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Original Article

Exercise stress test prognostic factors in Chagas cardiomyopathy with left ventricular dysfunction

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Abstract: Background: Chagas disease has multiple presentations, and only 10% progress to left ventricular (LV) dysfunction. The exercise stress test (EST) has been underutilized as a prognostic tool for this disease. Objective: To study the main prognostic variables of EST in Chagas cardiomyopathy with LV dysfunction using all-cause death as the endpoint. Methods: This was a prospective cohort study. The EST was performed with the modified Bruce protocol and passive recovery after exertion. The variables analyzed in the EST were stress time, chronotropic index, heart rate recovery (HRR), systolic blood pressure (SBP) recovery, SBP curve on stress, and electrocardiographic changes. We used Cox regression analysis to determine the risk of death after adjusting for demographic variables, cardiovascular risk factors, medications, and LV ejection fraction. Results: A total of 46 patients were eligible. The mean age was 57.70 (SD 9.22) years; 25 (54.3%) were women, and 42 (91.3%) were using beta-blockers. Fourteen (30.4%) deaths were recorded during the total follow-up period of 68 months. The variables found to be independently associated with lower risk of death were exercise time > 6.5 minutes (HR = 0.286; 95% CI 0.086-0.952; p = 0.041) and HRR ≥ 8 bpm (HR = 0.146; 95% CI 0.036-0.585; p = 0.007). Conclusion: EST can be a useful prognostic tool in Chagas cardiomyopathy with LV dysfunction in terms of stress time and HRR.

Keywords: Exercise stress test, Chagas disease, Chagas cardiomyopathy, left ventricular dysfunction

Introduction

Chagas disease, a parasitic infection caused by *Trypanosoma cruzi (T. cruzi),* is an important cause of heart dysfunction in countries that it is endemic in. It is estimated that 10-12 million people worldwide are infected by *T. cruzi,* of which 20-40% develop Chagas cardiomyopathy [1]. Of these, around 10% present with left ventricular (LV) dysfunction [2].

Clinically, it is characterized by two distinct phases: acute and chronic. The vast majority of patients are seen in the chronic phase, which includes the indeterminate form, in which there is no clinical, electrocardiographic, or radiological manifestation, and chronic Chagas cardiomyopathy, including mild to severe heart damage. Chagas cardiomayopathy has a peculiar form of myocardial damage characterized by incipient chronic myocarditis, leading to varying degrees of myocardial injury. Early manifestations are usually conduction system abnormalities, most frequently right bundle branch block and left anterior fascicular block, and segmental ventricular wall motion abnormalities, including the typical apical aneurysm. Later stages are characterized by a progressive enlargement and systolic dysfunction of the left ventricle. Complex ventricular arrhythmias and varying degrees of heart block are also common. The diagnostic standard of Chagas cardiomyopathy is based on epidemiological data and clinical features allied to complementary tests. The most commonly used are electrocardiogram, chest x-ray, and echocardiogram. The treatment depends on the stage of the disease. When there is systolic dysfunction, the drug

treatment is similar to other causes of cardiac dysfunction. A pacemaker may be indicated in cases with bradyarrhythmias. Nevertheless, the prognosis for these heart failure patients is poor. It is estimated that the annual mortality rate can be as high as 19.2% [2, 3].

Several studies have identified variables associated with a higher risk of death in this condition, which may help guide the management of the disease.

The exercise stress test (EST), a simple and widely available complementary method, presents multiple prognostic variables that have been widely studied in various clinical scenarios. However, information on the association between EST variables and the risk of death in patients with Chagas cardiomyopathy and LV dysfunction is very limited.

This study aimed to identify EST variables associated with the risk of all-cause death in patients with Chagas cardiomyopathy and LV dysfunction.

Methods

Study design

This prospective, longitudinal, observational study was conducted at the Myocardiopathies Outpatient Clinic and Functional Tests Section of Instituto Dante Pazzanese de Cardiologia. The study was conducted from October 2010 to June 2016. Patients were included until June 2013. The research ethics committee of the institution approved the study, and all participants signed an informed consent form.

Study group

The analyzed patients had been previously followed at our institution and were consecutively selected. We included individuals older than 18 years of age who were diagnosed with Chagas disease, had LV ejection fraction (LVEF) < 45%, and were clinically compensated. They were excluded if they had obstructive coronary artery disease, rheumatic heart disease, congenital heart disease, chronic atrial tachyarrhythmias, previous implantation of a cardiac electronic device (CED), malignant neoplasms, liver cirrhosis, chronic obstructive pulmonary disease, or absolute contraindications to EST.

The LVEF considered for patient inclusion was obtained from an echocardiogram taken as close as possible to the date of the EST.

Chagas disease was diagnosed based on epidemiological, clinical data, and serological tests.

Clinical data and conventional cardiovascular risk factors

All clinical and demographic data of the patients were obtained by reviewing medical records and interviewing the patients (by author S.P.F.) on the date of the EST. The medications used were tabulated during patient entry into the study. Age was recorded as years completed as of the EST date. The New York Heart Association (NYHA) functional classes were expressed as ordinal variables from I to IV according to symptom intensity. Current smoking was defined as smoking within the last 6 months. The diagnoses of diabetes mellitus, systemic arterial hypertension, and dyslipidemia were considered according to previous history and/or the use of medications.

EST method and variables

TEB® model Apex 2000 (São Paulo, Brazil) was used to perform the EST. Welch Allyn® (New York, USA) sphygmomanometers were duly calibrated and adjusted to the diameter of individuals' arms. All tests were performed by a single observer (S.P.F.) who was experienced in the method. There was no precise clinical indication, and any EST was performed for research purposes only. The modified Bruce protocol was primarily used. The exercise phase interruption was based on the Borg rating of perceived exertion > 17 [4]. Other reasons for exercise interruption were those recommended in the guidelines [5, 6]. EST was always performed under the presence of medications.

Throughout the EST, the electrocardiogram (ECG), blood pressure (BP), and heart rate (HR) were monitored. Records of the ECG, BP, and HR were obtained at rest in the supine and standing positions, at the end of each phase of the protocol, at peak exertion, and at minutes 1, 2, 4, and 6 after exercise. The exercise recovery phase was performed with the patient immediately placed in the supine position. ECG

was performed with 12 leads along with the MC5 lead. All tests were continuously recorded to better analyze the arrhythmias that were present.

The EST was used to detect patients at higher risk of all-cause death. For this purpose, the variables analyzed were exercise capacity, chronotropic index, HR recovery (HRR), systolic BP response on exertion, systolic BP recovery, ECG changes, and HR at rest.

Exercise capacity was not recorded as the metabolic equivalents (MET). Instead, we preferred to consider it as the total time during the effort phase, measured in minutes. The chronotropic index was obtained by the ratio between the chronotropic reserve achieved (peak HR - HR at rest) and the predicted chronotropic reserve (predicted maximum HR - HR at rest), expressed as percentage (%). The predicted maximum HR was obtained by the formula 220 - age. HRR referred to the difference between HR at peak exertion and HR obtained in the first minute of the passive recovery phase, expressed as bpm. Systolic BP response on exertion referred to the difference between systolic BP measured during peak effort and at rest in the standing position. Systolic BP recovery referred to the difference between the systolic BP at the first minute and the third minute of recovery. Heart rate at rest was obtained with the subject in the supine position. Analyzed ECG changes included arrhythmias and ST segment changes. Premature beats were considered frequent if > 10/min were present at any time during exercise or recovery. Ventricular premature beats were considered polymorphic if they presented with two or more distinct morphologies on the tracing. Ventricular tachycardia (VT) was considered in the presence of three or more consecutive ventricular complexes with HR > 100 bpm. Tachycardia was considered sustained if it persisted for > 30 s or if there was hemodynamic instability. An abnormal ST-segment response was defined as 1 mm or more of horizontal or down-sloping ST-segment depression measured at the J point. The ST-segment was interpreted only in the absence of conditions that might have impaired its analysis, such as left bundle branch block (LBBB) and left ventricular overload on ECG at rest.

Clinical outcomes

Information on death was obtained by reviewing medical records, death certificates, and data from the Department of Deaths of the Municipal Health Secretary of São Paulo.

Statistical analysis

The sample size was estimated based on a previously published study [7]. We determined that a total of 28 participants would be sufficient to detect a difference of 6 ml/kg/min in peak oxygen consumption (peak VO2) between survivors and non-survivors, considering a standard deviation (SD) of 4.9 ml/kg/min, an α of 5%, and a power of 0.95.

Quantitative variables were expressed as mean and SD or as median and interquartile range. Qualitative variables were expressed as frequency, with absolute numbers and proportions (%).

The normal distribution of data was verified using the Shapiro-Wilk test. The Mann-Whitney non-parametric test or the Student t-test were used to compare quantitative variables. Fisher's test or the chi-square test were used to compare qualitative variables.

The log-rank test was used to compare the Kaplan-Meier survival curves. The EST variables were dichotomized, and to obtain the cut-off points the criterion used was that which maximizes the difference between the survival curves. The univariate Cox model was also performed for the outcome and was expressed by the hazard ratio and its 95% confidence interval. After univariate analyses, variables with a p value < 0.10 were candidates for the multivariate Cox model. SPSS version 19 (IBM SPSS Statistics) was used for the analyses. The significance level was set at 5%.

Results

A total of 46 patients met the eligibility criteria for the study. **Table 1** shows the initial characteristics of these participants. The group was divided according to the variables analyzed and the outcome. In patients who had died, only one (7%) was taking amiodarone, and 13 (93%) were not (p = 0.035). An attenuated recovery of

Table 1. Characteristics of the sample according to the variables analyzed

Variables	Total Group
Female, n (%)	25 (54.3)
Age, mean (SD)	57.70 (9.22)
Diabetes, n (%)	7 (15.2)
Hypertension, n (%)	25 (54.3)
Dyslipidemia, n (%)	23 (50)
Smoker, n (%)	4 (8.7)
NYHA I, n (%)	12 (26.1)
NYHA II, n (%)	32 (69.6)
NYHA III, n (%)	2 (4.3)
Beta-blocker, n (%)	42 (91.3)
Amiodarone, n (%)	14 (30.4)
ACEI, n (%)	30 (65.2)
Left ventricular EF (%), mean (SD)	36.52 (4.96)
EST variables	
Exercise time (min), mean (SD)	9.64 (2.71)
HRR (bpm), mean (SD)	25.02 (14.11)
ΔSBP (mmHg), mean (SD)	21.96 (20.53)
SBP recovery (mmHg), mean (SD)	8.80 (15.81)
Chronotropic index (%), mean (SD)	53.48 (24.06)
NSVT, n (%)	10 (21.7)

SD = standard deviation; NYHA = New York Heart Association functional class; ACEI = angiotensin-converting enzyme inhibitor; EF = ejection fraction; HRR = heart rate recovery; ΔSBP = difference between peak systolic blood pressure and rest; SBP = systolic blood pressure; NSVT = non-sustained ventricular tachycardia.

systolic BP after exercise was also observed with a mean recovery of 2.5 (SD 12.83) mmHg for non-survivors and 11.56 (SD 16.38) mmHg for survivors (p = 0.046). No other variables were significantly different between the groups (**Table 2**).

Patients were followed up at the specialized outpatient clinic for cardiomyopathies. The follow-ups occurred at least every 6 to 12 months based on the clinical condition and the need for medication adjustments.

The main reasons for patient exclusion were refusal to perform the EST, stroke sequelae, implanted CED, and atrial fibrillation or flutter.

The exercise phase of the EST was discontinued due to physical exhaustion in 40 (87%) cases, non-sustained VT in four (8.7%) cases, and a drop in systolic BP in two (4.3%) cases.

The main electrocardiographic changes during the EST were ventricular arrhythmias, which was observed in 44 (95.6%) cases, of which frequent ventricular premature beats occurred in 11 (25%) participants and were polymorphic in 39 (88.6%). The presence of non-sustained VT was observed in 10 (22.7%) patients, with a mean heart rate of 136.2 (SD 27.7) bpm.

Supraventricular arrhythmias occurred in 23 (50%) cases, of which only three (13%) patients presented with supraventricular tachycardia. Significant ST segment depression occurred in only one patient. No case presented with second-degree or higher advanced atrioventricular block.

Survival analysis

Of the 46 participants, 14 (30.4%) died during the total follow-up period of 68 months (5.6 years). The mean period of follow-up was 38.3 (SD 15) months. The cumulative probability of death for this period (3 years) was 28.5% (**Figure 1**).

The main causes of death were HF decompensation and sepsis, which corresponded to approximately 64% of the total. Among other causes, three (21.5%) patients died from acute myocardial infarction, and two (14.3%) patients died from sudden death.

Univariate analysis

All clinical variables studied, including medications in use (beta blockers, ACE inhibitors, and amiodarone), LVEF, EST variables, and HR at rest, were included in the initial univariate analyses.

The following variables were included in the final multivariate model: HR at rest, amiodarone use, exercise capacity, and HRR. Increased survival was significantly associated with taking amiodarone (p = 0.030), exercise time > 6.5 minutes (p = 0.011), and HRR ≥ 8 bpm (p = 0.019), as shown in **Table 3**.

Multivariate analysis

In this study, there was no loss in patient follow-up. However, because multivariate analyses require a complete set of data for all participants, 45 cases were included. In one patient,

Table 2. Comparison of the variables analyzed according to the outcome

Variables	Survivors (n = 32)	Non-survivors (n = 14)	*p*-value
Female, n (%)	19 (59)	6 (43)	0.47
Age, mean (SD)	57.69 (9.45)	57.64 (9.02)	0.96
Diabetes, n (%)	3 (9)	4 (29)	0.17
Hypertension, n (%)	17 (53)	8 (57)	1.00
Dyslipidemia, n (%)	14 (44)	9 (64)	0.33
Smoker, n (%)	4 (12)	0 (0)	0.29
NYHA I, n (%)	9 (28)	3 (21)	0.15
NYHA II, n (%)	23 (72)	9 (64)	
NYHA III, n (%)	0 (0)	2 (14)	
Beta-blocker, n (%)	28 (88)	14 (100)	0.29
Amiodarone, n (%)	13 (41)	1 (7)	0.03
ACEI, n (%)	20 (62)	10 (71)	0.73
Left ventricular EF (%), mean (SD)	36.81 (5.22)	35.86 (4.40)	0.45
EST variables			
Exercise time (min), mean (SD)	10.13 (2.30)	8.52 (3.31)	0.28
HRR (bpm), mean (SD)	27.0 (11.84)	20.86 (18.62)	0.16
ΔSBP (mmHg), mean (SD)	25.16 (20.84)	14.64 (18.44)	0.12
SBP recovery (mmHg), mean (SD)	11.56 (16.38)	2.5 (12.82)	0.04
Chronotropic index (%), mean (SD)	54.44 (22.55)	51.36 (27.90)	0.53
NSVT, n (%)	5 (16)	5 (36)	0.24

SD = standard deviation; NYHA = New York Heart Association functional class; ACEI = angiotensin-converting enzyme inhibitor; EF = ejection fraction; HRR = heart rate recovery; ΔSBP = difference between peak systolic blood pressure and rest; SBP = systolic blood pressure; NSVT = non-sustained ventricular tachycardia.

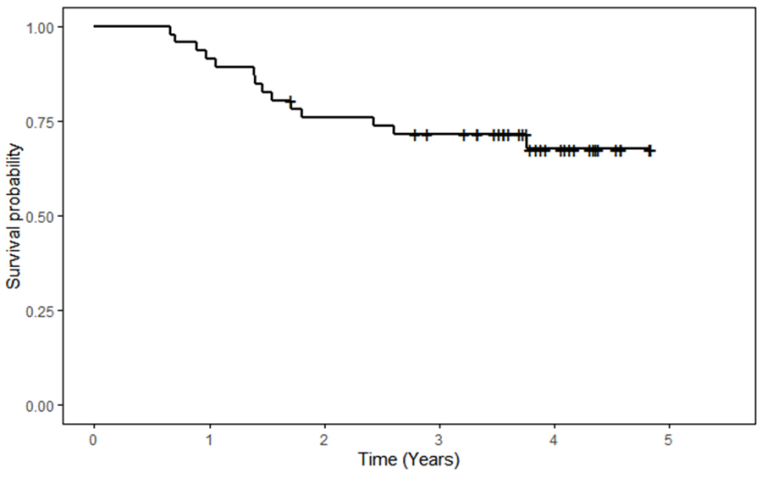

Figure 1. Cumulative survival curve for the total sample.

supraventricular tachyarrhythmias occurred at the peak of exertion, which made the HR measurement inaccurate.

In the final adjusted model, two variables remained associated with a lower risk of death: HRR ≥ 8 bpm and exercise time > 6.5 minutes (more details in **Table 3**).

Discussion

The main results found in this study were that two EST variables were associated with lower risk of all-cause death: exercise time and HRR. An exercise time > 6.5 min conferred a risk reduction of about 70%, while a HRR ≥ 8 conferred a risk reduction of about 85%. This association was independent of demographic variables, conventional cardiovascular risk factors, medication use, LVEF, and other EST variables. Amiodarone use was associated with a lower risk of death on univariate analysis but was not on multivariate analyses.

In this study, the exercise time was obtained exclusively from the modified Bruce protocol, which could limit the broad applicability of our results. However, this variable can be easily transformed into MET or VO2 estimated using widely known equations. By the equation derived from the FRIEND study, an exercise time > 6.5 min would be equivalent to > 6 MET or VO2 > 21 ml/kg/min [8].

Most deaths from Chagas disease are related to cardiac involvement. Sudden death has been reported in 55-65% of Chagas cardiomyopathy cases [7, 9, 10]. However, only two cases of sudden death, corresponding to 14.3% of total deaths, occurred in our study. The results of a study recently published by Costa et al. [11] supports our results; the authors studied 60 patients with Chagas disease and severe LV dysfunction and found only three cases of sudden death or 5.67% of total deaths. These findings may be explained, at

Table 3. Distribution of variables according to univariate analysis and the multivariate Cox regression model

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
HR rest	0.944 (0.886-1.007)	0.081	0.960 (0.897-1.027)	0.232
Amiodarone	-	0.030	0.129 (0.016-1.032)	0.054
Exercise time	-	0.011	0.286 (0.086-0.952)	0.041
HRR	-	0.019	0.146 (0.036-0.585)	0.007

95% CI = 95% confidence interval; HR = heart rate; HRR = heart rate recovery.

least in part, by the contemporary treatment of HF and the use of amiodarone [11].

A direct link between deaths in the patients and Chagas Cardiomyopathy could be determined only by high clinical suspicion. Furthermore, this observational study was not designed to determine the direct link between death and Chagas cardiomyopathy. We studied the risk of death from all causes in a group of patients with Chagas cardiomyopathy and left ventricular dysfunction who underwent EST.

The main causes of death in the studied group were HF decompensation and infectious conditions. In general, there is an overlap between infection and cardiac decompensation. Studies have shown that up to 50% of HF exacerbations are caused by infections, especially in the respiratory tract, and lead to high in-hospital mortality [12].

Exercise capacity is among the most studied variable of EST and has been consistently associated with the risk of all-cause and cardiovascular death [13-16]. However, evidence regarding this variable in Chagas cardiomyopathy with ventricular dysfunction is very limited. Mady et al. [7] conducted a prospective cohort study on 104 patients with HF due to Chagas disease. During the follow-up period of 47 months, around 50% of the participants died. Only exercise capacity and LVEF were associated with the risk of all-cause death on multivariate analyses. In this study the authors did not mention the analysis of other important variables obtained from the EST, such as HR and BP responses during the exercise and recovery periods.

The HRR is another important variable obtained from the EST and has been extensively studied in patients with and without LV dysfunction [17-20]. It is linked to vagal reactivation after exercise, and the imbalance of cardiac autonomic control has been associated with low HRR [21]. The HR response during conventional EST has been used to study the balance of cardiac autonomic control. It was observed that at the beginning of the exercise phase, at low and moderate intensities, the increase in HR was mainly mediated by the reduction of vagal tone, with little contribution of sympathetic activity. At high intensity exercise, it is estimated that vagal tone is reduced around to 90%, with adrenergic action being the most heavily responsible for the increase in HR. With the interruption of exercise, abrupt and intense parasympathetic activity, known as the rebound phase or vagal reactivation, was demonstrated and is responsible for the rapid decrease in HR [22].

We were not able to find studies associating HRR to the risk of death in patients with Chagas cardiomyopathy and ventricular dysfunction. Only cross-sectional studies have analyzed the HRR in individuals with Chagas cardiomyopathy but without ventricular dysfunction. For example, Alencar et al. [23] compared EST parameters among 46 patients with Chagas disease having right bundle branch block (RBBB), 65 patients in the undetermined form, and 38 healthy controls. They showed that attenuated HRR was significantly more prevalent in patients with RBBB when compared to that of the indeterminate form and control group.

Prospective studies analyzing other variables of EST have been rarely reported. In one study [24], the authors aimed to analyze the prognostic value of ventricular arrhythmias induced by exercise. They included 69 patients with a mean LVEF of 46.6% (SD 18.6%). There were seven deaths in the group with non-sustained exercise-induced VT and no deaths in the group without VT ($p < 0.05$). A regression analysis was not performed; hence, it was not possible to evaluate the independent association of this variable with death. In another work aimed at studying the role of exercise-induced VT, 130 patients with and without LV dysfunction were included. An increase in the risk of

death from cardiovascular causes was evidenced only in patients with an increased cardiothoracic ratio at chest x-ray (HR = 4.3; 95% CI 1.6-11.4; p = 0.004) [25]. Our work found no association between ventricular arrhythmias and risk of all-cause death in the group studied, which can be explained by the treatment instituted.

Strengths of the study

To the best of our knowledge, this was the first prospective study to analyze all the main prognostic variables of EST in a group with LV dysfunction due to Chagas disease.

An observer with extensive experience in the method followed the patients during EST to avoid measurement biases. All tests were performed in patients who were taking medications, allowing us to study their effects on the risk of death among other variables.

The variables analyzed are easily obtained from the EST. They were dichotomized, and their cutoff values were calculated from the group data itself for better applicability in clinical practice.

Limitations of the study

This study was conducted at a single center, which limits its external validity. Only patients with LV systolic dysfunction of Chagas etiology were included; hence, the results cannot be extrapolated to other forms of Chagas disease or to other etiologies of myocardial systolic dysfunction.

Drug treatment was not controlled during the follow-up period. However, as no medication showed a significant association in the final adjusted model, it is possible that its interference in the results was small.

The studied cohort had a relatively small number of patients. Although the confidence intervals were wide, the association with the outcome was demonstrated to be significant.

Clinical implications

The results of this study have important clinical implications. Studies have demonstrated that physical exercise acts on the cardiac autonomic balance and improves the physical fitness of individuals with LV systolic dysfunction [26, 27]. Thus, exercise-based cardiac rehabilitation may play an important role in patients with Chagas cardiomyopathy and LV systolic dysfunction.

Patients with Chagas disease and systolic dysfunction who present with low exercise capacity and/or attenuated HRR on EST should be followed more closely with maximized medication, because there may be benefits in reducing the risk of death.

Conclusion

This study demonstrated the usefulness of the EST, through its HRR and exercise capacity variables, as a possible marker of all-cause death in cases with Chagas cardiomyopathy and LV dysfunction.

Disclosure of conflict of interest

None.

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