Survival and Predictors of Survival in Patients With Congestive Heart Failure Due to Chagas’ Cardiomyopathy

Charles Mady, MD; Rita Helena Antonelli Cardoso, MSc; Antonio Carlos Pereira Barreto, MD; Protásio Lemos da Luz, MD, FACC; Giovanni Bellotti, MD; Fulvio Pileggi, MD, FACC

Background  The fundamental determinant of the natural history of Chagas’ disease is cardiac involvement.

Methods and Results  We studied 104 male patients with congestive heart failure due to Chagas’ disease to estimate the survival distribution function and to evaluate age, functional class (FC), maximal oxygen consumption (VO₂ max), and ejection fraction (EF) as predictors of survival. Statistical evaluation was performed through univariate (Student’s t test and χ² test) and multivariate analyses (Cox’s regression model). Overall survival was 66% at 1 year, 56% at 3 years, and 48% at 5 years. Ages were not statistically different (P = .9811) between survivors (40.3±8.7) and nonsurvivors (40.3±9.4) groups. The ejection fraction(s) were statistically different (P = .0001) between survival (43.6±9.9) and nonsurvival (30.6±8.1) groups, as was VO₂ max (P = .0001) (21.0±4.7 and 15.0±4.9, respectively). Most of the surviving patients were in FC II and most of the nonsurvivors were in FC IV (P = .0001). VO₂ max (P = .0001) and EF (P = .0008) are highly associated with survival time in the multivariate analysis, but FC (P = .0578) is less important. Age (P = .9811) did not influence survival.

Conclusions  We conclude that 50% of the patients with heart failure due to Chagas’ disease die in 47 months and that VO₂ max and EF are important indices of survival in this group. (Circulation. 1994;90:3098-3102.)

Key Words  • Chagas’ disease  • cardiomyopathy  • ejection fraction  • heart failure

Since the original description of Chagas’ disease,¹ there has been a great development in its understanding through research in several fields. The fundamental determinant of the natural history of the disease is cardiac involvement, and its several evolutive forms have been well studied from the morphological, etiopathogenic, and clinical points of view.²−⁷ However, studies regarding functional alterations are rare, and when performed, they were generally restricted to patients with advanced congestive heart failure (CHF); the milder forms deserved less attention.⁸−¹² The scarce information available about the functional status of these patients was not found to relate to survival. Because new therapeutic modalities are being proposed for the treatment of advanced Chagas’ cardiomyopathy, such as cardiomyoplasty¹⁴ and heart transplantation,¹⁵ it becomes important to identify and quantify cardiac dysfunctions, relating them to evolution and survival of such patients.

The aim of this work was to study patients with CHF due to Chagas’ cardiomyopathy, ranging from mild to severe forms, in order to analyze survival and some predictors of survival in individuals within this evolutive range of the disease.

Received February 16, 1994; revision accepted July 26, 1994.
From the Heart Institute, University of São Paulo Medical School, São Paulo, Brazil.
Reprint requests to Charles Mady, MD, Cardiopatias Gerais, Instituto do Coração, Av Dr Eneas C. Aguiar, 44, 05403-000-São Paulo, SP, Brazil.
© 1994 American Heart Association, Inc.

Methods  We studied 104 male patients, with ages ranging between 18 and 65 years (40.3±9.0). From these, 31 (29.8%) were in New York Heart Association (NYHA) functional class (FC) II, 41 (39.4%) in FC III, and 32 (30.8%) in FC IV. Follow-up times varied between 1 and 77 months (30.1±24.5, median of 24 months). All patients were treated and followed up in our hospital, and they received digitalis, diuretics, and vasodilator drugs whenever necessary and in the absence of side effects. Patients were not submitted to cardiomyoplasty and heart transplantation until the end of the study. The diagnosis of Chagas’ disease was based on epidemiological aspects, clinical history, physical findings compatible with cardiomyopathy, serological reactions (Machado-Guerreiro and immunofluorescence), and typical ECG abnormalities. The latter included 30 electrically inactive areas, 61 right bundle branch blocks, 49 left anterosuperior division branch blocks, 2 postero-inferior division branch blocks, 2 anteromedial division branch blocks, 6 left ventricular hypertrophies, 42 ventricular extrasystoles, 22 supraventricular extrasystoles, 5 first-degree atrioventricular (AV) blocks; 1 with second-degree AV block Mobitz type I, 2 left bundle branch blocks, and 9 atrial fibrillations. Patients with high-degree AV block were excluded.

The proposition was to study these patients in relation to survival and to evaluate age, FC, maximal oxygen consumption (VO₂ max), and ejection fraction (EF) as predictors of survival. The EF was obtained by Aloka SSD 720 and SSD 870 echocardiographic equipment and was calculated by the formula EF = EDV – ESV/EDV, in which EDV is the end-diastolic volume and ESV is the end-systolic volume.¹⁶ The volumes were calculated by the formula of Pombo in accordance with the American Society of Echocardiography,¹⁶ and the mean of five consecutive beats was used.

The evaluation of the VO₂ max was performed using a Beckman computerized gas analyzer, model MMC, which has a polarographic sensor (OM-11) and an infrared system.
The age, EF, \( V_0 \), and FC were subsequently included in a multivariate analysis that used Cox's multiple regression model. In the independent associations between these variables and mortality (Table 2), we noticed that \( V_0 \) (\( P = .0001 \)) and EF (\( P = .0008 \)) are highly associated with survival time. FC (\( P = .0578 \)) was of marginal statistical significance.

The Kaplan-Meier survival curve of all patients is in Fig 1. Each circle represents an individual event (death). The numbers under the graphic indicate the number of patients traced at that time. The 70% confidence limit is indicated by the vertical bar around the point estimate. Overall survival was 66% at 1 year, 56% at 3 years, and 48% at 5 years.

The probability of survival in relation to each individual prognostic variable was estimated by the Kaplan-Meier method. For this purpose, EF values were classified as mildly reduced (>50%), moderately reduced (31% to 50%), or severely reduced (<30%). Likewise, \( V_0 \) values were categorized as being normal (>20 mL·kg\(^{-1}\)·min\(^{-1}\)), moderately reduced (10 to 20 mL), or severely reduced (<10 mL·kg\(^{-1}\)·min\(^{-1}\)). The \( P \) values represent difference (log rank test) among the three groups.

Fig 2 represents the Kaplan-Meier survival curves of patients stratified according to NYHA class. Patients in FC II had predicted survival probability of 97% at 1 and 3 years. Patients in FC III had predicted survival probabilities of 73% and 58% at 1 and 3 years, respectively. Patiens in FC IV, therefore, had a considerably lower predicted survival: 38% at 1 year and 16% at 3 years. With increasing values of FC, there was a progressive increase in mortality (\( P = .0001 \)).

![Table 1](https://example.com/table1.png)

**Results**

The age, EF, \( V_0 \), and FC of the complete group and survivor and nonsurvivor subgroups are shown in Table 1. At the end of the study, there were 54 survivors and 50 nonsurvivors. All deaths were cardiac (64% sudden death and 36% due to pump failure). The ages in the survivor group varied between 24 and 58 years (40.3±8.7) and in the nonsurvivor group between 18 and 65 years (40.3±9.4). There were no statistical differences between the two subgroups (\( P = .9811 \)).

The EF in the survival group ranged between 17% and 63% (43.6±9.9%); it was smaller in the nonsurvivor group and varied between 14% and 62% (30.6±8.1%, \( P = .0001 \)). \( V_0 \) in the survival group ranged between 11.1 and 30.5 mL·kg\(^{-1}\)·min\(^{-1}\) (21.0±4.7) and in the nonsurvivor group between 7.2 and 28.2 mL·kg\(^{-1}\)·min\(^{-1}\) (15.0±4.9), a value that is significantly smaller than among survivors (\( P = .0001 \)). Most of the survivors were in FC II and most of the nonsurvivors were in FC IV (\( P = .0001 \)).

![Table 2](https://example.com/table2.png)
Fig 1. Kaplan-Meier survival curve of all patients. Each circle represents an individual event (death). Numbers indicate the remaining patients still being followed up at the time, with reference to the time scale of the x-axis; 70% confidence limit is indicated by vertical bars around the point estimate.

Fig 3 represents the Kaplan-Meier survival curves of patients stratified according to EF. There was a statistically significant difference among the three subgroups (P=.0001). Predicted survival was 100% at 1 and 3 years in patients with EF >50%. Only 31% of patients with EF ≤30% survived at 1 year and 16% at 3 years compared with 78% and 70% at 1 and 3 years, respectively, of those with EF between 31% and 50%.

Fig 4 represents the Kaplan-Meier survival curves of patients stratified according to $\dot{V}O_2$ max. There was also a highly significant statistical difference among the three subgroups (P=.0001). Survival was significantly better in patients with $\dot{V}O_2$ max >20 mL·kg$^{-1}$·min$^{-1}$. All patients in whom $\dot{V}O_2$ max was below 10 mL·kg$^{-1}$·min$^{-1}$ had died before 1 year. Patients presenting $\dot{V}O_2$ max between 10 and 20 mL·kg$^{-1}$·min$^{-1}$ had a predicted survival of 59% and 44% at 1 and 3 years, respectively. The corresponding values for patients with $\dot{V}O_2$ max >20 were 89% and 86%.

**Discussion**

Although the poor prognosis of patients with CHF due to Chagas' cardiomyopathy has long been appreciated, information concerning survival and predictors of survival in this disease is limited.

Survival curves from recent studies following patients with severe CHF due to several etiologies indicate 1 year survival rates of 40% to 70%.20-22 However, these data may not reflect the natural history of milder CHF. In addition, most studies have compared the prognosis of patients with CHF due to several etiologies, some of
them showing different or similar survival rates according to the underlying disease.\textsuperscript{23,24} In our group, there were only male patients with Chagas' disease. We studied only male patients because there are differences in evolution according to sex in other etiologies, and the maximal functional capacity is greater in male patients in relation to female patients.\textsuperscript{24,25} Some articles have suggested that elderly patients have poorer prognosis.\textsuperscript{25} We did not find differences between our two groups in relation to ages.

CHF ranged from mild to severe, with a similar distribution of patients among these categories. This is an important point, because in several studies there is no clear relation between symptoms and mortality except in the most extreme cases. In others, the severity of symptoms is an important prognostic variable.\textsuperscript{21,23-25} In our patients, we found overall survival rates of 66\% at 1 year, 56\% at 3 years, and 48\% at 5 years (Fig 1). However, when we divided the patients into subgroups according to FC, we noticed a clear relation between symptoms and mortality, showing an important prognostic significance (Fig 2).

Patients in FC II had the same predicted survival probability of 97\% at 1 year and 3 years, demonstrating the good prognosis of this subgroup. Patients in FC III had predicted survival probabilities of 73\% in 1 year and 58\% in 3 years. Patients in FC IV had a considerably lower predicted survival rates, 38\% at 1 year and 16\% at 3 years (Fig 2). Therefore, there is a clear difference in evolution of groups with this kind of cardiomyopathy according to the FC, from mild to severe. This point has considerable therapeutic implications. Other studies were not able to show this difference, probably because they do not have a single etiology.\textsuperscript{26}

Some investigators have shown that maximal oxygen uptake during exercise is related to long-term prognosis, whereas others have noted no significant difference in exercise capacity between groups of survivors and nonsurvivors with CHF.\textsuperscript{27,28} Many studies showed that the predictive value of the exercise test was related to the markedly reduced survival of patients with the most severe exercise limitation, with VO\textsubscript{2max} < 10 mL · kg\textsuperscript{-1} · min\textsuperscript{-1}. When such patients were excluded, exercise capacity provided little prognostic information, according to these authors.\textsuperscript{29}

All of our patients with VO\textsubscript{2max} of < 10 mL · kg\textsuperscript{-1} · min\textsuperscript{-1} died within 1 year of evolution. Other studies showed a death rate of 77\% during the same period.\textsuperscript{27} Otherwise, the survival rate of patients with VO\textsubscript{2max} between 10 and 20 mL · kg\textsuperscript{-1} · min\textsuperscript{-1} is 59\% in 1 year and 46\% in 3 years. Above 20 mL · kg\textsuperscript{-1} · min\textsuperscript{-1}, it improves to 89\% in 1 year and 86\% in 3 years. In conclusion, the demarcation between survivors and nonsurvivors is very distinct in our group. Therefore, VO\textsubscript{2max} is a strong predictor of survival in patients with heart failure due to Chagas' disease, even in individuals with mild dysfunction. These data also have potential clinical relevance. The value of EF also is a significant predictor of outcome,\textsuperscript{30} but in some studies no relation between resting left ventricular EF of survivors and nonsurvivors was found.\textsuperscript{30,31} In contrast, other investigators have found that greater degrees of depression of left ventricular EF are associated with a poorer prognosis.\textsuperscript{32,33}

In our group, a highly significant statistical difference between the EF of the survival and nonsurvival groups was found, that is, those with greatly reduced EF have the worst prognosis; even at 1-year follow-up their survival was only 30\%.

**Conclusions**

We can estimate the survival distribution function of patients with cardiomyopathy due to Chagas’ disease, and the FC, EF, and VO\textsubscript{2max} have been shown to be effective predictors of survival. It is noteworthy that EF and VO\textsubscript{2max} are stronger predictors of survival than FC. Perhaps subjective factors intrinsic to the FC determination may account for this difference. The central information from this study is relevant to long-term treatment of cardiomyopathy due to Chagas’ disease such as heart transplantation and cardiomyplasty.

**References**

16. Sahn DJ, de Maria A, Kisslo J, Weymann A. Recommendations regarding quantification in M-mode echocardiography: results of a

C Mady, R H Cardoso, A C Barretto, P L da Luz, G Bellotti and F Pileggi

*Circulation*. 1994;90:3098-3102
doi: 10.1161/01.CIR.90.6.3098

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/90/6/3098

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* 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* is online at:
http://circ.ahajournals.org/subscriptions/