indexes in the time domain over a 24-hour period were similar in both groups ( $p=0.72$ ,  $p=0.10$ , and  $p=0.17$ , respectively). Likewise, no statistically significant differences were found between the risk categories with respect to the delta indexes in the frequency domain (deep breathing:  $p=0.37$ ,  $p=0.59$ , and  $p=0.15$ ; Valsalva maneuver:  $p=0.98$ ,  $p=0.28$ , and  $p=0.47$ , respectively).

The rate of arrhythmias (i.e. the number of PVCs/24 hours) for the groups (low risk versus intermediate-to-high risk) is shown in Table 3 and Figure 3. Comparison of the results showed a statistically significant difference between the categories of risk: low risk: 141 (3-421) and intermediate-to-high risk: 1,431 (361-3,684) ( $p=0.02$ ).

## Discussion

This is the first study to analyze HRV indexes in the time domain and the second study to analyze them in the frequency domain in patients with chronic Chagas cardiomyopathy classified into different mortality risk

categories according to the Rassi score. Analysis of the HRV indexes in the time domain over a 24-hour period (SDNN, rMSSD, pNN50) and in the frequency domain in 5-minute periods of time (delta values of HF, LF, and the LF/HF ratio for deep breathing and the Valsalva maneuver) showed no statistically significant differences between the low risk group and the group of intermediate-to-high risk despite the gradual increase in the rate of the ventricular arrhythmias found ( $p=0.02$ ).

In the present sample of 43 patients, mean age was  $58\pm 8$  years, with 44% being male and 86% being classified as NYHA functional class I-II. In the study conducted by Rassi et al.,<sup>9</sup> the most consistent evaluation of prognosis in cases of chronic Chagas cardiomyopathy performed up to the present time, mean age was  $47\pm 11$  years, 58% were male and 56% were NYHA class I-II.<sup>9</sup> In the most recent study of HRV in chronic Chagas cardiomyopathy, published by Merejo Peña et al., the mean age of the 60 participants evaluated was 63 years, 37% were male and 80% were NYHA class I-II.<sup>31</sup> Nevertheless, this latter study involved patients over 70 years of age and patients with DM. despite the fact that Rassi had established these conditions as exclusion criteria. In the present study, there were differences between the groups in relation to functional class and to the

**Table 3 – Analysis of the rate of ventricular arrhythmias**

Index	Low risk (n = 23)	Intermediate-to-high risk (n = 20)	p-value*
Number of PVCs/24h (median, IQR)	141 (3 – 421)	1431 (361 – 3684)	0.02

\* Student's t-test. PVCs: premature ventricular contractions.

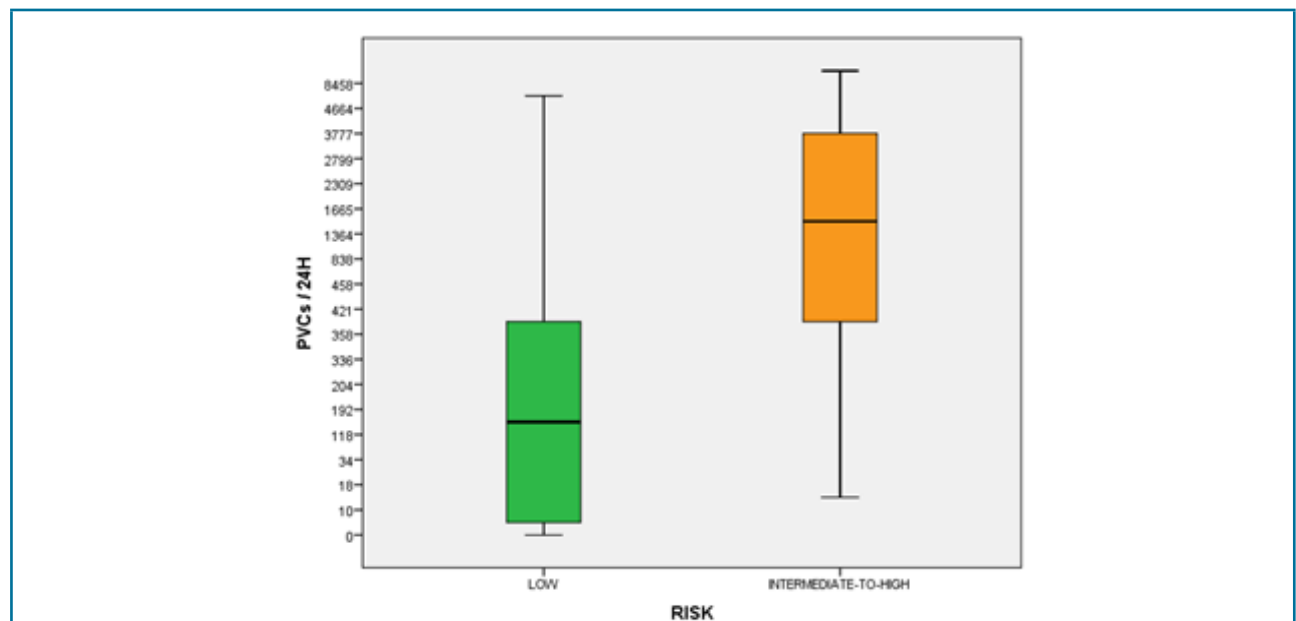


Figure 3 – Comparison of the number of PVCs/24 hours between the two risk groups.

degree of cardiologic involvement established using different supplementary methods. These findings were expected, since they reflect different categories of prognosis. The patients were using treatments that were adjusted according to their degree of cardiomyopathy, with differences being found between the groups with respect to their use of digitalis therapy and beta-blockers. The lack of uniformity in the use of beta-blockers by the patients was attenuated by treatment having been interrupted for 48 hours prior to the test, as specified in the study protocol.

Initial studies conducted by Guzetti et al.,<sup>32</sup> Menezes et al.,<sup>33</sup> Ribeiro et al.<sup>32-35,34</sup> among others evaluated HRV indexes in the time domain under a number of different conditions: healthy individuals versus patients with Chagas disease, patients with Chagas disease with and without cardiomyopathy, and even in different degrees of ventricular dysfunction; however,

results were largely inconsistent and conflicting. Furthermore, the objectives of those studies did not include establishing a possible association between autonomic dysfunction and prognosis<sup>32-35</sup> The present study, which found no statistically significant differences in HRV between the different categories of prognosis, appear to show that these indexes play no role in defining risk, further endorsing the previous findings reported by Rassi. In that study, dysautonomia (SDNN over a 24-hour period <100 milliseconds) was initially identified as a predictor of adverse outcome in the univariate regression model. Nevertheless, following multivariate analysis, the independent prognostic value of that variable as a predictor of adverse outcome was not confirmed, and it was not included in the final model of the score. Even fewer studies have evaluated the role of HRV in the frequency domain in Chagas disease. One such

study was that of Merejo Peña et al.,<sup>31</sup> who studied the behavior of the HF and LF/HF components between different Rassi risk categories following autonomic stimuli by means of controlled breathing and the tilt test. Those authors found that dysautonomia increased as a function of increasing risk.<sup>31</sup> The results of the present study failed to corroborate those findings.

The complex physiopathology that is characteristic of the disease includes processes of progressive neuronal depletion, persistent myocardial fibrosis, and consequent cardiac remodeling with neurohormonal activation and an increase in serum catecholamine levels, generating important substrates for arrhythmogenesis and resulting in a poorer prognosis compared to other cardiomyopathies.<sup>7-11</sup> In the present study, the progressive increase in the number of PVCs/24 hours found as a function of the increase in risk category gives further strength to this mechanistic model of an important association between ventricular arrhythmias and mortality in chronic Chagas cardiomyopathy. Nevertheless, it was impossible to demonstrate the role of the phenomenon of dysautonomia, as evaluated according to HRV, in this process. It is possible, however, that the very presence of arrhythmias, a common finding in this disease, could have hampered calculation of the HRV indexes. This may represent a limitation for the applicability of HRV in the evaluation of autonomic dysfunction in Chagas disease, differing from the well-established diagnostic and prognostic value of HRV indexes in other conditions.

Despite the apparent failure of HRV as a method with which to evaluate dysautonomia within the context of chronic Chagas cardiomyopathy, minor studies using scintigraphy with metaiodobenzylguanidine have shown not only the presence of autonomic dysfunction, but also the relevant role it plays. Associations have been found between denervation and: 1) early stages of the disease, 2) areas with fibrosis and abnormalities in motility, and 3) the rate/complexity of ventricular arrhythmias.<sup>16,18-20</sup>

Since few studies have been published on this subject and since those available were conducted using different diagnostic methods and yielded conflicting results, the existing evidence is insufficient and little is known regarding dysautonomia in Chagas disease. Major gaps persist in knowledge on the existence of a direct relationship between autonomic dysfunction and malignant arrhythmias/sudden cardiac death, as well as whether or not it could play a role in the prognosis of the disease. Moreover, unlike the case

with other cardiomyopathies, in chronic Chagas cardiomyopathy, individuals with preserved LVEF are still at a risk of death from arrhythmia, a risk that is under-quantified when evaluated only according to the conventional prognostic markers, as shown on some occasions by the finding of a low Rassi score in individuals who went on to die from sudden cardiac death.<sup>7,8,10,11</sup> These considerations highlight the need to improve the risk stratification model by identifying other predictive factors, including those associated with dysautonomia, in this population.

**Limitations:** The limited number of individuals in the high risk category and the consequent lack of homogeneity in the groups may have represented a limitation of this observational study. As found with other studies, this difficulty in the selection process could possibly be explained by the natural history of the disease itself, with prognosis being poor for the patients at this level of risk. With this in mind, the decision to perform the comparative analysis between two groups (low-risk versus intermediate-to-high risk) was already determined when the study was designed.

## Conclusion

The present results show that the evaluation of HRV by Holter monitoring failed to detect any difference in the patterns of dysautonomia in patients with chronic Chagas cardiomyopathy stratified into different risk categories. There was a progressive increase in the rate of arrhythmias as a function of increasing mortality risk, which could have hampered the performance of the method used.

## Author contributions

Conception and design of the research: Oliveira MAR, Rocha MS. Acquisition of data: Oliveira MAR, Nascimento TA. Analysis and interpretation of the data: Oliveira MAR, Nascimento TA, Rocha MS. Statistical analysis: Oliveira MAR. Obtaining financing: Oliveira MAR. Writing of the manuscript: Oliveira MAR, Rocha MS. Critical revision of the manuscript for intellectual content: Oliveira MAR, Nascimento TA, Feitosa-Filho GS, Ritt LEF, Cruz CMS, Rocha MS.

## Potential Conflict of Interest

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



## Sources of Funding

There were no external funding sources for this study.

## Study Association

This article is part of the thesis of master submitted by Michele Alves Rocha de Oliveira, from Escola Bahiana de Medicina e Saúde Pública.

## Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Santa Izabel under the protocol number 2738-073/CAAE: 91351918.7.0000.5520. 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.

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