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CME

# Influence of Etiology on Heart Failure With Preserved Systolic Function Mortality in a Population With High Prevalence of Chagas Cardiomyopathy

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## ABSTRACT

### Background
Heart failure with preserved systolic function is a clinical syndrome with the same signs and symptoms of classic heart failure. Chagas disease is a major cause of heart failure in Latin America, associated with dilated cardiomyopathy and progressive deterioration of systolic function. There are no previous assessment studies of patients with heart failure and preserved systolic function in an endemic area in which Chagas disease is the leading cause of heart failure.

### Objective
The aim of this study was to compare clinical characteristics and evolution of heart failure in patients with systolic dysfunction and with preserved systolic function in a population with high prevalence of Chagas disease.

### Methods
A prospective assessment was performed in patients with clinical diagnosis of heart failure admitted to a referral center in Salvador, Bahia (Brazil). Left ventricular ejection fraction > 45% by echocardiogram was considered as preserved systolic function. A one year follow-up was conducted through telephone or personal interview at the heart failure clinic.

### Results
Three hundred and eighty three patients were included in this study over a period of 16 months; 52.5% of patients were male and average age was 54.2 years. Systolic function was preserved in 138 patients (36%). Chagas disease was the main etiology of both types of heart failure (45.3% with systolic dysfunction and 44.2% with preserved systolic function). One year follow-up was completed by 93.5% (358) of patients. Patients with Chagas disease and preserved systolic function had lower mortality than patients with systolic dysfunction (10% vs. 23.6%, p = 0.039). In patients without Chagas disease and preserved systolic function, mortality was similar to that of those with systolic dysfunction (10.4% vs. 15.8%, p = 0.307).

### Conclusions
Preserved systolic function was very common in our population. Chagas disease is the leading cause of heart failure irrespective of left ventricular ejection fraction. Patients with Chagas disease and preserved systolic function have a better prognosis than those with systolic dysfunction, probably because they are in the initial phase of cardiac impairment.

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**Key words >** Heart failure, Diastolic heart failure; Chagas disease

**Abbreviations >**

| | | | |
|---|---|---|---|
| **HFPSF** | Heart Failure with Preserved Systolic Function | **LVEF** | Left Ventricle Ejection Fraction |

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## INTRODUCTION

Heart failure with preserved systolic function (HFPSF), also called diastolic heart failure, is a clinical syndrome that has the same signs and symptoms of classic heart failure associated with a normal left ventricular ejection fraction (LVEF). There is no consensus, but most studies consider normal LVEF when it is > 40-50%. The prevalence of this syndrome is approximately 50% in heart failure epidemiological studies, and it is more frequent in women, older patients and those with hypertension. (1-3)

Most studies agree that HFPSF is associated with hospital admission rates similar to systolic heart failure, but they disagree regarding mortality rates. Some studies have suggested that HFPSF has lower mortality in medium and long-term follow-up, but most recent investigations have shown a similar survival curve between the two types of heart failure. (4, 5)

Chagas disease is an important cause of heart failure in Latin America and is associated with dilated cardiomyopathy and progressive loss of systolic function. (6) No previous studies have evaluated patients with HFPSF from an endemic Chagas disease area, where it represents the main etiology of heart failure. This study aims to compare the clinical features and evolution of patients with heart failure with systolic dysfunction with those without systolic dysfunction from an endemic Chagas disease area.

## METHODS

Patients referred to a reference clinic for heart failure in Salvador-Bahia (Brazil) were prospectively evaluated during a 16-month period. Consecutive patients with diagnosis of heart failure and LVEF echocardiographic evaluation, and at least one telephone number for contact were included in the study. As the study was exclusively observational, there were no ethical issues and all patients signed the informed consent. The investigation was performed following the principles outlined in the Declaration of Helsinki. (7)

Major causes of heart disease were evaluated based on the following recommendations: Chagas cardiomyopathy with at least, two positive serological tests; ischemic cardiomyopathy based on history of classical chest pain, previous myocardial infarction or percutaneous coronary intervention, surgical revascularization, myocardial ischemia in functional tests or obstructive coronary lesions in angiography; hypertensive cardiomyopathy with previous history of uncontrolled hypertension, therapy with several antihypertensive drugs or presence of target organ damage. When ischemic and hypertensive etiologies were associated, the former was considered for the study data. Other cardiomyopathy etiologies (valvular, hypertrophic, restrictive, alcoholic, peripartum and viral) were diagnosed based on individual patient data. Dilated cardiomyopathy was considered by exclusion.

Patients were divided into two groups according to LVEF. The first group included patients with moderate to echocardiographic evidence of severe systolic dysfunction, defined by LVEF < 45%. The second group included patients with preserved systolic function defined by LVEF ≥ 45%. The LVEF cut-off point of 45% was the same used in other publications for definition of HFPSF. (8)

One year follow-up was obtained through phone contact or personal interview at the cardiac failure clinic.

### Statistical analysis

Variables with normal distribution were expressed as mean ± standard deviation and those with non-normal distribution as median. Data were compared using Student´s t test or the Mann-Whitney test, as appropriate. Categorical variables were described as proportions and compared with the chi-square test or Fisher`s exact test. Kaplan-Meier survival curves were built and compared with the log rank test. A two-tailed p value <0.05 was considered statistically significant. The Statistical Package for Social Sciences (SPSS), version 9.0 for Windows (SPSS, Chicago, IL) was used for statistical analyses.

## RESULTS

During the 16-month follow up, 533 new patients were admitted, 150 of whom did not fulfill heart failure criteria and were excluded. Thus, 383 patients were included in the analysis.

Ninety-three percent of patients (358) completed follow-up through a phone call one year after evaluation in the outpatient clinic.

Baseline characteristics of all included patients are described in Tables 1 and 2. Preserved systolic function was observed in 138 patients (36%). Most of these patients were women and had systolic hypertension (Table 2). The main etiology for both types of heart failure was Chagas Disease. However, in patients with HFPSF, hypertension was more prevalent than idiopathic etiology (Table 2).

Overall one-year mortality rate (for both groups) was 16.1%. Patients with HFPSF had lower mortality than patients with systolic dysfunction (10.2% vs. 19.3%; p=0.020). Mortality according to etiology differed among groups: patients with Chagas disease and HFPSF had lower mortality compared to those with systolic dysfunction (10% vs. 23.6%; p=0.039). In pa-

**Table 1.** Baseline patient characteristics

| | Patients (n=381) |
|---|---|
| Male (%) | 52.5 |
| Age at admission – years (Mean ± SD) | 54.2 ± 13.5 |
| Non-Caucasian race (%) | 82.6 |
| Years of formal education (median) | 4.0 |
| Hypertension (%) | 50.9 |
| Diabetes (%) | 10.7 |
| Stroke (%) | 15.8 |
| NYHA functional class IV at evaluation (%) | 47.7 |
| NYHA functional class III-IV at admission (%) | 17.0 |
| Etiology (%) | |
| Chagas disease | 45.1 |
| Hypertensive | 21.3 |
| Idiopathic | 11.5 |
| Ischemic | 10.8 |
| Others | 11.3 |

SD = standard deviation / NYHA = New York Heart Association

**Table 2.** Patient characteristics according to systolic function at admission (n=381).

| | Impaired n= 245 (64%) | Preserved n=138 (36%) | p Value |
|---|---|---|---|
| Female (%) | 42.9 | 55.8 | 0.019 |
| Age at admission – years (Mean ± SD) | 54.4 ± 13.0 | 52.2 ± 15.3 | 0.156 |
| Caucasian race (%) | 18.6 | 15.2 | 0.482 |
| Years of formal education ≤ 4 years (%) | 65.5 | 58.9 | 0.251 |
| Hypertension (%) | 47.3 | 57.4 | 0.069 |
| Diabetes (%) | 11.0 | 10.2 | 0.865 |
| Stroke (%) | 16.0 | 15.4 | 1.000 |
| NYHA functional class III-IV at admission (%) | 18.0 | 15.2 | 0.571 |
| Etiology (%) | | | |
| Chagas disease | 45.3 | 44.2 | 0.915 |
| Hypertensive | 17.6 | 27.5 | 0.027 |
| Idiopathic | 15.1 | 5.1 | 0.003 |
| Ischemic | 12.7 | 7.2 | 0.122 |
| Others | 9.3 | 16.0 | |
| One-year follow-up (%) | 93.5 | 93.5 | 1.000 |

SD = standard deviation / NYHA = New York Heart Association

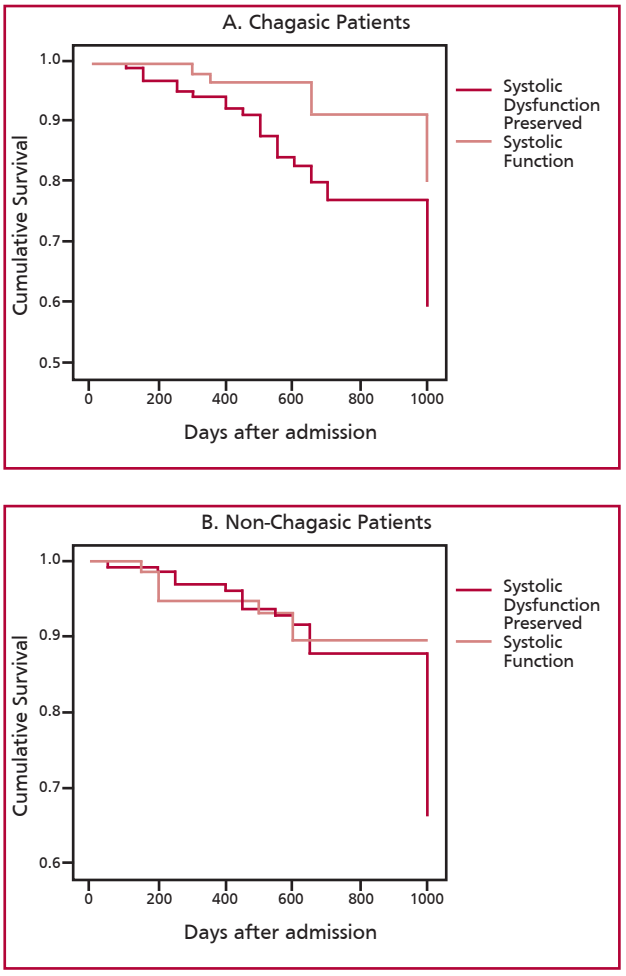


**Fig. 1.** Heart failure with systolic dysfunction versus preserved systolic function survival curves in chagasic **(A)** and non-chagasic patients **(B).**

tients without Chagas disease but with HFPSF, the mortality rate was similar to that of patients with systolic dysfunction (10.4% vs. 15.8%; p=0.307). Survival curves are shown in Figure 1.

## DISCUSSION

In our study, preserved systolic function had a higher prevalence, and was found in 36% of patients with heart failure. The main clinical features in these patients were similar to the ones found in previous studies: female gender, (9-13) systolic hypertension (11) and less treatment with moderate to high dose angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs). (10, 13) Masoudi et al. showed that among elderly patients with heart failure, preserved systolic function was strongly associated with female gender, independently of other clinical and demographic variables. (12) This difference is probably related to the loss of the protective effects of estrogens in postmenopausal women, which makes the female heart more susceptible to the hypertrophic stimuli of hypertension and obesity. (14)

Readmission rates (11, 15) and quality of life (16) at medium and long-term follow-up have been found to be similar to the ones reported for heart failure with systolic dysfunction. However, the prognosis of HFPSF is not well defined. Some authors have reported that patients with HFPSF have a higher mortality rate compared to the overall population, but better prognosis when compared to patients with heart failure and systolic dysfunction. (11, 17-19) Others have found similar survival rates in the two groups (10, 15, 20) or even a higher mortality in HFPSF patients. (21) Solomon et al. found that all-cause and cardiovascular mortality declined with increasing LVEF up to a threshold of 45%; and then the risk of death was maintained relatively stable despite increasing LVEF. (17) Owan et al. showed that the prevalence of HFPSF has been increasing since 1987 and while the survival of patients with systolic dysfunction has improved over time, the mortality rate for HFPSF has remained unchanged. (19) This emphasizes the importance of studies on the pathophysiology of HFPSF in order to develop novel therapeutic strategies to improve its prognosis.

The one-year mortality rate in non-chagasic patients with and without HFPSF was lower than in other studies on non-endemic Chagas disease areas. Bhatia et al. found a mortality rate of 22% at one-year follow-up in patients with LVEF > 50% versus 26% in those with LVEF < 40%. (20) Varela-Roman et al. reported one-year mortality rates of 17.2% and 20.3%

in heart failure patients with preserved systolic function and with systolic dysfunction, respectively. (10, 22) This difference is probably due to population features, as most studies included hospitalized patients with decompensated heart failure and we evaluated ambulatory outpatients, most of them with stable cardiac disease.

Of note, Chagas disease was the main etiology in both types of heart failure in our population. Previous studies have suggested that in patients with Chagas disease, diastolic dysfunction can precede systolic impairment.(23) Patients with preserved systolic function can present with electrocardiographic disorders and decreased maximal functional capacity. (24) These results suggest that patients with Chagas disease and no ejection fraction impairment are in the initial phase of cardiac disease and, according to our findings, should have a better prognosis when compared with those with systolic dysfunction. Moreover, many authors have demonstrated that LVEF is one of the most important factors that decrease the survival of patients with Chagas cardiomyopathy. (25, 26)

The influence of etiology on the prognosis of patients with HFPSF is not clear. Hernandez et al. evaluated 95 patients with HFPSF after a mean follow-up period of 53 months and found higher rates of hospital admission, overall mortality, mortality due to heart failure and sudden death in patients who had ischemic versus non-ischemic etiology. (27) Some authors have described a worse prognosis of systolic and overall heart failure in patients with Chagas disease when compared to other etiologies. (28, 29) However, no previous studies have investigated the effect of chagasic etiology on the prognosis of patients with HFPSF.

## CONCLUSIONS

We conclude that preserved systolic function was commonly found in our population, especially in women and hypertensive patients. Chagas disease was the main etiology of heart failure independently of LVEF. Patients with Chagas disease and HFPSF have a better prognosis than those with systolic dysfunction, probably because they are in the initial phases of cardiac impairment. In non-chagasic patients, the one-year mortality rates were similar for both types of heart failure. Further research is necessary to explore the effect of etiology on the prognosis of HFPSF and develop therapeutic strategies to improve the survival curve of these patients.

## RESUMEN

### Influencia de la etiología sobre la mortalidad en la insuficiencia cardíaca con función sistólica preservada en una población con alta prevalencia de cardiopatía chagásica


**Introducción**
En diversas publicaciones de los últimos años se señala una La insuficiencia cardíaca con función sistólica preservada es un síndrome clínico con los mismos signos y síntomas de la insuficiencia cardíaca clásica.

**Objetivo**
Comparar las características clínicas y la evolución de la insuficiencia cardíaca (IC) en pacientes con disfunción sistólica y con función sistólica preservada (FSP) en una población con alta prevalencia de enfermedad de Chagas.

**Materiales y métodos**
Se realizó una evaluación prospectiva de los pacientes con diagnóstico clínico de IC que ingresaron a un centro de referencia en Salvador, Bahía (Brasil). Se consideró FSP a una fracción de eyección del ventrículo izquierdo (FEVI) mayor del 45% por ecocardiograma. Se realizó seguimiento al año a través de contacto telefónico o entrevista personal en el consultorio de insuficiencia cardíaca.

**Resultados**
Se incluyeron 383 durante un período de 16 meses; el 52,5% eran hombres y la edad media fue 54,2 años. La función sistólica estuvo preservada en 138 pacientes (36%). La enfermedad de Chagas fue la principal etiología de ambos tipos de IC (45.3% con disfunción sistólica y 44,2% con FSP). El 93.5% (358) de los pacientes completaron un año de seguimiento. Los pacientes con enfermedad de Chagas y FSP presentaron menor mortalidad que los pacientes con disfunción sistólica (10% vs. 23,6%; p=0,039). En los pacientes sin enfermedad de Chagas y FSP, la mortalidad fue similar a la de aquellos con disfunción sistólica (10,4% vs.15,8%; p = 0,307).

**Conclusión**
La FSP fue muy frecuente en nuestra población. La enfermedad de Chagas es la principal etiología de insuficiencia cardíaca independientemente de la FEVI. Los pacientes con enfermedad de Chagas y FSP tienen mejor pronóstico que aquellos con disfunción sistólica, probablemente porque se encuentran en la fase inicial del compromiso cardíaco.



**Palabras clave >** Insuficiencia cardíaca, insuficiencia cardíaca diastólica, enfermedad de Chagas


**Conflicts of interest**
None declared.

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