Dynamic Coupling between Atrio-ventricular Duration and RR-interval Histogram Phase-rectification Analysis in Chronic Chagas Disease

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Abstract

This study investigated dynamic atrio-ventricular duration (AVD) and phase-rectification-driven RR-interval coupling to assess AV conduction facilitation in healthy and chronic Chagas disease (ChD) subjects. All subjects 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 600 ms to 1200 ms. For each class, mean of normal RR-intervals (MRR) and mean of the peak-to-peak P-to-R wave interval (MPR), representing AVD, 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 MPR vs. MRR were computed in the whole series, and in DC and AC phases, and respective slopes calculated (sMPR_T, sMPR_DC and sMPR_AC). Student t-test compared groups. MRR and MPR were larger in ChD group. In healthy subjects, sMPR_T, sMPR_DC and sMPR_AC significantly increased as a function of MRR in all phases. In subjects with Chagas disease, however, PR-interval increases only in DC phase, confirming loss of sympathetic driven RR-interval variation.

1. Introduction

Chagas disease (ChD) is a major cause of cardiomyopathy in Latin America. It has been estimated that that Trypanosoma Cruzi worldwide currently infects 8-11 million people, becoming a significant worldwide healthcare related problem due to migration [1]. Since myocardial damage is scattered throughout the heart in ChD, electrocardiogram (ECG) abnormalities (arrhythmias, conduction disturbances) reflects a widespread cardiac involvement [2]. A relevant pathophysiological aspect of chronic ChD is the abnormal atrio-ventricular (AV) conduction [9], commonly related to sustained supraventricular arrhythmia in different stages of the disease [2].

Atrio-ventricular duration (AVD) tends to adapt to changes in heart rate (HR) directly [3]. Dynamic coupling between AVD and RR-interval relates to AV conduction facilitation, particularly influenced by the strength of the autonomic input [4]. Thus, the relationship between AVD and cardiac cycle length may be a valuable tool to assess adaptation to autonomic input.

Recently, isolation of distinct autonomic contribution on HR has been feasible by assessing the capability of RR-intervals to accelerate (AC) or decelerate (DC), representing sympathetic and parasympathetic contributions, respectively [5, 6]. Additionally, separation of RR-intervals by histogram classes has demonstrated to be useful to compare different populations [7].

In a recent study, assessment of RR-interval in AC and DC in ChD groups added insights into the dependence of autonomic modulation on HR [8]. The objectives of the study were: i) To investigate dynamic AVD to RR-interval coupling, stratified by RR histogram classes, in healthy and chronic ChD, and ii) To analyse AC and DC phases of RR-interval series, discriminating sympathetic and parasympathetic effects on AVD.

2. Materials and methods

2.1. Study population

ECG signals were extracted from an existing high resolution ECG database [10]. 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 ± 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. Due to the exploratory nature of the study, the number of participants was arbitrarily defined and equally distributed between groups.

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 [11] 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 5 min [12].

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 parasympathetic during supine rest, and sympathetic during tilt [13].

High-resolution ECG signals were acquired using modified bipolar Frank XYZ orthogonal leads and digital data were processed with custom-made pattern recognition software [6]. The wave detection was carried out with the signal low-pass filtered at 15 Hz (Butterworth, 4th order). The analysis of the RR-interval length was carried out after detection of the QRS complex. Artefacts and ectopic beats were excluded by correlation, precocity and visual inspection, and confirmed by one expert. [6].

The AVD interval comprehended the distance between the apex of the P-wave and the peak of the R-wave in normal beats, defining PR-interval (Figure 1), which was employed in a sole purpose of analysing AVD adaptation over instantaneous cardiac cycle [14]. The RR- and PR-intervals were analysed on X lead.

![Diagram of ECG waves](Image)

Figure 1. Identification of the apex (point) on P- and R-waves, which allowed precise identification of the atrio-ventricular duration by PR-interval.

2.3. Instantaneous RR and PR interval analysis

The histogram was constructed for individual RR-interval series, and divided into classes of 100 ms width, ranging from 600 ms to 1200 ms. 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, and mean (MPR) and standard deviation (SDPR) of consecutive normal PR-intervals. Only pairs of consecutive normal RR and PR-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 Ni, class RR-intervals, the calculus of the mean (Mx, class), standard deviation (SDx, class) of the normal RR and PR-intervals was performed as follows:

\[
M_{x, class} = \frac{\sum_{k=1}^{N_{i, class}} x_k}{N_{i, class}} \\
SD_{x, class} = \sqrt{\frac{\sum_{k=1}^{N_{i, class}} (x_k - M_{x, class})^2}{N_{i, class} - 1}}
\]

where x represents either RR or PR 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, class and SDx, class were aggregated to the respective histogram class. The pooled mean (Mx, class) and standard deviation (SDx, class) of RR- and PR-intervals for each histogram class, weighted by respective degree-of-freedom (ηi, class), were calculated according to:

\[
M_{x, class} = \frac{\sum_{i=1}^{20} M_{x, i, class} \cdot (\eta_{i, class} + 1)}{\sum_{i=1}^{20} (\eta_{i, class} + 1)} \\
SD_{x, class} = \sqrt{\frac{\sum_{i=1}^{20} (SD_{x, i, class})^2 \cdot \eta_{i, class}}{\sum_{i=1}^{20} \eta_{i, class}}}
\]

where x represents either RR- or PR-interval.

The variables MPR 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-intervals 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, $PR$-intervals histograms were built, respectively, following the correspondent $RR$-intervals phases: $PR_{AC}$ derived from $RR_{AC}$ and $PR_{DC}$ from $RR_{DC}$ intervals.

![Figure 2](image-url)

Figure 2. Acceleration ($\bigcirc - RR_{AC}$) and Deceleration ($\bigdiamond - RR_{DC}$) pairs of $RR$-intervals are represented in $RR$ series signal. $RR$-interval histogram is represented on the right.

2.5. Statistical analysis

The $MPR$ and $MRR$ of each subject were pooled and averaged on a class-by-class basis in the control and ChD groups. $MPR$ was analysed in the whole series ($T$) as well as in the AC and DC phases, and respective $MRR$ vs $MPR$ slopes calculated ($sMPR_{T}$, $sMPR_{DC}$ and $sMPR_{AC}$). 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. All tests were considered significant at a level $< 0.05$.

3. Results

The pooled $RR$- and $PR$-intervals duration, $MRR$ and $MPR$ respectively, were presented in Table 1.

<table>
<thead>
<tr>
<th>Group</th>
<th>$MRR$ (ms)</th>
<th>$MPR$ (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>806±72</td>
<td>131±9</td>
</tr>
<tr>
<td>ChD</td>
<td>906±52</td>
<td>140±1</td>
</tr>
</tbody>
</table>

Table 1. $MRR$ and $MPR$ duration per group (mean±SD)

Linear correlation coefficient ($r$) and respective angular coefficient ($slope$) of regression lines between $MRR$ and $MPR$ variables computed in the whole series ($T$), and in DC and AC phases are presented in Figure 3.

The $sMPR_{T}$, $sMPR_{DC}$ and $sMPR_{AC}$ slope values significantly increased as a function of $MRR$ in Control (Figure 3) in all phases. In ChD, slope of $MPR$ was significant only in DC phase ($p < 0.05$).

The $MPR_T$, $MPR_{DC}$ and $MPR_{AC}$ were compared between groups, as a function of $MRR$. The values showed no significant difference between AC and DC phases for classes below 1000 ms.

![Figure 3](image-url)

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

4. Discussion

The relation between AVD and cardiac cycle length were studied in chronic ChD and healthy sedentary controls. The use of $PR$-interval (P-peak to R-peak) as a measure of AVD instead of the conventional $PR$ segment has been proved to be feasible and has several advantages [14]. The conventional $PR$ interval requires accurate identification of P-wave and Q-wave onsets, which is subject to controversies [14]. In fact, other studies indicate that AVD assessed by the peak of the P- and R-wave show high correlation with the AVD measured at standard $PR$ segment [14, 15].

By measuring the “$PR$ segment” from the apex of the $P$ wave to the peak of the $R$ wave, the pure AV conduction time has not been accurately measured, which includes effects of variation on $P$ wave morphology, bundle of His and early ventricular depolarization. Nevertheless, AV conduction is considered to be the most important determinant of the $PR$-interval [16].

$PR$-interval undergoes dynamic variations depending on age, HR, autonomic status, medications, posture,
respiratory frequency etc. [15], and abnormal AV conduction are often associated with life-threatening arrhythmia [2, 9].

In a previous study, the behavior of HRV time domain parameters that expresses energy was analyzed by grouping RR-intervals at different histogram classes [8]. Additionally, assessment of the capability to accelerate or decelerate enabled approximate isolation of sympathetic (AC) and parasympathetic (DC) phases contribution on RR-interval duration, respectively. Thus, by comparing control and ChD groups, the study introduced novel information that brought insights into the dependence of autonomic modulation on HR in a population of chronic ChD.

Chagas heart disease is an arrhythmogenic cardiomyopathy. Bradyarrhythmias are also prevalent and, among them, sick sinus syndrome and diverse AV blocks degrees are common. Not infrequently, ventricular tachyarrhythmia and AV conduction abnormalities coexist in the same patient [17].

In the present study, it can be assumed that sympathetic denervation, confirmed by MIBG scintigraphy, contributed to average RR- and RT^1-interval prolongation in ChD subjects (Table 1). In control group, PR-interval duration (MPR, MRP_{DC} and MPR_{AC}) showed significant dependence on the corresponding cardiac cycle length (Figure 3). AVD and RR-interval relationship showed strong linear dependence (r > 0.93). On the other hand, in ChD group, significant MPR to cardiac cycle length dependence was confirmed only on DC phase (MPR_{DC}).

The MPR values comparison between groups showed no significant differences between AC and DC phases for classes below 1000 ms, in both controls and ChD. Thus, a vagal-driven influence on AVD adaptations may predominate in the RR-interval range analyzed.

This study has additional limitations, including a relatively small sample size and application of the method using two physiologically well-defined groups.

5. Conclusion

In healthy subjects, PR-interval shows a direct RR-interval dependence, under different autonomic-driven inputs. In subjects with Chagas disease showing sympathetic denervation, however, PR-interval increases only in DC phase, confirming loss of sympathetic driven RR-interval variation.

Acknowledgements

This study received financial support from the Brazilian agencies CAPES, CNPq and FINEP.

References


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