Why do Patients with Chagasic Cardiomyopathy have Worse Outcomes than those with Non-Chagasic Cardiomyopathy?

Christiano Pereira Silva, Carlo Henrique Del Carlo, Mucio Tavares de Oliveira Junior, Airton Scipioni, Celia Strunz-Cassaro, José Antonio Franchini Ramirez, Antonio Carlos Pereira Barretto

Instituto do Coração, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP - Brazil

Summary

Background: Heart failure is a highly prevalent disease, the prognosis of which depends on different predictive factors.

Objective: Chagas disease is a predictor of poor prognosis in patients with chronic heart failure (HF). The purpose of this study is to investigate whether this condition also predicts poor outcome in acutely decompensated patients.

Methods: Four hundred and seventeen patients admitted for decompensated heart failure were studied. Mean age was 51.8 years, and 291 (69.8%) were male. They were divided into two groups: 133 (31.9%) patients with Chagas heart disease (CH) and 284 patients with heart failure of other etiologies. Cytokine and norepinephrine plasma levels were measured in a subgroup of 63 patients (15.1% with Chagas disease).

Results: At admission, 24.6% of the patients needed inotropic support, and one-year mortality was 54.7%. Mortality rates were higher in the CH group (69.2% vs. 47.9%, $p < 0.001$). When data were compared, patients with Chagas disease were younger (47.6 vs. 53.8 years, $p < 0.001$) and, on average, showed lower systolic blood pressure (96.7 vs. 111.2 mmHg, $p < 0,001$), ejection fraction (32.7 vs. 36.4%, $p < 0.001$), and serum Na (134.6 vs. 136.0, $p = 0.026$), in addition to higher TNF-α levels (33.3 vs. 14.8, $p = 0.001$). The presence of hypotension requiring inotropic support, left ventricular (LV) diastolic diameter, renal function findings, and interleukin-6 and norepinephrine plasma levels did not differ between both groups.

Conclusion: Chagas disease patients admitted with decompensated heart failure had worse prognoses than patients with heart failure of other etiologies. This may be owing to a greater degree of cardiac impairment (lower ejection fraction) and hemodynamic instability (lower systolic blood pressure and heart rate), increased activation of the renin-angiotensin system (lower sodium), and increased cytokine levels (TNF-α) (Arq Bras Cardiol 2008;91(6):358-362).

Key words: Chagas cardiomyopathy; heart failure, congestive; clinical evaluation.

Introduction

Heart failure (HF) is a chronic, insidious disease that results in varying degrees of functional impairment. Although great strides have been made over the past twenty years in the management of this condition, it still carries an unfavorable prognosis. Despite the clinical and pathophysiological diversity that characterizes heart failure patients, some prognostic predictors are well known, such as hypotension and elevated levels of nitrogenous waste products[1].

Among all etiologies of the disease, Chagasic cardiomyopathy seems to carry the worst prognosis[2,3]. This finding was reported by Freitas et al.[4] in a prospective study involving 1220 patients with heart failure in functional classes III and IV of the New York Heart Association (NYHA)[4]. Another study yielded similar results. Rassi et al followed up a cohort of 204 patients with heart failure during 46 months and identified some risk factors for cardiovascular death, including NYHA functional classes III and IV (2.7 times higher), an increase of 10 bpm in heart rate (1.6 times higher), increased serum creatinine (60% higher), and Chagas disease (4.1 times higher)[5].

Some predictors of cardiomyopathy severity were correlated with its prognosis in Chagas disease patients, such as clinically or echocardiographically diagnosed right ventricular dysfunction. This condition not only makes drug therapy significantly more difficult, but may increase more than fivefold the risk of death[6]. The primary purpose of this study was to evaluate whether Chagas disease portends poor prognosis in patients with advanced heart failure. The secondary purpose was to determine how Chagas patients differ from those with cardiomyopathies of other etiologies and whether these differences may account for their worse prognosis.

Methods

During 12 months, 417 consecutive patients admitted for decompensated heart failure were prospectively selected. All of them were in functional class III or IV according to the

Mailing Address: Christiano Pereira Silva •
Rua José Ramon Urtiza, 181 / 193A – 05717270 - Morumbi – São Paulo, SP - Brazil
E-mail: chrispsilva@hotmail.com, chrispsilva@cardiol.br
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NYHA classification and went voluntarily to the hospital with symptoms of heart failure, such as dyspnea, tiredness, and exercise intolerance.

At admission, all patients underwent clinical (anamnesis and physical examination), echocardiographic, and laboratory (blood count, renal function, electrolytes, and blood glucose) examinations. Sixty-three patients were assessed for neurohormone and cytokine serum levels. The study sample was divided into two groups: 133 (31.9%) patients with Chagas disease (CH) and 284 patients with other etiologies.

Clinical, echocardiographic, and laboratory data were analyzed using the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. A multivariate analysis was performed to determine prognostic factors in this population. P values < 0.05 were considered statistically significant.

This study was approved by the Research Ethics Committee of the Medical School of São Paulo Federal University under Nº. 1758/00/119.

Results

Table 1 summarizes the primary characteristics of the patients studied. These patients were followed-up during one year, with outpatient clinic visits. Afterwards, each patient was followed up through medical record review (paper-based and electronic) up to five years after hospital discharge.

Table 1 – Characteristics of the study sample (mean + SD)

Variablevel	Mean (SD)	Min.-Máx.
Physical examination:		
SBP (mm Hg)	105.9 ± 27.7	6.0-200.0
HR (bpm)	90.1 ± 19.0	46.0-150.0
Third heart sound	93 (26.3%)	
Mitral regurgitation	238 (67.2%)	
Atrial fibrillation	90 (25.4%)	
Echocardiogram:		
LVEF (%)	34.5 ± 8.1	11.0-58.0
LVEDD (mm)	72.1 ± 8.7	51.0-100.0
LA (mm)	48.9 ± 7.3	29.0-78.0
Laboratory tests:		
Sodium (mEq/L)	135.5 ± 5.3	112.0-151.0
Urea (mg/dL)	71.2 ± 30.8	26.0-185.0
Creatinine (mg/dL)	1.5 ± 0.5	0.7-7.7
Potassium (mg/dL)	4.5 ± 0.7	2.7- 6.9
Hemoglobin (g/dL)	13.7 ± 2.1	8.8-18.4
Albumin (g/dL)	3.5 ± 0.7	1.7-5.8
Leukocytes (n/mm^3)	8433.3 ± 3128.4	4.000-22.000
Use of dobutamine	87 (24.6%)	

SBP - systolic blood pressure; HR - heart rate; LVEF - left ventricular ejection fraction; LVEDD - left ventricular end-diastolic diameter; LA - left atrium; Min. - minimum; Max. - maximum

Study sample was predominantly male, with 291 men (69.8%) and 126 women (30.2%), ranging in age from 17 to 80 (mean age 51.8 + 14.2).

At hospital admission, 24.6% of the patients required inotropic therapy. There were no differences regarding the use of inotropic agents ($p = 0.70$) between groups. Overall one-year mortality was 54.7%.

Clinical data and characteristics of both groups, Chagas and non-Chagas, are shown in Table 2.

Chagasic cardiomyopathy patients were found to be younger ($p < 0.001$) and have lower systolic blood pressure ($p < 0.001$) heart rate ($p = 0.006$), left ventricular ejection fraction ($p = 0.005$), and serum sodium ($p = 0.049$). Laboratory tests showed that TNF levels were higher in Chagas patients ($p = 0.001$) (Figure 1).

Table 3 contains clinical, demographic, and laboratory data of the patients assessed for neurohormone and cytokine levels.

Table 2 – Mean characteristics of Chagas and non-Chagas patients (SD)

Variable	Chagas patients	Non-Chagas patients	p
N	122	232	
Age	47,5 (12)	53 (14,9)	<0,001
Male	90 (73,8%)	161 (69,4%)	0,389
Physical examination			
SBP (mm Hg)	97,0 (25,2)	110,3 (28)	<0,001
HR (bpm)	85,9 (20,5)	92,3 (17,9)	0,006
Third heart sound	33,6%	22,4%	0,109
MR	76,2%	62,5%	0,227
Atrial fibrillation	27%	24,6%	0,611
Echocardiogram			
LVEF (%)	32,9 (8,7)	35,3 (7,7)	0,005
LVEDD (mm)	72,4 (7,5)	71,9 (9,3)	0,261
LA (mm)	49,2 (6,1)	48,7 (7,9)	0,339
Laboratory data			
Sodium (mEq/L)	134,6 (5,7)	136,0 (5)	0,049
Urea (mg/dL)	65,8 (24,4)	74,0 (33,4)	0,110
Creatinine (mg/dL)	1,4 (0,3)	1,5 (0,6)	0,067
Potassium (mEq/L)	4,4 (0,7)	4,5 (0,7)	0,317
Hemoglobin (g/dL)	13,9 (2,0)	13,6 (2,1)	0,226
Inotropic agents	27,9%	22,8%	0,709
One-year mortality	67,2%	49,1%	0,001
Neurohormones and cytokines			
Norepinephrine (pg/mL)	847 (528)	872 (597)	0,926
Interleucina-6 (pg/ml)	27,7 (42,2)	21,1 (47,6)	0,713
TNF-alfa (pg/ml)	33,3 (17,6)	14,8 (47,6)	0,001

N - number of patients; SBP - systolic blood pressure; HR - heart rate; MR - mitral regurgitation; LVEF - left ventricular ejection fraction; LVEDD - left ventricular end-diastolic diameter; LA - left atrium.

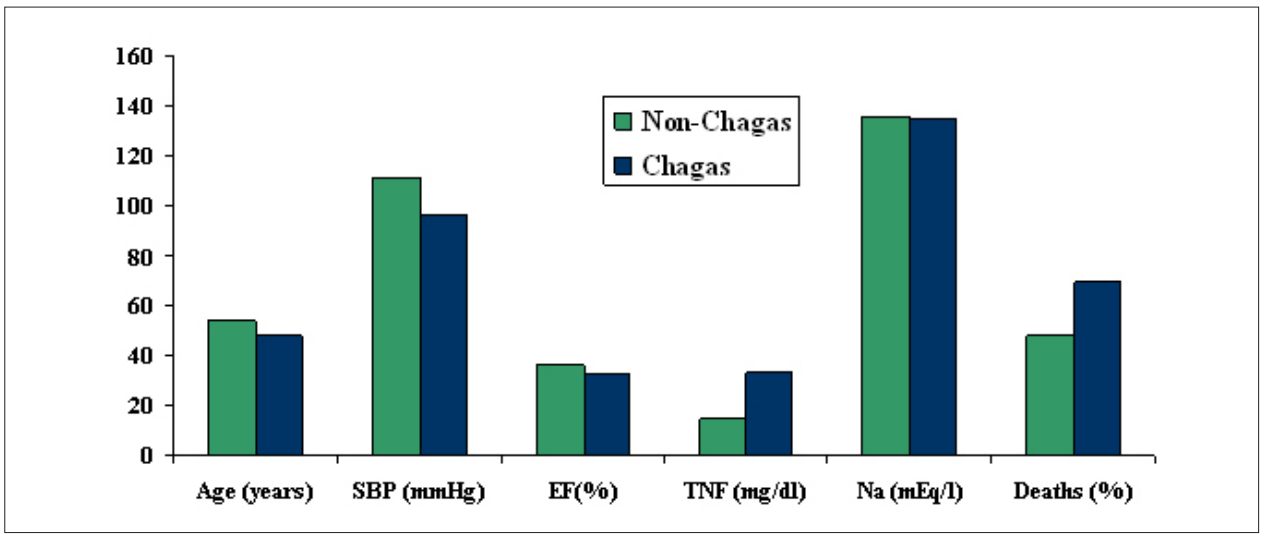

Figure 1 - Variables that were significantly different between Chagas and non-Chagas patients; BP - systolic blood pressure; EF - ejection fraction; TNF – tumor necrosis factor; Na – sodium; p < 0.001: age and SBP; p = 0.001: mortality and TNF; p = 0.005: LVEF; P = 0.006: HR; P = 0.049: sodium

Table 3 - Characteristics of Chagas (CH) and non-Chagas patients (non-CH) who underwent neurohormonal measurements

Variable	CH (n = 11)	Non-CH (n = 52)	P
Age (years)	49,1 ± 14,2	57,0 (15,8)	0,105
Male gender	63,6%	63,5	0,741
Body weight (kg)	63,0 (20,0)	69,7 (16,6)	0,110
Height (cm)	1,6 (0,1)	1,6 (0,1)	0,142
SBP (mm Hg)	94,5 (14,4)	113,7 (34,6)	0,087
DBP (mm Hg)	70.9 (11.4)	74.3 (20.6)	0.818
HR (bpm)	77.3 (14.9)	93.6 (21.6)	0.013
LVEF (%)	30.7 (6.4)	41.2 (13.9)	0.022
LVEDD (cm)	7.2 (0.7)	6.9 (1.4)	0.355
LA (cm)	5.4 (0.7)	5.3 (0.9)	0.690
Atrial fibrillation	18.2%	32.7%	0.480
Anemia	45.5%	21.2%	0.128
Hemoglobin (g/dL)	13.6 (2.0)	13.6 (2.0)	0.984
Urea (mg/dL)	60.2 (27.0)	73.7 (31.7)	0.250
Creatinine (mg/dL)	1.3 (0.5)	1.4 (0.5)	0.387
Sodium (mEq/L)	134.6 (4.8)	136.1 (4.5)	0.344
Potassium (mEq/L)	4.2 (0.6)	4.4 (0.6)	0.361
Norepinephrine (pg/mL)	847.1 (528.9)	872.6 (597.8)	0.926
Interleukin-6 (pg/mL)	27.7 (42.2)	21.1 (47.6)	0.732
TNF-a (pg/mL)	33.3 (17.6)	14.8 (47.6)	0.001

SBP - systolic blood pressure; DBP – diastolic blood pressure; HR - heart rate; LVEF - left ventricular ejection fraction; LVEDD - left ventricular end-diastolic diameter; LA - left atrium; Min. -

In a multivariate analysis including prognostic factors for the entire population (ejection fraction, systolic blood pressure, heart rate, hyponatremia, Chagas disease, and TNF), only Chagas disease was found to be predictive of poor prognosis. During the one-year follow-up period, mortality rates were significantly higher in the Chagas group ($p = 0.001$) (Figure 2).

Discussion

The primary purpose of this study was to evaluate whether patients with Chagasic cardiomyopathy do have poor prognosis for survival, as already demonstrated by earlier studies. It was also designed to identify variables related to heart failure that could justify that hypothetical poor outcome.

The attempt to predict clinical outcomes, unexpected or otherwise, in patients with ventricular dysfunction has been challenging cardiologists for quite some time. A number of prognostic factors were identified: clinical (systolic and diastolic blood pressure and heart rate), hemodynamic (pulmonary capillary pressure, cardiac output, and vascular resistance), electrocardiographic (ventricular hypertrophy and ventricular arrhythmia), and laboratory (increased BNP, low sodium, increased urea and creatinine), among others, such as non-use of beta-blockers. The potential role of the etiology in this prognosis has recently been studied and demonstrated.

Freitas et al.[4] followed up a cohort of 1220 patient during nine years. Twenty percent of them had Chagas disease, and the most common etiology of heart failure was idiopathic dilated cardiomyopathy (37%). All patients were in functional classes II to IV (NYHA). Seventy-eight percent were men (mean age 45.5) and had been referred from the heart failure outpatient clinic. At the end of the follow-up period, 34% patients had died, 6% had undergone heart transplantation and 2%, other type of interventions. Chagas heart disease and

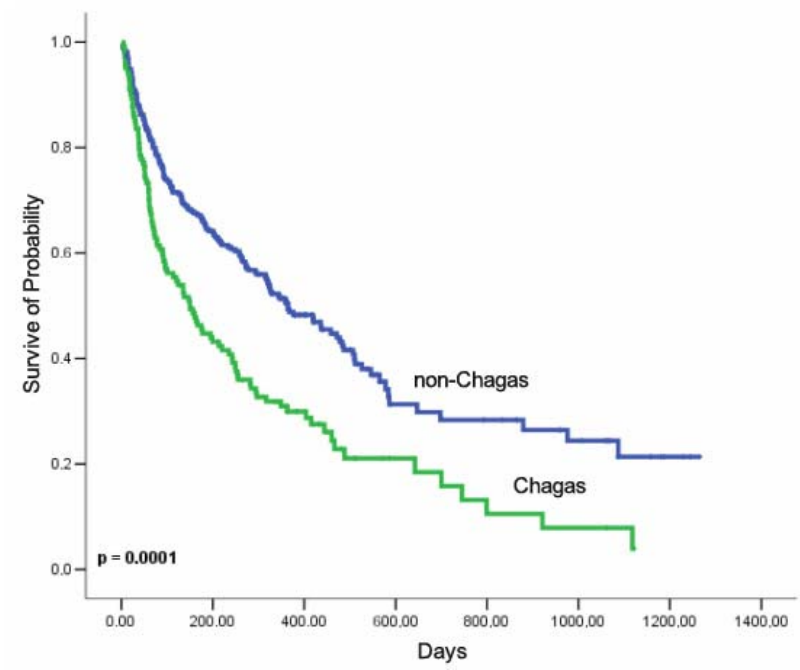

Figure 2 - Survival curve for Chagas and non-Chagas patients

left ventricular end-diastolic diameter and ejection fraction on echocardiogram were identified as predictors of mortality, particularly Chagas heart disease.

In a cohort of 204 patients with heart failure of recent onset followed up during 46 months, Chagas disease was also found to be predictive of poor prognosis. The multivariate analysis showed that NYHA functional classes III and IV (2.7-fold risk), systolic hypotension (each 10-mm Hg increment in BP decreases the risk of cardiovascular death in 25%), tachycardia (each 10 bpm-increase in HR increases the risk 1.6 times), elevation in serum creatinine (each 0.25 mg/dL leads to a 60% increase in cardiovascular risk, the presence of the third heart sound (three-fold increase), and Chagas disease ($p < 0.0001$) were predictive of shorter survival[5].

Chagasic cardiomyopathy has a unique pathophysiology that distinguishes it from the other etiologies. Its distinctive characteristics include male gender predominance, age between 30 and 60, right bundle branch block usually associated with left anterior hemiblock, excessive arrhythmias (atrial and ventricular), varying degrees of atrioventricular blocks, occurrence of both tachyarrhythmias, and bradyarrhythmias, biventricular dysfunction, apical left ventricular aneurysm containing thrombus, frequent thromboembolic events, and high incidence of sudden death. The clinical course of Chagas heart disease itself may play a key role in the poor outcome of these patients. The time course of the disease is longer than that of all other etiologies, often over twenty years, allowing the heart to optimize the compensatory mechanisms and thus keep the patient asymptomatic or mildly symptomatic for years or even decades. Decompensation occurs when myocardial damage overwhelms all compensatory mechanisms, aggravating the disease. This is unlikely to occur in most patients with heart failure of other etiologies, with shorter clinical course. In these cases, life-prolonging treatments allow compensatory mechanisms to be optimized thus improving the clinical course of the disease. The worse prognosis of patients with Chagas heart disease may be attributed to the following: more extensive myocardial damage, as compared with other etiologies, such as ischemic, hypertensive, or idiopathic[7]; social deprivation[8]; myocardial perfusion defects associated with autonomic dysfunctions[9]; the severity of ventricular arrhythmias[10]; and higher incidence of right ventricular dysfunction[11].

Rassi Jr. et al[12] followed up 424 patients during 7.9 years, 130 of whom died, and identified six independent prognostic factors of mortality in patients with Chagas heart disease[12]. Each prognostic factor was assigned a score according to its level of risk: NYHA functional class III or IV (5 points), evidence of cardiomegaly on chest X-ray (5 points), left ventricular dysfunction on echocardiogram (3 points), nonsustained ventricular tachycardia on 24-hour Holter monitoring (3 points), low QRS voltage on electrocardiogram (2 points), and male gender (2 points). Subsequently, three groups were defined: patients at low risk (0 to 6 points), intermediate risk (7 to 11 points), and high risk (12 to 20). Ten-year mortality rates among these groups were 10%, 44%, and 84%, respectively. In the validation group, these rates were 9%, 37%, and 85%, respectively.

Rassi Jr. et al.[13] performed a systematic literature review regarding predictors of mortality in patients with Chagas heart disease. By analyzing clinical trials published between 1985 and 2006, these authors found that impaired left ventricular function,

NYHA functional class III or IV, cardiomegaly, and nonsustained ventricular tachycardia are associated with poor prognosis in patients with chronic Chagas disease. Our results support the hypothesis that patients with Chagas disease and ventricular dysfunction have poor prognosis. Findings such as hyponatremia, impaired ejection fraction, elevated serum TNF-α, plus lower systolic BP and heart rate in patients with Chagas heart disease, compared with other etiologies, suggest that these patients are more severely ill, since all these predictors are known in the medical literature as indicative of worse outcome.

The difference - and we believe that this is the major contribution of this study - is that these results refer to acutely decompensated patients, something that had not yet been demonstrated. Large clinical trials of therapies for decompensated heart failure or even registration trials are usually conducted in countries with low incidence of Chagas cardiomyopathy, thus precluding consistent analyses of clinical outcomes of this disease. The remaining studies investigating Chagas heart disease as a prognostic factor of heart failure were performed with outpatients, making it impossible to infer that patients with Chagas disease also become more severely ill when decompensated, and not only during long-term outpatient follow-up.

Conclusion

Among patients with decompensated heart failure and similar clinical conditions, those with Chagas disease had worse prognoses, probably because of a higher degree of cardiac impairment (reduced ejection fraction), greater hemodynamic instability (lower systolic blood pressure and heart rate), increased activation of the rennin-angiotensin system (lower serum sodium), and increased levels of cytokines (TNF-α).

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any post-graduation program.

References

1. Yancy CW, Lopatin M, Stevenson LW, Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the acute decompensated heart failure national registry (ADHERE) Database. J Am Coll Cardiol. 2006; 47: 76-84.
2. Bestetti RB, Muccillo G. Clinical course of Chagas' heart disease: a comparison with dilated cardiomyopathy. Int J Cardiol. 1997; 60: 187-93.
3. Mady C, Cardoso RH, Barreto ACP, Da Luz PL, Bellotti G, Pileggi F. Survival and predictors of survival in patients with congestive heart failure due to Chagas' cardiomyopathy. Circulation. 1994; 90: 3098-102.
4. Freitas HF, Chizzola PR, Paes AT, Lima AC, Mansur AJ. Risk stratification in a Brazilian hospital-based cohort of 1220 outpatients with heart failure: role of Chagas' heart disease. Int J Cardiol. 2005; 102 (2): 239-47.
5. Rassi S, Barretto ACP, Porto CC, Pereira CR, Calaça BW, Rassi DC. Sobrevida e fatores prognósticos na insuficiência cardíaca sistólica com início recente dos sintomas. Arq Bras Cardiol. 2005; 4: 309-13.
6. Nunes MCP, Rocha MOC, Ribeiro ALP, Colosimo EA, Rezende RA, Carmo GA, et al. Right ventricular dysfunction is an independent predictor of survival in patients with dilated chronic Chagas' cardiomyopathy. Int J Cardiol. 2007, doi:10.1016/j.ijcard.2007.06.012.
7. Higuchi ML, de Morais CF, Pereira-Barreto AC, Lopes EA, Stolg N, Bellotti G, et al. The role of active myocarditis in the development of heart failure in chronic Chagas' disease: a study on endomyocardial biopsies. Clin Cardiol. 1987; 10: 665-70.
8. Lopes CBC. Influência de fatores socioeconômicos no prognóstico da insuficiência cardíaca. São Paulo: Ed USP; 2002.
9. Simões MV, Pintya AO, Bromberg-Marin G, Sarabanda AV, Antloga CM, Pazin-Filho A, et al. Relation of regional sympathetic denervation and myocardial perfusion disturbance to wall motion impairment in Chagas' cardiomyopathy. Am J Cardiol. 2000; 86: 975-81.
10. Martinelli M, De Siqueira SF, Moreira H, Fagundes A, Pedrosa A, Nishioka SD. Probability of occurrence of life-threatening ventricular arrhythmias in Chagas' disease versus non-Chagas' disease. Pacing Clin Electrophysiol. 2000; 23: 1944-6.
11. Rodriguez-Salas LA, Klein E, Acquatella H, Catalioti F, Dvalos VV, Gomez-Mancebo JR, et al. Echocardiographic and clinical predictors of mortality in chronic Chagas' disease. Echocardiography. 1998; 15: 271-8.
12. Rassi Jr A, Rassi A, Little WC, Xavier SS, Rassi SG, Rassi AG, et al. Development and validation of a risk score for predicting death in Chagas´ heart disease. N Engl J Med. 2006; 355: 799-808.
13. Rassi Jr A, Rassi A, Rassi SG. Predictors of mortality in chronic chagas disease: a systematic review of observational studies. Circulation. 2007; 115: 1101-8.