Dynamic Coupling between Ventricular Repolarization Duration and *RR*-Interval Phase-Rectification Analysis in Chagas Disease

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Abstract

Dynamic ventricular repolarization duration (VRD) and phase-rectification-driven RR-interval coupling was investigated aiming at assessing myocardial electrical stability in healthy and chronic Chagas disease (ChD) subjects. All were in sinus rhythm and underwent 60 min head-up tilt table test under ECG recording. ChD group underwent MIBG scintigraphy and confirmed sympathetic denervation. Histogram of RR-interval series was calculated, with 100 ms class, ranging from 500 ms to 1200 ms. For each class, mean of normal RR-intervals (MRR) and mean of the peak-to-peak R-to-T wave interval (MRT), representing VRD, were analyzed in RR-intervals pairs of acceleration (AC) and deceleration (DC) phases, reflecting sympathetic and parasympathetic influences on heart rate, respectively. Regression lines of MRT vs. MRR were computed in the whole series, and in DC and AC phases, and respective slopes calculated (sMRT$_T$, sMRT$_{DC}$ and sMRT$_{AC}$). Student t-test compared groups. RT-interval was larger in ChD group. sMRT$_T$, sMRT$_{DC}$ and sMRT$_{AC}$ function showed no difference between groups, and all increased directly to MRR. In both groups, MRT increased as a linear function of MRR. In ChD, RT-interval analysis was not able to confirm loss of sympathetic driven RR-interval variation.

1. Introduction

American trypanosomiasis or *Chagas* disease (*ChD*) is the principal cause of acquired cardiomyopathy in the American continent. It has been estimated that 8-11 million people worldwide if infected by *Trypanosoma cruzi*, becoming a significant healthcare related problem in Europe, North America and other continents due to migration [1]. A relevant pathophysiological aspect of chronic *ChD* is the impairment of the cardiac tissue repolarization [2]. On its turn, dynamic ventricular repolarization duration (VRD) and *RR*-interval coupling relates to myocardial electrical stability [3].

Electrocardiographic repolarization parameters are markers for arrhythmia and cardiovascular mortality in *ChD* [4]. Since myocardial damage is scattered throughout the heart in *ChD*, ECG abnormalities (arrhythmias, conduction disturbances, and repolarization changes) reflects a widespread cardiac involvement [5].

The relationship between VRD and cardiac cycle length is a valuable tool to assess cardiac adaptation to autonomic input [6]. Recently, isolation of distinct autonomic contribution on HR has been feasible by assessing the capability of RR-interval series to accelerate (AC) or decelerate (DC), representing sympathetic and parasympathetic contributions, respectively [7].

Previous studies reproduced the VRD dependence on the cardiac cycle lengths, indicating that the separation by *RR*-interval classes can be useful to compare different populations [3], [8]. Then, discriminating the stronger autonomic stimulus in DC and AC phase would determine faster ventricular adaptations (steepest curve) and vice-versa, potentially affecting the relation between them. The objectives of the study were: i) To investigate dynamic VRD to *RR*-interval coupling, stratified by *RR* histogram classes, assessing myocardial electrical stability in healthy and chronic *ChD*, and ii) To analyse AC and DC phases of *RR*-interval series, discriminating sympathetic and parasympathetic effects on VRD.

2. Materials and methods

2.1. Study population

ECG signals were extracted from an existing high resolution ECG database [9]. The study protocol was approved by Ethics Committee and informed consent was obtained. A group of age and gender-adjusted 11 healthy sedentary participants [Control group, (mean age $\pm$ SD) 58.3 ± 13.1 years] and 11 subjects with chronic *ChD* (Chagas group, 59.4 ± 12.3 years) were studied. Chronic *ChD* subjects were enrolled to the study based on spontaneous demand and all underwent MIBG scintigraphy to assess cardiac sympathetic innervation.

The following criteria were met: (i) no intake of nutritional supplements or potential ergogenic aids of any

type; (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.

2.2. Signal acquisition, processing and wave detection

All subjects underwent 60 min head-up tilt test (HUTT) under modified Westminster protocol [10] 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 supine position for 5 min [11].

ECG signal acquisition periods were characterized by 10 min of supine rest followed by 40 min HUTT and another 10 min supine rest. Accordingly, HR variability (HRV) was expected to be influenced by two predominant autonomic inputs: parasympathetic input during supine rest, and sympathetic input during tilt [12].

High-resolution ECG signals were acquired using modified bipolar *Frank XYZ* orthogonal leads and digital data were processed with custom-made pattern recognition software [8]. The R wave detection was carried out with the signal low-pass filtered at 15 Hz (Butterworth, 4th order). For the analysis of the *RR*-interval length, artefacts and ectopic beats were excluded by correlation, precocity and visual inspection, and confirmed by one expert. Additionally, any *RR*-interval that exhibited more than 20% change from the previous one were excluded, as they were likely to be related to measurement noise or ectopic beats [8].

The VRD interval comprehended the distance between the top of the QRS complex (*R-wave*) and the apex of the *T* wave (*T*) in normal beats defined *RT*-interval (Figure 1), which was employed in a sole purpose of analysing repolarization adaptation over instantaneous cardiac cycle [3]. The *RR*- and *RT*-intervals were analysed on *X* lead.
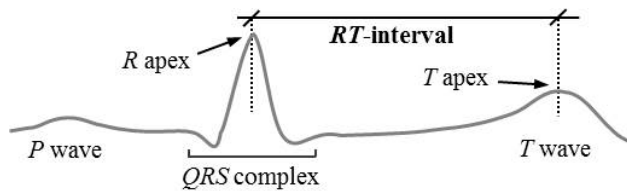

Figure 1. Identification of the apex (point) on *R*- and *T*-waves, which allowed precise identification of the ventricular repolarization duration by *RT*-interval.

2.3. Dynamic *RR* and *RT* interval analysis

The histogram was constructed for each individual *RR*-interval series, and divided into classes of 100 ms width, ranging from 500 ms to 1200 ms, which represented a variation between 50 and 120 bpm in HR. For each histogram class, and respective to each *RR*-interval series, it was calculated mean (*MRR*) and standard deviation (*SDRR*) of consecutive normal *RR*-intervals; mean (*MRT*) and standard deviation (*SDRT*) of consecutive normal *RT* intervals. Only pairs of consecutive normal *RR* and *RT* intervals for individual series that lied inside a particular class of the *RR* histogram were analysed together.

For a particular histogram class (*class*) of the ith series, containing $N_{i,\ class}$ *RR*-intervals, the calculus of the mean ($Mx_{i,\ class}$), standard deviation ($SD_{xi,\ class}$) of the normal *RR* and *RT* intervals was performed as follows:

$$Mx_{i,class} = \sum_{k=1}^{N_{i,class}} \frac{x_K}{N_{i,class}} \tag{1}$$

$$SDx_{i,class} = \sqrt{\sum_{k=1}^{N_{i,class}} \frac{(x_K - Mx_{i,class})^2}{N_{i,class} - 1}} \tag{2}$$

where *x* represents either *RR* or *RT* interval.

For each histogram, classes with 20 or less intervals were excluded of analysis to avoid bias due to lack of statistical precision.

The values of the variables $Mx_{i\ class}$ and $SDx_{i,\ class}$ were aggregated to the respective histogram class. The pooled mean ($Mx_{\ class}$) and standard deviation ($SD_{x\ class}$) of *RR*- and *RT*-intervals for each histogram class, weighted by respective degree-of-freedom ($\eta_{i,\ class}$), were calculated according to:

$$Mx_{class} = \frac{\sum_{i=1}^{20} Mx_{i,class} \cdot (\eta_{i,class} + 1)}{\sum_{i=1}^{20} (\eta_{i,class} + 1)} \tag{3}$$

$$SDx_{class} = \sqrt{\frac{\sum_{i=1}^{20} (SDx_{i,class})^2 \cdot \eta_{i,class}}{\sum_{i=1}^{20} \eta_{i,class}}} \tag{4}$$

where *x* represents either *RR*- or *RT*-interval.

The variables *MRT* were plotted and correlated with *MRR* class.

2.4. Instantaneous AC and DC analysis

RR-interval histograms in AC and in DC phases were also built, following the rules described above. *RR*-interval in AC (*RR*$_{AC}$) and in DC (*RR*$_{DC}$) phases were classified accordingly. To further accomplish this task, it was initially isolated the data points as either acceleration (AC) or deceleration (DC) phases. If a particular *RR*-interval increased relatively to the previous one, a DC interval occurred. As the instantaneous *RR*-interval increased, it

characterized parasympathetic input (DC; lozenge symbols in Figure 2). Conversely, a sympathetic effect on the cardiac cycle length was represented whenever the *RR*-interval decreased relatively to the previous one, and AC interval was defined (AC; circle symbols in Figure 2). After *RR*-intervals classification, *RT*-intervals histograms were built, respectively, following the correspondent *RR*-intervals phases: RT_{AC} derived from RR_{AC} and RT_{DC} from RR_{DC} intervals.
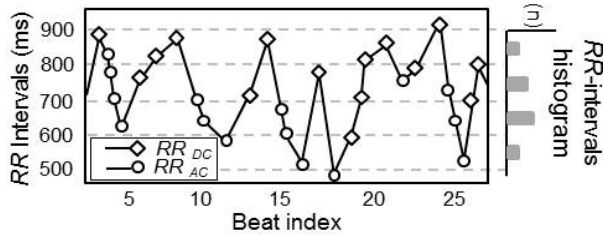

Figure 2. Acceleration (O - RR AC) and Deceleration (◇ - RR DC) pairs of RR-intervals represented in RR series signal. RR-interval histogram is represented on the right (reproduced from Benchimol-Barbosa PR *et al*. [13]).

2.5. Statistical analysis

The *MRT* and *MRR* of each subject were pooled and averaged on a class-by-class basis in the control and *ChD* groups. *MRT* was analysed in the whole series ($_T$) as well as in the AC and DC phases, and respective slopes calculated ($sMRT_T$, $sMRT_{DC}$ and $sMRT_{AC}$). Regression lines were analysed 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. The significance level α was always 0.05.

3. Results

The pooled *RR*- and *RT*-intervals duration, *MRR* and *MRT* respectively, were presented for each group in Table 1.

Table 1. *MRR* and *MRT* duration per group: (mean±SD)

Group	MRR (ms)	MRT (ms)
Control	806±72	265±12
Chagas	906±52	273±11

Linear correlation coefficient (*r*) and respective angular coefficient (*slope*) of regression lines between *MRR* and *MRT* variables computed in the whole series (T), and in DC and AC phases are presented in Figure 3 (a), (b) and (c). The $sMRT_T$, $sMRT_{DC}$ and $sMRT_{AC}$ slope values showed no significant difference between groups, and all regressions significantly increased proportionally to *MRR* ($p < 0.05$). The *r* values were significant for all regression

lines ($p < 0.05$). The *MRT* showed no significant intra-group differences between AC and DC phase, in all *MRR* classes ($p > 0.05$) (Figure 3).
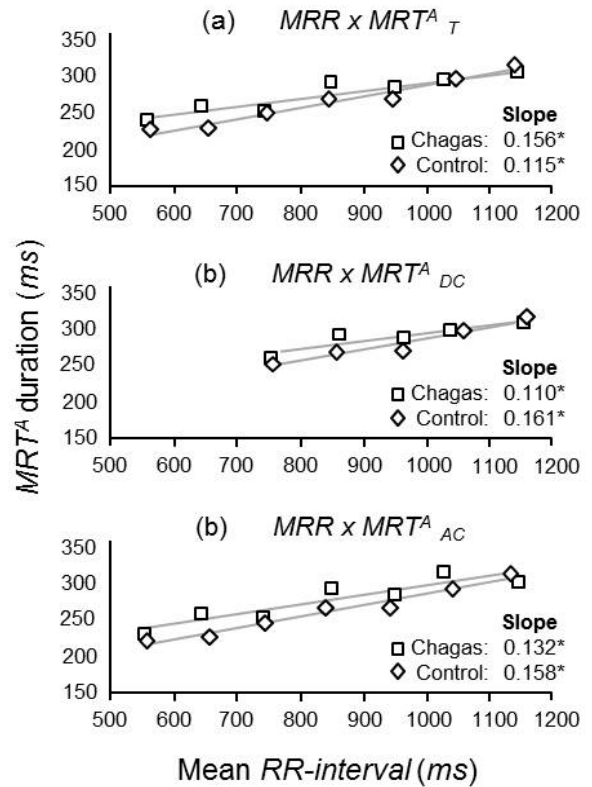

Figure 3. Pooled *MRT* group analyses (◇ Control and □ Athletes) as a function of mean *RR*-intervals for (a) whole series - T, (b) acceleration phase - AC and (c) deceleration phase - DC. * $p < 0.05$.

The $sMRT_{DC}$ and $sMRT_{AC}$ were compared in each group, as a function of *MRR*. The slopes showed no significant difference between AC and DC phases ($p > 0.05$).

4. Discussion

This study applied a computerized method to analyze the relation between VRD and cardiac cycle length in chronic *ChD* and healthy sedentary controls. Utilization of *RT*-interval as a measure of VRD instead of the conventional *QT* interval has been proved to be feasible and has several advantages [14]. The conventional *QT* interval requires accurate identification of the *Q*-wave onset and the T-wave offset, and the latter is subject to controversies related to optimal definition of reference offset point in visual identification processes [14]. Indeed, VRD offset assessed either at the peak of the *T*-wave or the inflexion point after the peak show high correlation with the VRD measured at the end of the *T*-wave, validating this measurement [14].

The performance of HRV time domain parameters has

been assessed in a previous study, by grouping *RR*-intervals in different histogram classes [15]. Furthermore, the capability of *RR*-intervals to accelerate or to decelerate allowed isolating sympathetic (AC) and parasympathetic (DC) phase contributions on heart rate variation, respectively. Thus, by comparing control and ChD groups, the study introduced novel information that brought insights into the dependence of heart rate on autonomic modulation in a population of chronic *ChD* [15].

Salles *et al.* [4] were the first to describe the prognostic importance of ECG parameters of ventricular repolarization in patients with *ChD*. Based on the results, both maximum *QT*-corrected duration (*Bazett's* formula) and the greatest *QT*-interval dispersion were independent predictors of all cause, *ChD* related, and sudden arrhythmic deaths.

In this study, sympathetic denervation, confirmed by MIBG scintilography, influenced average *RR*- and *RT*-interval prolongations in *ChD* subjects (Table 1). In both groups, *RT*-interval duration (MRT_T, MRT_{DC} and MRT_{AC}) showed significant dependence on the corresponding cardiac cycle length (Figure 3). Additionally, this relationship shows a strong linear dependence between VRD duration and *MRR* ($r > 0.91$).

The *MRT* intragroup comparison between AC and DC phases showed no significant differences either in controls or in *ChD*. In addition, it was not possible to isolate any potential hysteresis in VRD adaptation in the analyzed *RR*-interval range (500 to 1200 ms).

This study has its limitations, including a small sample size and two physiologically well-defined groups. Assessment of left ventricular systolic function was not carried out in the present study; however, in *ChD*, there are controversies in the relationship between autonomic and ventricular function [16].

5. Conclusion

RT-interval increases as a linear function of *RR*-interval, in a wide physiological range of *RR*-interval variation during tilt-table test. In Chagas disease showing sympathetic denervation, *RT*-interval stratified by *PRSA* of normal *RR*-intervals shows a similar behavior of *RT*-interval in control healthy subjects.

Acknowledgements

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