Clinical Predictors of Chronic Chagasic Myocarditis Progression

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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.

Matherial 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.*

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Indicadores clínicos de progresión de la miocarditis chagásica crónica

Introducción y objetivos. Los estudios de pronóstico efectuados sobre la mortalidad de la cardiopatía se han centrado en la etapa final de la enfermedad (insuficiencia cardíaca). Nuestro objetivo fue establecer los indicadores de progresión de la enfermedad de Chagas en estadios tempranos.

Material y método. Se incluyó a 856 pacientes con 3 pruebas reactivas anti-*Trypanosoma cruzi* y se excluyó a los pacientes con insuficiencia cardíaca. Se utilizó la siguiente estratificación clínica: grupo I, sin cardiopatía; grupo II, con cardiopatía y sin dilatación del ventrículo izquierdo (VI); grupo III, con dilatación del VI, sin insuficiencia cardíaca.

El punto final de evaluación fue la progresión hacia un grupo clínico de mayor severidad o la muerte cardiovascular. Se incluyeron las variables clínicas, electrocardiográficas y ecocardiográficas en un análisis multivariado (Cox) y se construyó una puntuación de riesgo.

Resultados. La edad promedio fue de 43,7 años y el seguimiento de 8 años. La edad (*hazard ratio* [HR] = 1,05; intervalo de confianza [IC] del 95%, 1,02-1,07; p < 0,001), el diámetro sistólico del VI (HR = 1,06; IC del 95%, 1,04-1,09; p < 0,001), los trastornos de conducción intraventricular (HR = 1,85; IC del 95%, 1,02-3,36; p = 0,04) y la taquicardia ventricular sostenida (HR = 3,97; IC del 95%, 1,65-9,58; p = 0,002) fueron predictores de progresión de la cardiopatía. El tratamiento con benznidazol redujo el riesgo de progresión (HR = 0,40; IC del 95%, 0,23-0,72; p = 0,002).

La puntuación de riesgo construido estratificó adecuadamente la probabilidad de progresión de la cardiopatía.

Conclusiones. Los indicadores clínicos y la puntuación propuesta pueden establecer el pronóstico de progresión de la miocarditis chagásica crónica sin insuficiencia cardíaca.

Palabras clave: *Cardiopatía. Enfermedades cardíacas. Insuficiencia cardíaca. Pronóstico.*

ABBREVIATIONS

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

INTRODUCTION

Chagas disease is the single most important infectious cause of myocarditis[1]; of the 15-20 million people infected in Latin America, some 25% suffer this heart complication.[2] The pathogenesis of chronic Chagas heart disease is not completely understood,[3] although 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 parasite) in cardiac tissue,[4-6] 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 damage,[7] followed by diffuse or focal chronic myocarditis with progression towards myocardial fibrosis.[8] From a clinical point of view, the disease has been classically described as passing through acute, indeterminate and chronic stages.[9] Manifest cardiomyopathy is seen in adults who were infected during childhood.[10] The presentation of chronic heart disease is polymorphic.[11] Patients may suffer intraventricular conduction problems, ventricular arrhythmias, sinus node disease, segmentary lesions of the left ventricle (LV), enlargement 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.[12]

The prognostic studies undertaken so far have largely focused on mortality due to cardiomyopathy in the final stages of the disease (heart failure).[13-15] In these studies, very important prognostic factors such as electrocardiographic variables and arrhythmias were not analyzed in conjunction with already established clinical 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.[16,17]

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

MATERIALS AND METHODS

The patients in this study all had Chagas disease, as confirmed by 3 serological tests (the Machado Guerreiro test or ELISA, indirect hemoagglutination, and immunofluorescence). Those presenting with concomitant heart disease (such as congenital heart disease) (n=4), high blood pressure (n=29), ischemia (n=8), other types of heart disease (n=3), or who were alcoholics (n=5), were excluded from the final sample (n=856). Those with enlargement of the LV and heart failure were also excluded since they were considered to be in the final stages (mortality among these patients was expected to be high); moreover, the prognostic factors pertinent to these patients have already been studied.[13-15] On entry to the study, patients were stratified into different clinical categories: group I—no heart disease, reactive serology, electrocardiogram (ECG) normal, chest x-ray normal, LV diastolic diameter ≤57 mm; group II—manifest heart disease with no enlargement of the LV, reactive serology, ECG normal, chest x-ray normal, LV diastolic diameter ≤57 mm; group III—manifest heart disease with enlargement of the LV, reactive serology, abnormal ECG, chest x-ray showing evidence of cardiomegaly (cardiothoracic index >0.50), and/or LV diastolic diameter >57 mm, but with no sign of heart failure.

The electrocardiographic anomalies considered to be related to Chagasic cardiomyopathy were: complete right bundle branch block, anterior left hemiblock, complete left bundle branch block, Lown grade II or higher ventricular extrasystole, areas of electrical inactivation, atrial flutter, atrial fibrillation, atrial tachycardia, sinus bradycardia <50 x', sustained or non-sustained ventricular tachycardia, and type II second degree and third degree atrioventricular (AV) block. Patients who received a pacemaker during the study were also regarded as showing electrocardiographic abnormalities. These ECG anomalies were significantly more common among patients with *T cruzi* antibodies than in uninfected individuals.[18] During the screening phase of the study (the first 2 months), all patients were subjected to the following examinations: ECG, ergometry, chest x-ray, and an echocardiogram (two-dimensional, M mode). Once stratified according to their clinical characteristics, the patients were monitored and followed-up according to the protocols adopted by our department: group I—one appointment with ECG every 6-12 months, Holter monitoring or repetition of ergometry, and echocardiography in accordance with symptoms or changes in baseline ECG (or every 5 years); group 2—one appointment with ECG every 4-6 months, Holter monitoring or repetition of ergometry, and echocardiography in accordance with symptoms or changes in baseline ECG (or every 5 years); group III—one appointment with ECG every 3 months, Holter monitoring or repetition of ergometry, and echocardiography in accordance with symptoms or changes in baseline ECG (or every 5 years), echocardiogram every 2 years. Patients who pro-

gressed 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), 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 these 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 colinearity 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 1. **Changes of Clinical Group and Deaths With Respect to Clinical Group at Entry to the Study**

Number of Patients at Entry		Changes in Clinical Group		Deaths
		Totals	New Clinical Group	
Group I	731	34 (4.6%)	Group II: 18 Group III: 4 Heart failure: 8 Died: 4	4 (0.5%)
Group II	35	5 (14%)	Heart failure: 4 Died: 1	1 (2.8%)
Group III	90	35 (39%)	Heart failure: 22 Died: 13	13 (14%)

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***

Variables	No Change in Group, n=782	Change in Group, n=74	*P*
Age at entry to study, mean ± SD	46.18±10.76	49.04±9.49	<.0001
Baseline heart rate, median (25%-75%)	75 (65-86)	68 (60-86)	0.78
Diastolic diameter of the LV, median, mm (25%-75%)	48 (43-52)	56 (48.7-64)	<.0001
Systolic diameter of the LV, median, mm (25%-75%)	28 (24-33)	36 (28-49)	<.0001
Systolic diameter of the LA, median, mm (25%-75%)	33 (27-37)	38 (31-45)	<.003
Etiological treatment, %	318 (41)	19 (26)	<.0001
Intraventricular conduction abnormalities, %	312 (40)	58 (78)	<.0001
Ventricular extrasystoles, %	257 (33)	38 (51)	.21
Non-sustained ventricular tachycardia, %	30 (4)	5 (7)	.23
Sustained ventricular tachycardia	5 (0.6)	8 (11)	<.0001
Segmental lesions of the LV	82 (10)	12 (16)	.32
Systolic dysfunction	34 (4)	20 (27)	<.0001

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

TABLE 3. **Multivariate Analysis (Cox) of the Predictors of Change in Clinical Group***

Variables	Changes in Clinical Group		
	Hazard Ratio	95% CI	*P*
Age at entry to study	1.05	1.02-1.07	.000
Diastolic diameter of the LV	1.01	–	.065
Systolic diameter of the LV	1.06	1.04-1.09	.000
Systolic diameter of the LA	1.01	–	.65
Etiological treatment	0.40	0.23-0.72	.002
Sustained ventricular tachycardia	3.97	1.65-9.58	.002
Intraventricular conduction abnormalities	1.85	1.02-3.36	.04
Systolic dysfunction†	2.85	1.53-5.31	.001

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

terquartile range (25%-75%) was 4.25-14 years. Three hundred and fifty five patients were male (42%) and 501 were female (58%). Clinical group 1 included 731 patients, group II contained 35, and group III contained 90 (therefore, only 10% of all patients showed enlargement of the heart at entry). During follow-up, 74 changes of clinical group were recorded (9% of patients), including 18 deaths (2%). Table 1 shows the distribution of changes of clinical group and deaths according to clinical group at entry. The number of group changes increased proportionally from group I to group III (*P*<.0001), i.e., with increasing severity of heart disease at entry.

Table 2 shows the univariate analysis for predictors of disease progression (change of clinical group). All variables that were significant in this analysis were included in the Cox regression analysis (Table 3).

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.

The 18 patients who died were older at entry than those who survived (49.39±11.48 years compared to 43.57±10.53 years; *P*=.02). The causes of mortality were sudden death in 9 patients (50% of those who died), heart failure in 6 (33%), cerebrovascular accident in 2 (11%), and pulmonary thromboembolism in 1 (6%). Figures 1 and 2 show the Kaplan-Meier curves for the variables "intraventricular conduction abnormalities" and "etiological treatment". Both figures show the curves to separate after four or 5 years of follow-up, reflecting the minimum length of time required to detect differences in the progression of chronic Chagasic cardiomyopathy.

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.

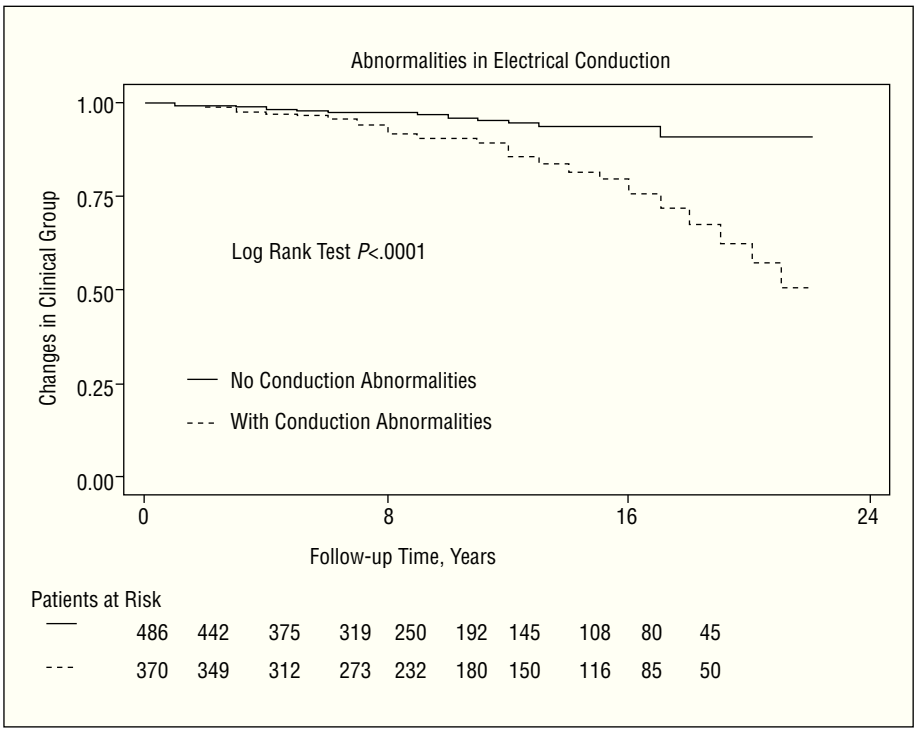

Figure 1. Kaplan-Meier curves for patients with and without conduction abnormalities at entry to the study).

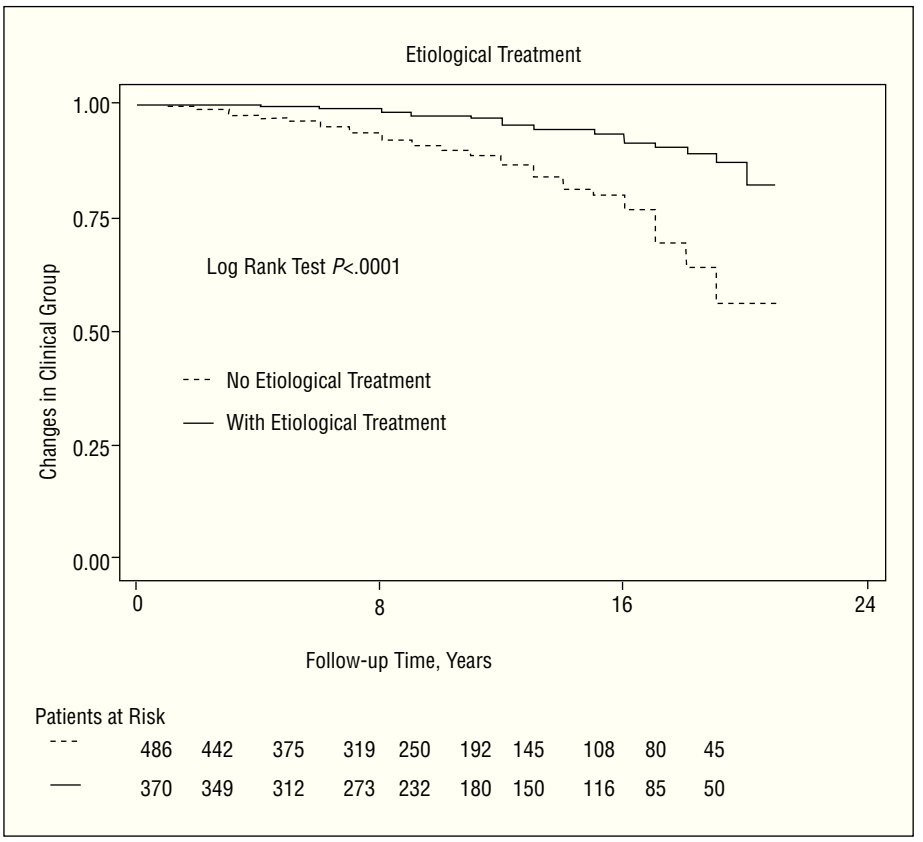

Figure 2. Kaplan-Meier curves for patients who received and who did not receive benznidazole treatment.

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-

TABLE 4. **Clinical Risk Score for Progression of Chronic Chagasic Myocarditis***

Score	Prevalence, Number of Patients, %	Change of Group (Progression), %
0	476 (56)	3.6†
1-3	234 (27)	6.9‡
4-6	106 (12)	16.0$
7-10	40 (5)	52.5

*Prognostic variables: age at entry to study ≥50 years (2 points), systolic diameter of the left ventricle ≥40 mm (3 points), intraventricular conduction abnormalities (2 points), sustained ventricular tachycardia (3 points), and etiological treatment with benznidazole (–2 points).
†*P*=.05 for a score of 0 compared to 1-3.
‡*P*<.008 for score of 1-3 compared to 4-6.
$*P*<.001 for a score of 4-6 compared to 7-10.

tients with these scores (prevalence), and the probability of patients with these scores progressing to a higher clinical severity group.

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.[19] 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.[20] 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[21] and parasympathetic[22] 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,[23] 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.[24]

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;[25] 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 electrocardiographic and echocardiographic 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[26] 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 radioisotopic 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.[27]

Etiological treatment with benznidazole was the only indicator of delay in the progression of cardiomyopathy. Our group[28] and other authors[29-31] 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.[26] The stratification of pa-

tients into clinical groups in this work was similar to that described by Kuschnir et al,[32] 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.[33,34]

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.

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