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

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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 survivor (40.3±8.7) and nonsurvivor (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.

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(LB-2) for evaluation of the oxygen and carbon dioxide expired fractions. Respiratory variables were obtained under conditions of standard temperature, pressure, and humidity (STPD), using appropriate correction factors. The group was submitted to a test of maximum exercise on a Quinton model 18-54 treadmill with variable speed (mph) and inclination (%), using the modified Naughton protocol. Values of $V_{O_2}$ max in mL·kg$^{-1}$·min$^{-1}$ were obtained. All patients agreed to take part in the study after presentation of the method and explanation of the purpose of the examination.

Statistical Analysis
The relation of the variables age, FC, EF, and $V_{O_2}$ max to mortality was assessed using both univariate and multivariate analyses. For univariate analysis, subgroups were defined as survivors and nonsurvivors. The quantitative variables were examined by Student's t test and the qualitative variables by $\chi^2$ test to determine differences between the subgroups.

To identify the variables that are independently predictive of survival, multivariate analysis using Cox's regression model was performed. Finally, patients were classified in different subsets according to the variables selected by Cox's analysis. Kaplan-Meier survival curves were constructed to approximate the life expectancy of each group, and the long rank test was used to assess the significance of differences in survival rates among the various groups. All statistics computations were provided by SAS (Statistical Analysis System).

Results
The age, EF, $V_{O_2}$ max, 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%, $P=.0001$). $V_{O_2}$ max 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 ($P=.0001$).

The EF, $V_{O_2}$ max, 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 $V_{O_2}$ max ($P=.0001$) 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, $V_{O_2}$ max values were categorized as 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. Patients 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. Age, Ejection Fractions, $V_{O_2}$ max, and NHYA Functional Class Data on Total Group and Survivor and Nonsurvivor Subgroups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Group (n=104)</th>
<th>Survivors (n=54)</th>
<th>Nonsurvivors (n=50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>40.3±9.0</td>
<td>40.3±8.7</td>
<td>40.3±9.4</td>
<td>.9811</td>
</tr>
<tr>
<td>Ejection fractions*</td>
<td>37.4±11.1</td>
<td>43.6±9.9</td>
<td>30.6±8.1</td>
<td>.0001</td>
</tr>
<tr>
<td>$V_{O_2}$ max</td>
<td>18.1±5.7</td>
<td>21.0±4.7</td>
<td>15.0±4.9</td>
<td>.0001</td>
</tr>
<tr>
<td>NYHA class†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>31 (29.8)</td>
<td>28 (51.9)</td>
<td>3 (6.0)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>41 (39.4)</td>
<td>22 (40.7)</td>
<td>19 (38.0)</td>
<td>.0001</td>
</tr>
<tr>
<td>IV</td>
<td>32 (30.8)</td>
<td>4 (7.4)</td>
<td>28 (56.0)</td>
<td></td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association.
Values are listed as mean±SD or frequency and percentage.
*Significant difference from means for survivors and nonsurvivors.
†Significant difference from proportions for survivors and nonsurvivors.

### Table 2. Independent Associations Between Variables and Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression Coefficient</th>
<th>$\chi^2$ for Independence</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction(s)</td>
<td>-0.08</td>
<td>11.15</td>
<td>.0008</td>
</tr>
<tr>
<td>$V_{O_2}$ max</td>
<td>-0.13</td>
<td>14.55</td>
<td>.0001</td>
</tr>
<tr>
<td>New York Heart Association class</td>
<td>0.56</td>
<td>3.60</td>
<td>.0578</td>
</tr>
</tbody>
</table>
Fig 3 represents the Kaplan-Meier survival curves of patients stratified according to EF. There was a statistically significant difference among the three subgroups ($P=0.0001$). Predicted survival was 100% at 1 and 3 years in patients with EF $>50%$. Only 31% of patients with EF $\leq 30%$ 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 $V_{O_2}\text{max}$. There was also a highly significant statistical difference among the three subgroups ($P=0.0001$). Survival was significantly better in patients with $V_{O_2}\text{max} > 20$ mL·kg$^{-1}$·min$^{-1}$. All patients in whom $V_{O_2}\text{max}$ was below 10 mL·kg$^{-1}$·min$^{-1}$ had died before 1 year. Patients presenting $V_{O_2}\text{max}$ 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 $V_{O_2}\text{max} > 20$ 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.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.24,25 Some articles have suggested that elderly patients have poorer prognosis.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.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.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.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 VO₂max <10 mL·kg⁻¹·min⁻¹. When such patients were excluded, exercise capacity provided little prognostic information, according to these authors.29

All of our patients with VO₂max of <10 mL·kg⁻¹·min⁻¹ died within 1 year of evolution. Other studies showed a death rate of 77% during the same period.27 Otherwise, the survival rate of patients with VO₂max between 10 and 20 mL·kg⁻¹·min⁻¹ is 59% in 1 year and 46% in 3 years. Above 20 mL·kg⁻¹·min⁻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, VO₂max is a strong predictor of survival in patients with heart failure due to Chagas’ disease, even in individuals with mild dysfunctions. These data also have potential clinical relevance. The value of EF also is a significant predictor of outcome,20 but in some studies no relation between resting left ventricular EF of survivors and nonsurvivors was found.30,31 In contrast, other investigators have found that greater degrees of depression of left ventricular EF are associated with a poorer prognosis.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 VO₂max have been shown to be effective predictors of survival. It is noteworthy that EF and VO₂max 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 cardiomyoplasty.

References


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