

# Predictors of Heart Failure in Chronic Chagasic Cardiomyopathy With Asymptomatic Left Ventricular Dysfunction

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**Introduction and objectives.** The development of asymptomatic left ventricular dysfunction signifies a worsening of chronic chagasic cardiomyopathy. Our objective was to identify factors that predict the development of heart failure and all-cause mortality.

**Methods.** The study included 95 patients with an echocardiographic diagnosis of asymptomatic left ventricular dysfunction. The patients' clinical, electrocardiographic, and echocardiographic characteristics were recorded. Factors associated with the development of heart failure were evaluated by Cox regression modeling. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Receiver operating characteristic (ROC) curves were used to evaluate the sensitivity and specificity of continuous variables identified as significant in the regression analysis.

**Results.** Patients (mean age, 55 [11] years) were followed up for a median of 63 months (interquartile range, 32-110 months). Univariate analysis showed that there were significant differences in mild and severe systolic dysfunction, age on admission, and E-point-to-septal separation, while the only significant predictors of heart failure found on Cox regression analysis were severe systolic dysfunction (HR=3.53; 95% CI, 1.21-10.30;  $P=.021$ ) and E-point-to-septal separation (HR=1.12; 95% CI, 1.02-1.23;  $P=.014$ ). The mortality rate was 3% (3/95) in patients who continued to have asymptomatic left ventricular dysfunction and 37% (10/27) in those who developed heart failure.

**Conclusions.** The E-point-to-septal separation and the presence of severe systolic dysfunction can serve as predictors of heart failure in patients with chronic chagasic cardiomyopathy and asymptomatic left ventricular dysfunction.

**Key words:** Heart failure. Ventricular dysfunction. Prognosis.

## Predictores de insuficiencia cardíaca en la miocardiopatía chagásica crónica con disfunción asintomática del ventrículo izquierdo

**Introducción y objetivos.** La disfunción ventricular izquierda asintomática representa un estadio de mala evolución en la miocardiopatía chagásica crónica. Nuestro objetivo fue establecer los posibles predictores de progresión hacia la insuficiencia cardíaca y mortalidad total.

**Métodos.** Se incluyó a 95 pacientes con diagnóstico ecocardiográfico de disfunción ventricular izquierda asintomática. Las variables estudiadas fueron clínicas, electrocardiográficas y ecocardiográficas. Para evaluar la progresión hacia la insuficiencia cardíaca se utilizó un modelo de regresión de Cox. Se calcularon las *hazard ratio* (HR) y sus intervalos de confianza del 95%. La curva *receiver operating characteristic* (ROC) se utilizó para valorar la sensibilidad y la especificidad de las variables continuas con significación en la regresión.

**Resultados.** El tiempo de seguimiento presentó una mediana de 63 meses y un rango intercuartílico de 32-110 meses, con una edad promedio de  $55 \pm 11$  años. El deterioro leve y severo de la función sistólica, la edad al ingreso y la distancia E-septum mostraron diferencias significativas en el análisis univariable, mientras que la disfunción sistólica severa ( $p = 0,021$ ; HR = 3,53 [1,21-10,3]) y la distancia E-septum ( $p = 0,014$ ; HR = 1,12 [1,02-1,23]) fueron las únicas variables predictoras de insuficiencia cardíaca en el análisis de regresión de Cox. La mortalidad fue del 3% (3/95) de los pacientes que permanecieron con disfunción ventricular izquierda asintomática y el 37% (10/27) de los pacientes que evolucionaron hacia la insuficiencia cardíaca.

**Conclusiones.** La distancia E-septum y el deterioro severo de la función sistólica pueden ser predictores de insuficiencia cardíaca en pacientes con miocardiopatía chagásica crónica y disfunción ventricular izquierda asintomática.

**Palabras clave:** Insuficiencia cardíaca. Disfunción ventricular. Pronóstico.

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**ABBREVIATIONS**

ALVD: asymptomatic left ventricular dysfunction  
 ECG: electrocardiogram  
 FC: functional class  
 LV: left ventricle  
 NYHA: New York Heart Association  
 ROC: receiver operating characteristic

**INTRODUCTION**

Chagas disease is one of the most worrying health care problems in Latin America and is the main cause of infectious myocarditis<sup>1</sup>; 18 to 20 million people are infected in Latin America.<sup>2</sup> Chagas disease is characterized by 3 phases—acute, indeterminate, and chronic<sup>3</sup>; the chronic phase tends to display a slow course in which chronic chagasic cardiomyopathy is the principal manifestation. The clinical presentation in the phase of chronic myocarditis is diverse, and heart failure is the most advanced, since it is indicative of extensive, severe, and irreversible damage to the myocardium preceding death.<sup>4</sup> Asymptomatic left ventricular dysfunction (ALVD) is an earlier stage, and the development of heart failure is indicative of worsening not only of the patient's symptoms but also of prognosis for survival.<sup>5</sup> Five-year mortality is approximately 70% in patients with Chagas disease and heart failure.<sup>6</sup> Development of the syndrome is linked to compensatory mechanisms triggered during the early stages of damage to the myocardium and that are initially adaptive before subsequently becoming harmful.

There are few methods available with which to assess ALVD in chronic chagasic cardiomyopathy and predict progression to heart failure, and those that are available are incomplete. We therefore sought to establish predictors of progression towards heart failure using simple clinical and echocardiographic variables normally used in follow-up of these patients. As a secondary objective, we analyzed overall mortality in this patient group.

**METHODS**

A prospective study was undertaken in our regional referral center for Chagas disease between 1993 and 2006 in which 95 patients aged over 18 years with a diagnosis of chagasic cardiomyopathy and ALVD were consecutively enrolled for subsequent follow-up. The study group was selected from a population of 2990 patients with ALVD (New York Heart Association

[NYHA] class I) and serologic diagnosis of Chagas disease seen in our hospital and comprised 95 patients (3.18%). Stress tests in those patients indicated a functional class equivalent to NYHA class I, with a maximum load achieved of at least 6 metabolic equivalents (MET) and its equivalent in kg; 27 (0.9%) had heart failure (NYHA II/IV); 762 (25.5%) only had electrical conduction abnormalities or arrhythmias; and 2033 (68%) were in the indeterminate phase of the disease.

Patients were excluded from the study if they had concomitant heart disease, such as congenital, hypertensive, ischemic, or alcoholic heart disease, valve disease, and others.

Diagnosis of the disease was established with a least 2 out of 3 positive serologic tests for *Trypanosoma cruzi*<sup>7</sup>: enzyme-linked immunosorbent assay, indirect hemagglutination, and immunofluorescence test. Deterioration of left ventricular systolic function was assessed by echocardiography according to the measures and variables employed in our hospital and also taking into account the subjective assessment of the operator regarding general systolic dysfunction as mild, moderate, or severe.

The following were performed at the beginning of follow-up: serology for Chagas disease, baseline electrocardiogram (ECG), frontal chest x-ray, stress test, and M-mode, and 2-dimensional echocardiography. During follow-up, patients attended appointments every 2 months or in the event of symptoms. ECG was repeated at each appointment and other tests were done once a year.

The following variables were considered in the study: sex, age on enrollment, length of follow-up, appearance or development of heart failure, ECG abnormalities associated with Chagas disease, complex ventricular arrhythmias (ventricular pairs, sustained, and nonsustained ventricular tachycardia), diastolic and systolic left-ventricular diameter, presence of segmental lesions in the left ventricle, shortening fraction, ejection fraction, E-point septal separation, and left ventricular systolic dysfunction defined semiquantitatively by the cardiologist responsible for echocardiography as mild, moderate, or severe.

The following were considered ECG anomalies related to Chagas disease: complete right bundle branch block, left anterior hemiblock, complete left bundle branch block, ventricular pairs, sustained and nonsustained ventricular tachycardia, areas of electrical inactivation, atrial fibrillation or flutter, atrial tachycardia, sinus bradycardia (<50 beats/min), type 2 second degree and third degree atrioventricular block, and definitive pacemaker implantation; all of these abnormalities displayed an incidence that differed significantly from the ECG findings in healthy individuals.<sup>8</sup>

Diagnosis of left ventricular systolic dysfunction was established when the cardiologist responsible for echocardiography reported mild, moderate, or severe

dysfunction (defined semiquantitatively) accompanied by at least 1 of the following quantitative parameters: E-point septal separation >10 mm, shortening fraction <25%, and ejection fraction <45%. The reference values used in our hospital for normal left ventricular systolic function are an E-point septal separation <7 mm, shortening fraction >28%, and ejection fraction >55%.

Heart failure was defined according to Framingham criteria, establishing the simultaneous presence of at least 2 major criteria or 1 major and 2 minor criteria.<sup>9</sup>

The study protocol was approved by the institutional review board and patients consented to inclusion in the study.

### Statistical Analysis

Continuous variables were expressed as means (SD) or median (interquartile range) according to whether they exhibited a gaussian distribution in the Shapiro-Wilk test, and categorical variables were expressed as proportions and/or percentages. The primary outcome measure was the development of heart failure and the secondary measure was overall mortality. Univariate and multivariate Cox regression were used to establish predictors of the development of heart failure. The assumption of proportionality was assessed by Kaplan-Meier analysis. The variables that displayed a significant association with the dependent variable ( $P < .10$ ) in the univariate analysis were incorporated in the multivariate model to confirm the independent predictive value of each variable, considering values of  $P < .05$  to be statistically significant. The hazard ratio (HR) and 95% confidence interval (CI)

was calculated for each variable included in the Cox regression model. The area below the receiver operating characteristic (ROC) curve was used to determine the sensitivity and specificity of the continuous variables that displayed statistical significance and the curve of the risk function (derived from the Kaplan-Meier curve) was used to display the differences. Analysis was performed with the programs Statistix 7.0 Analytical Software and SPSS version 10.0 Statistical Analysis Software for Windows (SPSS Inc, Chicago, Illinois, USA).

### RESULTS

The follow-up period for the 95 patients with chronic chagasic cardiomyopathy and ALVD had a median length of 63 months and an interquartile range of 32 to 110 months. The mean age of the patients was 55 (11) years and the group included 58 (61%) men and 37 (39%) women. The baseline characteristics of the patients included in the study are shown in Table 1. Severe systolic dysfunction was observed in 17% of the population and in 20% when considering an E-point septal separation of at least 20 mm as an indicator of severe systolic dysfunction. Most of the patients had mild or moderate systolic dysfunction on inclusion in the study. In 96.8% of cases, the patients received treatment with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists.

Twenty-seven patients (28%) developed heart failure during follow-up. Table 2 shows the results of the univariate analysis. The variables that were not associated with the primary outcome measure (development of heart

**TABLE 1. Baseline Characteristics of Patients With Chronic Chagasic Cardiomyopathy and Asymptomatic Left Ventricular Dysfunction Included in the Study**

Characteristic	Population (n=95)
Sex, men/total, %	58/95 (61)
Age at enrollment, mean (SD), y	54.7 (10.6)
Length of follow-up, median (interquartile range), mo	63 (32-110)
ECG abnormalities/total, %	85/95 (89)
Segmental lesions/total, %	71/95 (75)
Complex ventricular arrhythmias/total, %	60/95 (63)
Diastolic diameter of the left ventricle, median (interquartile range), mm	62 (58-66)
Systolic diameter of the left ventricle, mean (SD), mm	46.76 (6.5)
Shortening fraction, median (interquartile range), %	24 (20-29)
Ejection fraction, median (interquartile range), %	44 (36-51)
E-point septal separation, median (interquartile range), mm	15 (12-18)
Mild deterioration of systolic function/total, %	45/95 (47)
Moderate deterioration of systolic function/total, %	34/95 (36)
Severe deterioration of systolic function/total, %	16/95 (17)
Treatment with ACE inhibitors and/or angiotensin II receptor antagonists/total, %	92/95 (97)

ACE indicates angiotensin converting enzyme; ECG, electrocardiogram.

**TABLE 2. Univariate Analysis for the Development of Heart Failure and Distribution of Frequencies in Patients With Chronic Chagasic Cardiomyopathy and Asymptomatic Left Ventricular Dysfunction**

Variable	Distribution of Frequencies		Univariate Analysis	
	Without Heart Failure (n=68)	With Heart Failure n=27	P	HR (95% CI)
Age at enrollment, mean (SD), y	53.3 (11.5)	54.7 (8.4)	.08	1.04 (0.99-1.08)
Sex, men/total	44/68	14/27	.53	0.78 (0.37-1.67)
ECG abnormalities/total	61/68	24/27	.90	1.08 (0.32-3.63)
Segmental lesions/total	47/68	24/27	.51	1.51 (0.44-5.14)
Complex ventricular arrhythmias/total	40/68	20/27	.66	1.22 (0.51-2.91)
Diastolic diameter of the left ventricle, median (interquartile range), mm	61.5 (58-66)	63 (58-66)	.13	1.06 (0.98-1.15)
Systolic diameter of the left ventricle, mean (SD), mm	46.4 (6.5)	47.6 (6.8)	.28	1.04 (0.97-1.11)
Shortening fraction, median (interquartile range), %	24.5 (20-29)	23 (20-29)	.96	1 (0.94-1.07)
Ejection fraction, median (interquartile range), %	45 (36-51)	41 (34-54)	.86	0.67 (0.08-53.65)
E-point septal separation, median (interquartile range), mm	15 (12-16)	17 (14-21)	.001	1.15 (1.07-1.24)
Mild deterioration of systolic function/total, %	36/68 (53)	9/27 (33)	.03	0.41 (0.18-0.92)
Moderate deterioration of systolic function/total, %	22/68 (32)	12/27 (44)	.62	1.21 (0.57-2.6)
Severe deterioration of systolic function/total, %	10/68 (15)	6/27 (23)	.001	5.38 (2.06-14.07)

ECG indicates electrocardiogram; HR, hazard ratio; CI, confidence interval.

**TABLE 3. Multivariate Analysis for the Development of Heart Failure in Patients With Chronic Chagasic Cardiomyopathy and Asymptomatic Left Ventricular Dysfunction**

Variable	P	HR	95% CI
Age at enrollment	.31	1.02	0.98-1.07
Mild deterioration of systolic function	.83	0.89	0.32-2.45
E-point septal separation	.014	1.12	1.02-1.23
Severe deterioration of systolic function	.021	3.53	1.21-10.3

HR indicates hazard ratio; CI, confidence interval.

failure) were sex, ECG abnormalities, systolic left ventricular diameter, diastolic left ventricular diameter, presence of segmental lesions, complex ventricular arrhythmias, shortening fraction, ejection fraction, and moderate depression of systolic function. Age at enrollment, mild or severe depression of left ventricular systolic function, and E-point septal separation displayed statistically significant differences.

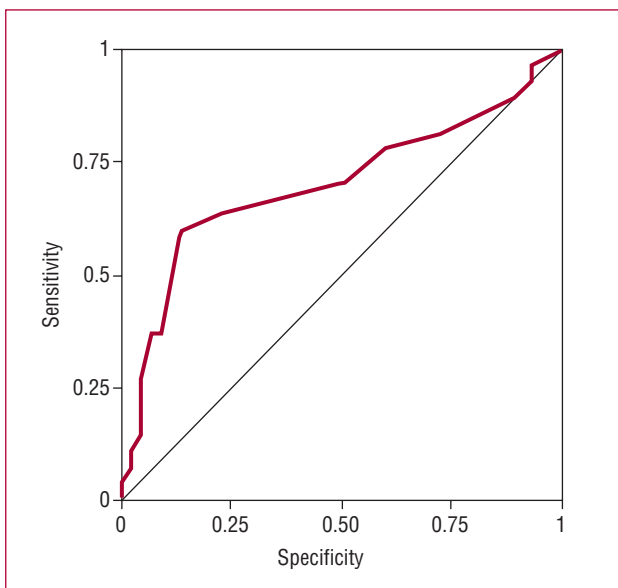
Table 3 shows the results of the multivariate analysis (Cox regression). Age and mild depression of left ventricular systolic function lost their independent predictive value for heart failure, while the presence of severe left ventricular systolic dysfunction and greater E-point septal separation maintained their prognostic value. The sensitivity and specificity of those variables was calculated: severe left ventricular systolic dysfunction had a sensitivity of 22% and a specificity of 85%. We used a ROC curve to determine the best cutoff for the

E-point septal separation and selected a value of 17 mm, which was associated with a sensitivity of 63% and a specificity of 75% for prediction of the development of heart failure (Figure 1). The area below the ROC curve was 0.68 (a test with no discriminative power has a value of 0.50). Figure 2 shows the risk of developing heart failure in relation to severe deterioration of systolic function.

The mortality at 63 months of follow-up was 3/95 (3%) patients who continued to have ALVD and 10/27 (37%) patients who had developed heart failure. The time from inclusion in follow-up to development of heart failure was 55 months, with an interquartile range of 23 to 117 months. The mean follow-up from the appearance of heart failure to death was 46 (37) months.

## DISCUSSION

Our study assessed the possible predictors of heart failure in a sample of 95 patients with chronic chagasic cardiomyopathy and asymptomatic ventricular dysfunction. Patients with severe left ventricular dysfunction had a 2.5-fold greater risk of developing heart failure than those with mild or moderate deterioration of left ventricular systolic function. In studies designed to assess mortality, this was found to increase with deterioration of left ventricular systolic function.<sup>10</sup> An E-point septal separation of at least 17 mm was associated with a 3.5-fold increased risk of developing heart failure compared to those in whom the distance was shorter. The data obtained in our hospital based on 2990 patients with Chagas disease reveal a wide range of clinical presentations of the disease and

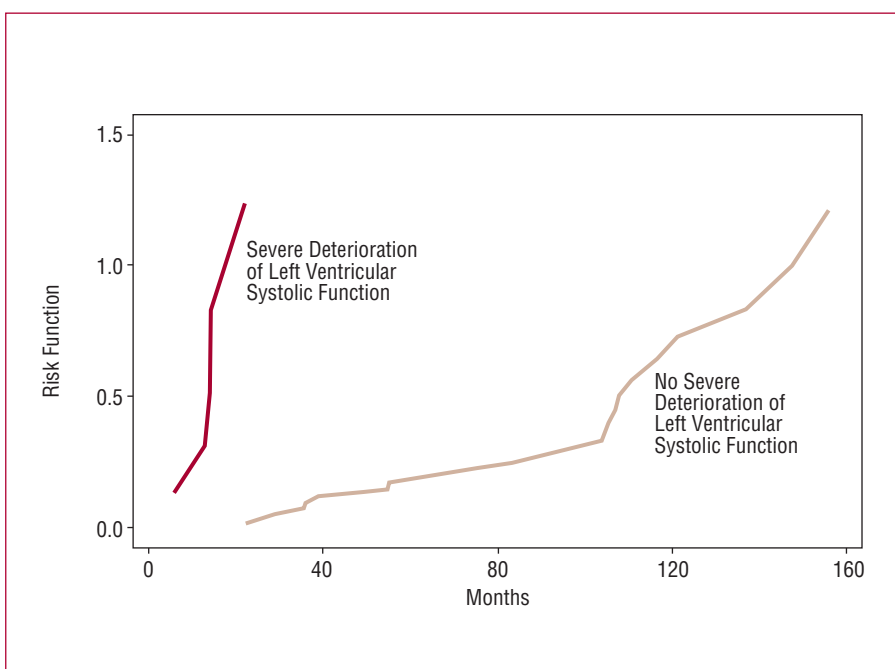


**Figure 1.** Receiver operating characteristic curve for the variable E-point septal separation in relation to the development of heart failure in patients with chronic chagasic cardiomyopathy and asymptomatic left ventricular dysfunction. An E-point septal separation of 17 mm represents the cutoff with the best combination of sensitivity and specificity.

a small number of patients who progress to more severe forms of the heart disease.

Various echocardiographic studies have demonstrated that segmental abnormalities of left ventricular wall motion in chronic chagasic heart disease contribute to general deterioration of left-ventricular systolic dysfunction,<sup>11</sup>

which in turn contributes to poor prognosis in those patients.<sup>12-14</sup> The number of affected segments generally shows a good correlation with general deterioration of systolic function.<sup>15</sup> It is known that the most common site of segmental abnormalities in chronic chagasic cardiomyopathy is the apex of the left ventricle.<sup>11-16</sup> This leads to shortening of basal segments being conserved or little affected, due to the compensatory mechanisms that are triggered. Depending on the method used to assess ventricular function—by measurement of systolic and/or diastolic left ventricular wall diameter, shortening fraction, and ejection fraction (Teichholz)—deterioration may be underestimated or overestimated, since those measurements are made in the basal segments and do not offer an adequate assessment of general function in ventricles with regional differences in contraction (Chagas disease and other segmental heart diseases).<sup>17</sup> In our study, these variables did not display statistical significance as predictors of heart failure, a finding that may be explained by the regional differences in contraction and the homogeneity of those variables in our sample of patients with ALVD. The E-point septal separation and severe general systolic dysfunction, as defined by the cardiologist, were the only factors with prognostic value for heart failure in the multivariate analysis. The E-point septal separation has the advantage of being a measure of general systolic function that is relatively independent of regional abnormalities in left ventricular wall motion,<sup>18</sup> with a good correlation with angiographic ejection fraction.<sup>19,20</sup> In addition, it displayed acceptable sensitivity and specificity when analyzed using a ROC curve. The semiquantitative assessment by the operator (cardiologist



**Figure 2.** Risk function for the development of heart failure in patients with chronic chagasic cardiomyopathy and asymptomatic left ventricular dysfunction in relation to severe deterioration of systolic function.

trained in echocardiography) can offer a more general interpretation of ventricular function, since it considers both M-mode measurements at the base of the left ventricle (shortening fraction, systolic diameter of the left ventricle, etc) and assessment of general and regional motion, influenced by the various echographic views.<sup>21</sup> This may explain the good correlation with ejection fraction estimated from radionuclide studies<sup>22</sup> and may even be better than that calculated by the Simpson method in terms of correlation with estimates from radionuclide imaging.<sup>23</sup> Calculation of the ejection fraction using the Simpson method requires adequate visualization of the endocardial borders and a considerable amount of time, which may not always be available. Due to technical limitations, we do not use this method, and the ejection fraction was calculated according to the Teichholz formula, in the knowledge of its limitations in the presence of segmental lesions. Another limitation was the lack of cardiac Doppler studies, which can improve the assessment of left ventricular systolic and diastolic function.

None of the clinical variables such as age and ECG abnormalities associated with Chagas disease displayed prognostic value for the development of heart failure in our study. In general, age is associated with greater mortality in patients with heart failure, but this was not the case in our group of patients with ALVD. ECG findings also showed no statistical significance for the prediction of heart failure, in contrast to the prognostic value associated with cardiac death.<sup>24</sup> Likewise, complex ventricular arrhythmias were not associated with development of heart failure, even though they are known to be closely associated with deterioration of left ventricular function and increased risk of death.<sup>13,25</sup> Segmental lesions did not seem to be independent predictors of heart failure, at least not in the patient sample studied here, with no classification of the lesion according to type or location.

Selection of patients with ALVD appears to have led to homogeneity of many of the variables studied, and they did not display an association with the outcome measures of the study. These same variables may have had a different significance if the outcome measure was mortality and the study group had heart failure.

## CONCLUSIONS

In patients with chronic chagasic cardiomyopathy and ALVD, 2 easily obtained echocardiographic variables—E-point septal separation and severe left ventricular dysfunction defined by the operator—can predict the development of heart failure.

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