

Assessment of Autonomic Function by Phase Rectification of RR-Interval Histogram Analysis in Chagas Disease

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Abstract

Background: In chronic Chagas disease (ChD), impairment of cardiac autonomic function bears prognostic implications. Phase-rectification of RR-interval series isolates the sympathetic, acceleration phase (AC) and parasympathetic, deceleration phase (DC) influences on cardiac autonomic modulation.

Objective: This study investigated heart rate variability (HRV) as a function of RR-interval to assess autonomic function in healthy and ChD subjects.

Methods: Control (n = 20) and ChD (n = 20) groups were studied. All underwent 60-min head-up tilt table test under ECG recording. Histogram of RR-interval series was calculated, with 100 ms class, ranging from 600–1100 ms. In each class, mean RR-intervals (MNN) and root-mean-squared difference (RMSNN) of consecutive normal RR-intervals that suited a particular class were calculated. Average of all RMSNN values in each class was analyzed as function of MNN, in the whole series (RMSNN_T), and in AC (RMSNN_{AC}) and DC (RMSNN_{DC}) phases. Slopes of linear regression lines were compared between groups using Student t-test. Correlation coefficients were tested before comparisons. RMSNN was log-transformed. ($\alpha < 0.05$).

Results: Correlation coefficient was significant in all regressions ($p < 0.05$). In the control group, RMSNN_T, RMSNN_{AC}, and RMSNN_{DC} significantly increased linearly with MNN ($p < 0.05$). In ChD, only RMSNN_{AC} showed significant increase as a function of MNN, whereas RMSNN_T and RMSNN_{DC} did not.

Conclusion: HRV increases in proportion with the RR-interval in healthy subjects. This behavior is lost in ChD, particularly in the DC phase, indicating cardiac vagal incompetence. (Arq Bras Cardiol. 2015; 104(6):450-456)

Keywords: Chagas Disease; Chagas Cardiomyopathy; Heart Rate; Organ Dysfunction Scores; Sympathetic Nervous System; Charts; Statistics as Topic.

Introduction

Chagas disease (ChD) is a major cause of cardiomyopathy in Latin America. It has been estimated that 8–11 million people are currently infected by *Trypanosoma cruzi* worldwide, potentially becoming a significant healthcare-related problem in Europe and in the United States due to migration^{1,2}. In chronic ChD, autonomic dysfunction has been associated with impairment of both parasympathetic and sympathetic limbs^{3–5}, with prognostic implications⁶.

Heart rate variability (HRV) analysis is a powerful and simple method for assessing autonomic influence on the sinus node and risk stratification in many cardiac diseases^{7,8}. On routine clinical assessment, parameters in time domain are usually estimated during a predefined time sequence

of normal-to-normal RR-intervals. Among the parameters usually employed, root-mean-squared difference (RMSNN) is particularly useful, as it expresses the amount of energy associated with data variability⁷. However, none of these indexes distinguish between vagal and sympathetic effects.

Recently, an approximate isolation of distinct autonomic contribution on heart rate (HR) has been possible by assessing the capability of RR-interval series to accelerate (AC) or decelerate (DC), representing sympathetic and parasympathetic contributions, respectively. To further accomplish this task, it was initially detected that if a particular RR-interval changed relative to the previous one, the corresponding RR-interval was separated in a new series^{9,10}.

In healthy subjects, it has been demonstrated that HRV indices tended to increase as RR-intervals enlarged^{11,12}. On the other hand, this relationship may be lost during a disease state and may further precipitate some forms of ventricular arrhythmia, such as long QT syndrome, and ischemic cardiomyopathy¹³. Thus, the aims of this study were (i) to assess RMSNN index on AC and DC phases of RR-interval series in order to isolate sympathetic and parasympathetic effects, respectively, and (ii) to correlate RMSNN and mean RR-intervals (MNN) to assess heart rate dependence of autonomic modulation index in chronic ChD.

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Methods

Study population

ECG signals were extracted from an existing high resolution ECG database¹⁴. The study protocol was approved by the Hospital Universitário Clementino Fraga Filho Ethics Committee and informed consent was obtained from each volunteer. A group of gender-matched 20 healthy sedentary participants [Control group, (mean age \pm SD) 51.1 ± 17.6 years] and 20 subjects with chronic ChD (Chagas group, 55 ± 10.3 years) were studied. Chronic ChD subjects were enrolled to the study based on spontaneous demand. Due to the exploratory nature of the study, the number of participants was arbitrarily defined and equally distributed between groups.

According to surface ECG data analysis, in ChD group, seven had normal ECG. Among 13 subjects with abnormal ECG, nine showed left atrial overload based on Morris criteria, nine had left anterior fascicular block, nine had complete right bundle branch block and one had first degree AV block. Two subjects showed isolated supraventricular tachycardia and four showed isolated ventricular premature beats.

Additionally, all participants met the following criteria: (i) no intake of nutritional supplements or potential ergogenic aids of any type (e.g., exogenous anabolic androgenic steroids); (ii) non-smokers; (iii) normal blood pressure; (iv) non-diabetic; (v) no history of alcohol addiction; (vi) no history of thyroid dysfunction; and (vii) not taking medications that affect cardiac electrical properties and/or autonomic function.

Signal acquisition and processing

All subjects underwent 60-min head-up tilt test (HUTT) under modified Westminster protocol¹⁵ at 70° and continuous high-resolution ECG recording in an acclimatized (27°C) and quiet room. Subjects were oriented to withhold exercise for 48 h before the exam, fast for at least 4 h, and avoid taking caffeine-containing beverages on the day of the exam. Before ECG recording, subjects remained in the supine position for at least 5 min in order to reduce orthostatic autonomic memory on spontaneous RR-interval variations^{16,17}.

ECG signal acquisition periods were characterized by 10 min of supine rest followed by 40-min HUTT and another 10-min supine rest. Accordingly, HRV was expected to be influenced by two predominant autonomic inputs: parasympathetic input during supine rest, and sympathetic input during tilt⁷.

High-resolution ECG signals were acquired using modified bipolar Frank XYZ orthogonal leads¹⁸. Digital data were processed with custom-made pattern recognition software¹⁹⁻²¹. The analysis of the HRV was done by extraction of the normal RR-intervals, after detection of the QRS complex using a low-pass triangular filter. Any RR-interval that exhibited more than 20% change from the previous RR-interval were excluded, as they were likely to be related to measurement noise or ectopic beats^{21,22}.

Instantaneous RR-interval analysis

The RR-interval histogram was constructed for each individual series and split into 100-ms width classes, ranging from 600–1100 ms. For each histogram class, and respective to each RR-interval series, *mean* (MNN) and *root-mean-square difference* ($RMSNN$) of consecutive normal RR-intervals suiting a particular class were calculated. Only the pairs of consecutive normal RR-intervals for individual series that were inside a particular class of the RR histogram were analyzed together.

For a particular histogram class (*class*) of the i^{th} series, containing $N_{i,class}$ RR-intervals, calculation of the mean ($M_{i,class}$) and the root-mean-squared difference ($RMS_{i,class}$) of the normal RR-intervals was performed as follows:

(1)

$$M_{i,class} = \frac{\sum_{k=1}^{N_{i,class}} RR_k}{N_{i,class}}$$

(2)

$$RMS_{i,class} = \sqrt{\frac{\sum_{k=1}^{N_{i,class}} (RR_k - RR_{k-1})^2}{N_{i,class}}}$$

For each histogram, classes with intervals of 30 or less were excluded to avoid bias due to lack of statistical precision.

The values of the variables $M_{i,class}$ and $RMS_{i,class}$ were aggregated to the respective histogram class. The ensemble mean (MNN_{class}) and root-mean-squared difference ($RMSNN_{class}$) of RR-intervals for each histogram class, weighed by the respective degree-of-freedom ($\eta_{i,class}$), were calculated according to:

(3)

$$MNN_{class} = \frac{\sum_{i=1}^{20} M_{i,class} \cdot (\eta_{i,class}^{+1})}{\sum_{i=1}^{20} (\eta_{i,class}^{+1})}$$

(4)

$$RMSNN_{class} = \sqrt{\frac{\sum_{i=1}^{20} (RMS_{i,class})^2 \cdot (\eta_{i,class}^{+1})}{\sum_{i=1}^{20} (\eta_{i,class}^{+1})}}$$

Instantaneous AC and DC analysis

RR-interval histograms in AC and DC phases were also built following the procedures described above; $RMSNN$ in AC ($RMSNN_{AC}$) and $RMSNN$ in DC ($RMSNN_{DC}$) phases were calculated accordingly. To further accomplish this task, data points were initially isolated as acceleration (AC) or deceleration (DC) capacities. If a particular RR-interval increased relative to the previous one, a DC interval occurred. As the instantaneous RR-interval increased, it represented a parasympathetic action (DC; lozenge symbols in Figure 1). Conversely, a sympathetic effect on the RR-interval was represented whenever the RR-interval decreased relative to the previous one, and AC interval was defined (AC; represented by circle symbols in Figure 1).

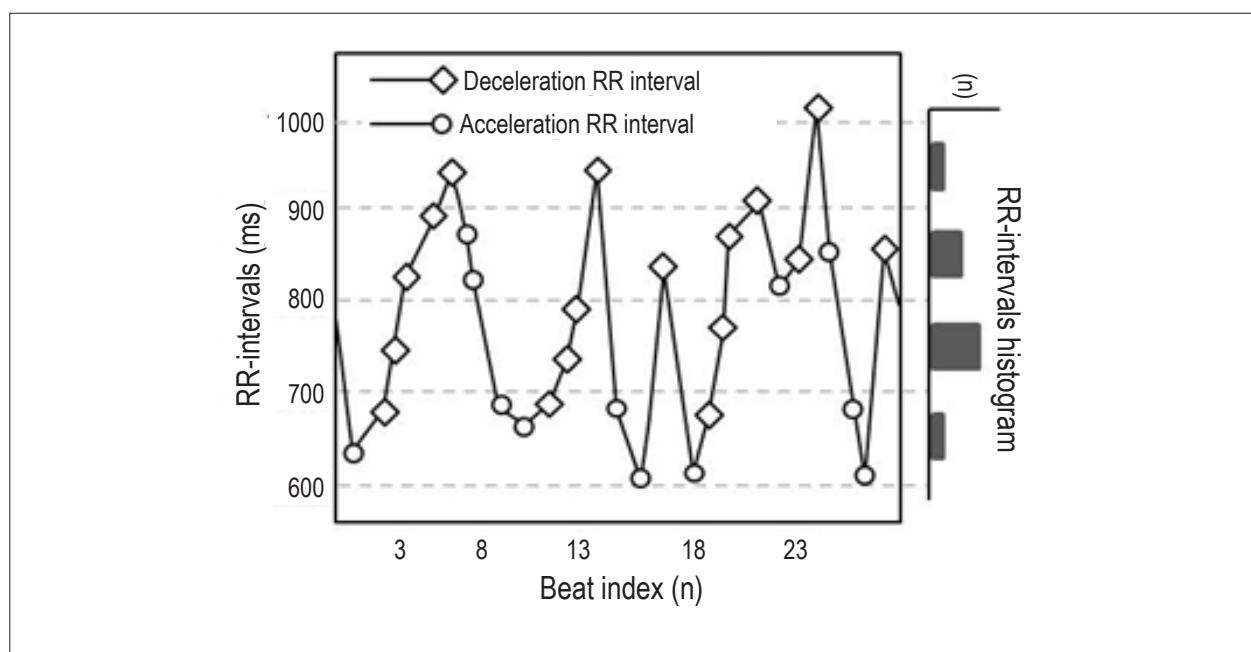


Figure 1 – Deceleration and Acceleration anchor points are represented in RR-intervals samples that were derived from an ECG recording. RR-interval histogram is represented on the right.

Statistical analysis

The *RMSNN* and *MNN* of each subject were pooled and averaged on a class-by-class basis in the control and ChD groups. *RMSNN* was analyzed in the whole series ($RMSNN_T$) as well as in the AC and DC phases. Regression lines were analyzed and angular coefficient was compared between ChD and control groups using non-paired Student's t-test. Correlation coefficients (r) were tested before each test. Due to strong asymmetry in their probability density functions, the *RMSNN* variables were log-transformed before analysis to fit appropriately in the parametric statistical analysis. All tests were considered significant at α level < 0.05 .

Results

Table 1 shows the linear correlation coefficient (r) and respective angular coefficient (*slope*) of the regression line between *MNN* and other each pooled variable. The r -values were significant in all regression lines ($p < 0.05$).

The log-transformed pooled *RMSNN* (T, AC, and DC), as a function of pooled *MNN*, were presented for each group (Figure 2). $RMSNN_{AC}$ were significantly different in both groups, whereas, in the control group, $RMSNN_T$, $RMSNN_{AC}$, and $RMSNN_{DC}$ significantly increased proportionally to *MNN* ($p < 0.05$); in the ChD group, only $RMSNN_{AC}$ showed significant increase as a function of *MNN*, whereas $RMSNN_T$ and $RMSNN_{DC}$ did not.

Based on the total number of RR-intervals suiting a particular histogram class, the percent value (mean \pm SD) of RR-interval pairs rejected as not pertaining to the same histogram class was $31.7\% \pm 21.7\%$ for the control group

and $27.0\% \pm 14.7\%$ for ChD. Figure 3 shows histograms of RR-interval pairs for each group according to the AC and DC phases, respectively.

Discussion

Cardiac autonomic dysfunction, characterized mainly by parasympathetic depression, is an important aspect of human ChD³⁻⁵. The observation of marked autonomic dysfunction in association with normality of most ventricular echocardiographic variables suggested that there was no clear relationship between autonomic and ventricular function²³. Additionally, autonomic dysfunction seemed to be a primary phenomenon, preceding ventricular mechanical changes in chronic ChD evolution^{6,24,25}.

In a previous study²², DC index adaptation was proposed to measure cardiac vagal modulation by a phase-rectified signal averaging (PRSA) procedure^{10,11} that was effective in distinguishing athletes from sedentary healthy volunteers. It was hypothesized that depending on vagal stimulus intensity, the rate of ascent of the RR-interval series would change accordingly, determining slope variation. Thus, the strongest vagal stimulus determined the steepest slope and vice-versa, potentially affecting the DC value. Although PRSA has been originally developed to risk-stratify subjects post myocardial infarction¹⁰, its application in assessing physiological conditions that are strongly related to vagal activity modulation has been shown to be highly pertinent and feasible as well.

In the present study, the behavior of RR-intervals was analyzed by grouping time domain *RMSNN* parameters calculated at different histogram classes. This procedure

Table 1 – Correlation of parameters: MNN vs. Variables

Group		Ln RMSNN _T	Ln RMSNN _{AC}	Ln RMSNN _{DC}
Control	r	0.96 *	0.99 *	0.99 *
	slope	0.0011 **	0.0012	0.0008 **
ChD	r	-0.55 *	0.96 *	-0.75 *
	slope	-0.0002	0.0010	-0.0003

(*) $p < 0.05$; (**) $p < 0.05$ for intergroup comparison. Log-transformed RMSNN_T, RMSNN_{AC} e RMSNN_{DC}

made it possible to cluster beats under the influence of similar instantaneous time factors. Additionally, assessment of the capacity of RR-interval series to accelerate or decelerate enabled the isolation of both sympathetic (AC phase) and parasympathetic (DC phase) contributions on the RR-intervals series.

The essential point of this study was to stratify HR and HRV according to instantaneous RR-interval difference using a parameter that expresses energy (RMSNN) from all series and to isolate sympathetic and parasympathetic contributions. Also, it introduced novel information that represents insights into the dependence of autonomic modulation on heart rate in a population of chronic ChD.

In the control group, HRV (RMSNN_T, RMSNN_{AC} and RMSNN_{DC}) was strongly dependent on the instantaneous RR-interval, confirming the previous findings of Benchimol-Barbosa et al.¹³. In the physiological range of RR-interval variation (600–1100 ms), RMSNN was lower during head-up tilt and higher during supine position, representing sympathetic and parasympathetic autonomic influences on HRV, respectively. Moreover, it was notable that RR-interval variation had average inter-beat “jumps” that were proportional to the average RR-intervals (Figure 2). This relation was also represented by a strong linear dependence between RMSNN and MNN ($r > 0.96$).

On the other hand, in the ChD group, only RMSNN_{AC} showed significant increase as a function of MNN ($p < 0.05$), which assessed the isolated contribution of sympathetic nervous system on HRV. RMSNN_{DC}, which assessed the isolated parasympathetic influence, not only had its mean value lower than the control group, but also showed no variations with changes in mean RR-interval. These findings indicate that not only vagal modulation was reduced in this population, but also the ability of parasympathetic system to modulate RR-intervals at different heart rates throughout a wide range of RR-intervals analyzed. We named this later observation as parasympathetic incompetence.

This study has its limitations, including a relatively small sample size and application of the method using two physiologically well-defined groups. Although the groups were not matched by age, both had their mean age above 40 years. Assessment of left ventricular systolic function was not carried out in the present study; however, in Chagas disease, there was no clear relationship between autonomic and ventricular function²⁴. Further studies are needed to confirm present findings.

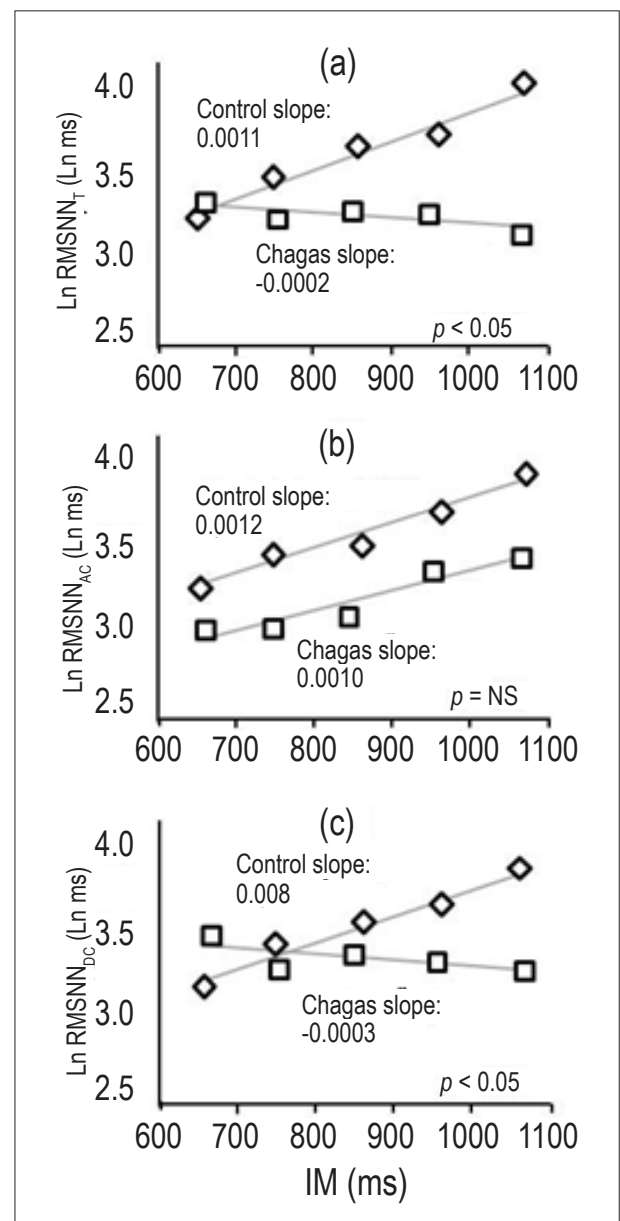


Figure 2 – Comparison of control and ChD groups in terms of log-transformed of pooled RMSNN_T (a), RMSNN_{AC} (b), and RMSNN_{DC} (c) as a function of pooled RR-intervals (MNN), and the respective angular coefficient (slope) of regression line. p value refers to Student's t-test significance for comparing slopes. Correlation was significant for all regression lines. (See text for details)

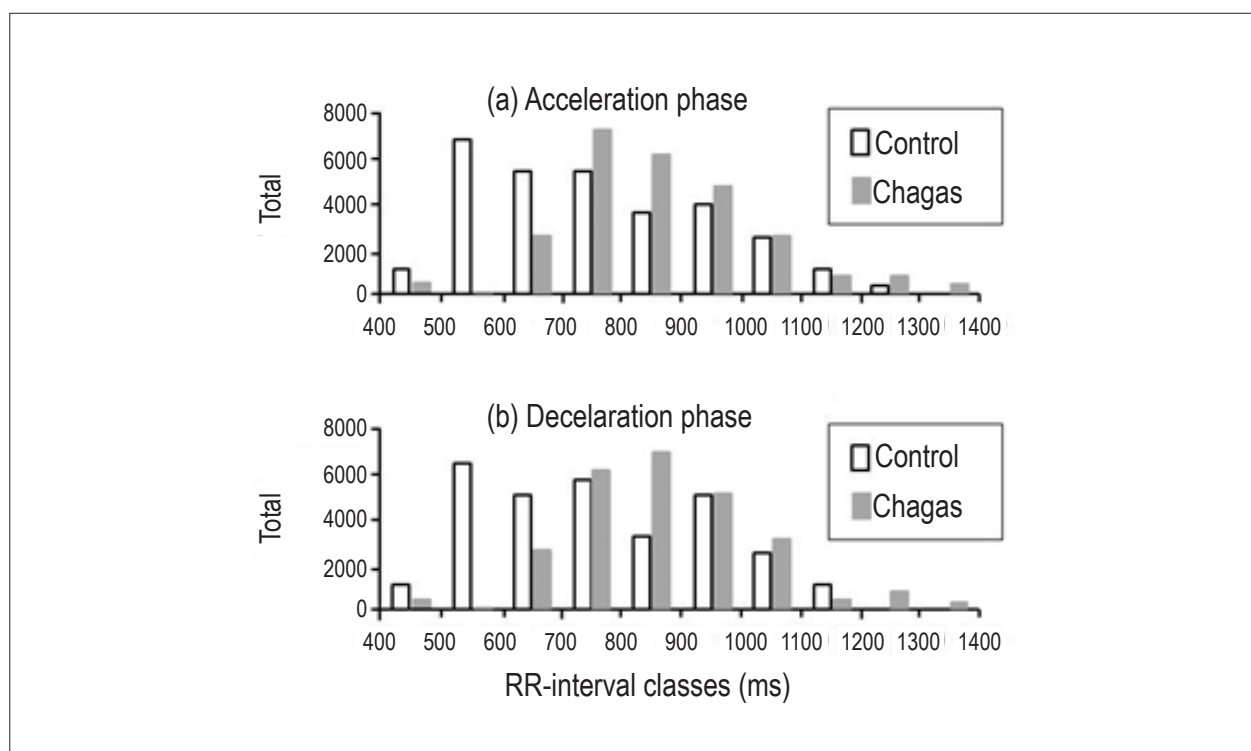


Figure 3 – RR-interval pairs histograms assessed for each group and phase: acceleration phase (a) and deceleration phase (b).

Conclusion

In subjects with chronic Chagas disease, a significant reduction of autonomic modulation of the heart is observed throughout a wide physiological range of RR-intervals.

Additionally, in healthy sedentary subjects, *RMSNN* increases proportionally with RR-interval. This relationship is not observed in chronic Chagas disease, particularly during parasympathetic stimulation phase, indicating parasympathetic incompetence in modulating heart rate variation in this scenario.

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Author contributions

Conception and design of the research: Nasario-Junior O, Benchimol-Barbosa PR. Acquisition of data: Pedrosa

RC. Analysis and interpretation of the data: Nasario-Junior O, Benchimol-Barbosa PR, Nadal J. Statistical analysis: Nasario-Junior O, Benchimol-Barbosa PR, Nadal J. Obtaining financing: Pedrosa RC, Nadal J. Writing of the manuscript: Nasario-Junior O, Benchimol-Barbosa PR, Pedrosa RC, Nadal J. Critical revision of the manuscript for intellectual content: Nasario-Junior O, Benchimol-Barbosa PR, Pedrosa RC, Nadal J. Supervision / as the major investigator: Nadal J.

Potential Conflict of Interest

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

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Study Association

This study is not associated with any thesis or dissertation work.

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