**β-Blocker Therapy and Mortality of Patients With Chagas Cardiomyopathy**

**A Subanalysis of the REMADHE Prospective Trial**

Victor S. Issa, MD; Alexandre F. Amaral, MS; Fátima D. Cruz, NR; Silvia M.A. Ferreira, MD; Guilherme V. Guimarães, MD; Paulo R. Chizzola, MD; Germano E.C. Souza, MD; Fernando Bacal, MD; Edimar A. Bocchi, MD

**Background**—Peculiar aspects of Chagas cardiomyopathy raise concerns about efficacy and safety of sympathetic blockade. We studied the influence of β-blockers in patients with Chagas cardiomyopathy.

**Methods and Results**—We examined REMADHE trial and grouped patients according to etiology (Chagas versus non-Chagas) and β-blocker therapy. Primary end point was all-cause mortality or heart transplantation. Altogether 456 patients were studied; 27 (5.9%) were submitted to heart transplantation and 202 (44.3%) died. Chagas etiology was present in 68 (14.9%) patients; they had lower body mass index (24.1±4.1 versus 26.3±5.1, *P*=0.001), smaller end-diastolic left ventricle diameter (6.7±1.0 mm versus 7.0±0.9 mm, *P*=0.001), smaller proportion of β-blocker therapy (35.8% versus 68%, *P*<0.001), and higher proportion of spironolactone therapy (74.6% versus 57.8%, *P*=0.003). Twenty-four (35.8%) patients with Chagas disease were under β-blocker therapy and had lower serum sodium (136.6±3.1 versus 138.4±3.1 mEq/L, *P*=0.05) and lower body mass index (22.5±3.3 versus 24.9±4.3, *P*=0.03) compared with those who received β-blockers. Survival was lower in patients with Chagas heart disease compared with patients with other etiologies. When only patients under β-blockers were considered, the survival of patients with Chagas disease was similar to that of other etiologies. The survival of patients with β-blockers was higher than that of patients without β-blockers. In Cox regression model, left ventricle end-diastolic diameter (hazard ratio, 1.78; CI, 1.15 to 2.76; *P*=0.009) and β-blockers (hazard ratio, 0.37; CI, 0.14 to 0.97; *P*=0.044) were associated with better survival.

**Conclusions**—Our study suggests that β-blockers may have beneficial effects on survival of patients with heart failure and Chagas heart disease and warrants further investigation in a prospective, randomized trial.

**Clinical Trial Registration**—clinicaltrials.gov. Identifier: NCT00505050.

(Circ Heart Fail. 2010;3:82-88.)

**Key Words:** heart failure ■ cardiomyopathy mortality ■ death, sudden ■ receptors, adrenergic, beta

A hundred years after the description of the first case of human infection by *Trypanosoma cruzi*, Chagas disease still plays a major epidemiological role in Latin America. Recently, the disease has acquired worldwide relevance, as new cases have been described in North America and Europe. According to an estimation in 1992, 370 000 people had *T. cruzi* infection in the United States and 75 000 of those had chronic Chagas cardiomyopathy. Chagas heart disease has particular pathophysiological aspects that distinguish it from other etiologies, mainly the persistence of a chronic myocardial inflammatory process in which the persistence of the parasite is thought to play an important role. Chagas heart disease has been associated with worse prognosis as compared with other etiologies.

### Clinical Perspective on p 88

Currently, the treatment of Chagas cardiomyopathy is similar to that used in patients with heart failure and other etiologies and is greatly based on the inhibition of renin-angiotensin-aldosterone and sympathetic systems. No etiology-directed treatment has been approved so far. However, peculiar aspects of the pathology and pathophysiology of Chagas cardiomyopathy raise concerns about efficacy and safety of these therapeutic options in these circumstances.

Specifically regarding the sympathetic nervous blockade, authors have reported lower levels of norepinephrine, increased parasympathetic tonus (decreasing heart rate), decreased vagal modulation, and bradycardia in patients with Chagas disease. Although some reports indicate that patients with Chagas may benefit from β-blocker treat-
ment,14–16 the inclusion of a small number of patients, retrospective analysis, presence of selection bias, and use of surrogate end points prevents a final conclusion. Therefore, we sought to study the influence of β-blocker therapy in patients with Chagas cardiomyopathy prospectively followed in ambulatory care setting.

Patients and Methods

Patients
We examined the patients included in the REMADHE trial; since its publication the trial database has been reviewed and extended for an ongoing analysis of quality of life. For the purpose of current study, patients were grouped according to etiology (Chagas versus non-Chagas groups) and presence of β-blocker therapy. Patients with Chagas disease were stratified according to the clinical score published by Bassi et al.17

REMADHE is a prospective, randomized, single-center open parallel trial controlled by nonintervention simple randomization and designed to compare a disease management program versus control in patients with chronic heart failure. Patients enrolled in the study were under ambulatory care in a tertiary referral center and were followed by a cardiologist with experience in heart failure. Patients were aged 18 years or older with irreversible chronic heart failure of at least 6-month duration. Exclusion criteria included patients’ inability to attend educational sessions and researchers’ inability to monitor patients because of the patients’ lack of transportation, social, or communication barriers; myocardial infarction or unstable angina within 6 months before randomization; cardiac surgery or angioplasty within 6 months before randomization; hospitalized patients or recently discharged patients; any severe systemic disease that could impair expected survival; procedures that could influence follow-up; and pregnancy or childbearing potential. The study protocol was approved by institutional ethics committee, and all patients or proxies provided written informed consent. The details of the rationale and design of REMADHE trial have been published elsewhere.18

Definitions
The diagnosis of Chagas disease was based on epidemiological information along with serological tests (indirect immunofluorescence, passive hemagglutination, and immunoenzymatic assay) positive for infection with T cruzi.19 Patients with an alternative diagnosis or a mixed etiology for the cardiomyopathy were not included in Chagas group. The diagnosis of heart failure was based on Boston criteria; all patients were submitted to transthoracic echocardiography at study entry; measurement of heart dimensions and indexes followed guidelines.20 Left ventricle ejection fraction was based on Simpson’ method; other measures included left ventricle end-diastolic volume and diameter. All patients received standard therapy for the treatment of heart failure that included both nonpharmacological and pharmacological therapies, according to current guidelines.21,22 In patients with Chagas cardiomyopathy, the prescription of β-blocker therapy is considered as a IIa indication according to Brazilian guidelines,22 irrespective to the disease severity; in REMADHE trial, the indication of β-blocker therapy in patients with Chagas disease was according to the clinician’s discretion; carvedilol was the β-blocker used in 89.6% of patients, followed by metoprolol (6.4%) and bisoprolol (4.0%).

End Point
The primary end point of the study was all-cause mortality or heart transplantation in UNOS I condition, which was obtained during the follow-up, either from the trial database, from review of medical records by matching the identification number of the patients with the National Death Registry, or by telephone contact with family members. In addition, time to first unplanned hospitalization was studied.

Statistical Analysis
Continuous variables are expressed as mean±SE, and categorical variables are expressed as percentages. For effects of group comparison the t test was used for normal distribution and Mann–Whitney test was used to compare variables without normal distribution. For categorical variables, χ² test or the Fisher exact test was applied. Survival was estimated by the Kaplan–Meier method, and differences in survival between groups were assessed by the log-rank test. Cox proportional-hazards models were used to determine the influence of the variables on patients’ survival. In the analysis, data on patients were censored at the time of cardiac transplantation. All analyses and graphs were performed with SPSS statistical software version 13.0 and Graphpad Prism software version 5.0.

Results
A total of 456 patients were enrolled. The first inclusion occurred in April 1999, and patients were followed until December 2000 with a mean follow-up of 38.5 days. Chagas cardiomyopathy was present in 68 (14.9%) patients; risk categorization of patients with Chagas disease22 indicated that they were at high risk (mean score, 13.4±4.4). Baseline characteristics of the patients are described in Table 1.

When compared with patients without Chagas disease, patients with Chagas disease had lower heart rate (71.2±1.7 bpm versus 79.1±1.8 bpm, P=0.03), lower mean blood pressure (86.6±3.0 mm Hg versus 92.1±2.1 mm Hg, P=0.04), lower prevalence of atrial fibrillation (11.5% versus 18%, P=0.001), higher prevalence of pacemakers (14.7% versus 4.2%, P=0.001), lower body mass index (24.1±0.5 versus 26.3±0.2, P=0.001), smaller end-diastolic left ventricle diameter (6.7±0.08 mm versus 7.0±0.05 mm, P=0.001), a smaller proportion of patients under β-blocker therapy (35.8% versus 68%, P<0.001), and a higher proportion of patients under aldosterone antagonist therapy (74.6% versus 57.8%, P=0.003). When left ventricle diameter was corrected for body surface, no difference between groups was found (4.0±0.06 mm/m² versus 4.0±0.07 mm/m², P=0.67).

β-Blocker Therapy in Patients With Chagas Disease
Twenty-four patients with Chagas disease (35.8%) were under β-blocker therapy, and when compared with patients who were not under β-blocker therapy, they had lower serum sodium level (136.6±6.0 mEq/L versus 138.4±4.0 mEq/L, P=0.05) and lower body mass index (22.5±0.7 versus 24.9±0.7, P=0.03). Clinical characteristics of patients with Chagas disease according to the use of β-blockers are shown in Table 2.

Survival Analysis and Unplanned Hospital Admissions
Altogether 202 patients (44.3%) died and 27 patients (5.9%) were submitted to heart transplant. The end point death or heart transplant occurred in 49 patients with Chagas disease (72%) and in 180 patients with other etiologies (45.6%).
Among patients with Chagas disease, death or heart transplant occurred in 11 patients under \( \beta \)-blocker therapy (45.8%) and in 34 patients (79.1%) not under \( \beta \)-blocker therapy.

Survival rate was lower in patients with Chagas heart disease when compared with other etiologies (Figure 1); when survival analysis was stratified according to \( \beta \)-blocker therapy, the difference in the survival rate between the groups persisted among patients not under \( \beta \)-blocker therapy (Figure 2). However, when only patients under \( \beta \)-blocker therapy were considered, the survival of patients with Chagas heart disease was similar to that of patients with other etiologies (Figure 3).

In addition, we analyzed the survival of patients with Chagas heart disease according to the \( \beta \)-blocker therapy. We found that the survival rate of patients under \( \beta \)-blockers was higher than that of patients not under \( \beta \)-blockers (Figure 4). The influence of \( \beta \)-blockade on mortality of patients with Chagas heart disease was further evaluated by Cox proportional-hazards regression model that included etiology, left ventricle ejection fraction, left ventricle end-diastolic diameter, serum creatinine, serum sodium, functional status, and \( \beta \)-blocker therapy; both left ventricle end-diastolic diameter (hazard ratio, 1.78; CI, 1.15 to 2.76; \( P = 0.009 \)) and \( \beta \)-blocker therapy (hazard ratio, 0.37; CI, 0.14 to 0.97; \( P = 0.044 \)) were independently associated with survival.

The survival free from unplanned hospital admissions was lower in patients with Chagas disease when compared with other etiologies. No difference was found regarding unplanned hospital admissions between patients with Chagas disease who were under \( \beta \)-blocker therapy and those who were not.

### Discussion

This study found that in the presence of a \( \beta \)-blocker agent, the worst prognosis of Chagas heart disease was attenuated, and survival was statistically similar to that of patients with other etiologies. Moreover, the survival of patients with Chagas heart disease who received \( \beta \)-blocker therapy was better than that of patients with Chagas heart disease who did not receive \( \beta \)-blocker therapy. In addition, findings of this study indicate that Chagas heart disease carries a poor prognosis when

### Table 1. Baseline Characteristics of Patients According to Etiology

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Chagas</th>
<th>Other Etiologies</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>456</td>
<td>68 (14.9)</td>
<td>388 (85.1)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>50.2±0.5</td>
<td>50.4±1.2</td>
<td>50.2±0.6</td>
<td>0.91</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>135 (29.6)</td>
<td>27 (39.7)</td>
<td>108 (27.8)</td>
<td>0.16</td>
</tr>
<tr>
<td>Male</td>
<td>321 (70.4)</td>
<td>41 (60.3)</td>
<td>280 (72.2)</td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>76.8±1.4</td>
<td>71.2±1.7</td>
<td>79.1±1.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>91.2±1.8</td>
<td>86.6±0.3</td>
<td>92.1±2.1</td>
<td>0.04</td>
</tr>
<tr>
<td>NYHA I–II*</td>
<td>157 (58.1)</td>
<td>26 (59)</td>
<td>131 (58)</td>
<td>0.20</td>
</tr>
<tr>
<td>NYHA III–IV*</td>
<td>113 (41.9)</td>
<td>18 (41)</td>
<td>95 (42)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>74 (16.3)</td>
<td>8 (11.5)</td>
<td>70 (18)</td>
<td>0.001</td>
</tr>
<tr>
<td>Artificial pacemaker</td>
<td>33 (7.2)</td>
<td>10 (14.7)</td>
<td>16 (4.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>NSVT/24 h</td>
<td>28.4±9.5</td>
<td>42.4±1.7</td>
<td>21.4±12.2</td>
<td>0.21</td>
</tr>
<tr>
<td>Body mass index</td>
<td>25.9±5.1</td>
<td>24.1±0.5</td>
<td>26.3±2.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Etiology ischemic</td>
<td>115 (25.3)</td>
<td>…</td>
<td>…</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>103 (22.6)</td>
<td>…</td>
<td>…</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>85 (18.6)</td>
<td>…</td>
<td>…</td>
<td></td>
</tr>
<tr>
<td>Chagas disease</td>
<td>68 (14.9)</td>
<td>…</td>
<td>…</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>85 (18.6)</td>
<td>…</td>
<td>…</td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>34.7±0.01</td>
<td>35.6±0.01</td>
<td>34.6±0.01</td>
<td>0.48</td>
</tr>
<tr>
<td>LV size, mm/m²</td>
<td>4.0±0.07</td>
<td>4.0±0.06</td>
<td>4.0±0.07</td>
<td>0.67</td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>138.0±0.1</td>
<td>137.6±0.4</td>
<td>138.1±0.2</td>
<td>0.24</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.8±0.07</td>
<td>13.7±0.2</td>
<td>13.8±0.1</td>
<td>0.24</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.3±0.03</td>
<td>1.2±0.05</td>
<td>1.3±0.03</td>
<td>0.16</td>
</tr>
<tr>
<td>Medication†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \beta )-blocker</td>
<td>287 (68)</td>
<td>24 (35.8)</td>
<td>263 (91.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACEI/AT₂ inhibitor</td>
<td>405 (95.9)</td>
<td>67 (98.5)</td>
<td>338 (95.2)</td>
<td>0.14</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>242 (57.8)</td>
<td>50 (74.6)</td>
<td>192 (54.5)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean±SE. LV indicates left ventricle; ACEI, angiotensin-converting enzyme inhibitor; AT₂, angiotensin II; NSVT, nonsustained ventricular tachycardia.

*Information available in 270 patients: 44 with Chagas disease and 226 with other etiologies.

†Information available in 422 patients: 67 with Chagas and 355 with other etiologies.
compared with other etiologies—patients with Chagas cardiomyopathy had higher rates of mortality as well as higher rate of unplanned hospital admission, despite the fact that patients with Chagas disease had similar age and left ventricle function and smaller left ventricle size. The prescription of the recommended drug therapy differed between patients with Chagas heart disease when compared with other etiologies, namely, patients with Chagas disease were less likely to receive a β-blocker agent and more likely to receive spironolactone.

Some distinctive clinical aspects of Chagas cardiomyopathy have been attributed to be responsible for the excessive mortality found in patients with Chagas disease when compared with other etiologies, such as the presence of a more intense inflammatory process, different degrees of bundle branch block, increased rate of atrial and ventricular arrhythmias, varying degrees of atrioventricular blocks, biventricular dysfunction, apical left ventricular aneurysm and thrombus formation, and higher incidence of sudden death. These distinctive characteristics have been pointed as putative reasons why β-blockers could not be as effective in Chagas as in other etiologies. However, there are also similarities between Chagas cardiomyopathy pathophysiology and the mechanisms described in heart failure syndrome in general. Specifically, authors have reported that intracardiac sympathetic overactivity seems to occur in patients with Chagas disease and chronic heart failure, and that catecholamines levels are increased in patients with Chagas disease and correlated with disease severity, suggesting that the sympathetic activity play a significant role in the disease progression. In resonance with this rationale, our results do support the use of β-blockers therapy in patients with Chagas cardiomyopathy. Our findings are also in accord with results reported by other authors. Data derived from observational studies indicate that the lack of a β-blocker agent is independently associated with all-cause mortality in patients with Chagas disease. Recently, a double-blind, placebo-controlled trial found that the β-blockade in patients with Chagas disease was safe, hemodynamically well tolerated, not associated with bradycardia, and associated with a trend toward an increase in left ventricle ejection fraction. However, these data are based on a retrospective analysis, small number of patients, and surrogate end points. This study suggests that β-blockers have beneficial effects on survival of patients with heart failure and Chagas heart disease.

In addition, the rate of unplanned hospital admission was higher among patients with Chagas disease when compared with other etiologies; this is an original finding not previously reported and adds to the recognition of a condition of high morbidity. In our study, the use of β-blockers in patients with Chagas disease did not modify the rate of unplanned hospital admission. Arguably, this finding could be related to how the β-blockade influence mechanisms of disease progression—namely, the occurrence of sudden death versus the progression of ventricular dysfunction. Taken together our results warrant further investigation in this area.

It is noteworthy that in our study, the left ventricle ejection fraction was similar in both etiologic groups; moreover,
patients with Chagas disease had smaller left ventricle end-diastolic diameter; that is to say that even in the face of similar left ventricular function and remodeling, the disease still carries worst prognosis. This finding is in resonance with other reports and could be related to specific physiopathological aspects of the disease, such as right ventricle dysfunction, myocardial inflammation, persistence of parasites, fibrosis, ventricular arrhythmia, and systemic conditions. Interestingly, patients with Chagas disease had lower body mass index and lower serum sodium, suggesting that this group could have a more pronounced systemic effect of the disease and more intense inflammatory and neurohumoral activation, which could also contribute to the excessive mortality found in this study.

The authors have reported a lower rate of use of $\beta$-blockers in patients with Chagas disease, mainly due to arterial hypotension and bradycardia. Consistently, in our study, the frequency of $\beta$-blocker use was lower in patients with Chagas disease, suggesting the existence of medical circumstances that could raise safety concerns in clinicians when prescribing this class of medication. The increased rate of use of spironolactone likely represents an attempt to counterbalance this limitation perceived by physicians in face of a group of patients with a poor prognosis. However, our results challenge this hesitant behavior of clinicians and warrant the use of $\beta$-blockers therapy in patients with Chagas cardiomyopathy based on a significant beneficial impact on prognosis.

**Limitations**

This study contains some limitations that should be acknowledged. First, individuals enrolled in the study were not randomized for $\beta$-blocker therapy or placebo, and physicians and patients were not blinded to the medical intervention. In addition, despite the fact that patients were prospectively followed in the REMADHE trial, this study represents a retrospective subgroup analysis.

**Conclusions**

Taken together, our results indicate that despite the pathophysiological and clinical peculiarities of Chagas heart disease, the use of $\beta$-blockers may become an important therapeutic option in this circumstances, which can reduce
mortality of patients. These findings challenge the current conservative hesitation by clinicians to prescribe \(\beta\)-blockers to patients with Chagas disease and warrant further studies in a randomized, double-blind fashion.

**Sources of Funding**

No external funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the article, and its final contents.

**Disclosures**

None.

**References**

8. Guimarães GV, d’Avila VM, Silva MS, Ferreira SA, Carvalho OV, Ciocla EG, Bocchi EA. A cutoff point for peak oxygen consumption in the prognosis of heart failure patients with beta-blocker therapy. *Int J Cardiol*. In press.
The treatment of Chagas cardiomyopathy is similar to that of other heart failure etiologies and is based on the inhibition of renin-angiotensin-aldosterone and sympathetic systems. However, peculiar aspects of the pathology and pathophysiology of Chagas cardiomyopathy raise concerns about efficacy and safety of these therapeutical options. Therefore, we sought to study the influence of β-blocker therapy in patients with Chagas cardiomyopathy prospectively followed in ambulatory care setting. We found that in the presence of a β-blocker agent, the worst prognosis of Chagas heart disease was attenuated, and survival was statistically similar to that of patients with other etiologies. Moreover, the survival of patients with Chagas heart disease who received β-blocker therapy was better than that of patients with Chagas heart disease who did not receive β-blocker therapy. The prescription of the recommended drug therapy differed between patients with Chagas heart disease when compared with other etiologies, namely, patients with Chagas disease were less likely to receive a β-blocker agent and more likely to receive spironolactone. Taken together, our results indicate that despite the pathophysiological and clinical peculiarities of Chagas heart disease, the use of β-blockers may become an important therapeutical option in these circumstances, which can reduce mortality of patients. These findings challenge the current conservative hesitation by clinicians to prescribe β-blockers to patients with Chagas disease, and warrant further studies in a randomized, double-blind fashion.
β-Blocker Therapy and Mortality of Patients With Chagas Cardiomyopathy: A Subanalysis of the REMADHE Prospective Trial
Victor S. Issa, Alexandre F. Amaral, Fátima D. Cruz, Silvia M.A. Ferreira, Guilherme V. Guimarães, Paulo R. Chizzola, Germano E.C. Souza, Fernando Bacal and Edimar A. Bocchi

Circ Heart Fail. 2010;3:82-88; originally published online November 20, 2009; doi: 10.1161/CIRCHEARTFAILURE.109.882035
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/3/1/82

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Heart Failure can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Heart Failure is online at:
http://circheartfailure.ahajournals.org//subscriptions/