Effects of Exercise Training on Heart Rate Variability in Chagas Heart Disease

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Abstract

Background: **Heart rate variability (HRV) is a marker of autonomic dysfunction severity. The effects of physical training on HRV indexes in Chagas heart disease (CHD) are not well established.**

Objective: **To evaluate the changes in HRV indexes in response to physical training in CHD.**

Methods: **Patients with CHD and left ventricular (LV) dysfunction, physically inactive, were randomized either to the intervention (IG, N = 18) or control group (CG, N = 19). The IG participated in a 12-week exercise program consisting of 3 sessions/week.**

Results: **Mean age was 49.5 ± 8 years, 59% males, mean LVEF was 36.3 ± 7.8%. Baseline HRV indexes were similar between groups. From baseline to follow-up, total power (TP): 1653 (IQ 625 – 3418) to 2794 (1617 – 4452) ms, p = 0.02) and very low frequency power: 586 (290 – 1565) to 815 (610 – 1425) ms, p = 0.047) increased in the IG, but not in the CG. The delta (post – pre) HRV indexes were similar: SDNN 11.5 ± 30.0 vs. 3.7 ± 25.1 ms. p = 0.10; rMSSD 2 (6 – 17) vs. 1 (21 – 9) ms. p = 0.43; TP 943 (731 – 3130) vs. 1780 (921 – 2743) Hz. p = 0.46; low frequency power (LFP) 1.0 (150 – 197) vs. 60 (111 – 146) Hz. p = 0.85; except for high frequency power, which tended to increase in the IG: 42 (133 – 92) vs. 79 (61 – 328) Hz. p = 0.08).**

Conclusion: **In the studied population, the variation of HRV indexes was similar between the active and inactive groups. Clinical improvement with physical activity seems to be independent from autonomic dysfunction markers in CHD. (Arq Bras Cardiol. 2014; 103(3):201-208)**

Keywords: **Chagas Cardiomyopathy; Exercise; Heart Rate.**

Introduction

Chagas disease is an infection caused by the *Trypanosoma cruzi*, transmitted primarily by insects of the Triatominae family. It is estimated than 8-10 million people are infected worldwide, especially in Latin America, where the disease is still endemic[1,2]. Chagas cardiomyopathy (CHD) affects 20-40% of patients with the chronic form, and its pathogenesis is closely linked to neurogenic mechanisms, microvascular dysfunction, autoimmune processes and direct injury by the parasite[2-4].

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Cardiac autonomic dysfunction is known to be a characteristic and early finding of Chagas disease[5-9], possibly related to deposits of autoantibodies[10], causing desensitization of cardiac neurotransmitter receptors, early affecting cardiac vagal control[11]. The heart rate variability (HRV) is an indirect measure of the interactions between the sympathetic and parasympathetic systems, mediated by several physiological mechanisms such as reflex arcs, release of cytokine and vasoactive substances, among others. The values of HRV measurements in the time and frequency domains are known diagnostic, prognostic markers and predictors of complications, including mortality, in several systemic diseases, such as heart failure and sepsis[12-14].

Among the non-pharmacological measures in the treatment of cardiovascular diseases, regular physical activity as a factor of vagal tone increase has shown a major impact on HRV indices and association with training intensity[15,16]. Significant HRV impairment has been demonstrated in CHD[17], but studies suggest that, unlike other forms of heart failure, there seems to be a change in the association between physical exercise and HRV[18], with no significant improvement of their indices being observed after supervised training programs[5].

The objective of this study is to evaluate the changes of HRV indexes in the time and frequency domains in patients with Chagas heart disease and left ventricular dysfunction undergoing supervised exercise training for 12 weeks, compared with the inactive group of patients with the same clinical characteristics.

Methods

Study population and inclusion criteria

A complete description of the study design has been published previously[19]. Briefly, 145 subjects were recruited from the Cardiology and Chagas Disease Outpatient Clinics of Hospital das Clinicas, Universidade Federal de Minas Gerais. The volunteers were interviewed to obtain clinical history and current life habits. To be eligible for the study, patients had to have a previous diagnosis of CHD, based on at least two positive serologic tests for Trypanosoma cruzi antibodies, along with the presence of left ventricular dysfunction and capacity to attend the training program fully[4]. Patients with comorbidities, patients with pacemaker or resynchronization device and those that self-reported to be physically active were excluded. Forty patients met the inclusion criteria.

All patients had been clinically stable for at least three months, had sinus rhythm and were receiving standard medical therapy[20]. After randomization, carried out through an electronic system, patients were allocated to the intervention group (IG) or control group (CG). Informed consent was obtained from all patients, and the study was approved by the Research Ethics Committee of Universidade Federal de Minas Gerais, in accordance with the Declaration of Helsinki.

Study design and procedures

At the moment of inclusion, all patients underwent clinical examination, laboratory tests, 12-lead ECG, symptom-limited exercise stress test to establish training heart rate (HR) intensity, 6-minute walk test (6MWT), echocardiography and 24-h Holter monitoring to assess HRV indices. Functional capacity was assessed by Goldman and New York Heart Association (NYHA) criteria. Severity of cardiac impairment was determined by echocardiographic indices (ejection fraction, EF, and left ventricular end diastolic volume, LVEDV). All tests were performed in a two-week period before and after aerobic training. Examiners were blinded to the results of the other tests.

A symptom-limited exercise stress was performed on a treadmill (Digistress Pulsar Micromed, Brasilia, Brazil) using the Bruce protocol. Continuous monitoring was performed with 12-lead ECG, recorded every minute. Blood pressure was measured manually with a cuff in the standing position in the last 30 seconds of each stage and for four minutes in the recovery period. Heart rate was determined by ECG and the chronotropic response was calculated as the achieved percentage of heart rate predicted for age, according to the Astrand formula (220 - age) at peak exercise. The 6-minute walk test (6MWT) was performed according to standard protocol[21] with two walks at maximum walking speed in a 30-meter corridor, separated by a 15-minute interval. A HR monitor (Polar FS2, Electro, Kempele, Finland) and a pulse oximeter (NoninOnyx 9500, Plymouth, Minnesota, USA) were used in the assessment.

24 h-Holter monitoring was performed using a portable three-channel tape recorder (Dynamics, Cardios, São Paulo, Brazil), at the beginning and end of the study. Subjects were instructed to maintain their normal daily activities during the recording. HRV analysis was performed when a good quality tracing of at least 18 h was available on a Burdick/DMI/Cardios Hospital Holter System (Spacelabs Burdick, Deerfield, Wisconsin, Sao Paulo, Brazil). Tracings were analyzed for five minutes every hour, and the sleep period with the loweat HR was used as reference.

The HRV indices were calculated in the time domain (SDNN: standard deviation of normal RR intervals; rMSSD: Root Mean Square of Successive Differences) and frequency domain (TP, total power; VLFP: very low frequency power; LFP: low frequency power; HFP, high frequency power).

Physical training protocol

The IG patients participated in a supervised program consisting of three sessions per week, on alternate days, totaling 36 sessions in 12 weeks, as detailed in a previous publication[19]. Briefly, the protocol consisted of warm-up exercises for 15 minutes, followed by a 30 minute-walk and 15 minutes of cooling down. Exercise intensity was based on peak HR achieved on a treadmill test limited by symptoms and calculated by the Karvonen formula (maximal HR - HR at rest) 50-70% + resting HR[22] and was adjusted throughout the program. The CG patients were instructed to maintain their daily routines and were asked about physical activities during consultations.

Statistical Analysis

Statistical analysis was performed using SPSS software version 20.0 for Mac OSX (SPSS Inc., Chicago, Illinois, United States of America). For this analysis, a sample of 36 patients was calculated to detect a 15% difference in SDNN variation between groups, with α error = 5% and β error = 20%. Descriptive analysis of continuous and categorical variables was performed. The presence or absence of normal distribution of variables was performed with the Shapiro-Wilk's test. Continuous data were expressed as mean ± standard deviation or as median and interquartile (IQ) range Q1 - Q3 (25-75%) when presenting with non-normal distribution. Categorical variables were expressed as absolute values and percentages. Variations in measurements at the beginning and end of the study were expressed as delta values (Δ).

To evaluate the changes in continuous variables in relation to baseline, the paired Student's *t* test was used for normally distributed variables or paired Wilcoxon test if the distribution was not normal. The comparison of means between groups was performed using Student's *t* test for continuous variables with normal distribution and the Mann-Whitney test for those with non-normal distribution. The comparison of categorical variables between groups was performed by Chi-square test. When necessary, analysis of variance transformations were performed. A two-tailed significance level of 0.05 was considered statistically significant.

Results

Of the 145 patients evaluated, 40 met the inclusion criteria. Throughout the study, two patients died (one patient in each group) and one patient did not complete the proposed procedures. The final sample consisted of 37 subjects: 18 in the IG and 19 in the CG. Demographic, clinical and echocardiographic characteristics of the groups are shown in Table 1. The male gender predominated and most patients had NYHA functional class I, with mean left ventricular ejection fraction (LVEF) < 40%. The only characteristic that differed between IG and CG was body mass index (BMI). Regarding medication, all patients received angiotensin-converting enzyme inhibitors (ACEI); 22.2% and 21.1% (p = 1.00), respectively, were taking beta-blockers; 22.2% and 15.8% (p = 0.693) were taking digitalis; 77.8% and 84.2% (p = 0.62) used amiodarone. The IG patients had complete adherence to the training program and, in the event of non-attendance, a new session was scheduled.

In relation to the baseline 12-lead ECG, the characteristics were similar between the IG and CG groups (Table 2), except for lower HR in IG and greater PR interval in this group. Regarding the 24-h Holter variables, the groups were also similar (Table 2), except for mean and minimum HR, which were lower in the IG (Table 2).

At the functional assessments at the end of the study, there was a significant improvement in Goldman functional classification in IG patients. At the stress test, although baseline and post-training VO_2 max was similar between the groups, its variation was significantly higher in IG, as well as a significantly greater increase in test time in the IG compared to the CG (Table 3). At 6-minute walk test, the distance walked at baseline was similar between the groups, but at the end of the study this distance was significantly higher in IG; the variation was also higher when compared to the baseline (Table 3).

When evaluating the HRV indices in the time domain (SDNN and rMSSD), no statistically significant variations were observed in the values at the end of the study when compared to the baseline in both groups, and ΔSDNN and ΔrMSSD were similar between them (Table 4). Regarding HRV indices in the frequency domain (TP, VLFP, LFP and HFP), there was significant increase in TP and VLFP compared to baseline in IG, but not in CG. The ΔTP and ΔVLFP values, however, were similar between groups. Regarding HFP, there was an increase in IG and decrease in the CG (no significant difference compared to baseline) and there was a non-statistically significant trend of ΔHFP difference between groups: 79 (61-328) vs. -42 (-133 - 92) Hz, p = 0.083.

Discussion

In this prospective, randomized therapeutic study in patients with Chagas cardiomyopathy and left ventricular dysfunction, exercise training resulted in no significant changes in HRV indices, although it resulted in improved functional class, as well as stress 6-minute walk test variables. We observed an increase in only two indices of HRV in the frequency domain (TP and VLFP) compared to the baseline in the IG, but with statistically similar variation between groups. Additionally, there was a trend towards greater positive variation of HFP in IG compared to CG.

HRV is reduced in Chagas patients with and without the cardiac form (including the indeterminate form)[6,7,9,18,23], and the reduction in its indices is correlated with levels of antimuscarinic antibodies[10], which are increased in infected patients. The levels of these antibodies seem to be associated with clinical markers of autonomic dysfunction[24], including the reduction of the chronotropic response to stress, suggesting clinical and physiopathological significance in Chagas disease[25]. It is controversial the existence of an association between reduced HRV autonomic dysfunction marker and severity of ventricular dysfunction or the evolutionary stage of the disease[26-31].

Table 1 – Comparison of clinical, demographic and echocardiographic characteristics between the control and intervention groups

Characteristic	Control Group (n = 19)	Intervention Group (n = 18)	p
Male gender (n, %)	12 (63.2%)	10 (55.6%)	0.74
Age, years (mean ± SD)	50.1 ± 6.6	48.6 ± 9.0	0.55
BMI (kg/m², median IQ)	22.5 (21.5-24.8)	24.6 (23.7-27.9)	0.042*
SBP at rest (mmHg, median IQ)	120 (110-130)	115 (110-120)	0.13
DBP at rest (mmHg, median IQ)	80 (70-80)	80 (70-80)	0.987
Functional class NYHA I/II (n, %)	14 (73.7%)/5 (26.3%)	10 (55.6%)/8 (44.4%)	0.31
Functional class Goldman I/II/III (n, %)	12 (63.2%)/5 (26.3%)/2 (10.5%)	10 (55.6%)/7 (38.9%)/3 (8.1%)	0.66
LVEF (%, mean ± SD)	37.1 ± 7.6	36.6 ± 7.4	0.84
LVDD (mm, mean ± SD)	50.3 ± 5.4	50.9 ± 7.3	0.77
LVDS (mm, mean ± SD)	64.0 ± 4.9	64.2 ± 5.6	0.90

SD: standard deviation; LVEF: left ventricular ejection fraction; BMI: body mass index; IQ: interquartile range (25-75); NYHA functional class - New York Heart Association; DBP: diastolic blood pressure; SBP: systolic blood pressure; LVDD: left ventricular diameter during diastole; LVDS: left ventricular diameter during systole.

Table 2 – Comparison of electrocardiographic baseline and 24-h Holter variables between the control group and the intervention group

Variable	Control group (n = 19)	Intervention group (n = 18)	p
Baseline ECG			
HR (bpm, median IQ))	64 (55-73)	56 (52-60)	0.036*
PRi Interval (ms, median IQ)	160 (151-194)	192 (175-230)	0.029*
QRS duration (ms, median IQ)	135 (96-150)	147 (118-154)	0.343
QTc Interval (ms, mean ± SD)	437 ± 31	448 ± 33	0.300
LBBB (n, %)	1 (5.3%)	0	1.000
RBBB (n, %)	10 (52.6%)	14 (77.8%)	0.170
LAHB (n, %)	5 (26.3%)	10 (55.5%)	0.099
Baseline 24-h Holter			
Mean HR (mean ± SD)	67,7 ± 7,7	61.7 ± 7.5	0.023*
Minimum HR (mean ± SD)	47,2 ± 5,7	42.8 ± 7.2	0.044*
AVB (1st and 2nd degree)	3 (15,8%)	5 (27.8%)	0.447
Supraventricular ectopic beats	58 (10-697)	133 (16-401)	0.903
Supraventricular tachycardia	0 (0-1)	0 (0–1)	0.679
Ventricular ectopic beats	851 (583-2137)	1347 (314-2624)	0.738
Ventricular tachycardia	0 (0-1)	2 (0-8)	0.252

*AVB: atrioventricular block; RBBB: right bundle branch block; LBBB: left bundle-branch block; SD: standard deviation; HR: heart rate; LAHB: left anterior hemiblock; IQ: interquartile range 1–3 (25-75%). * significant p value.*

Table 3 – Comparison of changes in clinical functional variables, of exercise stress test and the six-minute walk test between the control group and the intervention group

Variable	Control group (n = 19)	Intervention Group (n = 18)	p
Improvement in NYHA functional class (n, %)	0	2 (11.1%)	0.23
Improvement in Goldman functional class (n, %)	1 (5.3%)	8 (44.4%)	0.008*
ST: VO_2 maximal pre/post-training (ml/kg/min, mean ± SD)	31.4 ± 7.2/33.5 ± 6.8	27.3 ± 5.7/34.3 ± 4.9	0.07/0.71
ST: ΔVO_2 maximal (ml/kg/min, mean ± SD)	2.2 ± 4.8	7.0 ± 3.6	< 0.001*
ST: time of test pre/post-training (min, mean ± SD)	9.4 ± 3.0/10.2 ± 3.0	7.6 ± 2.4/10.6 ± 2.2	0.05/0.68
ST: Δ time of test (min, mean ± SD)	0.8 ± 2.0	3.0 ± 1.6	< 0.001*
6MWT: distance walked pre/post-training (m, mean ± SD)	521.8 ± 91.1/530.3 ± 69.1	525.4 ± 85.5/593.3 ± 78.5	0.902/0.014*
6MWT: Δ of walked distance (m, mean ± SD)	8.4 ± 49.1	67.8 ± 54.7	0.001*

*SD: standard-deviation; NYHA: New York Heart Association; ST: stress test; VO_2: maximal oxygen uptake; 6MWT – six-minute walk test. * Statistically significant p value.*

Although the prognostic value of HRV reduction has not been demonstrated in Chagas' disease, it is known that in several cardiac and systemic diseases, reduced HRV is a strong and independent prognostic marker, with good prediction of adverse events[12-14]. In heart failure from other causes, there is an association between reduced indices with adverse events, such as decompensation, hospital readmissions, ventricular dysfunction progression and mortality[32-34].

Some methodological issues should be considered in the analysis of our data, especially regarding the variability of HRV indices between different measures. The reproducibility of these variables at rest and during stress has been previously demonstrated[35], but other studies suggest that although the indices in the time domain (SDNN and rMSSD) are reproducible, the same is not true in relation to the frequency domain variables obtained by spectral analysis[36,37]. Thus, considering the sample size calculation based on the time domain index, the interpretation of negative results in the frequency domain should be made with caution. Furthermore, our data dispersion was generally higher than that observed in those studies.

Table 4 – Indices of heart rate variability at baseline and at the end of the study

Variable	Group	Pre	Post	Delta (Δ)	p (pre vs. post)	p (dif.)
SDNN (ms. mean ± SD)	CG (n = 19)	126.4 ± 31.3	137.9 ± 43.0	11.5 ± 30.0	0.112	0.102
	IG (n = 18)	163.9 ± 54.7	160.2 ± 50.0	-3.7 ± 25.1	0.536	
rMSSD (ms. median IQ)	CG (n = 19)	27 (23–44)	39 (19-53)	2 (-6-17)	0.542	0.429
	IG (n = 18)	44 (30-83)	41 (32-74)	-1 (-21-9)	0.678	
TP (Hz. median IQ)	CG (n = 19)	1526 (709-2850)	2423 (1132-4234)	943 (-731-3130)	0.091	0.521
	IG (n = 18)	1653 (625-3418)	2794 (1617-4452)	1780 (921-2743)	0.017*	
VLFP (Hz. median IQ)	CG (n = 19)	666 (427-1230)	1215 (527-3003)	682 (-208-2019)	0.126	0.849
	IG (n = 18)	586 (290-1565)	815 (610-1425)	371 (27-1171)	0.047*	
LFP (Hz. median IQ)	CG (n = 19)	124 (77-447)	202 (50-482)	-1.0 (-150-197)	0.629	0.849
	IG (n = 18)	192 (38-418)	161 (76-292)	60 (-111-146)	0.733	
HFP (Hz. median IQ)	CG (n = 19)	166 (86-291)	154 (62-422)	-42 (-133-92)	0.494	0.083
	IG (n = 18)	190 (87-443)	256 (207-462)	79 (-61-328)	0.156	

*SD: standard-deviation; CG: control group; IG: intervention group; HFP: high-frequency power; IQ: interquartile range (25-75); LFP: low-frequency power; pre-post: comparison of the results of the group at the beginning and end of the study; rMSSD: root mean square of successive differences; SDNN: standard deviation of NN intervals; TP: total power; VLFP: very low-frequency power. * Statistically significant p value.*

Regular physical activity is known to be beneficial in heart failure[38], with improved functional capacity and possible prognostic impact. Pooled data suggest an effect on serum prognostic markers such as B-type natriuretic peptide and functional variables in specific subgroups[39]. Moreover, supervised activity programs have a beneficial effect on HRV indices in healthy subjects and in patients with ventricular dysfunction of different etiologies at different stages and clinical contexts[15,16,40,41], data that somehow have biological plausibility, considering the abnormal behavior of the sympathetic and parasympathetic modulation in the disease. In a way, it would be possible to propose the assessment of HRV as an objective marker of the beneficial effects of physical training.

Similarly to ventricular dysfunction from other etiologies, physical training seems to have a beneficial effect in patients with Chagas cardiomyopathy, both in functional capacity and mortality[8,19,42]. However, the beneficial effect of exercise training on cardiac autonomic control, observed in other diseases, has not been demonstrated in Chagas heart disease.

Sousa et al[18] verified that the strong association observed in normal individuals between the intensity of physical activity and vagal HRV indices was not present in chagasic patients, suggesting that in Chagas disease, the usual vagotonic effect of exercise is not observed. More recently, Souza et al[18] evaluated indices of the time domain before and after a supervised exercise program in 18 chagasic patients and found no differences in the indices after training[5]. This lack of response expected from the increased vagal tone with aerobic training could be explained by the characteristics of the autonomic dysfunction in early Chagas disease, relatively independent from left ventricular dysfunction and associated to antimuscarinic autoantibodies[1]. Another possibility is that the impairment of the cardiac excitoconductive system, particularly the sinus node[1], impair the capacity of the parasympathetic ANS to modulate the beat-to-beat variation, typical of HRV.

At any rate, one might suspect that the clinical benefits observed with aerobic training in patients with Chagas cardiomyopathy do not involve the potential benefits of increased vagal tone, such as a decrease in the risk of sudden death[18]. Despite methodological considerations in the evaluation of HRV, this hypothesis has been consistently tested in our study, with an exercise program of which effectiveness was assessed clinically and functionally, and which application did not result in any significant changes in HRV indices.

Limitations

The analysis of HRV indices showed greater variability than initially expected, which may be related to physiopathological characteristics of Chagas heart disease. For this reason, sampling limitations may have hindered the detection of statistical differences between the groups (type I error). The trend to the difference observed between the groups regarding ΔHFP could be confirmed or not with a larger sample. Furthermore, in spite of the sample randomization and considerable similarity between the groups, small differences in baseline (such as mean and minimum HR at Holter) can influence the interpretation of results.

The time of exercise training may also have been insufficient for the detection of changes, considering the sample size, as well as its intensity (mild to moderate). However, longer training periods also did not result in significant changes in HRV indices, as shown in a previous study[5]. Moreover, the absence of isometric exercises, as recommended by guidelines for cardiac rehabilitation, may also have contributed to the negative result. Finally, the effect of training in the IG could have been more objectively evaluated through functional testing with analysis of expired gases.

Conclusions

In the studied population, exercise training did not significantly alter HRV indices in Chagas patients with LV dysfunction, although it resulted in functional improvement. The only changes observed in relation to baseline were increased TP and VLFP in the IG, with no significant difference in changes between groups. The data are consistent with previous publications and suggest that the clinical benefits of physical conditioning in Chagas heart disease are independent from HRV indices. Future studies in larger populations are needed in order to reach more definitive conclusions about the behavior of HRV during physical conditioning in Chagas heart disease.

Author contributions

Conception and design of the research: Nascimento BR, Lima MMO, Rocha MOC, Ribeiro AL; Acquisition of data: Lima, MMO, Nunes MCP, Alencar MCN, Costa HS, Pinto Filho MM, Cota VES; Analysis and interpretation of the data: Nascimento BR, Lima MMO, Pinto Filho MM, Cota VES; Obtaining financing: Rocha MOC, Ribeiro AL; Writing of the manuscript: Nascimento BR, Lima MMO; Critical revision of the manuscript for intellectual content: Rocha MOC, Ribeiro AL.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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References

1. Nunes MC, Dones W, Morillo CA, Encina JJ, Ribeiro AL; Council on Chagas Disease of the Interamerican Society of Cardiology. Chagas disease: an overview of clinical and epidemiological aspects. J Am Coll Cardiol. 2013;62(9):767-76.
2. Biolo A, Ribeiro AL, Clausell N. Chagas cardiomyopathy: where do we stand after a hundred years? Prog Cardiovasc Dis. 2010;52(4):300-16.
3. Ribeiro AL, Nunes MP, Teixeira MM, Rocha MO. Diagnosis and management of Chagas disease and cardiomyopathy. Nat Rev Cardiol. 2012;9(10):576-89.
4. Rocha MO, Teixeira MM, Ribeiro AL. Anupdateonthe management of Chagas cardiomyopathy. Expert Rev Anti Infect Ther. 2007;5(4):727-43.
5. Amaral da Silva Souza MV, Santos Soares CC, Rega de Oliveira J, Rosa de Oliveira C, Hargreaves Fialho P, Cunha DM, et al. [Heart rate variability: analysis of time-domain indices in patients with chronic Chagas disease before and after an exercise program]. Rev Port Cardiol. 2013;32(3):219-27.
6. Resende LA, Carneiro AC, Ferreira BD, Silva RA, Silva VJ, Prata A, et al. Análise temporal da variabilidade da frequência cardíaca no estado basal em idosos chagásicos na forma indeterminada em área endêmica. Rev Soc Bras Med Trop. 2003;36(6):703-6.
7. Guzzetti S, Iosa D, Pecis M, Bonura L, Prosdocimi M, Malliani A. Impaired heart rate variability in patients with chronic Chagas' disease. Am Heart J. 1991;121(6 Pt 1):1727-34.
8. Ritt LE, Carvalho AC, Feitosa GS, Pinho-Filho JA, Andrade MV, Feitosa-Filho GS, et al. Cardiopulmonary exercise and 6-min walk tests as predictors of quality of life and long-term mortality among patients with heart failure due to Chagas disease. Int J Cardiol. 2013;168(4):4584-5.
9. Rocha AL, Lombardi F, da Costa Rocha MO, Barros MV, Val Barros Vda C, Reis AM, et al. Chronotropic incompetence and abnormal autonomic modulation in ambulatory Chagas disease patients. Ann Noninvasive Electrocardiol. 2006;11(1):3-11.
10. Ribeiro AL, Gimenez LE, Hernandez CC, Carvalho AC, Teixeira MM, Guedes VC, et al. Early occurrence of anti-muscarinic autoantibodies and abnormal vagal modulation in Chagas disease. Int J Cardiol. 2007;117(1):59-63.
11. Ribeiro AL, Moraes RS, Ribeiro JP, Ferlin EL, Torres RM, Oliveira E, et al. Parasympathetic dysautonomia precedes left ventricular systolic dysfunction in Chagas disease. Am Heart J. 2001;141(2):260-5.
12. Bauer A, Barthel P, Schneider R, Ulm K, Muller A, Joeinig A, et al. Improved stratification of autonomic regulation for risk prediction in post-infarction patients with preserved left ventricular function (ISAR-risk). Eur Heart J. 2009;30(5):576-83.
13. La Rovere MT, Pinna GD, Maestri R, Barlera S, Bernardinangeli M, Veniani M, et al; GISSI-HF Investigators. Autonomic markers and cardiovascular and arrhythmic events in heart failure patients: still a place in prognostication? Datafromthe GISSI-HF trial. Eur J Heart Fail. 2012;14(12):1410-9.
14. Nascimento BR, Coelho TO, Ribeiro AL. Variabilidade da frequência cardíaca em pacientes criticamente enfermos. In: Botoni FA, Dias FS. (eds.). PROAMI. Programa de atualização em medicina intensiva. Porto Alegre: Artmed Panamericana; 2009.
15. Larsen AI, Gjesdal K, Hall C, Aukrust P, Aarsland T, Dickstein K. Effect of exercise training in patients with heart failure: a pilot study on autonomic balance assessed by heart rate variability. Eur J Cardiovasc Prev Rehabil. 2004;11(2):162-7.
16. Iellamo F, Manzi V, Caminiti G, Sposato B, Massaro M, Cerrito A, et al. Dose-response relationship of baroreflex sensitivity and heart rate variability to individually-tailored exercise training in patients with heart failure. Int J Cardiol. 2013;166(2):334-9.
17. Vasconcelos DF, Junqueira Jr LF. Distinctive impaired cardiac autonomic modulation of heart rate variability in chronic Chagas' indeterminate and heart diseases. J Electrocardiol. 2009;42(3):281-9.
18. Sousa L, Rocha MO, Britto RR, Lombardi F, Ribeiro AL. Chagas disease alters the relationship between heart rate variability and daily physical activity. Int J Cardiol. 2009;135(2):257-9.
19. Lima MM, Rocha MO, Nunes MC, Sousa L, Costa HS, Alencar MC, et al. A randomized trial of the effects of exercise training in Chagas cardiomyopathy. Eur J Heart Fail. 2010;12(8):866-73.
20. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: The task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the heart failure association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008;29(19):2388-442. Erratum in: Eur Heart J. 2010;12(4):416, Eur Heart J. 2010;31(5):624.

21. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS Statement: guidelines for the six-minute test. Am J Respir Crit Care Med. 2002;166(1):111-7.

22. Myers J. Principles of exercise prescription for patients with chronic heart failure. Heart Fail Rev. 2008;13(1):61-8.

23. Ribeiro AL, Cassini P, Peixoto SV, Lima-Costa MF. Vagal impairment in elderly Chagas disease patients: a population-based study (the Bambui study). Int J Cardiol. 2011;147(3):359-65.

24. Thiers CA, Barbosa JL, Pereira Bde B, Nascimento EM, Nascimento JH, Medei EH, et al. Autonomic dysfunction and anti-M2 and anti-beta 1 receptor antibodies in Chagas disease patients. Arq Bras Cardiol. 2012;99(2):732-9.

25. Talvani A, Rocha MO, Ribeiro AL, Borda E, Sterin-Borda L, Teixeira MM. Levels of anti-M2 and anti-beta1 autoantibodies do not correlate with the degree of heart dysfunction in Chagas' heart disease. Microbes Infect. 2006;8(9-10):2459-64.

26. Ribeiro AL, Lombardi F, Sousa MR, Lins Barros MV, Porta A, Costa Val Barros V, et al. Power-law behavior of heart rate variability in Chagas' disease. Am J Cardiol. 2002;89(4):414-8.

27. Villar JC, Leon H, Morillo CA. Cardiovascular autonomic function testing in asymptomatic T. cruzi carriers: a sensitive method to identify subclinical Chagas' disease. Int J Cardiol. 2004;93(2-3):189-95.

28. Tundo F, Lombardi F, Rocha MC, Botoni F, Schmidt G, Barros VC, et al. Heart rate turbulence and left ventricular ejection fraction in Chagas disease. Europace. 2005;7(3):197-203.

29. Vasconcelos DF, Junqueira Jr LF. Funções autonômica e mecânica ventricular na cardiopatia chagásica crônica assintomática. Arq Bras Cardiol. 2012;98:111-119.

30. Davila DF, Inglessis G, Mazzei de Davila CA. Chagas' heart disease and the autonomic nervous system. Int J Cardiol. 1998;66(2):123-7.

31. Molina RB, Matsubara BB, Hueb JC, Zanati SG, Meira DA, Cassolato JL, et al. Dysautonomia and ventricular dysfunction in the indeterminate form of Chagas disease. Int J Cardiol. 2006;113(2):188-93.

32. Tanindi A, Olgun H, Celik B, Boyaci B. Heart rate variability in patients hospitalized for decompensated diastolic heart failure at admission and after clinical stabilization. Future Cardiol. 2012;8(3):473-82.

33. Arsenos P, Gatzoulis K, Manis G, Gialernios T, Dilaveris P, Tsiachris D, et al. Decreased scale-specific heart rate variability after multi resolution wavelet analysis predicts sudden cardiac death in heart failure patients. Int J Cardiol. 2012;154(3):358-60.

34. Ho YL, Lin C, Lin YH, Lo MT. The prognostic value of non-linear analysis of heart rate variability in patients with congestive heart failure: a pilot study of multiscale entropy. PloS One. 2011;6(4):e18699.

35. McNarry MA, Lewis MJ. Heart rate variability reproducibility during exercise. Physiol Meas. 2012;33(7):1123-33.

36. Tannus LR, Sperandei S, Montenegro Júnior RM, Carvalho VR, Pedrosa HC, Félix MT, et al. Reproducibility of methods used for the assessment of autonomous nervous system's function. Auton Neurosci. 2013;177(2):275-9.

37. Ginsburg P, Bartur G, Peleg S, Vatine JJ, Katz-Leurer M. Reproducibility of heart rate variability during rest, paced breathing and light-to-moderate intense exercise in patients one month after stroke. Eur Neurol. 2011;66(2):117-22.

38. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al; ESC Committee for Practice Guidelines. Esc guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the heart failure association (HFA) of the ESC. Eur J Heart Fail. 2012;14(8):803-69. Erratum in Eur J Heart Fail. 2013;15(3):361-2.

39. Cipriano G Jr, Cipriano VT, da Silva VZ, Cipriano GF, Chiappa GR, de Lima AC, et al. Aerobic exercise effect on prognostic markers for systolic heart failure patients: a systematic review and meta-analysis. Heart Fail Rev. 2013 Oct 16. [Epub ahead of print].

40. Murad K, Brubaker PH, Fitzgerald DM, Morgan TM, Goff DC Jr, Soliman EZ, et al. Exercise training improves heart rate variability in older patients with heart failure: a randomized, controlled, single-blinded trial. Congest Heart Fail. 2012;18(4):192-7.

41. Routledge FS, Campbell TS, McFetridge-Durdle JA, Bacon SL. Improvements in heart rate variability with exercise therapy. Can Jo Cardiol. 2010;26(6):303-12.

42. Fialho PH, Tura BR, Sousa AS, Oliveira CR, Soares CC, Oliveira JR, et al. Efeitos de um programa de exercícios sobre a capacidade funcional de pacientes com cardiopatia chagásica crônica, avaliados por teste cardiopulmonar. Rev Soc Bras Med Trop. 2012;45(2):220-4.