Original Article

Active Orthostatic Stress and Respiratory Sinus Arrhythmia in Patients with Chagas' Disease with Preserved Left Ventricular Global Systolic Function

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Objective

To assess the use of the active orthostatic stress test for detecting vagal dysfunction in patients with Chagas' disease with preserved overall systolic function, and to compare it with the respiratory sinus arrhythmia test.

Methods

Sixty-one chagasic patients (Ch) and 38 nonchagasic (NCh) patients with no significant evidence of heart disease or systemic diseases underwent Doppler echocardiography and autonomic function tests. The respiratory sinus arrhythmia test was performed through electrocardiographic recording during deep breathing, at 6 ripm, calculating the E:I ratio (mean ratio between the longest expiratory RR interval and the shortest inspiratory RR interval at each cycle). The electrocardiogram was recorded during the act of standing and during the following 30 seconds (active orthostatic stress test), and the max RR/min RR ratio (the longest and shortest RR intervals right after change in posture) was calculated. The indices were adjusted for significant covariables.

Results

The max RR/min RR ratio (NCh: 1.52 [1.44-1.74] x Ch: 1.43 [1.33-1.51], P < 0.001) and the E:I ratio (NCh: 1.38±0.02 x Ch: 1.25±0.02, P<0.001) were lower among chagasic patients. A high correlation was observed between the adjusted max RR/ min RR ratio and E:I ratio (r = 0.628, P < 0.001), but neither significantly correlated with left ventricular ejection fraction.

Conclusion

Chagasic patients with preserved left ventricular overall systolic function showed a significant reduction in the vagal indices obtained on short-lasting tests, as compared with normal controls. The active orthostatic stress test that, showed a good correlation with the respiratory sinus arrhythmia maneuver, constituted a valid option for the outpatient care assessment of vagal control.

Key words

Chagas' disease, autonomous nervous system, orthostatism

Chagas' disease persists as a major public health problem in our country, affecting approximately 4 million Brazilians[1]. Sudden death accounts for approximately 50% of the deaths caused by the disease, and it may affect young individuals halfway through their productive life years[2]. Autonomic dysfunction, a typical abnormality of the disease, has been implicated as playing an important role in the genesis of arrhythmic death in Chagas' disease[3]. Recent studies[4-8] have reported that vagal dysfunction can be observed in patients with no left ventricular dysfunction, occurring early in some patients with the disease. It can be recognized with the study of heart rate variability on 24-hour Holter, of respiratory sinus arrhythmia, and the Valsalva maneuver. Although these methods are established indicators of parasympathetic activity, they have specific limitations, such as the need for Holter equipment and for software for analysis, or the patient's collaboration.

The active orthostatic stress test consists of the evaluation of the response of heart rate when the standing position is actively assumed[9]. When the individual stands up, from a horizontal position, approximately 300 to 800 mL of blood are rapidly transferred from the thorax to the lower limbs. A few seconds after assuming a standing position, tachycardia is observed, caused mainly by suppression of the vagal influence, related to voluntary muscle contraction and the transient reduction in blood pressure[9-11]. The baroreflex activation that follows leads to recovery of blood pressure and a vagus-mediated reduction in heart rate, which is completed at 30 seconds of orthostatism. Subsequent increases in heart rate and maintenance of blood pressure are mainly due to cardiac and vasomotor sympathetic control, in addition to neuroendocrine activation[9]. Active orthostatic stress is believed to be better than the passive tilting test to trigger vagus-mediated reflexes[9]. Because the highest heart rate usually occurs around the 15th beat after assuming the standing position, followed by maximum bradycardia around the 30th beat, Ewing et al[12] standardized an autonomic test of the parasympathetic division based on the 30:15 ratio (the longest RR interval around the 30th beat divided by the shortest RR around the 15th beat). Wieling et al[11,13], considering that the 30:15 ratio underestimates the maximal variability in heart rate occurring after orthostatism, have proposed the use of a ratio between the maximum RR interval and the minimum RR interval (max:min RR index).

The present study aims at assessing whether the active orthostatic stress test, obtained through the max:min RR index, allows the detection of vagal dysfunction in chagasic patients

with preserved left ventricular overall systolic function, in addition to assessing its correlation with the respiratory sinus arrhythmia test, here considered the gold standard for the diagnosis of vagal dysfunction.

Methods

A cross-sectional study was carried out in the referral outpatient care clinic for Chagas' disease of the Hospital das Clínicas of the UFMG, after approval of the research project by the committee on ethics in research of the institution [4]. The patients were screened up from January 1992 to August 1994, and those, chagasic or not, in the age group from 15 to 50 years with a defined serology for Chagas' disease were recruited. Their initial evaluation did not suggest the presence of heart disease or other significant diseases. These patients underwent anamnesis and physical examination according to the standardized protocol, and their serological status was not known by the examiner. Twelve-lead electrocardiography and chest teleradiography were performed, in PA and left profile. They were analyzed in a blind and standardized form. The following laboratory tests were also performed: complete hemogram; serum levels of creatinine, urea, potassium, and sodium; fasting glycemia; and TSH level measurement. Other examinations were later asked for according to clinical need, such as free T4 measurement and glucose tolerance curve. The individuals with positive serology for *Trypanosoma cruzi* according to 2 or more different techniques, including the reactions of indirect immunofluorescence, indirect hemagglutination, fixation of complement, and ELISA, were considered chagasic. The inclusion criteria for the study were as follows: age between 15 and 50 years; defined serologic status for Chagas' disease; and no evidence of heart disease on anamnesis, physical examination, electrocardiography, or chest radiography.

The exclusion criteria were as follows: 1) impossibility of or no availability for performing the examinations proposed; 2) systemic arterial hypertension operationally defined as blood pressure level during physical examination of 160/95 mm Hg, or between 140-159/90-94 mm Hg in association with a history of systemic arterial hypertension; forth heart sound on physical examination; probable left ventricular overload on the electrocardiogram according to the Romhilt-Estes criterion; or evidence of aortic dilation on chest radiography; 3) history compatible with coronary heart disease, according to directed anamnesis; 4) a previous episode suggestive of acute rheumatic disease; 5) diabetes mellitus or decreased tolerance to glucose, according to anamnesis, measurement of fasting glycemia, and, if necessary, a test of oral glucose tolerance; 6) thyroid dysfunction; 7) renal failure; 8) chronic obstructive pulmonary disease; 9) hydroelectrolytic disorders; 10) significant anemia, arbitrarily defined as hemoglobin < 10 g/dL; 11) alcoholism defined as mean week alcohol consumption above 420 g of ethanol; 12) any other chronic or acute significant systemic disease, which could interfere with the results of the specific tests; 13) pregnancy, defined by laboratory criteria; 14) use of medications with an effect on the cardiovascular system or on the autonomous nervous system.

Of the initial 144 patients, 45 were excluded according to the criteria already cited, leaving 99 patients available for undergoing the specific examinations, 61 of whom were chagasic and 38 of whom were nonchagasic. The respiratory sinus arrhythmia test always preceded orthostatic stress, both being performed on the same day, in the morning, after at least an 8-hour fast.

The respiratory sinus arrhythmia test was performed with the patient in a sitting position connected to the Hewlett-Packard electrocardiograph, 1504 model, with a nasal clip to avoid nasal respiratory losses. The environmental temperature was monitored (mean of 25±3°) to allow corrections of the current volume. The patient was maintained at rest, sitting for at least 2 minutes before the beginning of the test. Continuous electrocardiographic recording at 25 mm/s was initiated 10 seconds before the maneuver and maintained for at least 1 minute of deep breathing controlled by a metronome, at 6 ripm, with simultaneous recording of the current volume on graph paper in a Collins spirograph, DSII model. Each patient was prompted to slowly perform maximum respiratory movements, each respiratory cycle lasting 10 seconds. A simply codified manual mark was performed on the electrocardiogram at the beginning of each inspiration and expiration in each respiratory cycle [4,12-16].

The analysis of the electrocardiogram was performed manually, including the pretest period and the minute corresponding to the 6 respiratory incursions performed, using the Del Mar Avionics rulers of electrocardiographic measurement.

The ratios between the longest expiratory RR interval and the shortest inspiratory RR interval (E:I ratio) for each respiratory cycle were calculated, as were the mean values referring to the 6 cycles. The mean cardiac interval and mean heart rate, immediately before initiating the maneuver, were obtained for the 10 RR intervals immediately preceding the beginning of the maneuver. All calculations were based on the original maximum and minimum cardiac intervals.

The patient was maintained resting in the horizontal position for 5 minutes, and then asked to stand up rapidly (3 to 5 seconds). The electrocardiographic recording was initiated 10 seconds before initiating the maneuver, and was maintained for 40 seconds. The tracing was manually analyzed a posteriori, measuring the RR intervals as in the previous tests, including the pretest periods, the act of standing, and the following 40 seconds. The 10 RR intervals immediately preceding maneuver onset were computed to obtain the mean cardiac interval and mean heart rate at baseline immediately before starting the maneuver. The longest and shortest RR intervals were recorded right after the maneuver, and the max:min RR index was calculated [4,8-16].

Doppler echocardiography was performed with a Siemens echocardiograph, Sonoline CF model, using unidimensional (M mode) mode, two-dimensional mode in real time, color Doppler, pulsed Doppler, and continuous Doppler. All examinations were performed by the same echocardiographer, in a standardized manner, without knowing the patient's serological status. The global and regional diastolic and systolic left ventricular function was assessed with details. The present study comprised only data referring to left ventricular ejection fraction.

Descriptive statistics of the variables chosen was performed. The distribution of the absolute and relative frequency of the qualitative variables, and the mean, variance, standard deviation, median, amplitude, and mean dispersion of the continuous quantitative variables were obtained. In all quantitative variables, the histogram of distribution was performed to detect the deviations

41

from normality and the extreme values, excessively distant from the measures of central trend (outliers). In this case, the original electrocardiographic recordings or tracings were reassessed in the search for errors in the measurements, in the recording, or in data typing. The graph of normal probability for each continuous variable was built, and the Ryan-Joiner statistical test, similar to the Shapiro-Wilk test, was performed for detecting deviations from normality. For the continuous variables, the homogeneity of the variances in the 2 groups was compared using the Bartlett test; nonparametric tests were chosen if the distribution of the variable was different from the normal or if heterogeneity of variances existed in the 2 groups. The variables with nonnormal distribution or heterogeneous variances underwent logarithmic transformation, using the natural logarithm [17]. The proportions, means, and medians of the independent and dependent variables of the chagasic and nonchagasic groups were compared using the appropriate statistical tests, such as the chi-square test, Fisher exact test, Student t test, and Wilcoxon-Mann-Whitney test. In all tests, the probability of significance (P) lower than 0.05 was required for rejecting the null hypothesis.

Because the autonomic tests are influenced by varied factors, such as age, current volume (in the respiratory sinus arrhythmia test), and, possibly, the presence of depression in left ventricular systolic function, the analysis was performed through multiple linear regression. The model of regression was defined using the computed algorithm that allows the selection of variables more significantly related to the autonomic indices (Best-subset selection procedure, software Minitab, version 9). On multivariate analysis, the max:min RR index (obtained during active orthostatic stress) was observed to relate to age, while the E:I ratio (respiratory sinus arrhythmia) was also influenced by age and the current volume achieved in each patient. Through analysis of covariance, the means of the autonomic indices in both groups were corrected for the significant covariables and again compared, and the corrected indices derived from the autonomic tests were again compared through the Pearson product moment correlation [17].

Results

Table I shows the clinical, radiological, and echocardiographic characteristics of the patients in the chagasic and nonchagasic groups. The mean age was slightly more significantly lower in the control group (P = 0.002). Mild abnormalities on esophagogram

with barium occurred in some patients in both groups, with a slight retention of contrast medium and no significant dilation. The ejection fraction was close to normal in almost all patients, and no significant difference was observed in the groups also in regard to the cardiothoracic index and left ventricular end-diastolic diameter on echocardiography. No patient in any of the groups had ejection fraction below 50%.

The max:min RR ratio obtained during active orthostatic stress was substantially lower in the chagasic group (median: 1.43, quartile interval 1 – quartile 3 1.33-1.51) than in the nonchagasic group (1.52, 1.44-1.74, P < 0.0001). In 3 patients, the max:min RR ratio could not be calculated due to loss of the tracing (1), frequent artifacts (1), and the presence of arrhythmia (1). The E:I ratio during the respiratory sinus arrhythmia test was also significantly lower in the Ch group (mean 1.38, standard deviation 0.02) than in controls (1.25, 0.02). One patient could not perform the respiratory maneuvers, even after training. After correction for the covariables, the medians of the values of the max:min RR ratio and the means of the E:I ratio were significantly lower in the chagasic group as compared with those in the nonchagasic group. The results were not significantly different after exclusion of those with mild radiological alterations in the esophagus. An elevated correlation between the max:min RR ratio and the adjusted E:I ratio was observed (r = 0.628, P < 0.001, fig. 1).

Table II shows the matrix of correlation for the autonomic indices and the echocardiographic variables in control and chagasic patients. Both the E:I ratio and the max/min RR index did not significantly correlate with the echocardiographic variables assessed, such as ejection fraction and left ventricular end-diastolic diameter.

Discussion

The cardiovascular response to orthostatism in Chagas' disease has already been previously studied, using both passive and active orthostatic stress. In passive orthostatic stress, the individual's postural change is obtained through inclination of the table on which the patient is lying down [18-20]. In active orthostatic stress, the posture is actively changed [21-23] in a similar way to that in the present study. However, we know no report about the use of the max:min RR ratio for detecting vagal dysfunction in Chagas' disease on an outpatient care basis. The active orthostatic stress test is sensitive, specific, reproducible, and easily performed, being con-

| Table I - Clinical, radiological, and echocardiographic characteristics of patients in the chagasic and control groups			
	Controls (n=38)	Chagas' disease (n=61)	P
Age (years)	33 ± 8	38 ± 8	0.00
Sex (man/woman)	33/5	46/15	0.17
Weight (kg)	71.1 ± 11.4	67.1 ± 9.8	0.06
Heart rate (bpm)	69 ± 10	69 ± 7	0.86
Systolic blood pressure (mmHg)	118 ± 11	122 ± 12	0.10
Diastolic blood pressure (mmHg)	76 ± 10	78 ± 9	0.12
Cardiothoracic index	0.42 ± 0.04	0.43 ± 0.03	0.67
Retention of barium on esophagography (%)	19	11	0.41
Ejection fraction (%)	68 ± 6	68.0 ± 7	0.99
LV end-diastolic diameter (cm)	5.17 ± 0.07	5.07 ± 0.04	0.39
LV - left ventricle. Data expressed as mean and standard deviation or proportions			
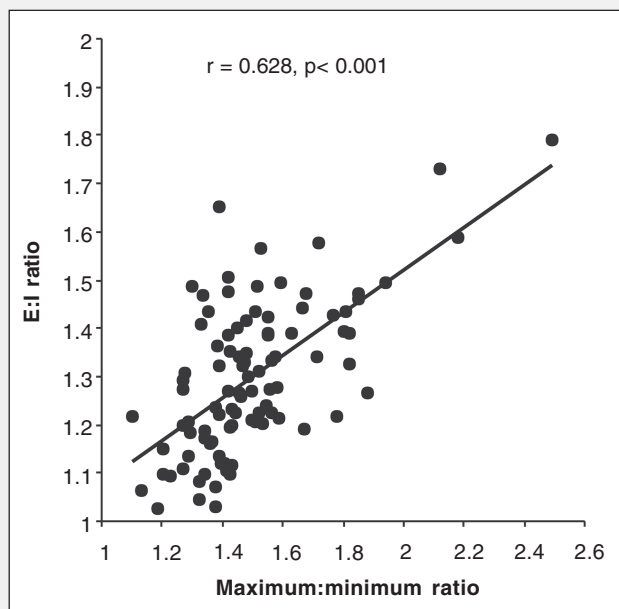
Fig. 1 - Correlation between the max:min RR ratio on active orthostatic stress and the E:I ratio on respiratory sinus arrhythmia maneuver in 99 chagasic and nonchagasic patients with no apparent heart disease.

Table II - Coefficients of correlation between the autonomic indices and the variables selected in 99 chagasic and nonchagasic patients with no apparent heart disease				
	Max:min RR ratio		E:I ratio	
	r	P	r	P
Ejection fraction	0.056	0.860	- 0.121	0.239
LV end-diastolic diameter	-0.066	0.71	- 0.012	0.904
LV - left ventricle				

sidered better than the head-up tilt test as a methodology for assessing vagal control of orthostatism [9].

The results of the active orthostatic stress test in chagasic patients with no heart disease, as compared with that in normal controls, confirm the findings of our previous study performed in the same group of patients [4-6], and in another sample later studied [7,8], and also the findings reported by other authors [24-27]. The different methods used, such as the variability in heart rate (assessed with different techniques) [5,7,8,22], the Valsalva maneuver [6,23,24,26], and respiratory sinus arrhythmia [5,26], showed that autonomic dysfunction is present in patients with no evidence of heart disease and with preserved left ventricular function. The set of these results definitively answers a question that has pervaded the literature during the last 2 decades: whether autonomic dysfunction precedes or not left ventricular dysfunction in Chagas' disease [26-30]. Although these results do not provide any causal inference, early autonomic dysfunction certainly exists in Chagas' disease.

The influence of digestive impairment in the genesis of autonomic dysfunction, emphasized in other studies [26], was not an object of evaluation in our study. However, it is worth noting that the patients studied had no clinical or radiological manifestations of significant digestive disease, indicating that this was not the major determinant of the abnormalities found in the autonomic tests.

In the present study, 2 classical tests were used for assessing cardiac vagal control. The indices obtained, the E:I ratio adjusted to the respiratory sinus arrhythmia test and the max:min ratio to

orthostatic stress, are strongly correlated (r = 0.632), but did not show identical results. Gautschy et al [31], studying 120 healthy individuals, found an identical coefficient of correlation between these 2 indices: r = 0.63. Discordance between the results of different autonomic tests has been reported by other authors in the literature, and usually indicates the need for using more than 1 autonomic function test for detecting the autonomic dysfunction, and deserves to be discussed [13-16]. Such variability in the response to autonomic tests depends not only on neural control, but also on different hemodynamic and methodological aspects. Although predominantly related to the vagus, the immediate cardioaccelerating response that follows the beginning of the standing maneuver is also linked to hemodynamic modifications subject to reflex adjustments, and also influenced by sympathetic stimulation [9-11]. The initial increase in heart rate (3 seconds after beginning the maneuver) is related to the removal of vagal influence by voluntary abdominal muscle contraction; a second peak of increase in heart rate (around 12 seconds) is mediated by both vagal inhibition and sympathetic stimulation, elicited by the decrease in the arterial baroreflex activation, caused by the drop in blood pressure associated with the decrease in venous return [11]. The hemodynamic and autonomic response is influenced by the resting time that precedes the examination, as well as by the velocity and effort made in the act of standing [32], factors that may vary from patient to patient, being difficult to standardize. Although respiratory sinus arrhythmia also relates to complex mechanisms, the respiratory stimulus is subject to standardization and control. The hemodynamic changes are less pronounced and the sympathetic influence has minimal importance. Therefore, respiratory sinus arrhythmia is presumed to provide a more precise indication of vagal control of the heart [33,34].

Although in laboratory conditions with spirometric control of the current volume and maintenance of a fixed respiratory rate, the respiratory sinus arrhythmia test provides a clear advantage as compared with the active orthostatic stress test, the situation is different in the outpatient care context. The control of current volume is not possible inside a primary care medical office, and the performance of the test with maximal and regular breathing at 6 cycles per minute requires training and patient's collaboration. On the other hand, calculation of the variability in heart rate on 24-hour Holter, an important marker of autonomic dysfunction, requires the patient to undergo monitoring for 24 hours, demanding equipment and specific abilities of the attending physician. The active orthostatic stress test becomes, then, an attractive alternative for the ambulatory assessment of cardiac autonomic control, both in isolation and in association with other short-lasting autonomics tests.

The lack of information about the reproducibility of the test in chagasic patients is one of the limitations of the present study. However, studies performed in other population groups suggest that the reproducibility of the method is excellent. In addition, information on the evolution of those patients was not provided; therefore, we could not infer whether an additional deterioration in the autonomic function occurred, or, more importantly, whether the patients with abnormal tests had an unfavorable evolution when compared with that of those with preserved function.

Chagasic patients with preserved left ventricular overall systolic function have a significant reduction in the vagal indices obtained on short-lasting tests as compared with normal controls. However, the indication of such procedures for the clinical assessment of

43

the autonomic function in clinical practice is still pending, because the clinical and prognostic significance of autonomic dysfunction in Chagas' disease is yet to be known. While in diabetic patients, and after infarction, the autonomic dysfunction assessed through both rapid methods [35,36] and variability in heart rate [37] is a strong and independent indicator of the increased risk of death, the implications in Chagas' disease are not clear. If autonomic dysfunction in Chagas' disease is also recognized to allow a better stratification of the risk of death in patients followed up on an outpatient care basis, the active orthostatic stress test should be an option for ambulatory assessment of vagal control.

Acknowledgements

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44