Heart rate turbulence and left ventricular ejection fraction in Chagas disease

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Abstract Aims Chagas disease patients often present premature ventricular complexes (PVCs), depression of left ventricular ejection fraction (LVEF) and autonomic dysfunction, which is generally evaluated by heart rate variability (HRV) analysis. As frequent PVCs may complicate HRV computation, we measured heart rate turbulence (HRT) and evaluated the correlation between ejection fraction and HRT or HRV in Chagas disease.

Methods We studied 30 patients (47 ± 11 years, 20 men) with Chagas cardiomyopathy and left ventricular dilatation who underwent clinical evaluation, ejection fraction (EF: 45 ± 14%) determination and 24-h Holter monitoring (median PVC = 1781). In all patients, the standard deviation of normal RR intervals (SDNN), the square root of the mean square differences of successive RR intervals (RMSSD) and values of turbulence onset (TO) and turbulence slope (TS) were calculated.

Results HRT indices were independent of mean RR interval and presented high correlation with EF: TO (−0.11 ± 0.01%, r = −0.60, P < 0.001) and TS (5.8 ± 3.7 ms/RR-interval, r = 0.73, P < 0.001). Of HRV parameters, only SDNN, corrected for mean RR interval, showed a weak but not significant correlation with EF (r = 0.41). The comparison of HRT/EF and HRV/EF correlation coefficients, indicated the presence of a significant difference (P = 0.017).

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Conclusions

HRT indices appear to correlate better with EF than SDNN in Chagas disease. Thus, an analysis based on heart rate transient adaptation seems to perform better than HRV in detecting the autonomic alterations that parallel left ventricular dysfunction in Chagas disease patients. The high number of PVCs observed in these patients further support the use of HRT methodology.

Introduction

Chagas disease, an illness caused by the infection by the protozoan *Trypanosoma cruzi*, has high prevalence in Latin American countries, where nearly 20 million people are affected [1]. In the overt phase of its cardiac form, but also in the absence of previous clinical manifestations, this chronic cardiomyopathy [2] is potentially lethal, with 60% of all deaths from Chagas disease occurring as sudden cardiac death, generally from ventricular tachyarrhythmias [3]. There is evidence [4] that, in the course of the disease, there occurs a progressive functional deterioration of both autonomic nervous system and left ventricular function.

Heart rate variability (HRV) analysis is a powerful and simple method for assessing alteration of autonomic modulation of the sinus node and for risk stratification in many cardiac diseases [5]. In Chagas disease, HRV analysis [6–9] suggests that autonomic dysfunction seems to precede clinical and echocardiographic manifestations of left ventricular dysfunction. Nonetheless, the relationship between HRV indices and left ventricular ejection fraction (LVEF) is not well defined [6–9]. A possible explanation is related to the fact that HRV analysis could be hampered by the presence of a high number of premature ventricular complexes that is usual in Chagas disease also in absence of severe left ventricular dysfunction [5,10].

Heart rate turbulence (HRT) is a new method [11] for risk stratification that is based on the analysis of spontaneous changes in heart rate that occur after premature ventricular complexes (PVCs). In normal subjects after a PVC, sinus rhythm exhibits a typical biphasic pattern characterised by an early acceleration (defined by the “Turbulence Onset” value) and late deceleration (defined by the “Turbulence Slope” value), largely dependent upon vagal and sympathetic mechanisms presumably initiated by arterial baroreflexes [12–16]. An altered HRT response has been proved as a potent marker of high risk of arrhythmic death in post-infarction patients [17] and its prognostic value has been confirmed in other cardiac diseases [18,19]. We have previously reported [20] that, in comparison with controls, Chagas disease patients showed abnormal HRT indices, although their relation with ejection fraction was not specifically addressed.

In the present study we analysed HRV and HRT in Chagas patients to evaluate the correlation between indices obtained from these non-invasive methodologies and LVEF, i.e. the most powerful prognostic indicator in Chagas disease.

Methods

Study population

The recruitment of patients was carried out at the Chagas Disease Outpatient Reference Center of the Federal University of Minas Gerais, Brazil, between January and April of 2003. From the 42 screened, we selected 30 (20 males) consecutive patients with a mean age of 47 ± 11 years (range 20–70 years), with a definite serological status for Chagas disease (>2 different positive reactions to *T. cruzi* in patients at risk of infection), and who presented dilated cardiomyopathy with either LV end-diastolic diameter > 55 mm (or > 27 mm/m² body surface area) or LVEF < 55% on echocardiogram. These patients were in the recruitment phase of a clinical trial on carvedilol in Chagas disease patients and were on ACE inhibitors (80%), diuretics (80%), aldosterone antagonist (33%), digoxin (20%) and amiodarone (50%). None of the patients was on beta-blocker therapy. Those who agreed to participate and signed a written informed consent were submitted to a standard screening protocol that included clinical and laboratory examinations, electrocardiogram, and chest X-ray. Exclusion criteria were: (i) any evidence of other cardiovascular disease, diabetes, thyroid dysfunction, chronic obstructive pulmonary disease, renal or hepatic failure, anaemia, or any significant systemic disease; (ii) alcoholism; (iii) pregnancy; (iv) use of beta-blockers; (v) presence of chronic atrial fibrillation (one patient) or pacemaker rhythm on basal ECG (three patients), inadequate Holter monitoring.
tracings (three patients), high frequency of ventricular ectopies (>15% of cardiac cycles; two patients) and (vi) refusal of participation in the study (three patients).

Study protocol

The Ethical Committee of the Federal University of Minas Gerais approved the study protocol. Patients were submitted to Doppler echocardiography with colour flow using ATL HDI 5000 equipment (Bothell, WA, USA), according to the recommendations of the American Society of Echocardiography, with a 16-segment model. LVEF was obtained through Simpson’s method using the software provided with the equipment [21].

Twenty-four-hour Holter monitoring was performed using a portable 3-channel cassette tape recorder (Dynamis, Cardios, São Paulo, Brazil). Subjects were encouraged to continue with their normal everyday activities during the recordings, with the avoidance of physical exercise or drugs that could interfere with autonomic function. Analysis of HRV was performed when at least 18 h of good quality tracings and 85% or more sinus rhythm beats were available. The recordings were analysed on a Burdick/DMI Hospital Holter System (Spacelabs Burdick, Deerfield, WI, USA) by a semi-automatic technique, with the sampling frequency of 200 Hz. For each tape, the entire recording was carefully reviewed and the QRS complexes were classified as normal beats, artifacts, and PVCs, in order to create a time series of RR intervals. The standard deviation of normal RR intervals (SDNN) and the square root of the mean square differences of successive RR intervals (RMSSD) were calculated according to the Task Force guidelines of the European Society of Cardiology and the North American Society of Cardiac Pacing and Electrophysiology [5].

HRT was evaluated on the entire 24-h heart rate time series, as previously described [11,18] using the source code and the filter algorithm available at the website ”www.h-r-t.com” (HRT Source Code version 1.11). The filter algorithm ensured that the sinus rhythm immediately preceding and following the index PVC is free from arrhythmia and artifacts. Two indices of HRT were calculated: the turbulence onset (TO) and the turbulence slope (TS). TO is the percentage difference between the heart rate immediately following a PVC and the heart rate immediately preceding the same PVC. Turbulence onset is determined for each PVC and then averaged. Positive values for TO indicate deceleration; negative values indicate acceleration of the sinus rhythm. TS is defined as the steepest slope of the linear regression line for each sequence of five consecutive normal intervals in the local tachogram. The turbulence slope calculations are based on the average tachogram and expressed in milliseconds per RR interval [11].

Statistical analysis

Data obtained from continuous variables are expressed as mean ± standard deviation or median with the interquartile range. When necessary, mathematical transformation of non-normal data was performed to allow subsequent analysis. Pearson correlation coefficients were used to measure correlation between the variables. Since mean 24 h RR interval is strongly related to conventional HRV indices, their correlation coefficients with LVEF were adjusted for its value. In order to compare the strength of the correlation between the HRV and HRT indices with LVEF we tested the null hypothesis that the correlation between LVEF and SDNN was the same as the correlation between LVEF and HRT indices by applying the method proposed by Kleinbaum et al. [22]. A P value of <0.05 was considered significant. When the Bonferroni correction for multiple comparisons was applied (Table 2) a corrected P value of <0.01 was used.

Results

We studied 30 patients with Chagas disease with a mean LVEF of 45 ± 14% (range 18—71%) and a median number of PVCs of 1781 (IQR 580-3497). Most of the patients were in New York Heart Association (NYHA) Class I. The results of HRV and HRT analysis are presented in Table 1. In particular, 23 patients had a preserved HRV as indicated by a SDNN > 100 ms; whereas both indices of HRT were within normal limits in 22 subjects. No relation was observed between drug treatment and HRV or HRT parameters.

The Pearson correlation matrix of HRT TO and TS indices, SDNN and natural log of the root mean square of successive differences in normal RR intervals (In RMSSD), LVEF, natural log of PVCs and age is presented in Table 2. As SDNN and In RMSSD were highly correlated with mean RR interval, their correlation coefficients were displayed after adjusting for this variable. Age and number of PVCs were not significantly correlated with either SDNN or HRT indices. Mean RR interval did not correlate with LVEF (Fig. 1), whereas a significant correlation between LVEF and either SDNN or RMSSD was observed only before correction for mean RR
interval. After correction (Table 2), both ln RMSSD and SDNN failed to be significantly correlated with LVEF. Turbulence onset ($-0.11 \pm 0.01$) and slope ($5.8 \pm 3.6$ ms/RR-interval), were highly correlated with LVEF, but not with mean RR interval and natural log of premature ventricular complexes (ln PVCs) number. The correlation coefficient between TS/LVEF was significantly greater than the SDNN/LVEF coefficient ($P = 0.017$), whereas no significant difference ($P = 0.112$) was observed between TO/LVEF and SDNN/LVEF correlation coefficients.

### Discussion

The present study indicates that in Chagas disease patients, changes in cardiac cycle induced by a transient perturbation such as a premature ventricular complex are highly correlated with LVEF, thus suggesting that this methodology might be more suitable than traditional HRV analysis to detect those alterations in autonomic control that are associated with progression of Chagas cardiomyopathy.

### Autonomic dysfunction, LVEF and Chagas disease

An abnormal autonomic modulation of the sinus node has been consistently observed in Chagas disease patients [6–8]. Using traditional autonomic tests, a reduction in respiratory sinus arrhythmia [6] and an abnormal response to Valsalva manoeuvre [23] were reported. By using HRV analysis, a reduction in the percent of RR interval with a length difference greater than 50 ms (pNN50) and RMSSD of 24-h Holter recording were described [7–9]. More recently [24], a reduced baroreflex sensitivity in sero-positive Chagas disease patients independent of the characteristic electrocardiographic abnormalities was also reported. All these findings were interpreted as indirect evidence of abnormal vagal modulation of the sinus node which

### Table 1 Clinical, HRV and HRT parameters in Chagas patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA (class I)</td>
<td>16</td>
</tr>
<tr>
<td>NYHA (class II)</td>
<td>7</td>
</tr>
<tr>
<td>NYHA (class III)</td>
<td>4</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>30 45.4 ± 14.3</td>
</tr>
<tr>
<td>PVCs (number)</td>
<td>30 1781 (580–3497)*</td>
</tr>
<tr>
<td>NSVT (% of patients)</td>
<td>23 (77 %)</td>
</tr>
<tr>
<td>Mean RR interval (ms)</td>
<td>30 869.13 ± 135.5</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>30 140 ± 44</td>
</tr>
<tr>
<td>ln RMSSD (ms)</td>
<td>30 26.5 (18.7–50.2)*</td>
</tr>
<tr>
<td>TO (%)</td>
<td>30 $-0.011 \pm 0.011$</td>
</tr>
<tr>
<td>TS (ms/RR-interval)</td>
<td>30 5.752 ± 3.588</td>
</tr>
</tbody>
</table>

HRV: heart rate variability; HRT: heart rate turbulence; NYHA Class: New York Heart Association Class; LVEF: left ventricular ejection fraction; PVCs: premature ventricular complexes; NSVT: non-sustained ventricular tachycardia; SDNN: standard deviation of normal RR intervals; ln RMSSD: natural log of root mean square of successive differences in normal RR intervals; TO: turbulence onset; TS: turbulence slope. *Median and interquartile ranges.

### Table 2 Pearson’s correlation coefficients among clinical, HRV and HRT parameters adjusted for mean RR interval

| TS  | -0.67 (0.000) |
| SDNN (corrected for RR interval) | -0.19 (0.314) 0.32 (0.085) |
| In RMSSD (corrected for RR interval) | 0.03 (0.866) -0.01 (0.944) 0.34 (0.067) |
| LVEF | -0.60 (0.001) 0.73 (0.000) 0.41 (0.025) 0.22 (0.239) |
| ln PVCs | 0.03 (0.875) -0.07 (0.705) -0.17 (0.361) 0.16 (0.395) -0.33 (0.073) |
| Age | 0.30 (0.12) -0.23 (0.223) -0.25 (0.191) 0.03 (0.871) -0.26 (0.171) 0.14 (0.439) |
| TO  | -0.01 (0.944) 0.34 (0.067) |
| TS  | 0.03 (0.866) -0.01 (0.944) 0.34 (0.067) |
| SDNN (corrected for RR interval) | 0.03 (0.866) -0.01 (0.944) 0.34 (0.067) |
| In RMSSD (corrected for RR interval) | 0.03 (0.866) -0.01 (0.944) 0.34 (0.067) |
| LVEF | 0.03 (0.866) -0.01 (0.944) 0.34 (0.067) |
| ln PVCs | 0.03 (0.866) -0.01 (0.944) 0.34 (0.067) |

P values are within brackets; significant correlation coefficients are in bold. HRV: heart rate variability; HRT: heart rate turbulence; TO: turbulence onset; TS: turbulence slope; SDNN: standard deviation of normal RR intervals; ln RMSSD: natural log of root mean square of successive differences in normal RR intervals; LVEF: left ventricular ejection fraction; ln PVCs: natural log of premature ventricular complexes.
appeared to be detectable from the initial manifestations of this cardiomyopathy. More controversial was the interpretation of SDNN values in Chagas disease patients. We previously reported [7] that more global HRV indices such as SDNN or the standard deviation of averaged 5 min differences greater than 50 ms (SDANN) were not significantly reduced, in comparison with age matched controls, in Chagas patients with either a preserved or reduced LVEF, whereas a loss of normal non-linear dynamics of 24-h HRV was associated with progressive deterioration of left ventricular function. Thus, SDNN, the most easy to compute HRV index and powerful predictor of mortality in a variety of cardiovascular diseases, appeared to be unsuitable to detect the progressive alterations of autonomic modulation associated with Chagas disease. This point has several pathophysiological and clinical implications. First of all, it confirms the complexity of alterations of cardiac autonomic control in Chagas disease [6–9]; second, that the correlation between LVEF and HRV indices commonly observed in post-myocardial infarction [5,25,26] or heart failure [5,27] patients could be made less robust by factors such as the presence of frequent PVCs that may affect HRV analysis; third, that the predictive value of a reduced SDNN to identify patients at risk for sudden cardiac death cannot be directly applied to Chagas patients.

In the present study, carried out on a limited number of subjects but in whom SDNN, RMSSD and LVEF were analysed as continuous variables, we were unable to observe a significant correlation between LVEF and HRV indices after correction for mean RR interval. In this regard it is important to note that SDNN values were within normal range (>100 ms) in almost all subjects, whereas LVEF presented a wide range of values.

**HRT and Chagas disease**

HRT is a relatively new non-invasive methodology to study autonomic control of the sinus node and to identify patients at greater arrhythmic risk [11,17–19]. At variance with time domain analysis of HRV, which is essentially based on the quantification of steady-state physiological variations of cardiac cycles, HRT quantifies the biphasic response of the sinus node to a PVC, according to a transient stimulus–response model. Early acceleration and late deceleration are mainly mediated by baroreflex mechanisms [12,13]. In a previous study [20] we reported that, in comparison with controls, Chagas disease patients had a significant

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**Figure 1** Correlation between ejection fraction and, respectively, turbulence onset, mean RR interval, turbulence slope and SDNN. $r$ values and significance levels are presented in each panel.
alteration of HRT. However, when comparing patients with LVEF > or <0.5 no significant differences were detectable. When HRT indices were analysed as continuous variables, in both the present and previous studies, a significant correlation between LVEF and TS was noticed.

In the present report, which included patients with a greater range of LVEF values, both TO and TS were highly significantly correlated with LVEF, thus indicating a tight correlation between the extent of left ventricular dysfunction and the pattern of adaptation of the cardiac cycle to premature ventricular complexes. When comparing the correlation coefficients among LVEF and either HRV or HRT parameters, a significant difference was observed indicating a more robust association between TS and LVEF. This result is of relevant clinical interest taking into account the high incidence of PVCs in Chagas patients that prevents, in absence of appropriate and time-consuming data editing, a valid computation of time domain parameters of HRV. It also suggests that autonomic dysfunction in Chagas disease involves reflex response mechanisms that affect HRT and HRV to different extents. In the former case, rate acceleration and deceleration following PVCs mainly depend upon baroreflex control of efferent vagal and sympathetic activity [12–15], in the latter one, neural and non-neural factors play a major role in determining 24-h HRV [28].

Of interest was the finding that we were unable to observe a significant correlation between HRT indices and other electrocardiographic measurements such as mean RR interval or PVC number. It seems, therefore, that the information on autonomic control mechanisms that can be derived by HRT analysis is indeed based on different mechanisms of autonomic function assessment, which could be particularly useful in this clinical condition characterised by both a reduction of left ventricular function and frequent PVCs.

**Study limitation**

The small number of patients represents the major limitation of the study. This point was partially counterbalanced by the possibility of performing a careful evaluation and editing of 24-h Holter recordings with frequent PVCs. The absence of a follow-up period also prevented an appropriate evaluation of the predictive value of HRV and HRT parameters. To accomplish this objective, a completely different study design and patient population would have been necessary. No evaluation of the digestive tract was performed in these patients, a fact that does not reduce the strength of the correlation between HRT indices and LVEF.

In spite of these limitations, we compared, in Chagas disease patients with a greater range of left ventricular dysfunction, the correlation between LVEF and two non-invasive methodologies commonly used for the evaluation of autonomic dysfunction. The observed results indicate that HRT analysis is more suitable than traditional HRV parameters in detecting the changes of cardiac autonomic control that parallel left ventricular dysfunction in Chagas disease patients. The high number of PVCs observed in these patients further supports the use of the HRT methodology.

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