

## Baroreflex Sensitivity and its Association with Arrhythmic Events in Chagas Disease

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### Abstract

**Background:** Sudden death is the leading cause of death in Chagas disease (CD), even in patients with preserved ejection fraction (EF), suggesting that destabilizing factors of the arrhythmogenic substrate (autonomic modulation) contribute to its occurrence.

**Objective:** To determine baroreflex sensitivity (BRS) in patients with undetermined CD (GI), arrhythmogenic CD with nonsustained ventricular tachycardia (NSVT) (GII) and CD with spontaneous sustained ventricular tachycardia (STV) (GIII), to evaluate its association with the occurrence and complexity of arrhythmias.

**Method:** Forty-two patients with CD underwent ECG and continuous and noninvasive BP monitoring (TASK force monitor). The following were determined: BRS (phenylephrine method); heart rate variability (HRV) on 24-h Holter; and EF (echocardiogram).

**Results:** GIII had lower BRS (6.09 ms/mm Hg) as compared to GII (11.84) and GI (15.23). The difference was significant between GI and GIII ( $p = 0.01$ ). Correlating BRS with the density of ventricular extrasystoles (VE), low VE density ( $< 10/h$ ) was associated with preserved BRS. Only 59% of the patients with high VE density ( $> 10/h$ ) had preserved BRS ( $p = 0.003$ ). Patients with depressed BRS had higher VE density ( $p = 0.01$ ), regardless of the EF. The BRS was the only variable related to the occurrence of SVT ( $p = 0.028$ ).

**Conclusion:** The BRS is preserved in undetermined CD. The BRS impairment increases as disease progresses, being more severe in patients with more complex ventricular arrhythmias. The degree of autonomic dysfunction did not correlate with EF, but with the density and complexity of ventricular arrhythmias. (Arq Bras Cardiol. 2014; 102(6):579-587)

**Keywords:** Chagas Disease; Arrhythmias, Cardiac; Death, Sudden; Baroreflex / physiology; Analysis of Variance.

### Introduction

The arrhythmogenic form of chronic Chagas heart disease has a high ventricular arrhythmia density, which not only causes symptoms<sup>1</sup>, but is a frequent cause of sudden death (SD)<sup>2,3</sup>. It is worth noting the scarcity of symptoms and the normal cardiac size in contrast to the anatomicopathological changes found<sup>4</sup>. Determining the mechanism of SD in Chagas disease remains a challenge. However, evidence has shown that, because it is a fibrosing pathology<sup>5,6</sup>, the appearance of unidirectional block and slow conduction zones is common, which is the ideal scenario for reentrant ventricular arrhythmias, which can be confirmed during programmed ventricular stimulation<sup>7-10</sup>.

Of the factors that contribute to the occurrence of malignant ventricular arrhythmias, in addition to myocardial structural abnormalities, ventricular extrasystoles (VE), which initiate the reentrant process, stand out. However, not every patient with ventricular arrhythmia dies suddenly. Probably the model is only complete when functional factors appear, favoring the occurrence of arrhythmias (heart baroreflex control and autonomic dysfunction supposed to play an important role in the genesis of sudden death)<sup>11-14</sup>. The following tools of cardiovascular autonomic evaluation have been used: analysis of baroreflex sensitivity (BRS), which quantifies the incremental capacity of vagal activity; and heart rate variability (HRV), which assesses the tonic vagal activity on the heart. The BRS has been consolidated as an independent marker of mortality risk in ischemic patients, being used as a clinical and prognostic tool in a variety of cardiovascular diseases.

Special attention should be given to the asymptomatic subgroup, which, despite the lack of triggering factors or of structural myocardial changes, corresponds to a significant number of cases of SD<sup>15-17</sup>.

The autonomic dysfunction of Chagas disease can be detected prior to ventricular dysfunction, at all phases of the disease<sup>18,19</sup>. Thus, the detailed study of the autonomic

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function in several forms of Chagas disease is mainly aimed at determining possible elements that can identify individuals at risk for developing complex arrhythmias and/or SD.

## Objective

The primary objective of this study was to determine BRS in patients with the following forms of Chagas disease: undetermined (Group I); arrhythmogenic with nonsustained ventricular tachycardia (NSVT) (Group II); arrhythmogenic with spontaneous sustained ventricular tachycardia (SVT) (Group III). In addition, it was aimed at assessing the association between ventricular arrhythmia severity and the impairment degree of BRS.

The secondary objective was to assess the HRV by using 24-hour Holter monitoring, and, by using Doppler two-dimensional echocardiography, the left ventricular ejection fraction (LVEF) and the dimensions of cardiac left cavities.

## Case series and methods

This study selected 42 individuals with positive serology for Chagas disease, confirmed by the presence of at least two serologic reactions (indirect hemagglutination, indirect immunofluorescence or immunoenzymatic assay – ELISA), mainly originated from the outpatient clinic of the Instituto do Coração, of the Hospital das Clínicas of the Medical School of the Universidade de São Paulo (InCor-FMUSP) (Clinical Unit of Arrhythmia and Unit of Cardiomyopathies). The research protocol was approved by the Scientific Committee of the InCor-FMUSP and the Committee on Ethics and Research (CAPPesq) of the InCor-FMUSP.

The individuals were divided into three groups: Group I (GI), individuals with the undetermined form of Chagas disease; Group II (GII), patients with Chagas disease and complex ventricular arrhythmia, including NSVT; Group III (GIII), patients with Chagas disease and complex ventricular arrhythmia and at least one spontaneous SVT recording, after preliminary cardiologic evaluation with 12-lead electrocardiogram, echocardiogram, 24-hour Holter monitoring and exercise testing. The undetermined form of the disease was defined according to the already established criteria: asymptomatic individuals with at least two positive serological tests for Chagas disease and normal results of electrocardiogram, chest X-ray and esophageal and colon contrast-medium tests<sup>20</sup>. The ventricular arrhythmia recordings for inclusion in GII and GIII came from previous tracings of 24-hour Holter and 12-lead electrocardiogram performed at emergency rooms or triggered during exercise testing.

Group I comprised 16 individuals [11 (68.75%) females and 5 (31.25%) males]. Group II comprised 19 patients [14 females (73.68%) and 5 males (26.32%)] as follows: 17 with NSVT recorded on 24-hour Holter and 2 recorded during exercise testing. Group III comprised 7 patients [4 (57.14%) females and 3 (42.86%) males] as follows: 5 with SVT recorded on 12-lead electrocardiogram and 2 recorded on 24-hour Holter.

All GI patients were asymptomatic, while 84.2% of GII and 43% of GIII patients had symptoms, the most frequent being palpitations, dyspnea and chest pain. Syncope was reported by two GII individuals. Of the 7 GIII individuals, 3 had unstable SVT, requiring electrical cardioversion.

The medicines, such as beta-blockers, calcium channel blockers, digoxin and aldosterone antagonists, were suspended for at least three half-lives before the procedure, and the patients were instructed to have a light caffeine-free breakfast, in addition to avoid alcoholic beverage in the 24 hours preceding the exam.

Noninvasive cardiovascular monitoring was performed with the Task Force® Monitor system (CNSysteSD Medizintechnik GmbH, version 2.2.12.0, Austria)<sup>21</sup>. The parameters assessed were HRV, systolic and diastolic blood pressure (SBP and DBP, respectively) and BRS, blood pressure (BP) being measured via digital photoplethysmography<sup>22,23</sup> and electrocardiogram acquired by using three adhesive electrodes attached to the chest, to analyze the intervals between R waves (R-R intervals). A digital cuff with continuous pressure was positioned around the middle phalanx of the right third and fourth fingers, and another, on the left forearm. The oscillometric measures of BP were transformed into absolute values for each consecutive beat. The acquired signs were shown on screen, and, by the end of the procedure, they were printed or stored in a file under a format of easy conversion.

After a rest period, consecutive, continuous 15-minute recordings of SBP and HR were obtained for spontaneous BRS analysis, which was performed according to the sequence methodology<sup>24</sup>. That methodology involves a computer program and is based on the identification, on the time domain, of the spontaneous occurrence of sequences of at least three consecutive heartbeats, in which there is a progressive increase of SBP and consequent R-R interval prolongation or a progressive decrease of SBP and consequent R-R interval shortening. To be considered by the program, the modifications in SBP and R-R interval should be equal to or greater than 1 mm Hg and 5 ms, respectively. Linear regression was applied to all sequences, and the mean of the values obtained in all sequences was calculated for each patient, representing the measure of spontaneous BRS (in ms/mm Hg). Those values were automatically provided by the Task Force® Monitor system.

After spontaneous BRS recording, the volunteers had their BP and HR continuously monitored, as previously described. Then, phenylephrine was infused rapidly (30 seconds) and intravenously, at the dose of 2-4 mcg/kg, in at least three bolus, at 10-minute intervals, to increase SBP by 15 to 40 mm Hg<sup>25</sup>. If SBP did not increase as expected (> 15 mm Hg), a new infusion was performed with 25-50 increments up to the maximum dose of 10 mcg/kg.

Consecutive SBP values and corresponding changes in R-R intervals (with beat delay) were plotted, resulting in the slope of a line of linear regression. The measures chosen for analysis were those with a strong linear correlation coefficient (coefficient  $r \geq 0.7$ ). The BRS measure considered (expressed as ms/mm Hg) was equivalent to the calculated mean of the values obtained in the infusions with the greatest reproducibility for each patient (semiautomatic method).

The following dimensions of the left cardiac cavities were assessed on echocardiography and expressed in millimeters (mm): end-systolic left ventricular diameter (ESLVD); end-diastolic left ventricular diameter (EDLVD); and left atrial diameter (LAD). Ejection fraction (EF) was calculated by using the Teichholz method<sup>26</sup>.

## Statistical analysis

Data were organized in tables, graphs and charts of descriptive measures. For inferential statistical analysis, the following tests were performed: Kolmogorov-Smirnov test, aimed at analyzing the normality of the BRS variable; and Levene's test to assess the equality of the variances for the three groups. The means of the groups were compared by use of analysis of variance (ANOVA), and multiple comparisons used Tukey test (equal variances) or Games-Howell test (unequal variances). Pair analysis was performed with Student *t* test.

The correlation between continuous variables was performed with Pearson linear correlation coefficient (*r*), and the association between categorical variables, by use of chi-square test or maximal likelihood ratio. The odds ratio (OR) and their confidence intervals (95%CI) for SVT and probable factors influencing its appearance were calculated. Backward stepwise logistic regression analysis was performed, and the final adjusted model was obtained with a 5% significance level. Analyses with  $p < 0.05$  were considered statistically significant.

The SPSS software, version 14.0, was used for data processing.

## Results

Group I comprised 16 individuals, GII, 19 patients, and GIII, 7 patients. No significant difference was observed between the groups regarding sex distribution. The mean ages in the groups were as follows: GI, 49.5 years; GII, 50.26 years; and GIII, 41.86 years. Table 1 shows the clinical characteristics of the groups.

Statistically significant differences were observed between GI and GIII regarding EDLVD ( $p = 0.001$ ), and between the three groups regarding ESLVD.

Regarding LVEF, statistical difference was observed between GI and GIII ( $p = 0.000$ ), and between GII and GIII ( $p = 0.02$ ).

### 24-hour Holter

Graph 1 shows the distribution and density of VE observed on 24-hour Holter monitoring. The greatest ventricular ectopia density was found in GII.

### Measures of spontaneous BRS

Table 2 shows the characteristics of the groups studied regarding spontaneous BRS.

### Measures of induced baroreflex sensitivity

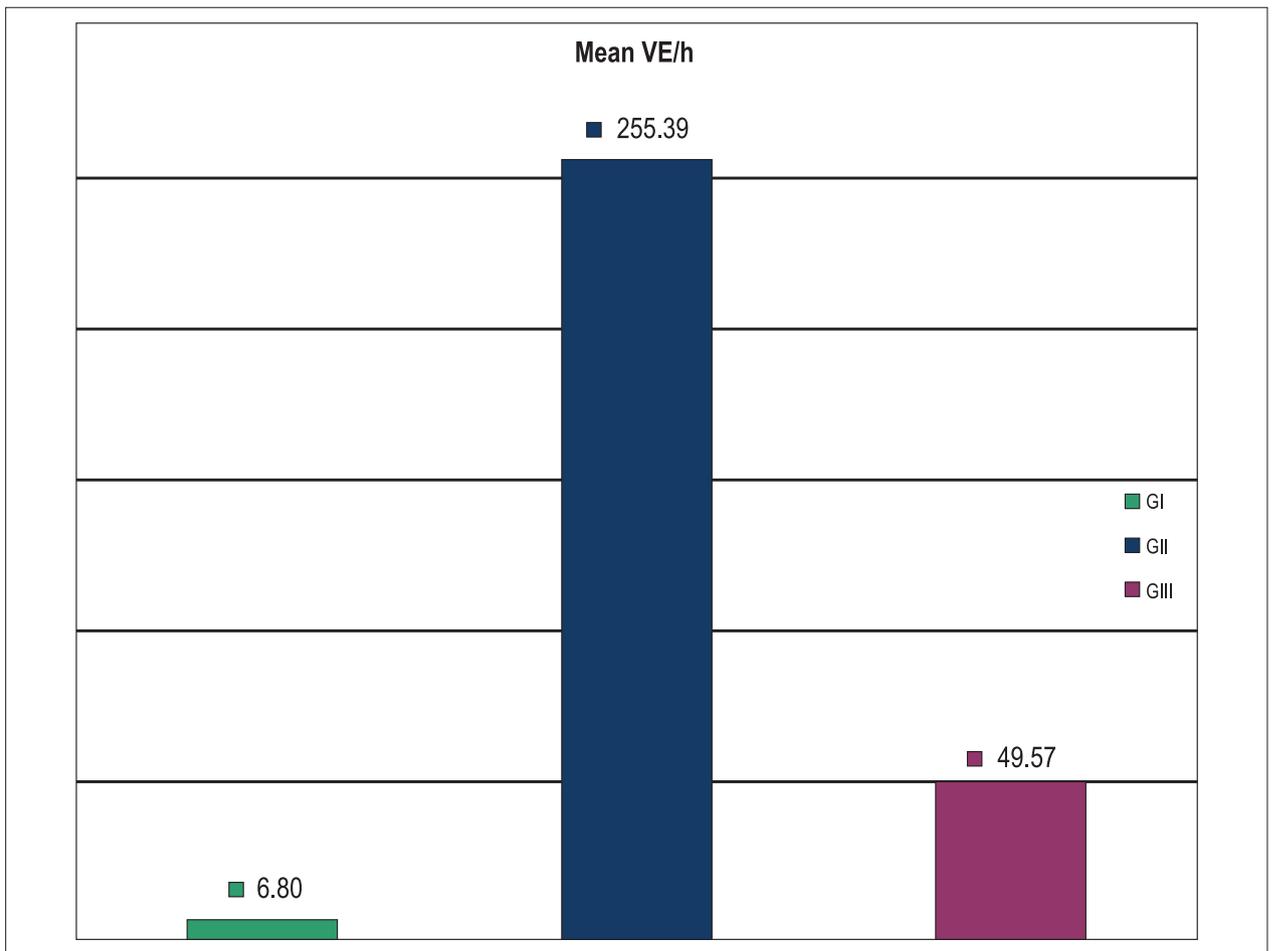
Statistically significant difference was observed between the groups regarding the assessment of BRS in response to phenylephrine (Table 3).

After comparing the groups, statistically significant difference was observed between GI and GIII ( $p = 0.01$ ), but no difference was observed between GI and GII. Pearson's correlation coefficient *r* was used to assess the correlation between the variables. Correlating BRS and density of ventricular ectopias, a higher density of ventricular ectopias ( $p = 0.01$ ) was observed in the subgroup with moderately depressed BRS (3.0 – 6.0 ms/mm Hg). A positive association between low ventricular ectopia density and preserved BRS was also observed ( $p = 0.003$ ) (Graph 2).

**Table 1 – Clinical data of the sample studied (n = 42)**

|                          | GI             | II             | GII           | P        |
|--------------------------|----------------|----------------|---------------|----------|
| Age (years)              | 49.50 ± 6.70   | 50.26 ± 7.65   | 41.86 ± 7.66  | 0.037    |
| BMI (kg/m <sup>2</sup> ) | 25.70 ± 3.09   | 26.50 ± 4.09   | 23.67 ± 5.55  | 0.293    |
| Race (B/NB)              | (16/00)        | (18/01)        | (7/00)        | -        |
| SBP (mm Hg)              | 115.94 ± 14.74 | 117.26 ± 14.74 | 117.14 ± 7.55 | 0.943    |
| DBP (mm Hg)              | 75.00 ± 8.16   | 76.58 ± 8.17   | 71.43 ± 12.15 | 0.431    |
| HR (beats/min)           | 70.99 ± 6.29   | 68.53 ± 9.31   | 58.43 ± 7.20  | 0.003    |
| NYHA FC I                | 100%           | 94.7%          | 85.7%         | 0.286    |
| Mean VE/24 h             | 6.8            | 255.39         | 49.5          | -        |
| LVEF (%)                 | 68.63 ± 8.29   | 59.37 ± 13.08  | 44.86 ± 14.98 | < 0.0001 |
| EDLVD (mm)               | 48.13 ± 4.09   | 52.95 ± 6.74   | 59.29 ± 7.45  | 0.001    |
| ESLVD (mm)               | 30.50 ± 3.46   | 36.79 ± 8.46   | 44.86 ± 8.74  | < 0.0001 |
| LAD (mm)                 | 33.94 ± 3.15   | 36.21 ± 5.77   | 36.14 ± 5.46  | 0.357    |
| Amiodarone (200 mg/d)    | 0 (0%)         | 3 (15.8%)      | 3 (42.9%)     | 0.016    |
| Amiodarone (400 mg/d)    | 0 (0%)         | 0 (0%)         | 3 (42.9%)     | 0.002    |

Values shown as mean ± SD; GI: group I; GII: group II; GIII: group III; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; NYHA FC: New York Heart Association functional class (%); ESLVD: end-systolic left ventricular diameter; EDLVD: end-diastolic left ventricular diameter; LVEF: left ventricular ejection fraction (%); LAD: left atrial diameter.



Graph 1 – Distribution of ventricular extrasystoles (VE) in the groups studied.

Table 2 – Characterization of the groups studied regarding spontaneous baroreflex sensitivity (ms/mm Hg)

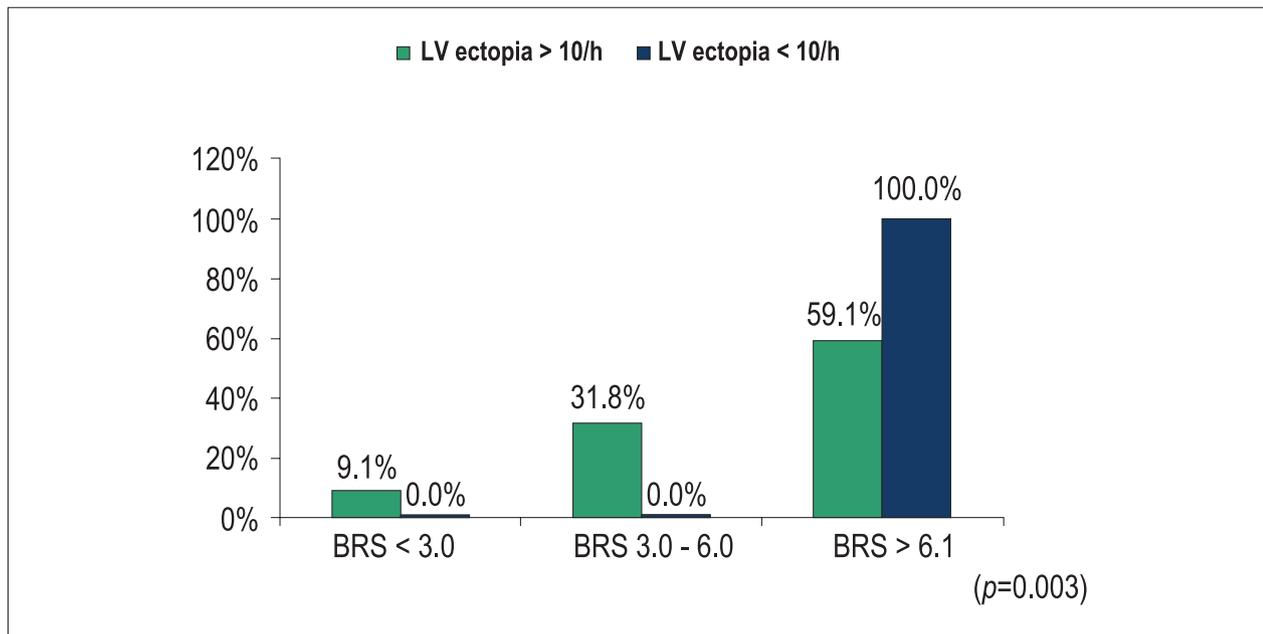
| Group | n  | Descriptive measures |         |         |
|-------|----|----------------------|---------|---------|
|       |    | Mean ± SD            | Minimum | Maximum |
| GI    | 13 | 13.38 ± 5.08         | 6.34    | 23.32   |
| GII   | 18 | 12.95 ± 4.29         | 5.93    | 21.04   |
| GIII  | 5  | 9.54 ± 3.63          | 3.25    | 12.21   |

Note: values expressed as mean ± standard deviation; GI: group I; GII: group II; GIII: group III.  
p = 0.265

Table 3 – Measures of baroreflex sensitivity (BRS) in the groups studied (ms/mm Hg)

| Group | n  | Descriptive measures |         |         |
|-------|----|----------------------|---------|---------|
|       |    | Mean ± SD            | Minimum | Maximum |
| GI    | 16 | 15.23 ± 7.61         | 6.12    | 30.27   |
| GII   | 19 | 11.84 ± 6.62         | 3.08    | 27.65   |
| GIII  | 7  | 6.09 ± 3.38          | 2.78    | 10.84   |

Note: values expressed as mean ± standard deviation; GI: group I; GII: group II; GIII: group III.  
p = 0,01



**Graph 2** – Correlation between the measure of baroreflex sensitivity (BRS) and density of ventricular arrhythmias.

Note: BRS: baroreflex sensitivity; LV ectopia > 10/h: left ventricular ectopia greater than 10 per hour; LV ectopia < 10/h: left ventricular ectopia smaller than 10 per hour.

The variables BRS, LVEF, EDLVD and VE/h were tested in the logistic regression model. After multivariate analysis, BRS was the only variable related to SVT appearance ( $p = 0.028$ ).

## Discussion

Sudden death is the major cause of death in Chagas disease, present in 55% to 65% of the cases<sup>27</sup>. It is worth noting that many of such SD affect patients with normal or close-to-normal left ventricular function. The risk of SD is known not to be the same for all patients with Chagas disease. Participation of the autonomic nervous system, mainly decreased parasympathetic activity, has been evidenced as a contributing factor in the genesis of ventricular arrhythmias and SD in ischemic heart disease<sup>28</sup>. Early identification of patients with chronic Chagas heart disease at risk of developing potentially lethal arrhythmic events is extremely important<sup>29</sup>, and autonomic function determination could be used as a noninvasive method for risk stratification in that population.

In this study, the three groups of patients did not differ regarding most of the clinical characteristics evaluated. However, the mean age of GIII patients (41.86 years) was lower than those of GI and GII patients (49.50 and 50.26 years, respectively). Vagal activity is known to decrease with age in healthy individuals. In our case series, GIII patients, although younger and probably with a shorter exposure to disease, showed a more impaired parasympathetic activity, in addition to higher arrhythmia complexity, which is in accordance with the findings of the ATRAMI study<sup>30</sup>. That study encompassed 1284 patients with recent myocardial infarction, whose HRV had been quantified as standard deviation of normal to normal RR intervals (SDNN) and BRS measurement with the phenylephrine method. The BRS measurement had

no prognostic value in the subgroup of patients older than 65 years; however, it showed a strong statistical power in the younger subgroup. Thus, advanced age was an exclusion criterion in our population.

Our observations reveal a way to identify worse disease progression, since GIII patients had more severe clinical manifestations, although they were younger, most in functional class I and with relatively preserved ventricular function. Our data revealed that, although most patients studied had preserved EF, the means were lower in GIII as compared with those in GI and GII, the same occurring with EDLVD. The clinical progression of the disease is dynamic, involving both autonomic function deterioration and progressive structural myocardial impairment. It is still unknown to what extent those two factors develop concomitantly or in an independent way. Further more detailed studies assessing the interdependence between structural and autonomic injuries are required.

### Phenylephrine-induced baroreflex sensitivity

In our study, phenylephrine-induced BRS was significantly reduced in the subgroup of patients with more complex arrhythmia (GIII), such as spontaneous SVT. It is worth noting that those changes in baroreflex were mainly shown in patients with NYHA functional class I. Over the past two decades, cardiac BRS has been recognized as a cardiovascular risk marker. The first clinical evidence has been identified in a study performed with 78 patients after myocardial infarction<sup>31</sup>, whose BRS was assessed in a 24-month follow-up. All 7 patients dead during follow-up had an extremely decreased BRS. However, that method has been consolidated as an independent marker of mortality risk in ischemic patients only after the multicenter

ATRAMI study<sup>30</sup>. Since then, it has been largely used for risk stratification in several populations, such as those with hypertension, diabetes and dilated cardiomyopathies.

In chronic Chagas heart disease, the autonomic nervous system involvement, both sympathetic and parasympathetic, has been well demonstrated from the histopathological and functional viewpoints. However, only a few studies have used BRS as a marker of the autonomic function in that population, and, to our knowledge, it has not been used to stratify the risk of arrhythmic events. Autonomic dysfunction is more exuberant in the cardiodigestive and digestive forms of the disease<sup>32</sup>. However, in the undetermined form of Chagas disease, the autonomic function assessment has conflicting results, which have varied from the single sympathetic or mainly parasympathetic involvement<sup>33</sup>, to no impairment at all. Junqueira Júnior et al.<sup>32</sup>, in 1985, demonstrated that BRS was significantly lower in 14 chagasic patients as compared with a control group (healthy); however, when only patients with the undetermined and digestive forms of the disease were studied, BRS was normal. In 2004, Villar et al.<sup>34</sup>, studying 31 asymptomatic chagasic patients, one group with electrocardiographic changes and the other with no changes, concluded that cardiovagal dysfunction can be early documented by measuring BRS, even in those with no electrocardiographic changes. In addition, they showed that cardiac autonomic assessment could be useful to identify subclinical disease.

In 1998, Marin Neto et al.<sup>19</sup>, assessing 31 chagasic patients at the initial phase of the disease, studied cardiac autonomic control and biventricular function by using radionuclide angiography, Valsalva maneuver, tilt testing and BRS. Their results showed that cardiac autonomic dysfunction is prominent in patients with the digestive form, but not in those with the undetermined form of the disease. In our case series, patients with the undetermined form showed preserved BRS measures.

### Spontaneous baroreflex sensitivity

Our results showed greater impairment of spontaneous BRS in GIII patients. Despite being only a tendency, such difference should be valued. Considering GI, GII and GIII and based on spontaneous BRS determination, autonomic impairment increases as disease progresses.

In addition to being simple and easily obtained, an advantage of the method is that it is based on standardized, automated and computerized measures, which almost eliminate the intra- and interobserver variations. The sequence methodology used to determine spontaneous BRS was applied in this study. According to Parlow et al.<sup>24</sup>, the method reflects primarily the baroreflex control of cardiac vagal activity (because most sequences are smaller than six beats) and was proposed as a reliable alternative to determine BRS in healthy<sup>35</sup> and in hypertensive patients<sup>36</sup>. However, despite the strong linear association, the agreement between spectral measures and phenylephrine in estimating BRS is weak. The baroreflex response to the sinus node is believed to be different under the influence of different methodologies<sup>37</sup>. Although provocation with vasoactive drugs has been considered the gold-standard method to assess BRS, the use of those drugs can cause

mechanical changes in the arterial wall, where baroreceptors are located, and result in a more intense and less physiological stimulus of reflex HR adaptation in face of a BP change<sup>24</sup>. By using the vasoactive drug, relatively greater BP changes are observed, and can alter not only the linear portion of the stimulus-response curve, but can also reach the portions where baroreceptor activity approaches saturation, and where the BRS is lower<sup>24</sup>. Another contributing factor is the fact that BP changes in spontaneous measurements have smaller amplitudes, and, thus, the method cannot assess the baroreflex function in its entire extension<sup>24</sup>. Thus, both techniques are considered non-exclusionary, but complementary, in assessing baroreflex function.

### The correlations

Previewing the occurrence of sustained ventricular arrhythmias in individuals with preserved ventricular function is a great challenge in chagasic cardiomyopathy, because of the high risk of SD in that population. The high density of ventricular ectopias and the presence of NSVT are known predictive criteria of cardiovascular risk in ischemic patients. However, in chagasic patients with relatively preserved ventricular function, its significance remains controversial.

Rassi et al.<sup>38</sup> have recently published a score to stratify the mortality risk of chagasic patients. In that cohort, the authors have found, after uni- and multivariate analyses, six clinical variables that predict poor prognosis, such as NSVT. In addition, they have reported that the combination of NSVT with left ventricular dysfunction was associated with a 15-time greater risk of death in the patients studied.

Our data revealed a direct correlation between the autonomic dysfunction degree and the density of ventricular ectopias on 24-hour Holter monitoring. In addition, 100% of the patients with preserved BRS (> 6.0 ms/mm Hg) had density of ventricular ectopias smaller than 10 per hour, being then considered at lower risk for events<sup>39</sup>. An inverse correlation between the SDNN index and the density of ventricular ectopias was also observed.

When assessing different noninvasive methods of risk stratification for a certain cardiovascular condition, data regarding ischemic cardiopathy are usually extrapolated from the literature. However, the pathophysiological peculiarities of chagasic cardiomyopathy are not necessarily comparable to those of coronary arterial disease or dilated disease of other etiologies.

Up to now, there is no method that alone can definitively predict the risk of ventricular arrhythmias and of SD in the most varied clinical situations, in the different populations studied. In addition, the cardiovascular risk has not evolved in a linear way, changing with disease progression and/or the treatment used. Therefore, the combination of various tests available is the best way to increase the risk stratification accuracy, and, consequently, to optimize the treatment and cost-effectiveness of therapeutic interventions.

### Conclusions

Baroreflex sensitivity is preserved in the undetermined form of Chagas disease. The BRS impairment is progressive

and accompanies the disease evolution, being more intense in patients with more complex ventricular arrhythmias. The degree of autonomic dysfunction did not correlate with ventricular function, but with the density and complexity of spontaneous ventricular arrhythmias.

### Clinical implications

We believe that BRS analysis, a simple low-cost methodology, can be clinically used to identify, among chagasic patients with the arrhythmogenic form and preserved ventricular function, those at higher risk to develop potentially malignant arrhythmias, and, thus, to guide earlier interventions.

### Study limitation

Because of the small sample size, prospective studies, involving a greater number of patients, should be conducted to confirm the results.

### Author contributions

Conception and design of the research: Santos AM, Scanavacca MI, Darrieux F, Ianni B, Melo SL, Santos Neto F,

Sosa E, Hachul DT; Acquisition of data: Santos AM, Ianni B, Santos Neto F, Hachul DT; Analysis and interpretation of the data: Santos AM, Scanavacca MI, Darrieux F, Melo SL, Pisani C, Hachul DT; Statistical analysis: Santos AM, Scanavacca MI, Pisani C, Hachul DT; Writing of the manuscript: Santos AM, Santos Neto F, Hachul DT; Critical revision of the manuscript for intellectual content: Santos AM, Scanavacca MI, Darrieux F, Ianni B, Melo SL, Pisani C, Santos Neto F, Sosa E, Hachul DT.

### Potential Conflict of Interest

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

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### Study Association

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