

## Echocardiographic Parameters and Survival in Chagas Heart Disease with Severe Systolic Dysfunction

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### Abstract

**Background:** Echocardiography provides important information on the cardiac evaluation of patients with heart failure. The identification of echocardiographic parameters in severe Chagas heart disease would help implement treatment and assess prognosis.

**Objective:** To correlate echocardiographic parameters with the endpoint cardiovascular mortality in patients with ejection fraction < 35%.

**Methods:** Study with retrospective analysis of pre-specified echocardiographic parameters prospectively collected from 60 patients included in the Multicenter Randomized Trial of Cell Therapy in Patients with Heart Diseases (Estudo Multicêntrico Randomizado de Terapia Celular em Cardiopatias) – Chagas heart disease arm. The following parameters were collected: left ventricular systolic and diastolic diameters and volumes; ejection fraction; left atrial diameter; left atrial volume; indexed left atrial volume; systolic pulmonary artery pressure; integral of the aortic flow velocity; myocardial performance index; rate of increase of left ventricular pressure; isovolumic relaxation time; E, A, Em, Am and Sm wave velocities; E wave deceleration time; E/A and E/Em ratios; and mitral regurgitation.

**Results:** In the mean 24.18-month follow-up, 27 patients died. The mean ejection fraction was  $26.6 \pm 5.34\%$ . In the multivariate analysis, the parameters ejection fraction (HR = 1.114;  $p = 0.3704$ ), indexed left atrial volume (HR = 1.033;  $p < 0.0001$ ) and E/Em ratio (HR = 0.95;  $p = 0.1261$ ) were excluded. The indexed left atrial volume was an independent predictor in relation to the endpoint, and values > 70.71 mL/m<sup>2</sup> were associated with a significant increase in mortality (log rank  $p < 0.0001$ ).

**Conclusion:** The indexed left atrial volume was the only independent predictor of mortality in this population of Chagasic patients with severe systolic dysfunction. (Arq Bras Cardiol. 2014; 102(3):245-252)

**Keywords:** Echocardiography / diagnosis; Survivorship (Public Health); Chagas Cardiomyopathy; Chagas Disease.

### Introduction

One hundred years after been first described, Chagas disease remains a serious health and economic problem in most countries in Latin America. Ten million people are estimated to be infected worldwide, most of them in Latin America, where the disease is endemic. More than 25 million people are at risk for the disease. Chagas disease has killed more than 10 thousand people according to an estimate made in 2008<sup>1</sup>.

This parasitic disease is transmitted to man by means of infected feces of hematophagous insects in endemic areas and, occasionally, by blood transfusion. Its diagnosis is

made based on a history suggestive of contact and on two or more positive specific serological tests<sup>2,3</sup>.

Chagas disease has two phases: the acute and chronic phases. The acute phase commonly manifests as a self-limited febrile syndrome lasting for 2 to 8 weeks, with clinical symptoms in less than 1% of patients. In the chronic phase, approximately half of these patients remain in the indeterminate form, which has low mortality and a good prognosis, whereas the other half progresses to the chronic form, with cardiac and/or digestive impairment 10 to 30 years after the initial infection<sup>2,4,5</sup>.

The cardiac form is the most common and severe manifestation of Chagas disease in its chronic phase. The myocardial abnormalities in the chronic phase are extremely variable, ranging from mild forms, such as digitiform apical aneurysms and abnormalities of the left ventricular diastolic function only, to significant cardiac chamber dilatation, with severe systolic dysfunction<sup>5-8</sup>.

Echocardiogram is a well-established test in the clinical practice and provides parameters by which chagasic patients can be analyzed and stratified. In our study, patients with

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severe systolic dysfunction, who already have a poor prognosis, were analyzed. The objective was to identify markers of a poor prognosis that would help us start a more aggressive and optimized treatment in an attempt to improve the unfavorable outcome of these patients<sup>9,10</sup>.

## Methods

### Population and study site

This is a study with retrospective analysis of pre-specified data collected prospectively from patients included in the Multicenter Randomized Trial of Cell Therapy in Heart Diseases (*Estudo Multicêntrico Randomizado de Terapia Celular em Cardiopatias – EMRTCC*) – Chagas heart disease arm, conducted from February 2006 to February 2009. The EMRTCC was a prospective randomized double-blind study, which, in our Institution, had a sample of 60 patients with severe systolic dysfunction (ejection fraction – EF < 35%) and NYHA functional classes III and IV. The exclusion criteria were: heart valve diseases, except for functional tricuspid or mitral regurgitation; coronary arteriography showing significant lesion (obstruction of 50% or more in one or more coronary artery); presence of a functioning implantable cardioverter/defibrillator; diseases that could impact the life expectancy or any other comorbidity impacting on the 2-year survival; and echocardiographic images inappropriate for a correct interpretation. The echocardiographic measurements were performed when the patients were randomized. At that moment, optimization of the medical treatment had been achieved, and the patients were hemodynamically stable. The result of the EMRTCC – Chagas heart disease arm, did not show elevation of the EF in the group receiving stem cell implantation, and the population of 60 patients was considered homogeneous, with no influence of the intervention between the two groups<sup>11</sup>.

The primary endpoint of our study was defined as cardiovascular mortality. Cardiovascular mortality was considered as sudden death, when occurring less than 1 hour after the change in symptoms, or as death for progressive worsening of heart failure, when resulting from worsening of symptoms or previous hemodynamic deterioration.

The study was conducted in the Clinics Hospital of the Federal University of Goiás (HC-UFG). The patients were selected from the heart failure outpatient clinic of the institution. Clinical assessments and follow-up of these patients were carried out in this outpatient clinic. Echocardiography was performed in the imaging service of the institution. The project was approved by the Scientific and Ethics Commission of HC-UFG, and the patients gave written informed consent.

### Echocardiographic assessment

Echocardiograms were performed in a Xsario ultrasound scanner (Toshiba) available in the department of echocardiography of HC-UFG, with images digitally recorded. Images were obtained according to the criteria established by the American Society of Echocardiography (ASE)<sup>12</sup>. All tests

were performed by one single highly experienced examiner duly trained to obtain the parameters measured, and in one single scanner of the institution.

The following parameters of the echocardiographic study were assessed: left ventricular end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD); LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV); EF as estimated by the Simpson's method; left atrial diameter (LA); LA volume (LAV); LAV indexed for body surface (LAV/m<sup>2</sup>); pulmonary artery systolic pressure (PASP); integral of the aortic flow velocity (IFV Ao); derivative of pressure/derivative of time (dP/dT); isovolumic relaxation time (IVRT); myocardial performance index (MPI); E and A wave velocities (by pulsed Doppler); E/A ratio and E wave deceleration time (DCT); myocardial tissue velocity of Em, Am and Sm waves (by tissue Doppler in the basal segment of the inferoseptal wall); and E/Em wave ratio.

### Statistical analysis

The survival curves were calculated using the Kaplan-Meier product-limit method, and compared using the log-rank test. Survival probabilities were estimated with a 95% confidence interval (CI). Quantitative variables were dichotomized using the optimal cut-off point obtained from the ROC (Receiver Operating Characteristic) analyses. Non-adjusted and adjusted hazard ratios (HR) with 95% CI were estimated in the Cox univariate and multivariate regression analyses, respectively. The multiple regression model used the proportion of number of events per variable of 9:1, with confirmed balanced estimates. Normality of variables was assessed using the Kolmogorov-Smirnov test, and were represented as mean  $\pm$  standard deviation or median and 95% CI, depending on a normal or non-normal distribution, respectively. All probabilities of significance (p values) presented are two-sided and values < 0.05 were considered statistically significant. P values between 0.05 and 0.10 were interpreted as marginally significant. The statistical analysis of data was carried out using the Stata 11 (Stata Corp, College Station, TX) and SAS 9.2 (Statistical Analysis System, Cary, NC) software programs.

## Results

Clinical and echocardiographic characteristics of the study group are shown in Tables 1 and 2, respectively.

Cardiovascular deaths occurred in 27 (45%) of the 60 patients in a mean follow-up of 24 months (Figure 1). All remained with optimized drug therapy and did not receive resynchronization therapy or implantable cardio-defibrillator during the follow-up.

### Analysis of the echocardiographic parameters

The association between the echocardiographic parameters and the endpoint was initially assessed by univariate analysis (Table 3).

Based on the clinical relevance and aiming to include anatomical and functional data, three echocardiographic parameters were selected for the multivariate analysis (Table 4).

Among the parameters assessed, only LAV/m<sup>2</sup> proved to be an independent predictor in relation to the endpoint.

**Table 1 - Clinical characteristics of the group**

Characteristic	Mean ± SD
Age (years)	50.9 ± 9.3
Gender (%)	n = 60
Male	70
Drug therapy (%)	n = 60
Diuretics	88.3
ACEI	60
ARB	21
Betablocker	60
Spironolactone	85
Digoxin	61
Amiodarone	58.33
Rhythm in atrial fibrillation (%)	6.6
Pacemaker (%)	30

SD: standard deviation; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker.

**Table 2 - Echocardiographic characteristics of the group**

Variable	p (KS)	Parameters		
		Mean ± SD	Median	95% CI
EF (%)	0.617	26.7 ± 5.3	27.4	25.3 - 28.1
LVEDD (mm)	0.667	78.9 ± 8.7	78.6	76.7 - 81.2
LVESD (mm)	0.485	67.4 ± 8.0	67.3	65.3 - 69.5
LVEDV (mL)	0.724	271.3 ± 94.5	265.6	246.9 - 295.7
LVESV (mL)	0.855	189.3 ± 73.0	186.8	170.5 - 208.2
LA (mm)	0.833	48.3 ± 8.5	48.0	46.1 - 50.5
LAV (mL)	0.375	104.9 ± 42.3	98.7	93.9 - 115.8
LAV/m <sup>2</sup> (ml/m <sup>2</sup> )	0.330	62.9 ± 24.4	58.8	56.6 - 69.2
PASP (mmHg)	0.022*	38.1 ± 13.4	33.6	34.3 - 41.9
IFV Ao (cm)	0.002*	13.2 ± 8.7	12.0	10.9 - 15.5
DCT (ms)	0.122	188.0 ± 92.3	160.0	164.2 - 211.8
MPI	0.026*	0.89 ± 0.40	0.82	0.79 - 0.99
dP/dT	0.286	489.6 ± 162.3	444.0	447.7 - 531.5
IVRT (ms)	0.005*	116.9 ± 72.1	100.0	98.3 - 135.6
A (cm/s)	0.426	46.8 ± 23.3	41.3	40.5 - 53.1
E (cm/s)	0.522	63.9 ± 25.0	61.4	57.5 - 70.4
Am (cm/s)	0.853	4.8 ± 2.1	4.5	4.3 - 5.4
Em (cm/s)	0.395	4.8 ± 1.7	4.5	4.4 - 5.3
Sm (cm/s)	0.774	4.6 ± 1.2	4.7	4.3 - 4.9

\* Significant: variables with non-normal distribution. KS: Kolmogorov-Smirnov normality test; SD: standard deviation; 95% CI: 95% confidence interval; EF: ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LA: left atrial anteroposterior measurement; LAV: left atrial volume; LAV/m<sup>2</sup>: left atrial volume indexed for body surface; PASP: pulmonary artery systolic pressure; IFV Ao: integral of the aortic flow velocity; DCT: E wave deceleration time; MPI: myocardial performance index; dP/dT: derivative of the pressure/derivative of time; IVRT: isovolumic relaxation time; A: transmitral flow velocity of late ventricular filling; E: transmitral flow velocity of early ventricular filling; Em and Am: diastolic tissue velocities; Sm: systolic tissue velocity.

When an LAV/m<sup>2</sup> value of 70.71 mL/m<sup>2</sup> was obtained, a larger distance between the study population was observed in relation to the endpoint mortality (Figure 2), with an area under the curve of 0.827 (95% CI = 0.708 – 0.913) (Figure 3).

## Discussion

Most of the echocardiographic studies involving patients with chronic chagasic cardiomyopathy sought to correlate echocardiographic parameters with survival, using proportional hazards models (Cox models). The populations assessed in these studies had varying expressions of the disease ranging from no cardiac impairment to severe disease with significant symptoms. In our study, exclusively patients presenting with severe structural cardiac involvement and significant systolic dysfunction were selected<sup>10</sup>.

Our results did not demonstrate a correlation between increased left ventricular diastolic and systolic diameters and decreased survival rates. This is consistent with Bestetti et al<sup>13</sup>, Viotti et al<sup>14</sup>, and Salles et al<sup>15</sup> findings. Evidences of segmental or global wall motion abnormalities and increased LVEDD significantly correlated with the endpoint mortality in a retrospective cohort of 424 patients evaluated by Rassi et al<sup>16</sup>. We may have not confirmed these findings in our cohort because it was comprised of patients with severe

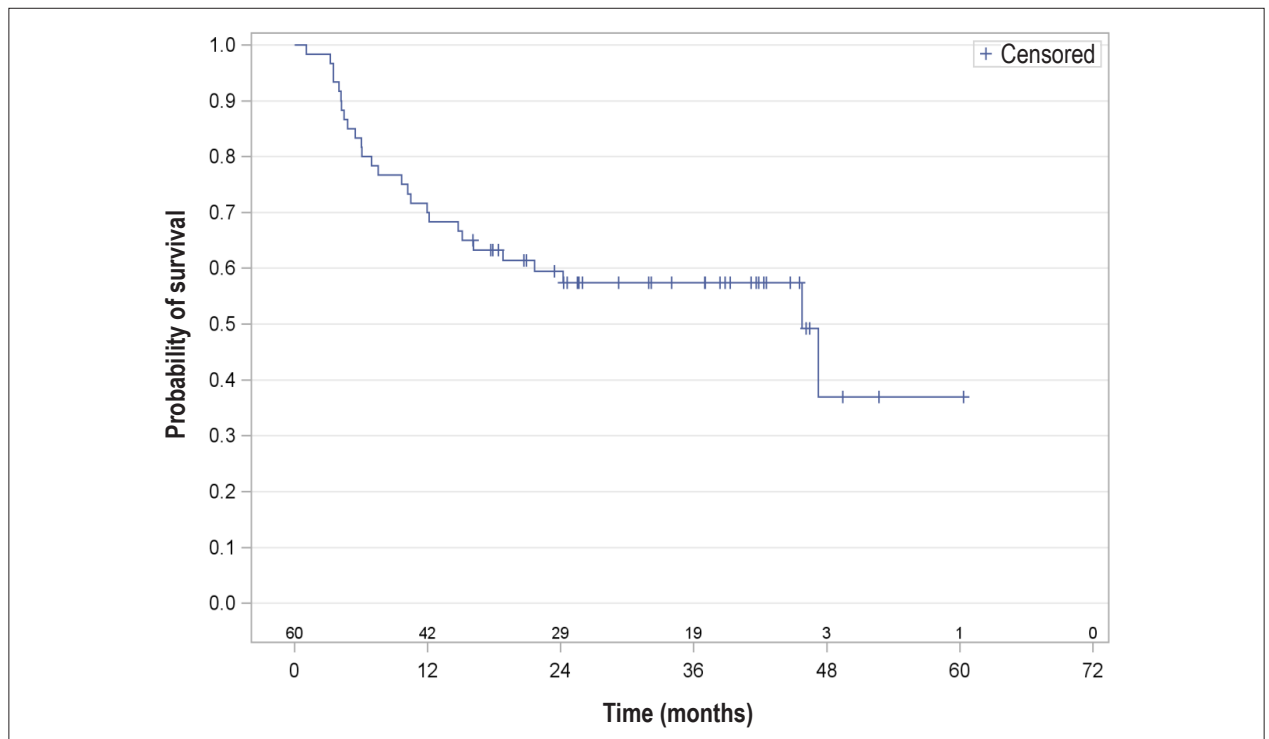


Figure 1 - Kaplan-Meier curve with analysis of overall survival in the study population.

systolic dysfunction and segmental or global wall motion abnormalities invariably present, unlike Rassi's cohort<sup>16</sup>. Increases in LVEDV and LVESV, as well as decrease in EF, correlated with the survival rate in the univariate analysis of this group of patients; however this was not confirmed in the multivariate analysis<sup>13-16</sup>.

The variable most commonly described as an independent predictor of death among the studies previously conducted is EF. This variable assesses the left ventricular systolic function and may be obtained by echocardiography using different methods. Several studies have evaluated the impact of the decrease in EF in relation to the survival of chagasic patients. In a meta-analysis of six echocardiographic series involving 3,135 patients, Aquatella<sup>10</sup> clearly demonstrated these findings.

Specifically, in the series involving chagasic patients with severe heart failure, the only echocardiographic finding that proved to be statistically significant among survivors, in the multivariate analysis, was the decrease in left ventricular EF (LVEF). The first of them was conducted by Mady et al<sup>17</sup>, in which 104 patients in functional class from II to IV were assessed, with a 50% mortality in a 47-month follow-up. The second was conducted by Bestetti et al<sup>13</sup>, in which 56 patients in functional classes III and IV were evaluated, with a 28% mortality in a 24-month follow-up.

In another study conducted in the modern era of the treatment for heart disease, Theodoropoulos et al<sup>18</sup> evaluated 127 patients diagnosed with systolic heart failure secondary to chagasic cardiomyopathy and observed that LVEF, as well

as the use of betablockers, digoxin, serum sodium level, and functional class IV on admission were independent predictors of mortality in a mean 25-month follow-up<sup>18</sup>.

The right ventricular systolic function was not assessed in our study, because it was part of the echocardiographic parameters of the protocol established by EMRTCC. However, we should point out that the presence of right ventricular systolic dysfunction is also an independent predictor of mortality in chagasic cardiomyopathy, as demonstrated by Nunes et al<sup>19</sup> in a study of 158 patients and a mean 34-month follow-up, in which this parameter was assessed using the Tei index.

In our study, there was a significant correlation of the anteroposterior LA diameter, LAV, and LAV/m<sup>2</sup> with the survival rate of these patients. LAV/m<sup>2</sup> was the only echocardiographic parameter in the multivariate analysis that proved to be an independent predictor of cardiovascular mortality in this population. When obtained, using an optimal cut-off point of 70.71 mL/m<sup>2</sup> by means of the ROC analysis, we observed an area under the curve of 0.827 (95% CI = 0.708 – 0.913).

These results corroborate those of a recent study conducted by Nunes et al<sup>20</sup>, who evaluated 192 chagasic patients retrospectively in a follow-up of 33.8 months. The authors showed that the increase in LAV/m<sup>2</sup> is an independent predictor of cardiovascular mortality (HR = 1.037 mL/m<sup>2</sup>) and increments the value of other parameters such as EF and Doppler-derived measurements in the assessment of diastole<sup>20</sup>.

**Table 3 - Univariate analysis of predictors of cardiovascular events**

Parameter	n	Events	HR	Lowest 95%CI	Highest 95%CI	p value
EF	60	27	0.932	0.873	0.994	0.031*
LVEDD	60	27	1.036	0.988	1.087	0.1464
LVESD	60	27	2.573	0.972	6.81	0.057
LVEDV	60	27	1.005	1.001	1.009	0.0275*
LVESV	60	27	1.005	1	1.01	0.0403*
LA	60	27	1.064	1.021	1.109	0.0031*
LAV	60	27	1.015	1.008	1.021	< 0.0001*
LAV/m <sup>2</sup>	60	24	1.036	1.021	1.051	< 0.0001*
PASP	50	27	1.039	1.012	1.067	0.0039*
IFV Ao	59	26	0.947	0.852	1.053	0.3151
DCT	60	27	0.993	0.987	0.998	0.0093*
MPI	60	27	2.423	1.032	5.689	0.0421*
dP/dT	60	27	1	0.998	1.003	0.7342
IVRT	60	27	0.997	0.99	1.004	0.3499
A	56	23	0.976	0.956	0.996	0.0212*
E	60	27	1.029	1.013	1.046	0.0004*
E/A	56	23	1.589	1.205	2.096	0.001*
Am	56	23	0.847	0.687	1.044	0.1192
Em	60	27	1.003	0.805	1.249	0.9815
Sm	60	27	0.726	0.514	1.026	0.07*
E/ EM	59	27	1.083	1.019	1.151	0.0104*
MR 1 vs. 2	60	27	0.325	0.146	0.728	0.0063*

\* Significant: variables statistically significant. HR: hazard ratio; 95% CI: 95% confidence interval; EF: ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LA: left atrial anteroposterior measurement; LAV: left atrial volume; LAV/m<sup>2</sup>: left atrial volume indexed for body surface; PASP: pulmonary artery systolic pressure; IFV Ao: integral of the aortic flow velocity; DCT: E wave deceleration time; MPI: myocardial performance index; dP/dT: derivative of the pressure/derivative of time; IVRT: isovolumic relaxation time; A: transmitral flow velocity of late ventricular filling; E: transmitral flow velocity of early ventricular filling; E/A: E and A wave ratio; Em and Am: diastolic tissue velocities; Sm: systolic tissue velocity; E/Em: E and Em wave ratio; MR 1 vs. 2: mild versus moderate mitral regurgitation.

**Table 4 - Multivariate analysis of predictors of cardiovascular events**

Parameter	Regression coefficient (beta)	HR	Lowest 95%CI	Highest 95%CI	p value
EF	-0.0508945	0.95	0.89	1.014	0.1261
LAV/m <sup>2</sup>	0.0321653	1.033	1.017	1.049	< 0.0001*
E/Em	0.0337537	1.034	0.961	1.114	0.3704

\* Significant: variables statistically significant. HR: risk ratio; 95% CI: 95% confidence interval; EF: ejection fraction; LAV/m<sup>2</sup>: left atrial volume indexed for body surface; E/Em: E (transmitral flow velocity of filling) and Em (diastolic tissue velocity) wave ratio.

LAV abnormalities also have an impact on the survival in heart diseases of other causes, such as ischemic heart disease. Møller et al<sup>21</sup> followed up 314 patients for a mean of 15 months and showed that LAV mL/m<sup>2</sup> > 32 mL/m<sup>2</sup> was an important predictor of mortality, even after adjustment for clinical factors, systolic function, and Doppler-derived parameters of diastolic function<sup>21</sup>.

As for patients with severe systolic dysfunction, Rossi et al<sup>22</sup> conducted a meta-analysis with 1157 patients from 18 studies

on heart failure and demonstrated that increased LA area was associated with a worse prognosis, regardless of age, NYHA functional class, EF, or restrictive filling pattern<sup>22</sup>.

In our group of patients, no statistically significant correlation was demonstrated between Em and Am wave velocity abnormalities and survival. There was a tendency for a correlation between Sm wave and survival rate (p = 0.07). Tissue velocities were evaluated in the inferoseptal wall (basal segment); many chagasic patients may show greater impairment in this region,

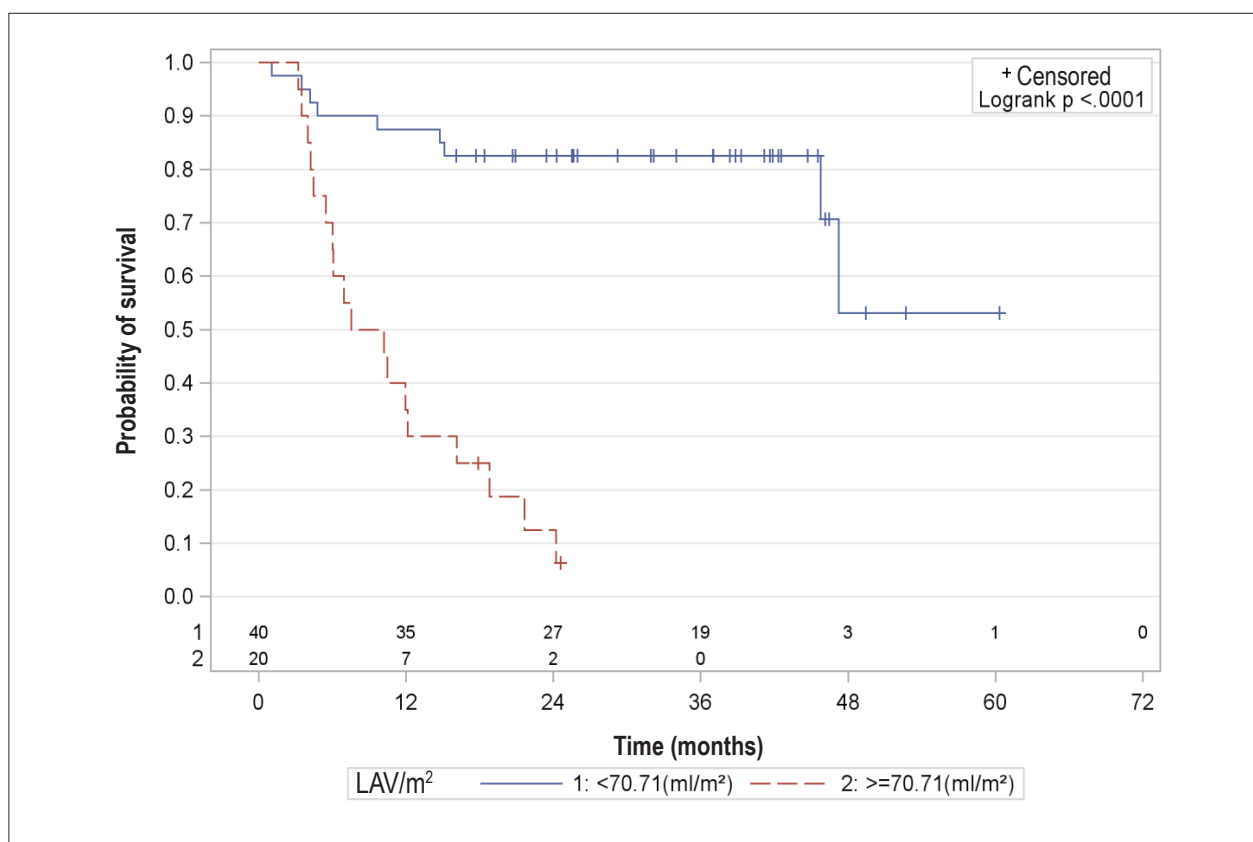


Figure 2 - Relationship between survival and Indexed Left Atrial Volume (LAV /m<sup>2</sup>).

as well as in the basal segment of the inferior and inferolateral wall and apex. Perhaps the most appropriate site for these measurements is another wall, where the probability of segmental impairment is lower. Another factor that may have compromised our tissue parameters was that approximately 30% of patients used pacemakers and 6.6% had rhythm in atrial fibrillation. These factors also compromise tissue assessment during diastole.

### Limitation

This was a study of retrospective analysis of data prospectively collected, and this implies in limitations inherent to this type of analysis.

There was no sample calculation for the analysis of endpoints, because the cohort available was of 60 patients. This limits possible additional conclusions, because of the small number of primary endpoint (mortality).

### Conclusion

Increased indexed left atrial volume proved to be the only echocardiographic parameter to independently correlate with cardiovascular mortality in this population of severely ill chagasic patients.

### Author contributions

Conception and design of the research: Rassi DC, Vieira MLC, Arruda ALM, Furtado RG, Rassi DT, Rassi S; Acquisition of data: Rassi DC, Rassi DT, Rassi S; Analysis and interpretation of the data, Critical revision of the manuscript for intellectual content and Writing of the manuscript: Rassi DC, Vieira MLC, Arruda ALM, Hotta VT, Furtado RG, Rassi DT, Rassi S; Statistical analysis: Rassi DC, Vieira MLC, Arruda ALM, Hotta VT, Furtado RG, Rassi S; Obtaining funding: Rassi S.

### Potential Conflict of Interest

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

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### Study Association

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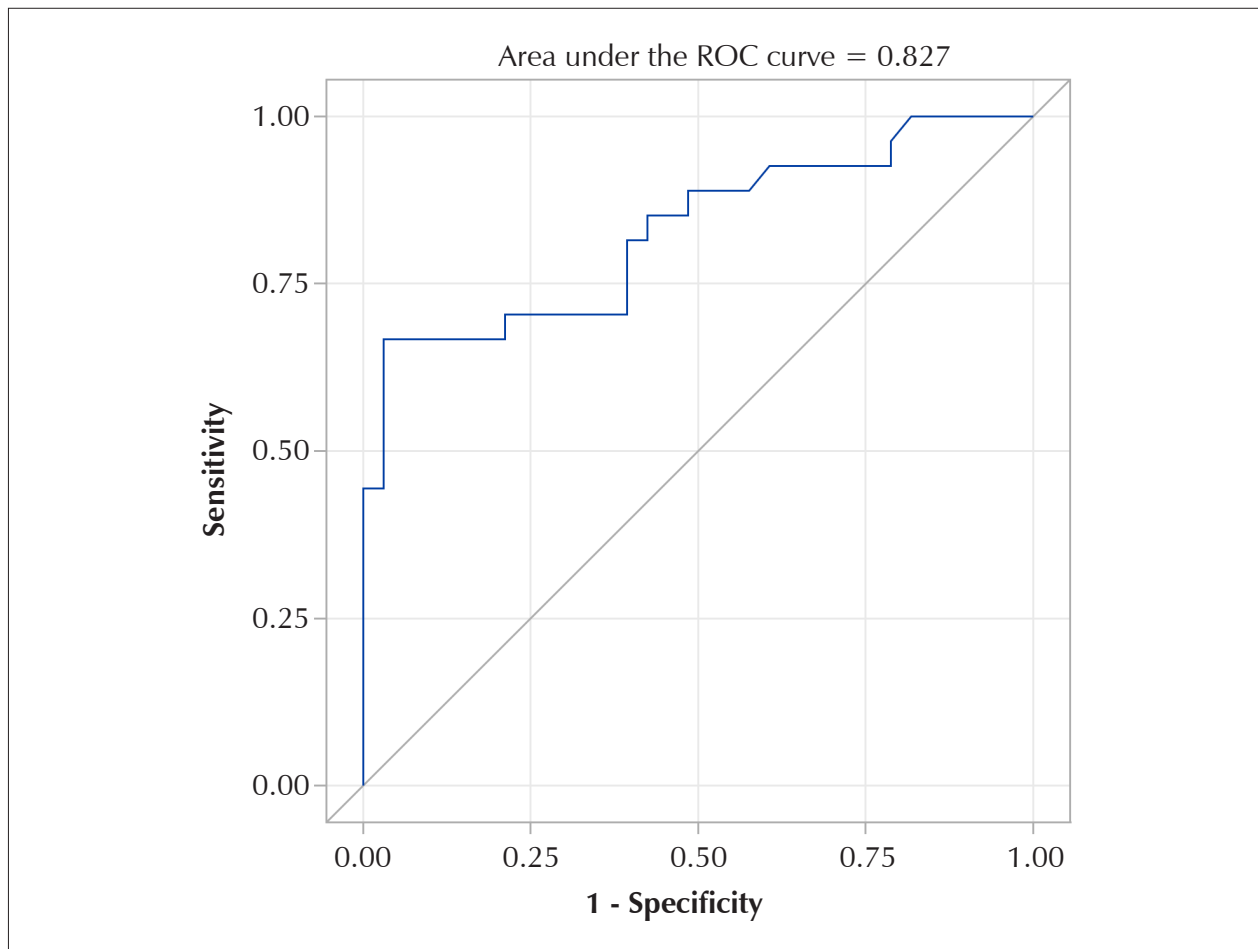


Figure 3 - ROC curve of the indexed left atrial volume.

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