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Prognostic impact of Chagas' disease in patients awaiting heart transplantation

Natália D. Bertolino, MD, Daniel F. Villafanha, MD, Augusto Cardinalli-Neto, MD, PhD, José A. Cordeiro, PhD, Milena J. Arcanjo, MD, Tatiana A.D. Theodoropoulos, MD, PhD, and Reinaldo B. Bestetti, MD, PhD

From Hospital de Base, São José do Rio Preto city, Brazil.

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BACKGROUND: The role of Chagas' etiology of chronic heart failure in predicting patient outcomes while awaiting heart transplantation is unknown. Accordingly, in this study we compare outcomes in Chagas' disease with non–Chagas'-disease-related advanced heart failure among patients on the waiting list for heart transplantation.

METHODS: We reviewed the clinical outcomes of 103 consecutive patients with chronic heart failure listed for heart transplantation from August 2000 to January 2008 at a single institution. Forty-six (44%) patients were diagnosed with Chagas' disease on the basis of positive serology. A Cox proportional hazards model was used to establish independent predictors of mortality, whereas competing risk analysis was used to estimate time-related prevalence of death and heart transplantation in Chagas' disease and non–Chagas' disease patients.

RESULTS: In the multivariate model, inotropic support ($p < 0.0005$; hazard ratio = 5.96; 95% confidence interval [CI] 2.41 to 14.71) and Chagas' disease etiology of heart failure ($p = 0.02$; hazard ratio = 2.27; 95% CI 1.14 to 4.52) were retained as independent predictors of mortality. Prevalence of death at 100 days after listing was 30% in Chagas' disease and 16% in non–Chagas' disease patients ($p = 0.02$), despite no difference in the competing rates of transplantation (30% in Chagas' and 37% in non-Chagas' patients, $p = 0.5$).

CONCLUSIONS: Chagas' disease etiology serves as an independent predictor of mortality in patients listed for heart transplantation, with a worse outcome when compared with non–Chagas' disease patients.

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Chagas' disease affects an estimated 11 million people in South America and 90 million are at risk of acquiring the disease.[1] Because of international immigration, Chagas' disease can now be found throughout the world, mainly in the USA, Europe and Australia.[2] The disease is caused by the protozoan *Trypanosoma cruzi*, which is transmitted to humans through the feces of a sucking parasite, usually deposited on eye mucosa or damaged skin. Initial infection occurs in early infancy, but the clinical manifestations of Chagas' disease appear many years later, up to 20 years after infection.[3]

Chagas' cardiomyopathy is the most frequent clinical manifestation of Chagas' disease, accounting for 30% of infected patients. Chronic heart failure is a protean clinical manifestation of Chagas' disease, affecting about 3% of a general, unselected population of patients with this condition, and up to 70% of patients followed in tertiary referral centers.[4] Outcomes of patients with chronic heart failure secondary to Chagas' disease are dismal, with an annual

Reprint requests: Reinaldo B. Bestetti, MD, Hospital de Base, Avenida Faria Lima 5544, São José do Rio Preto city 15090-000, Brazil. Telephone: 0055 17 32015746. Fax: 0055 17 32015000 Ext. 1493.

E-mail address: rbestetti@netsite.com.br

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mortality of about 20%,[5] worse than that seen in patients with non–Chagas' disease heart failure.[6,7]

Heart transplantation is the treatment of choice for patients with end-stage chronic heart failure due to Chagas' disease.[8] Comparison of prognosis of patients with Chagas' and non–Chagas' disease heart failure listed for heart transplantation is lacking. It is also unknown whether Chagas' disease etiology of chronic heart failure is, by itself, an independent predictor of mortality for patients on the waiting list for heart transplantation.

Accordingly, in this study we aimed to determine the impact of Chagas' disease etiology in patients with chronic heart failure who are on the waiting list for heart transplantation.

Methods

Patients

We reviewed the medical charts of 103 consecutive patients with chronic heart failure listed for heart transplantation from August 2000 to January 2008 at our center. Forty-six (44%) patients were diagnosed as having Chagas' disease on the basis of positive serology. The remaining patients were diagnosed as having non-Chagas' dilated cardiomyopathy.

All patients underwent medical history and physical examination on admission. Standard laboratory tests, 12-lead electrocardiogram (ECG), chest X-ray, Doppler echocardiography, heart catheterization, socioeconomic status analysis and psychologic data were obtained for all patients. Except for patients on inotropic or mechanical support, left ventricular ejection fraction was measured by radionuclide ventriculography. Indices of pulmonary vascular resistance were determined by right ventricular catheterization.

Indications for heart transplantation were as follows: (1) need of inotropic support or mechanical support with intra-aortic balloon pump; (2) persistent Class IV status despite proper medical therapy; and (3) maximal oxygen consumption rate <12 ml/kg/min in patients on β-blockers or <14 ml/kg/min in patients not receiving β-blocker therapy.[9] However, only 49 (47%) patients underwent cardiospirometry to determine maximal oxygen consumption rate due to their poor clinical condition. Aaronson's index was not used in patients' selection for heart transplantation because it has not been validated for Chagas' disease patients.[10] No patient had received a left ventricular assist device while on the waiting list for heart transplantation.

Statistical analysis

We used the unpaired *t*-test or the Mann–Whitney *U*-test for comparison of continuous variables with a normal distribution in the Chagas' and non–Chagas' disease groups. Either the chi-square test or Fisher's exact test was employed to compare categorical variables of the Chagas' and non-Chagas' groups. Pearson's correlation test was used to establish a correlation ($r > 0.50$) between two continuous variables.

The Cox proportional hazards model was used to evaluate whether etiology of heart failure was an independent predictor of all-cause mortality for patients on the waiting list for heart transplantation. All variables known to have prognostic significance in Chagas' disease patients with chronic heart failure were entered the univariate model. In this sense, however, it is important to emphasize that only variables available for all patients were included in the univariate analysis. Therefore, use of β-blockers as well as maximal oxygen consumption rate at cardiospirometry, important predictors of mortality for Chagas' disease patients with chronic heart failure, were not included in the univariate analysis because of the small sample size. Variables that presented an association with mortality at the $p < 0.05$ level were entered into the multivariate analysis. In the case in which several variables univariately associated with mortality were shown to have correlation among themselves, only the one with the highest Wald's coefficient was entered the multivariate model.

A competing-risk analysis was performed to provide time-related prevalence of deaths in the Chagas' and non-Chagas' groups, as previously described.[11,12] This method was used because patients enrolled in this study were simultaneously at risk for mutually exclusive outcomes: death, heart transplantation, and removal from the waiting list due to improved clinical status.

Differences at the $p < 0.05$ level were considered statistically significant in all analyses.

Results

Comparisons between the baseline non-invasive characteristics of Chagas' and non–Chagas' disease patients listed for heart transplantation are given in Table 1. With regard to invasive variables, the transpulmonary gradient was lower in Chagas' (8.9 ± 4 mm Hg) than in non-Chagas' dilated cardiomyopathy patients (12.8 ± 6.2 mm Hg, $p < 0.0005$); cardiac index was also lower in Chagas' than in non-Chagas' patients (2.32 ± 0.68 vs 2.54 ± 0.66 liters/min/m^2, $p < 0.0005$). No difference was observed regarding cardiac output (3.7 ± 1.1 liters/min in Chagas' and 4.4 ± 1 liters/min in non-Chagas' patients, $p > 0.05$), pulmonary capillary wedge pressure (31.8 ± 9.4 mm Hg in Chagas' vs 24.2 ± 0.5 mm Hg in non-Chagas' patients, $p > 0.05$), systemic vascular resistance ($1{,}561.8 \pm 592.2$ dyne/s/m^2 in Chagas' vs $1{,}432.7 \pm 470.3$ dyne/s/m^2 in non-Chagas' patients, $p > 0.05$) and pulmonary arterial resistance (678.7 ± 429.7 dyne/s/m^2 in Chagas' vs 626.1 ± 379.6 dyne/s/m^2 in non-Chagas' patients, $p > 0.05$).

Variables univariately associated with mortality for patients on the waiting list for heart transplantation included inotropic support ($p = 0.0005$), Chagas' disease etiology of heart failure ($p = 0.008$), serum sodium levels ($p = 0.002$), left anterior fascicular block ($p = 0.03$) and cardiac index ($p = 0.02$). In the multivariate model, however, only inotropic support ($p < 0.0005$; hazard ratio = 5.96; 95% confidence interval [CI] 2.41 to 14.71) and Chagas' disease