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ORIGINAL ARTICLE

Early detection of cardiac autonomic dysfunction using the respiratory sinus arrhythmia accentuation maneuver in patients with stage B1 of Chagas Disease

Detecção precoce da disautonomia cardíaca pela manobra de acentuação da arritmia sinusal respiratória de pacientes no estágio B1 da doença de Chagas

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Abstract

Introduction: The maneuver to accentuate respiratory sinus arrhythmia (RSA) demonstrates to be a convenient instrument to evaluate the autonomic modulation of individuals with chronic Chagas disease cardiomyopathy (CCC), even with medication influence, as T-cruzi causes an inflammatory process creating lesions in the cardiac nerve endings of patients affected by Chagas disease. *Objective:* To evaluate the autonomic modulation of heart rate (HR) at rest and during the respiratory sinus arrhythmia accentuation maneuver (RSA-M) in patients with CCC in stage B1. *Methods*: thirty-six individuals were evaluated, divided into the CCC group, composed of 18 patients with Chagas heart disease, and the control group, formed by 18 healthy individuals. Heart rate variability (HRV) was collected beat by beat using the electrocardiography system Wincardio USB, supine for 10 minutes, and during the RSA-M for 6 minutes. *Results:* We observed higher values of statistical significance in Control group for mean HR (p = 0.005), IRR (p = 0.007), and worse autonomic adjustments related to SD2 / SD1 (p = 0.001) concerning CCC group in a supine position. However, evaluating the RSA-M, we observed a statistical difference in the delta I-E (p = 0,039) and the E / I rate (p = 0.045) of the Control group in relation to

the CCC group. Conclusion: Patients with CCC showed better cardiovascular condition and HR control compared to the group of healthy individuals at rest. However, when subjected to RSA-M, the results showed a reduction in vagal balance in the autonomic control of individuals with CCC.
Keywords: respiration; heart rate; chagas cardiomyopathy; autonomic nervous system diseases.

Resumo

Introdução: A manobra de acentuação da arritmia sinusal respiratória (ASR) demonstra ser um instrumento conveniente para avaliar a modulação autonômica de indivíduos com cardiomiopatia chagásica crônica (CCC), mesmo com influência medicamentosa, pois o T-cruzi provoca um processo inflamatório gerando lesões nas terminações nervosas cardíacas de pacientes acometidos pela doença de Chagas. *Objetivo:* Avaliar a modulação autonômica da frequência cardíaca (FC) em repouso e durante a manobra de acentuação da arritmia sinusal respiratória (M-ASR) em pacientes com CCC estágio B1. *Métodos:* foram avaliados trinta e seis indivíduos, divididos em grupo CCC, composto por 18 cardiopatas chagásicos, e grupo controle, formado por 18 indivíduos saudáveis. A variabilidade da frequência cardíaca (VFC) foi coletada batimento a batimento por meio do sistema de eletrocardiografia Wincardio USB, em posição supina por 10 minutos e durante a RSA-M por 6 minutos. *Resultados:* Observamos maiores valores de significância estatística no grupo Controle para FC média (p = 0,005), IRR (p = 0,007) e piores ajustes autonômicos relacionados ao SD2/SD1 (p = 0,001) em relação ao grupo CCC em posição supina. Porém, avaliando o M-ASR, observamos diferença estatística no delta I-E (p = 0,039) e na razão E/I (p = 0,045) do grupo Controle em relação ao grupo CCC. *Conclusão:* Pacientes com CCC apresentaram melhor condição cardiovascular e controle da FC em comparação ao grupo de indivíduos saudáveis em repouso. Porém, quando submetidos à M-ASR, os resultados mostraram redução do equilíbrio vagal no controle autonômico de indivíduos com CCC.
Palavras-chave: respiração; frequência cardíaca; cardiomiopatia chagásica; doenças do sistema nervoso autônomo.

Introduction

Chronic Chagas disease cardiomyopathy (CCC) affects 20% to 30% of infected people (Bern, 2015), resulting from an incessant, low-intensity inflammatory process caused by *Trypanosoma cruzi*. The disorders resulting from the inflammatory process cause lesions in the cardiac nerve endings, especially parasympathetic tones [1].

One consequence of CCC is the appearance of cardiac dysautonomia, which represents the denervation of areas in the myocardium. This denervation may cause ventricular arrhythmias and reduced parasympathetic entry leading to an increased risk of sudden death [2]. Chronic chagasic patients experience impairment, in heart rate (HR) adjustment in response to physiological stimuli, such as changes in posture, breathing maneuvers, and physical exercise, mediated by the vagal system [3-5].

These changes can be evaluated by a non-invasive and safe technique known as heart rate variability (HRV). There is a description of the

oscillations in the period between consecutive heartbeats (RR intervals) and oscillations between consecutive instant heart rates [3,6,7]. Moreover, HRV is a clinical measure sufficient for identifying patterns to indicate adverse health conditions and providing helpful information about the adaptive capacity of individuals. Hence, a pattern with high HRV signals good cardiovascular health, with a nervous system autonomous (NSA) functioning correctly, while a reduced HRV can signal an improper functioning of the NSA, demonstrating poor autonomic modulation [8].

A strategy that enables the evaluation of the parasympathetic modulation using the HRV technique also has a more practical view of the modulation in the NSA is the respiratory sinus arrhythmia accentuation maneuver (RSA-M) [3]. This tool consists of improving and identifying vagal integrity, especially this sympathovagal balance, to keep changes in respiratory frequency by changing the inspiratory and expiratory cycles. It can be performed in healthy individuals or those with cardiovascular, respiratory and degenerative diseases [9]. Consequently, the HRV emerges as a valuable instrument to evaluate cardiovascular events such as sudden death [8,10], low survival in patients with left ventricular dysfunction, heart failure, or previous heart attack [8]. It also shows that a reduction in daily HRV was associated with hospitalization and death of cardiac patients [5,11]. In this context, successful strategies for rapid assessment of changes in HRV caused by CCC in earlier stages may represent assertive planning to control and interrupt the progression of the disease through pharmacological and non-pharmacological approaches, such as physical exercise. Thus, the aim of the study was to evaluate and compare the autonomic modulation of HR in patients with CCC stage B1 with healthy individuals at rest and during the RSA-M.

Methods

This is an observational and cross-sectional study with a control group. Initially, patients with stage B1 CCC (CCC group) with positive serology for Chagas disease were recruited and followed up at the Chagas heart disease outpatient clinic at Hospital Clementino Fraga Filho of Universidade Federal do Rio de Janeiro. The inclusion criteria were: i) age between ≥ 20 years and ≤ 70 years; ii) New York Association functional class between I and II; iii) with preserved left ventricular ejection fraction; iv) patients who had been away from the endemic area for more than 20 years and who still underwent active and regular clinical monitoring at the outpatient clinic; v) with optimized medication. Regarding the exclusion criteria, the following were considered: i) Hemodynamic instability; ii) Current smoking; iii) Change of medications; iv) Use of a cardiac resynchronizer or pacemaker; v) History of acute heart attack in the last six months; vi) Patients with neurological pathologies and chronic renal failure. While in the Control group, the volunteers were healthy, excluding smokers, users of illicit drugs and/or any medication, and individuals with cardiopulmonary, musculoskeletal, neurological, autoimmune, metabolic disease, diabetes mellitus, and/or hypertension.

All participants were evaluated in the same period of the day - the afternoon period - to avoid possible bias in the results by the variation of the circadian cycle. This study was carried out at the Laboratório do Grupo de Pesquisa em Avaliação e Reabilitação Cardiorrespiratória (GECARE) at the

Federal University of Rio de Janeiro (UFRJ). The team responsible for this study consists of a cardiologist, physiotherapists, and physical education professionals with extensive experience in ambulatory blood pressure monitoring, cardiopulmonary exercise testing, and cardiac rehabilitation activities. The approval for the realization of this study was granted by the Research Ethics Committee at Hospital Universitário Clementino Fraga Filho to the UFRJ (CAAE No. 26421619.1.0000.5257). Patients signed informed consent forms before the start of any study-related procedures.

Procedures

Functional Evaluation

The patients were submitted to a detailed evaluation (anamnesis and physical examination). Measurements of body mass (in kilograms - kg), height (in centimeters - cm), body mass index (BMI), and waist circumference (in centimeters - cm) were performed. The individuals' body mass and height were measured on the same anthropometric scale with a coupled stadiometer (P150C, Líder Balanças®, Araçatuba / SP). BMI was calculated from the collected body weight and height, calculated by the formula: BMI = M / Height², where M = body mass (in kilograms - kg) and Height (in meters – m) [12].

Evaluation of cardiac autonomic modulation

Following the laboratory's routine HRV collect protocol, some orientations will be given to research volunteers: firstly, the volunteers were familiarized with the experimental ambiance and the researchers involved. Before starting the protocol, volunteers were evaluated and examined to certify that the given orientations (like avoiding the consumption of stimulating drinks, ensuring a good night's sleep, and avoiding strenuous exercise on the day before and the test day) were strictly followed. Subsequently, vital signs (HR and blood pressure) were collected during and after each test.

HR and R-R intervals (R-Ri) were collected beat by beat using the Wincardio USB electrocardiography system (Micromed, Brasília, Brazil) - in derivations MC5, DII, DIII, aVR, aVL, and aVF modified as well as from V1 to V6. Subsequently, the data were transported and stored on a microcomputer (Pentium III, 1100MHz) for later analysis. The transition points of the protocol were also duly marked for the adequate analysis of the data.

The data collection was carried out in the following steps: 1st. Stage: Rest in the supine position for 10 min, during which the volunteers were instructed not to talk, not to sleep, and to avoid limb movements; 2nd. Stage: During RSA-M - in the supine position, the total collection time was 6 minutes: 1 minute at rest with spontaneous breathing; 4 minutes performing RSA-M and 1 minute final resting. During RSA-M, the volunteer was instructed to perform a series of deep inspirations and slow expirations, varying the lung volume from total lung capacity (maximum inspiration) to residual volume (maximum expiration), in such a way that each cycle is performed in 10 seconds (10s), controlled by a hand clock, with 5s of inspirations and 5s of expirations, totaling 5 to 6 breathing cycles per minute [9].

Then, the data was exported to the Kubios HRV software. A visual inspection was performed to ensure the data was free of artifacts and any noise was eliminated. The linear methods - HR, RRi, SDNN (standard derivation of NN normal), RMSSD (the square root of the mean square of the

differences between adjacent normal RRi), high frequency (HF) and low frequency (LF) - and nonlinear methods (SD1 and SD2) were applied to stretches of five minutes or 256 points [13] of the rest and in sections of the RSA-M. Additionally, to evaluate the magnitude of the RSA-M response, the expiration/inspiration (E/I) ratio was used, which is the average of the highest R-Ri values obtained in the expiratory phase divided by the average of the smallest R-Ri values obtained in the inspiratory phase; and the inspiratory-expiratory difference (∆EI) was calculated, which is the difference between the average of the highest HR value obtained in the inspiratory phase and the average of the lowest HR value obtained in the expiratory phase [9].

Statistical analysis

The data were analyzed using the Sigmaplot 11.0 statistical program. Initially, Shapiro-Wilk normality tests and Levene homogeneity of variances were applied to determine the sample distribution. The results are presented as mean ± standard deviation. For values that don't follow a Gaussian distribution, the medians (25th - 75th percentiles) are presented. The analysis test comparing the CCC group with the Control group was the unpaired t-test for parametric measures and the Mann-Whitney test for non-parametric data, with values with $p < 0.05$ considered significant.

Results

The initial population of this study was constituted by 36 eligible patients divided into two groups each comprising 18 individuals. This way, all of them completed the evaluations, the CCC group, with a mean age of 65 ± 10.9 years, and the Control group, with a mean age of 58 ± 10.1 years. All patients in the CC group used medications before starting the study with the same doses for at least six months. There were no differences in characteristics such as age or anthropometric values between the two groups. However, when comparing the values of systolic pressure between CCC group and Control group, a significant difference was observed. The Control group had no comorbidities and did not use daily medications (Table 1).

Table 1 – *Characteristics obtained from volunteers during collection, spirometry, anthropometric, clinical, and hemodynamic values of the Chagas and control groups*

Characteristics	CCC Group (n=18)	Control Group (n=18)
Age (years)	65±10.9	58±10.1
Gender		
Female (n)	8	9
Male (n)	10	9
FVC (L)	12,9±44,5	102 ± 15

VEF_1/FVC	89,9±8,6	101±7
FEV_1 (% of predicted)	88,5±13,9	91±5.6
NYHA I/II	13/5	-
FEVE (%)	51±5	-
Anthropometric and Clinical		
Body Mass (kg)	68.7±14.6	72,6±11,3
BMI (kg/m²)	23,2 (26.2-29.2)	24,8 (26.1-28.3)
SBP (mmHg)	132±11	110 (120-130) *
DBP (mmHg)	84±8	70 (80-90)
Medicament		
Carvedilol (n)	17	-
Captopril (n)	7	-
Enalapril (n)	2	-
Lozartana (n)	2	-
Hidroclorotiazida (n)	2	-
Metformina (n)	1	-
Alodipina (n)	1	-

Legend: BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure; NYHA: New York Heart Association; FVC: Forced vital capacity; FEV_1: the forced expiratory volume in 1 second. *SBP CCC group X Control group p=0,005

Figure 1 (A, C, D, E and F) presents the linear indices of the time and frequency domain. During the assessment at rest, patients with CCC showed better autonomic modulation of HR ($p<0.05$). This can be observed from better HR values, the BF/AF ratio, the SD2 index and the SD2/SD1 ratio when compared to the Control group. On the other hand, the HF presented significantly higher values in patients with CCC.

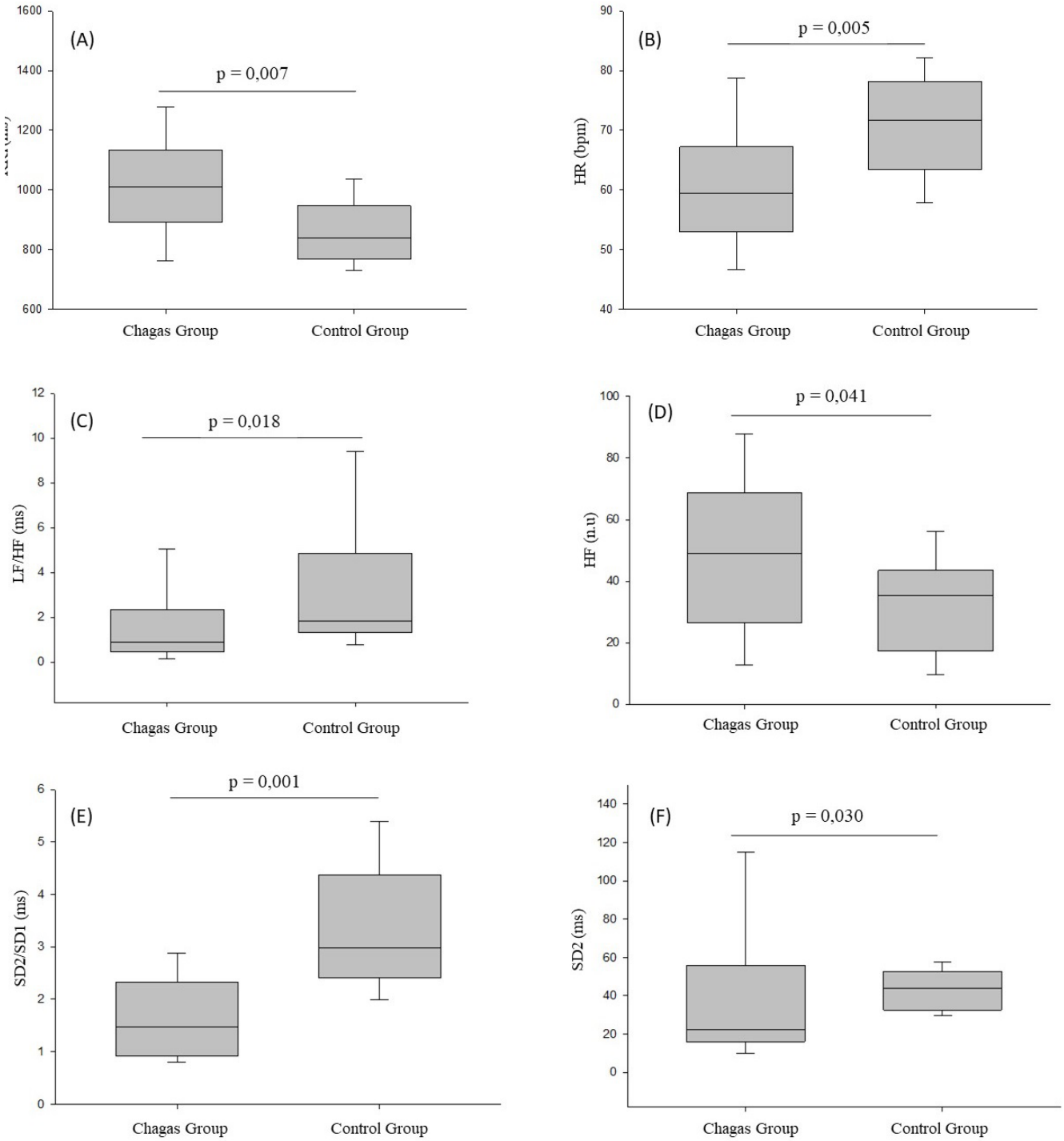

Figure 1 - *Heart rate variability at rest in patients with Chagas disease and healthy individuals: (A) RR intervals (RRi); (B) heart rate (HR); (C) low frequency and high frequency LF/HF ratio; (D) High frequency in standardized unit; (E) SD2/SD1 ratio; (F) SD2 index. Mann-Whitney test with p < 0.05*

Interestingly, during the RSA-M (figure 2: A, B and C), the SDNN indices, expiration/inspiration ratio and delta expiration/inspiration revealed significantly lower values in the patient group when compared to the control group. This may reflect a worse ability to adjust vagal modulation during RSA-M performance by the patients.

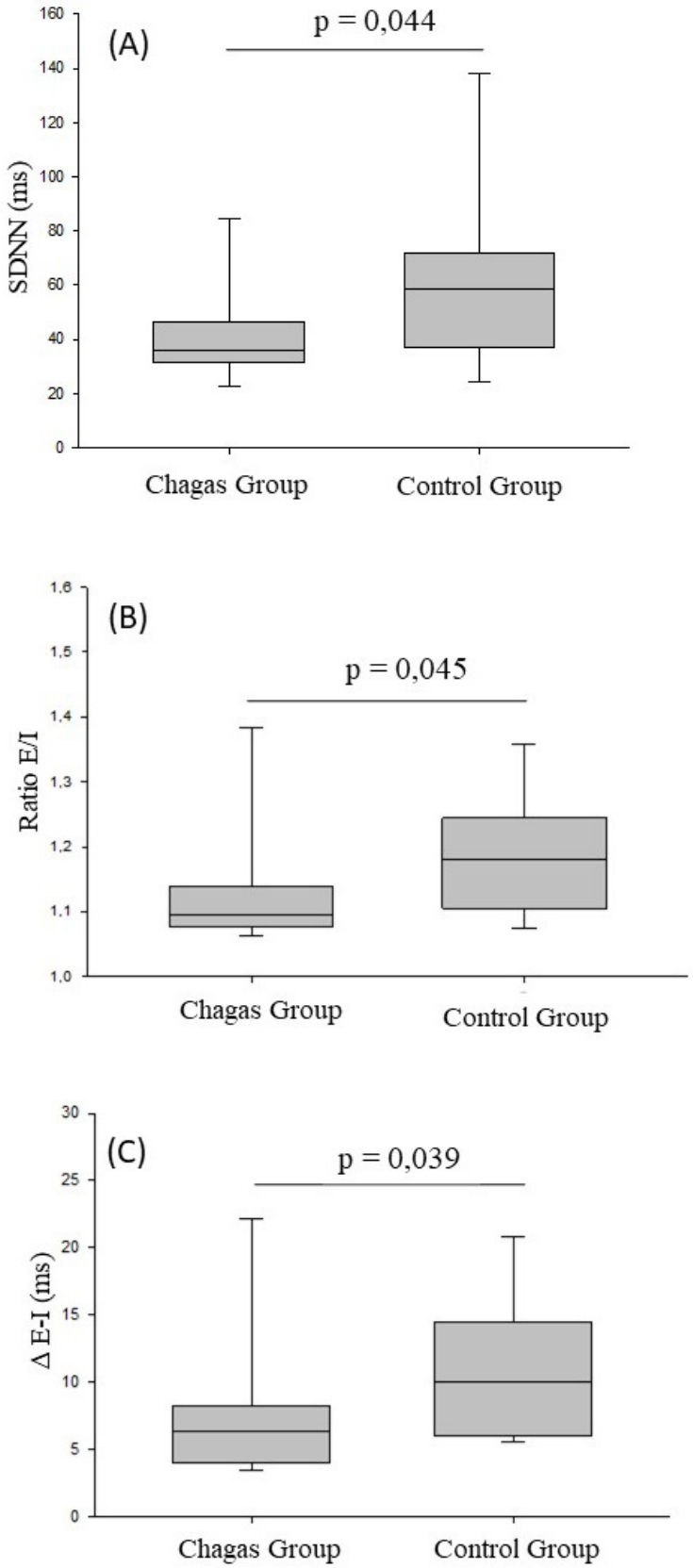

Figure 2 - *Heart rate variability and respiratory sinus arrhythmia accentuation maneuver (ASR-M) indices. E/I ratio: Expiration/inspiration ratio; Delta E-I: Delta expiration/inspiration. Mann-Whitney test with p=0.05*

Discussion

The results of this study showed that individuals with CCC stage B1 have impaired HRV with impaired vagal modulation when compared to healthy individuals during maneuvers to accentuate respiratory sinus arrhythmia. However, the values presented by the CCC group without RSA-M showed a better response than the Control group. However, when individuals were subjected to RSA-M that induced more consistent cardiovascular responses, patients with CCC showed a worse ability to adjust hemodynamic responses.

RSA-M has proven to be an easy-to-use tool for assessing vagal modulation and autonomic control of HR. This strategy aims to identify the sympathovagal balance in patients with chronic heart failure, hypertension, diabetes mellitus and chronic obstructive pulmonary disease [3]. In this study, it was possible to observe how RSA-M influences HRV, because while the groups were assessed at rest, the CCC group had a better cardiovascular condition and lower HR control than the Control group. However, when a technique that stimulates the sympathovagal balance was applied, the Control group showed an expected response and the CCC group showed a reduced response. This suggests that RSA-M was an important strategy for revealing HR autonomic dysfunction in individuals with CCC. In addition, the good sympathovagal balance at rest presented by the patients can be explained by the influence of medications - especially beta-blockers - on autonomic control.

With regard to the lower response of cardiac autonomic modulation, the present study showed similar to the findings of Peña et al. [2]. The authors identified a reduction in HRV compared to healthy individuals, which indicates a reduction in vagal balance in autonomic control. The mechanisms that supposedly explain the findings have been the subject of several studies. The natural evolution of the disease and the possible presence of agonist antibodies to muscarinic and beta-adrenergic receptors, which are present in patients with CCC, may be the most enlightening pathway. In this context, sympathovagal involvement could also explain the increase in ventricular arrhythmogenic potential, associated with myocardial remodeling and changes in size observed during CCC [14,15].

According to the available evidence, a reduction in total HRV indices or indices that represent vagal modulation such as HF, LF/HF and SD2 predict adverse cardiovascular events, including all-cause cardiovascular death [13,16]. In autonomic modulation, both vagal withdrawal and sympathetic hyperactivity can contribute to a reduction in HRV, and the pathogenesis of autonomic dysfunction in this population can be multifactorial, such as increased sympathetic activity and/or reduced vagal activity due to ANS hyperactivity and afferent signals released due to vagal denervation that stimulate sympathetic outflow [17]. Thus, the loss of vagal modulation presents in the CCC group identified by RSA-M indicated that possible morphological changes in the myocardium already represent alterations in autonomic function and protection of the heart.

In this context, it is worth noting that the patients with CCC in our study were stage B1 - people with Chagas disease with mild structural cardiomyopathy, without impaired ejection fraction - which strengthens the case for systematically applying strategies to assess autonomic modulation of HR. This could lead to earlier detection of HRV alterations, which could better clarify the electrophysiological and mechanical conditions of the heart and support more assertive approaches to mitigate the rapid evolution of the cardiac remodeling process induced by CCC.

In addition, it is important to recognize that the evaluation tool proves to be valid for patients with CCC, represents a low-cost and easy-to-use evaluation, and can be recommended for reference centers for the disease, settings known to have limited financial resources, compatible with the neglected way in which CD has been treated in Brazil and around the world.

Some limitations should be recognized. Firstly, it would be important to carry out specific evaluations with results that could corroborate dysautonomia by investigating markers that represent the loss of muscarinic receptors and greater activation of beta-adrenergic receptors. However, the lack of financial resources and the absence of experienced human resources meant that these parallel investigations were not possible. Another relevant aspect is the influence of the medication used by the patients on HRV behavior. However, the patients evaluated were on medication optimized by the same medical team and should remain so without discontinuation.

Conclusion

In conclusion, individuals with CCC who underwent RSA-M had reduced HRV with impaired vagal modulation when compared to healthy individuals, even under the influence of drugs that alter autonomic control. However, in the absence of RSA-M, the group with CCC had a higher HRV than the group of healthy individuals, which demonstrates the influence of regular medication. Our findings reinforce the importance of applying autonomic tests (such as RSA-M) to assess autonomic modulation of HR as an early strategy for detecting dysautonomia in patients with CCC.

Interest conflicts

The authors declare that they have no conflicts of interest of any nature.

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Authors' contribution

Conception and development of the research: VAN BAVEL, D; REIS, MS,; Data queue: VAN BAVEL, D; TRAVASSOS, JB; ANDRÉ, CRF; SILVA, CCF; PINTO, EF; Data analysis and interpretation: VAN BAVEL, D; TRAVASSOS, JB; ANDRÉ, CRF; SILVA, CCF; PINTO, EF; Statistical analysis: VAN BAVEL, D; REIS, MS; Manuscript writing: VAN BAVEL, D; REIS, MS; Critical review of the manuscript for important intellectual content: VAN BAVEL, D; REIS, MS; PEDROSA, RC.

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