Introduction and objectives. Previous prognostic studies of Chagas' disease have focused on mortality associated with end-stage cardiopathy (i.e., heart failure). Our aim was to identify indicators of progression in early-stage Chagas' heart disease.

Material and method. The study included 856 patients with 3 positive anti-*Trypanosoma cruzi* test results. Those with heart failure were excluded. Patients were divided into 3 clinical groups: those without heart disease (Group I); those with heart disease but without left ventricular enlargement (Group II); and those with left ventricular enlargement but without heart failure (Group III). The endpoint was progression to a more severe clinical stage or death due to cardiovascular disease. A Cox regression model was used to derive a clinical risk score from clinical, electrocardiographic and echocardiographic variables.

Results. At study entry, the patients' mean age was 43.7 years. They were followed up for a mean of 8 years. The following were predictors of heart disease progression: age at entry (HR=1.05; 95% CI, 1.02-1.07; P<.001), left ventricular systolic diameter (HR=1.06; 95% CI, 1.04-1.09; P<.001), intraventricular conduction abnormalities (HR=1.85; 95% CI, 1.02-3.36; P=.04), and sustained ventricular tachycardia (HR=3.97; 95% CI, 1.65-9.58; P<.002). Treatment with benznidazole reduced the risk of progression (HR=0.40; 95% CI, 0.23-0.72; P=.002). The devised clinical risk score was effective in stratifying the likelihood of cardiopathy progression.

Conclusions. Specific clinical indicators and a derived clinical risk score can be used to predict the progression of chronic chagasic myocarditis in patients without heart failure.

Key words: Cardiopathy. Cardiac disease. Heart failure. Prognosis.
MATERIALS AND METHODS

The patients in this study all had Chagas disease, as confirmed by 3 serological tests (the Machado Guer-

ABBREVIATIONS
ECG: electrocardiogram.
HR: hazard ratio.
LV: left ventricle.

INTRODUCTION

Chagas disease is the single most important infec-
tious cause of myocarditis; of the 15-20 million peo-
ple infected in Latin America, some 25% suffer this
heart complication. The pathogenesis of chronic Cha-
gas heart disease is not completely understood, al-
though the possible course of events (manifested only
very slowly and progressively) is thought to involve
the presence of the etiological agent Trypanosoma
cruzi or its antigenic components (the DNA of the pa-
rasite) in cardiac tissue, an abnormal response on the
part of the immune system which fails to control or
cure the infection and acts as a mediator of cell da-
mage, followed by diffuse or focal chronic myocardi-
tis with progression towards myocardial fibrosis. From
a clinical point of view, the disease has been clas-
sically described as passing through acute, indeter-
minate and chronic stages. Manifest cardiomyopathy
is seen in adults who were infected during childhood. The
presentation of chronic heart disease is polymor-
phic. Patients may suffer intraventricular conduction
problems, ventricular arrhythmias, sinus node disease,
segmentary lesions of the left ventricle (LV), enlarge-
ment and dysfunction of the LV with or without heart
failure, or combinations of the above. The main causes
of death are heart failure or sudden death—70% and
30% respectively of nearly all Chagas deaths. The
prognostic studies undertaken so far have large-
ly focused on mortality due to cardiomyopathy in the
final stages of the disease (heart failure). In these
studies, very important prognostic factors such as elec-
trocardiographic variables and arrhythmias were not
analyzed in conjunction with already established clini-
cal variables. Other studies have focused on complex
ventricular arrhythmias without taking into account the
progress of the disease or non-arrhythmic variables of
prognostic importance.

The aim of the present study was to establish the
prognostic indicators of the progression of heart dis-
ease in patients with indeterminate stage Chagas dis-
ease and with manifest cardiomyopathy but without
heart failure.

ABBRIVIATIONS
ECG: electrocardiogram.
HR: hazard ratio.
LV: left ventricle.
gessed towards heart disease underwent an ECG monthly and an echocardiogram annually.

In the determination of indicators of the progression of chronic Chagasic cardiomyopathy, the end point (dependent variable) was taken as movement into a more severe clinical group or death due to cardiovascular causes (both defined as changes in clinical group). Such progression required the appearance of an ECG abnormality, enlargement of the LV, the appearance of heart failure, or death.

The prognostic importance of the following variables were determined with respect to heart disease progression: age at entry, etiological treatment with benznidazole 5 mg/kg/day for 30 days (undertaken before entry to the study), intraventricular conduction abnormalities, complete right bundle block, left anterior hemiblock, complete right bundle block associated with left anterior hemiblock and complete left bundle block, baseline heart rate at entry, ventricular extrasystole diagnosed in ECG monitoring or in ergometric tests, non-sustained ventricular tachycardia (diagnosed from the baseline ECG, ergometry testing or Holter monitoring), the systolic and diastolic diameters of the LV, the diastolic diameter of the left atrium, systolic dysfunction of the LV, and the presence of segmentary lesions of the LV detected by echocardiography (two-dimensional, M mode).

Clinical Risk Score

To establish the individual risk of the progression of chronic Chagasic cardiomyopathy, the hazard ratios (HR) obtained in multivariate analysis were transformed into scores reflecting their prognostic significance. For this, continuous variables were transformed into dichotomous variables, establishing a cut-off point representative of the risk.

Loss to Follow-up

During the study, 221 patients (26% of the total) were lost to follow-up, the majority because of internal migration. Postal appointments were sent to try to recover those patients 5 and 10 years into the study; 84 were recovered (38% of those originally lost). Median follow-up time was 4.9 years in those lost to follow-up; the interquartile range (25%-75%) was 1.8-7.7 years.

Statistical Analysis

The results for continuous variables were expressed as the mean and standard deviation (SD) or the median and interquartile range (25%-75%). Dichotomous variables were expressed as result/total. For univariate analysis, all variables recorded in the study were analyzed using the Cox proportional risk model and with respect to the dependent variable of change in clinical group. For multivariate analysis the Cox regression model was used. This included all the variables found to be significant (P<.05) in the univariate analysis. When collinearity was seen between 2 variables, the regression was repeated including both variables separately in order to assess their significance with respect to the dependent variable. Survival was analyzed using the Kaplan-Meier method; the log-rank test was used to determine significance. All calculations were performed using Statistix 7.0 Analytical Software and SPSS 6.1 Statistical Analysis Software for Windows (SPSS Inc).

The study protocol was approved by the Research and Ethics Committee of our institution. All patients gave their consent to be included in the study.

RESULTS

The mean age of the patients at entry was 43.7±10.8 years. Overall median follow-up was 8 years; the in-

<table>
<thead>
<tr>
<th>Number of Patients at Entry</th>
<th>Changes in Clinical Group</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I 731</td>
<td>34 (4.6%)</td>
<td>Group II: 18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Group III: 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heart failure: 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Died: 4</td>
</tr>
<tr>
<td>Group II 35</td>
<td>5 (14%)</td>
<td>Heart failure: 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Died: 1</td>
</tr>
<tr>
<td>Group III 90</td>
<td>35 (39%)</td>
<td>Heart failure: 22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Died: 13</td>
</tr>
</tbody>
</table>

Group I indicates patients without cardiomyopathy; group II, patients with manifest cardiomyopathy but no enlargement of the left ventricle; group III, patients with manifest cardiomyopathy and enlargement of the left ventricle.
Table 2: Univariate Analysis (Cox) of the Predictors of Change of Clinical Group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Changes in Group</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at entry to study, year</td>
<td>46.18±10.76</td>
<td>1.05</td>
<td>1.02-1.07</td>
<td>.000</td>
</tr>
<tr>
<td>Baseline heart rate, median (25%-75%)</td>
<td>75 (60-86)</td>
<td>1.01</td>
<td>1.04-1.09</td>
<td>.000</td>
</tr>
<tr>
<td>Diastolic diameter of the LV, median (25%-75%)</td>
<td>48 (43-52)</td>
<td>1.06</td>
<td>1.01</td>
<td>.05</td>
</tr>
<tr>
<td>Systolic diameter of the LV, median (25%-75%)</td>
<td>26 (24-33)</td>
<td>1.01</td>
<td>1.00</td>
<td>1.86</td>
</tr>
<tr>
<td>Etiological treatment</td>
<td>318 (41)</td>
<td>1.40</td>
<td>0.23-0.72</td>
<td>.02</td>
</tr>
<tr>
<td>Sustained ventricular tachycardia</td>
<td>5 (0.6)</td>
<td>1.85</td>
<td>1.03-3.36</td>
<td>.04</td>
</tr>
</tbody>
</table>

*LA indicates left atrium; SD, standard deviation; LV, left ventricle.

Table 3: Multivariate Analysis (Cox) of the Predictors of Change of Clinical Group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Changes in Group</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at entry to study, year</td>
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<td>.000</td>
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<tr>
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<td>.000</td>
</tr>
<tr>
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<td>1.01</td>
<td>.05</td>
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<tr>
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<tr>
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<td>0.23-0.72</td>
<td>.02</td>
</tr>
<tr>
<td>Sustained ventricular tachycardia</td>
<td>5 (0.6)</td>
<td>1.85</td>
<td>1.03-3.36</td>
<td>.04</td>
</tr>
<tr>
<td>Systolic dysfunction†</td>
<td>34 (4)</td>
<td>2.85</td>
<td>1.53-5.31</td>
<td>.000</td>
</tr>
</tbody>
</table>

*LA indicates left atrium; LV, left ventricle; CI, confidence interval.
†Colinear with the systolic diameter of the LV.

The predictors of progression of chronic Chagasic cardiomyopathy were age at entry to the study, increased systolic diameter of the LV, intraventricular conduction abnormalities, and sustained ventricular tachycardia. Etiological treatment with benznidazole was associated with a reduced risk of progression. Systolic dysfunction of the LV showed colinearity with the systolic diameter of the LV, and thus shares its significance as a prognostic factor.

Clinical Risk Scores

Those variables that were significant in multivariate analysis were used to construct individual clinical risk scores. For this, significant continuous variables were transformed into dichotomous variables. Thus, the systolic diameter of the LV was transformed into the variable systolic diameter of the LV ≥40 mm, and age at entry was transformed into age at entry ≥50 years. The scores assigned to each variable were: age at entry ≥50 years =2 points (HR=1.86), systolic diameter of the LV ≥40 mm =3 points (HR=5.09), intraventricular conduction abnormalities =2 points (HR=1.85), sustained ventricular tachycardia =3 points (HR=3.97), and etiological treatment with benznidazole =2 points (HR=0.4). Systolic dysfunction of the LV (HR=2.85) appears as an alternative to systolic diameter of the LV≥40 mm, and was accordingly assigned 3 points.
The maximum risk score on this scale is 10, a score of 0 represents no risk. Final scores were obtained by adding together the scores for each variable. For the variable "etiological treatment with benznidazole," 2 points were subtracted from the total. Table 4 shows a number of risk score categories, the number of pa-
Viotti R, et al. Progression of Chronic Chagasic Myocarditis

DISCUSSION

The high mortality rate associated with cardiomyopathies of different etiology can be explained by a number of related and non-exclusive factors, including the extension of myocardial damage, the deterioration of heart function, and the appearance of lethal ventricular arrhythmias. Chronic Chagasic cardiomyopathy is different, however, to other kinds of heart disease. It is defined as a chronic myocarditis or a state of inflammation with periods of progression, changing in nature at certain moments with the unexpected appearance of complex ventricular arrhythmias. It is commonly accompanied by segmental lesions of the LV, whose association with ventricular arrhythmias is well known. Conduction abnormalities, especially in association with complete right bundle block and anterior left hemiblock, are also common (although not exclusive to this disease). Finally, the enlargement of the LV and the deterioration in overall systolic function which appears in the final stages of the disease is a route common to all cardiomyopathies advancing towards their final outcome. However, chronic Chagasic myocarditis also compromises the autonomic, sympathetic and parasympathetic nervous systems, which, in a context of inflammation, fibrosis and conduction abnormalities, is thought to be a factor in sudden death. This same damage to the autonomic nervous system determines the rare clinical appearance of uncompensated heart failure with bradycardia or normal heart rate (similar to beta-adrenergic block).

Patients in the indeterminate stage of Chagas disease or who suffer no cardiomyopathy generally have a good prognosis, but they can change group and even die, as occurred in the present cohort. The present results should be interpreted bearing in mind the composition of the patient sample—80% had no cardiomyopathy and fell into group 1, and 90% had either no or only mild cardiomyopathy at entry to the study (groups I and II). This starting point was important because it allows the progression of the disease to be followed from its early stages or, using the above terminology, from the indeterminate stage towards the appearance of manifest cardiomyopathy.

The chances of the progression of chronic Chagasic cardiomyopathy were greater the more the heart was compromised. Chronic myocarditis is slow and progressive, and it might be speculated that patients with some degree of cardiomyopathy are those most likely to see the progression of their disease; once myocardial damage occurs it tends to get worse.

The multivariate analysis shows the importance of assessing all the variables of potential prognostic potential (including clinical symptoms, and echocardiographic and electocardiographic signs).

The systolic diameter of the LV and systolic dysfunction of the LV are both variables associated with systolic function, which explains the colinearity between them. Both were indicators of progression and either can be used for determining final risk scores. The systolic diameter of the LV is a very useful measurement and is quite easy to record compared to the ejection fraction. In the presence of segmental lesions, the ejection fraction should only be measured by radionuclide ventriculography or the Simpson echocardiographic method. However, these methods could not be used in the present study given the large size of the sample.

The only arrhythmia variable with prognostic value for the patients of the present study was the presence of sustained ventricular tachycardia. Neither ventricular extrasystoles nor self-limiting ventricular tachycardia were of predictive value. Other important variables such as the diastolic diameter of the LV, the systolic diameter of the left atrium and the existence of segmental lesions were not independently predictive either. Conduction abnormalities were found to be predictors of advancing disease independent of all echocardiographic findings. This result returns one to the hypothesis that bundle branch blocks are the electrical expression of the complex process defined as chronic myocarditis.

Etiological treatment with benznidazole was the only indicator of delay in the progression of cardiomyopathy. Our group and other authors have described the possible effects of this anti-T. cruzi treatment on the clinical and serological course of the disease.

Changes in clinical severity group are a reliable measure of disease progression since they clearly reflect worsening heart disease; indeed, they have been used before in this context. The stratification of pa-

<table>
<thead>
<tr>
<th>Score</th>
<th>Prevalence, Number of Patients, %</th>
<th>Change of Group (Progression), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>476 (56)</td>
<td>3.6%</td>
</tr>
<tr>
<td>1-3</td>
<td>234 (27)</td>
<td>6.9%</td>
</tr>
<tr>
<td>4-6</td>
<td>106 (12)</td>
<td>16.0%</td>
</tr>
<tr>
<td>7-10</td>
<td>40 (5)</td>
<td>52.5%</td>
</tr>
</tbody>
</table>

*Prognostic variables: age at entry to study ≥50 years (2 points), systolic diameter of the left ventricle ≥50 mm (3 points), intraventricular conduction abnormalities (2 points), sustained ventricular tachycardia (3 points), and etiological treatment with benznidazole (<2 points).

†P < 0.05 for a score of 0 compared to 1-3.
‡P < 0.01 for scores of 1-3 compared to 4-6.
§P < 0.001 for a score of 4-6 compared to 7-10.
tients into clinical groups in this work was similar to that described by Kuschner et al., with the incorporation of the diastolic diameter of the LV. This better differentiates patients with enlarged and normal size hearts.

The clinical risk score, calculated using the results of the multiple regression analysis, was useful for identifying risk groups with respect to the progression of cardiomyopathy. However, when used with individual patients it should only be regarded as a guide, as are score systems used to stratify the prognosis of other forms of heart disease.3,4

Chronic Chagasic cardiomyopathy is a serious disease but it can be diagnosed early. Several indicators are available that should alert clinicians to the progression of the disease. Patients thus affected can be identified and given appropriate clinical attention.

REFERENCES