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Short Communication

Is autonomic function associated with left ventricular systolic function in Chagas heart disease patients undergoing treatment for heart failure?

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ABSTRACT

Introduction: The association between cardiac autonomic and left ventricular (LV) dysfunction in Chagas disease (ChD) is controversial. **Methods:** A standardized protocol that includes the Valsalva maneuver, a respiratory sinus arrhythmia (RSA) test, and an echocardiographic examination was used. Spearman correlation coefficients (rho) were used to investigate associations. **Results:** The study population consisted of 118 ChD patients undergoing current medical treatment, with an average LV ejection fraction of 51.4±2.6%. The LV ejection fraction and diastolic dimension were correlated with the Valsalva index (rho=0.358, p<0.001 and rho=-0.266, p=0.004, respectively) and the RSA (rho=0.391, p<0.001 and rho=-0.311, p<0.001, respectively). **Conclusions:** The impairment of LV function is directly associated with a reduction of cardiac autonomic modulation in ChD.

Keywords: Chagas disease. Autonomic function. Valsalva index.

Chagas disease (ChD) continues to be a major health problem in Latin America despite the implementation of prevention programs and a reduction in its prevalence[1]. Dysautonomia is a well-known complication of ChD, which may occur early during the natural history of the disease[2]. The clinical significance of cardiac autonomic dysfunction in ChD is not completely understood, but it has been related to the risk of sudden death[3].

In other cardiac diseases, the degree of vagal dysfunction is directly related to the decrease of the left ventricular ejection fraction (LVEF)[4]. In ChD, parasympathetic dysfunction precedes left ventricular (LV) dysfunction[2], and autonomic and myocardial dysfunction may be independent phenomena. Previous studies have yielded controversial results regarding the relationship between vagal dysfunction and LV function[5-9].

We hypothesize that autonomic function is associated with left ventricular function in ChD. In other words, although patients with normal LV function may have autonomic impairment, those with more severe LV function impairment may have a more pronounced reduction of autonomic control of the heart. Therefore, we evaluated the correlation between autonomic indexes (the respiratory sinus arrhythmia [RSA] test and Valsalva maneuver) and LV function measurements, namely, LVEF and LV diastolic diameter (LVd) values.

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In this study, we combined the data from two different previous studies that used the same clinical protocol[8,10] to increase the statistical power of analysis and to evaluate the patients representing the entire spectrum of LV function. The data were collected from patients who were referred from blood banks or primary care units to the Outpatient Reference Center at the University Hospital of the Universidade Federal de Minas Gerais (UFMG). The data used in this study were previously used in other studies related to Chagas disease and autonomic function, and the protocols were approved by the Ethics Committee of UFMG during the period 1997-2004[8,10]. At the time of recruitment, the patients provided informed consent for data collection and use. After a confirmed diagnosis of ChD using at least two different serologic tests, the patients were evaluated using a standardized protocol that included a questionnaire (including a list of current medication), the Valsalva maneuver, an RSA test, and an echocardiographic study.

All of the autonomic tests were performed in a quiet room. Patients were still taking their current medications on a normal basis but fasted for 2h and abstained from caffeine use, smoking, and medication for at least 12h before the tests. Before the Valsalva maneuver was performed, all of the patients were provided instructions on how to perform it and were allowed to practice it a few times. The patients were instructed to blow into a mouthpiece with a closed glottis following deep inspiration. The mouthpiece was connected to a tube that was connected to an aneroid manometer to maintain an intraoral pressure of 40mmHg for 15sec. The Valsalva maneuver was considered to be effective when facial plethora, neck vein distension, and abdominal muscle contraction were observed. An electrocardiogram was performed, and the electrocardiogram recording was analyzed in a blinded fashion. The Valsalva ratio was

calculated as the ratio of the longest R-R interval recorded during phase 4 to the shortest R-R interval recorded during phase 2[11].

For the RSA test, the subjects were instructed to breathe deeply at a rate of 6 cycles per minute with the help of a metronome, and the R-R interval was recorded with an electrocardiogram. The E/I ratio (the ratio of the longest expiratory R-R interval to the smallest inspiratory interval) was calculated for each cycle, and the mean value was calculated[2].

The echocardiographic study was performed by experienced echocardiographers, using a standardized protocol as previously described[8,10]. For this study, we used the data associated with LV function, specifically LVEF and LVd.

Data were analyzed using Statistical Package for the Social Sciences (SPSS) software, version 18 (SPSS Inc. Released 2009, Chicago, IL, USA), at the University Hospital of UFMG in Belo Horizonte. Continuous variables are described as means and standard deviations, and categorical variables are described as percentages. We analyzed the association between the autonomic function indexes and left ventricular function measurements using Spearman correlation coefficients (rho) because of the asymmetric distribution of most of the variables.

The total population in this study consisted of 118 ChD patients, with complete data derived from 2 different databases. Our population, with a mean age of 49.9 (±8.5) years, consisted of 58% males, with an average LVEF of 51.4% (±14.8). The majority of our population belonged to Goldman functional class I, and most used at least one medication for the treatment of heart failure, such as angiotensin-converting enzyme inhibitors or amiodarone **(Table 1)**.

TABLE 1 - Clinical and functional features of Chagas disease patients.

Variables		
Age (years), mean (SD)	49.9	(8.5)
Male (%)	0.58	
Goldman functional class (%)		
I	74.2	
II	18.9	
III	6.8	
Amiodarone (%)	33.0	
Beta blockers (%)	14.0	
Digoxin (%)	9.0	
Angiotensin-converting enzyme inhibitors (%)	62.0	
Diuretics (%)	49.0	
LVEF (%), mean (SD)	51.4	(14.8)
LVEF greater than 45% (%)	65.0	
Left ventricular diastolic diameter (mm), mean (SD)	57	(8.0)
Valsalva index, mean (SD)	1.41	(0.24)
Respiratory sinus arrhythmia, mean (SD)	1.13	(0.10)

SD: standard deviation; LVEF: left ventricular ejection fraction.

Figure 1 displays the association between the LV measurements and autonomic indexes. The LVEF is correlated with the Valsalva index (rho=0.358, p<0.001) and the RSA (rho=0.391, p<0.001). The strength of the correlation between autonomic indexes and LVd is similar to that between the autonomic indexes and LVEF; however, the correlation between autonomic indexes and LVd is opposite to that between the autonomic indexes and LVEF (Valsalva index [rho=-0.266, p=0.004] and RSA [rho=-0.311, p=0.001]). **Table 2** shows the Spearman correlation coefficients for the association between LV measurements and autonomic indexes stratified by the sample of origin (datasets 1 and 2). Although some variation of the magnitude of the association could be observed, no systematic bias could be detected.

Our data indicated that the autonomic function was directly correlated with left ventricular function in ChD. Previous studies on this subject have produced contradictory results. Ribeiro et al.[6] and Villar et al.[7] reported that the intensity of vagal dysfunction is not related to the presence of cardiomyopathy, whereas Davila et al.[5,] Tundo et al.[8], and Vasconcelos and Junqueira Junior[9] reported an association between autonomic indexes and LV function. The reasons for the absence of a significant correlation in some of the previous studies are most likely related to a small sample size and lack of patients with severe LV dysfunction. In the present study, a wider range of LV function values provided a better understanding of the effects of ChD on EF. Our results are in accordance with the findings of studies in patients with other heart diseases, in which a direct relationship between LV function and autonomic heart control has been observed[4]. Nevertheless, in contrast to the studies of other cardiopathies, previous studies in our group indicate that in ChD, autonomic dysfunction precedes LV dysfunction, and this phenomenon may be observed even in asymptomatic patients with cardiopathy[2]. Indeed, specific processes may occur in ChD leading to parasympathetic impairment, which occurs because of the destruction of the vagal ganglia and nerve terminations due to the inflammatory process[12] and the inhibition of muscarinic receptors by autoantibodies[13]. However, our data indicate that as LV dysfunction and heart failure progress, vagal heart dysfunction worsens because of mechanisms that appear to be common with those of other heart diseases.

The strength of the present study is the use of a large database with a full spectrum of LV ejection fractions and the standardization of the autonomic tests. A limitation of the present study is the use of two different databases and the fact that all of the patients are from the same hospital; thus, possible regional differences in the *T. cruzi* strains were not considered. The sample included a few elderly patients and many subjects taking cardiovascular medications, which can potentially modify autonomic indexes. Moreover, it should be stressed that despite the fact that there was a significant and linear correlation between autonomic function and left ventricular function in ChD, the correlation coefficients were relatively low, indicating that this association is relatively weak and that LV impairment may be associated but not necessarily be the cause of vagal dysfunction.

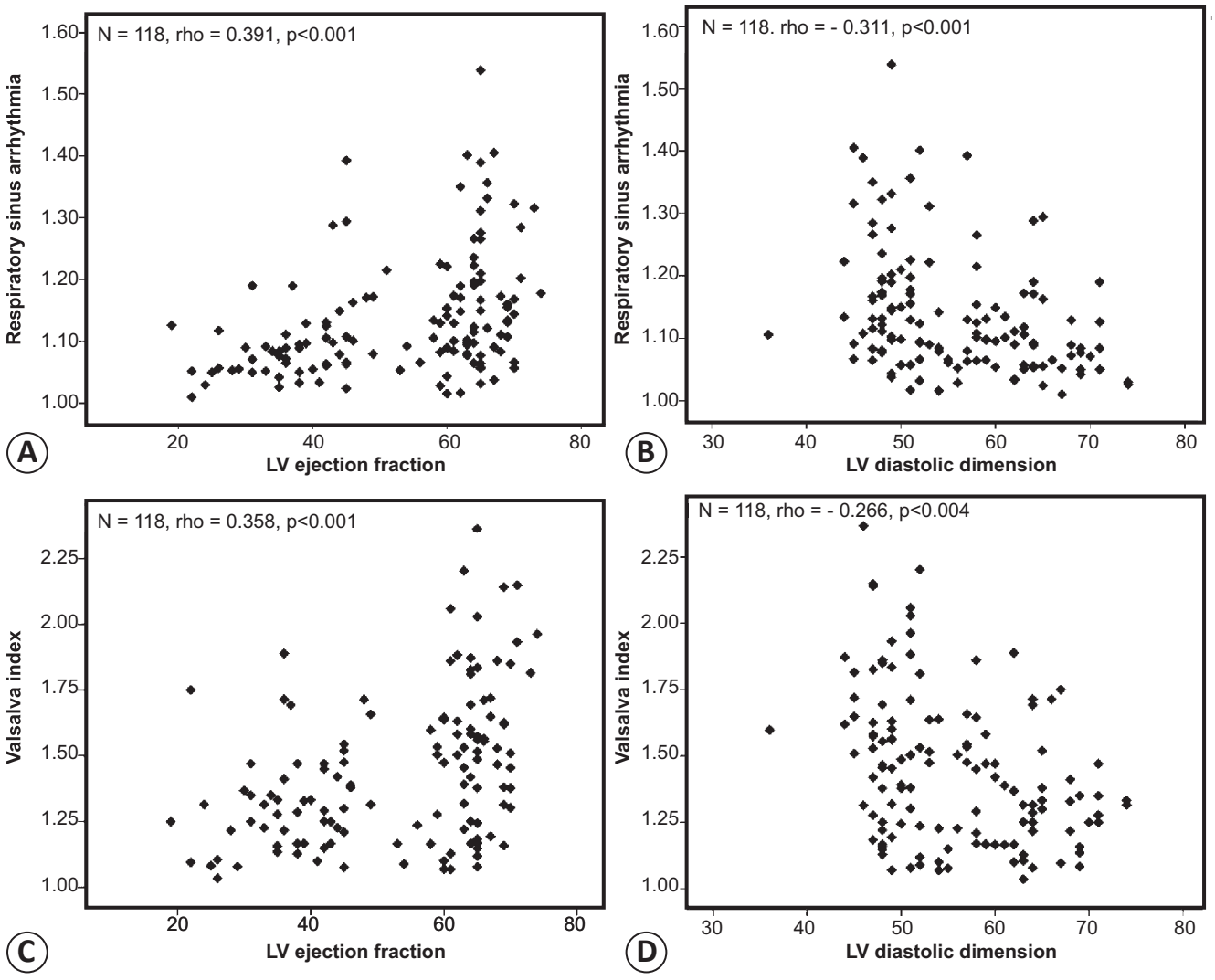

FIGURE 1 - Association between left ventricular measurements and autonomic tests: (a) left ventricular (LV) ejection fraction and respiratory sinus arrhythmia, (b) LV ejection fraction and Valsalva index, (c) LV diastolic diameter and respiratory sinus arrhythmia, and (d) LV diastolic diameter and Valsalva index.

TABLE 2 - Association between left ventricular measurements (left ventricular ejection fraction and diastolic diameter) and autonomic tests (respiratory sinus arrhythmia and Valsalva index) in the two datasets of Chagas heart disease patients used in this study.

		Respiratory sinus arrhythmia		Valsalva index	
		rho	p-value	rho	p-value
Left ventricular ejection fraction	Dataset 1	0.247	0.029	0.355	0.002
	Dataset 2	0.41	0.01	0.216	0.18
Left ventricular diastolic diameter	Dataset 1	-0.182	0.11	-0.261	0.024
	Dataset 2	-0.223	0.17	0.043	0.79

Rho: Spearman correlation coefficients.

In conclusion, autonomic function is related to left ventricular function in ChD, although patients with normal LV function could have vagal impairment. The prognostic significance of autonomic dysfunction is still unknown and warrants further investigation in prospective studies.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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