Long-Term Follow-Up of Patients with Chronic Chagas Disease and Implantable Cardioverter-Defibrillator

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Background/Objectives: Chronic Chagas heart disease (ChHD) is associated with ventricular tachyarrhythmias and an increased risk of sudden cardiac death. Little is known about the effectiveness of implantable cardioverter-defibrillator (ICD) therapy in this population. The objective of this study was to evaluate the efficacy of ICD in patients with ChHD and to identify predictors of mortality and appropriate ICD shocks.

Methods: The cohort study included 65 patients with ChHD and ICD for primary and secondary prevention of sudden death. The Cox model was applied to evaluate the predictors of mortality, and survival was assessed by Kaplan-Meier analysis.

Results: The median age was 56 ± 11.9 years. The median follow-up was 40 ± 26.8 months. Among the patients 23 (36.5%) had appropriate shocks. A total of 13 (20%) patients died (6.1% of annual mortality rate), and there was no sudden death. In univariate Cox model, functional class IV (hazard ratio [HR] = 1.99; 95% confidence interval [CI], 1.05–3.76; P = 0.034), primary prevention (HR = 0.29; 95% CI, 0.09–0.99; P = 0.048), lower education (HR = 2.51; 95% CI, 1.05–5.99; P = 0.038), and ejection fraction <30% (HR = 2.80; 95% CI, 1.09–7.18; P = 0.032) were predictors of worse prognosis (death). In the multivariate Cox model, an ejection fraction <30% and low education remained predictors of poor prognosis. Predictors of appropriate shocks were not found.

Conclusions: The ICD was effective for the prevention of sudden cardiac death in patients with chronic ChHD. An ejection fraction <30% and low education were predictors of poor prognosis. (PACE 2014; 37:751–756)

CRT, VT, defibrillation-ICD

Introduction

Chagas heart disease (ChHD) is caused by the protozoan Trypanosoma cruzi, which is endemic in South America and Central America, where 10–20 million people are infected and nearly 100–120 million are at risk of contracting the disease. This parasitic disease is transmitted to humans through the feces of infected bloodsucking insects (triatominae) in endemic areas and occasionally by nonvectorial mechanisms such as blood transfusion. Chronic Chagas cardiomyopathy is the most important manifestation of the disease due to its high morbidity and mortality.1,2 Sudden death is responsible for 60–65% of deaths by this disease and may occur in patients with normal ejection fraction or mild dysfunction.3 There are conflicting data regarding the efficacy of the implantable cardioverter-defibrillator (ICD) in patients with chronic ChHD. The evidence is based on the results of two reports4,5 and two retrospective studies of secondary prevention.6,7 The annual mortality reported in these four studies...
ranged from 5.5% to 16.6%. The aim of this paper was to evaluate, over a long-term follow-up period, the efficacy of ICD in primary and secondary prevention of sudden cardiac death in chronic ChHD patients from a tertiary center and to identify poor prognostic factors and predictors of appropriate shock.

**Materials and Methods**

The inclusion criteria were patients diagnosed with chronic ChHD by positive serological test and implanted with ICD for primary or secondary prevention of sudden cardiac death, according to the Brazilian guidelines. Those patients who received an ICD for primary prevention were the ones with indication for cardiac resynchronization and who had never presented syncope, sustained ventricular tachycardia (VT), or aborted sudden death by VT or ventricular fibrillation (VF). The study included all patients with chronic ChHD who received an ICD during the period of January 2003 to November 2011 at the Walter Cantidio Hospital of the Federal University of Ceará (HUWC) in Brazil. Follow-up was closed in July 2012. The exclusion criteria were: age under 18 years and patients with associated coronary artery disease. The presence of coronary artery disease was excluded through cardiac catheterization or myocardial scintigraphy. This retrospective cohort study was approved by the ethics committee of the above-mentioned institution in January 2010. A database was designed to include the clinical and epidemiological characteristics of the patients, indication of ICD, and functional outcomes of ICD at implant and during follow-up. These data were collected from medical records and during clinical visits. The ICD programming included antitachycardia stimulation, followed by shocks for VT and VF. It was considered VT in the presence of a sustained tachycardia with a cycle interval ranging 300–400 ms, not discriminated as supra-VT by specific algorithms. It was considered VF when the cycle interval was inferior to 300 ms with compatible electrogram analysis. ICD therapy was classified as appropriate for VT/VF if the recorded intracardiac electrogram for the intervention was compatible with the clinical manifestation, on medical discretion. ICD-stored electrograms were reviewed to determine type of arrhythmia as well as type of therapy delivered by two experienced electrophysiologists and differences resolved by a third electrophysiologist. The shock therapy was considered inappropriate when ICD therapy was applied to supra-VT, noise, myopotential oversensing, or double counting of R-wave. The follow-up protocol included regular clinical visits and evaluation of the device three times a year or in shorter terms when considered necessary. The circumstances of death were classified as a cardiac or a noncardiac cause, and the classification of Hinkle and Thaler was used to evaluate the suspected mechanism of death. The primary outcome was death from all causes and appropriate shocks.

Potential risk factors for appropriate shocks and long-term mortality were analyzed. We used χ² and Fisher’s exact test, with presentation of tables with absolute value (n) and their ratio (%). We constructed Kaplan-Meier curves for variables with P < 0.05 compared with the two-tailed log rank test between strata. The cumulative survival was evaluated by using the Cox proportional hazards models. To assess the proportionality of risk associated with the predictors, we used the Schoenfeld test and the graphic inspection of Cox-Snell residuals. The software used was SPSS version 17.0 for Windows (IBM Corp., Armonk, NY, USA).

**Results**

The study cohort consisted of 65 patients, of whom 44 were men. The mean age of patients was 56 ± 11.9 years. The functional classes II-III of the New York Heart Association were present in 66% and left ventricular ejection fraction was less than 30% in 50.8% of patients. Regarding education, 10 patients (15.4%) were illiterate and 38 (58.5%) had completed the first degree; that is, 48 patients had lower education (73.9%). The monthly income was less than three minimum wages in 51 (78.5%) patients. Perioperative complications were observed in two patients (3.07%); pneumothorax occurred in one case, hemothorax occurred in another case. No patient died in the immediate postimplantation time. Forty-two (64.6%) of the patients reported the presence of bloodsucking insects (contact with triatomine) in their homes at some point. Regarding the type of device used, one patient received a single-chamber ICD, 49 received a dual-chamber ICD, and 14 had a cardiac resynchronization defibrillator (CRT-D). Two patients were lost to follow-up. Of the remaining 63 patients, 13 (20.6%) used amiodarone, and 44 (69.8%) used amiodarone associated with β-blockers.

Resuscitated from sudden death due to VF or unstable VT was the indication for ICD in 31 patients. Syncope with induction of unstable VT in the electrophysiological study was the purpose of the implant in 20 patients. Fourteen patients had ICD implantation for primary prevention (they also received resynchronizers associated with defibrillators). The incidence of electrical storm was 12.7% and there was 6.3% of inappropriate shocks (all with sinus tachycardia with heart rate
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Table I.
Clinical and Epidemiological Characteristics of Patients with Chronic Chagas Disease and ICD

| Characteristics                  | (n = 65)                      |
|----------------------------------|-------------------------------|
| Age                              | 56.7 ± 11.9                   |
| Men                              | 44 (67.7%)                    |
| Schooling                        |                               |
| Illiterate                       | 10 (15.4%)                    |
| First grade                      | 38 (58.5%)                    |
| Second grade                     | 15 (23.1%)                    |
| Third grade                      | 2 (3.1%)                      |
| Contact with *Triatoma* sp.      | 42 (64.6%)                    |
| Type of device                   |                               |
| SR                               | 1 (1.5%)                      |
| DR                               | 49 (75.4%)                    |
| CRT-D                            | 15 (23.1%)                    |
| Ejection fraction                |                               |
| Normal (>55%)                    | 12 (18.5%)                    |
| Mild (45–55%)                    | 5 (7.7%)                      |
| Moderate (30–44%)                | 15 (23.1%)                    |
| Severe (<30%)                    | 33 (50.8%)                    |
| Function class                   |                               |
| I                                | 13 (20%)                      |
| II                               | 25 (38.5%)                    |
| III                              | 18 (27.5%)                    |
| IV                               | 9 (13.8%)                     |
| Prevention level                 |                               |
| Primary                          | 14 (21.5%)                    |
| Secondary                        | 51 (78.5%)                    |
| Loss of follow-up                | 2 (3.1%)                      |
| Time of follow-up (mean; n = 63) | 40 ± 26.8                     |
| Death (n = 63)                   |                               |
| Annual mortality rate (n = 63)   | 6.1%                          |
| Incidence of sudden death (SD) (n = 63) | 0 (0.0%)                   |
| Incidence of electrical storm (n = 63) | 8 (12.7%)                  |
| Incidence of appropriate shocks (n = 63) | 23 (36.5%)                |
| Incidence of appropriate therapies (appropriate shocks + ATP; n = 63) | 27 (42.9%)                   |
| Use of BB (n = 63)               | 4 (6.3%)                      |
| Use of amiodarone (n = 63)       | 13 (20.6%)                    |
| Use BB and amiodarone (n = 63)   | 44 (69.8%)                    |

ATP = antitachycardia pacing therapy; BB = β-Blocker; CRT-D = cardiac resynchronization therapy-defibrillator; DR = dual chamber ICD; ICD = implantable cardiac defibrillator; SD = standard deviation; SR = single-chamber.

During the mean follow-up of 40 ± 26.8 months, 13 deaths (20%) occurred (Table II), corresponding to an annual mortality rate of 6.1%. In the univariate Cox model, the variables of age, sex, education level, monthly income, ejection fraction, type of prevention, functional class, isolated use of β-blocker, administration of isolated amiodarone, and use of β-blockers associated with amiodarone were evaluated.

The functional class IV (hazard ratio [HR] 1.99; 95% confidence interval [CI], 1.05–3.76; over 200 beats per minute [bpm]). The clinical characteristics of the cohort are listed in Table I.
Table V.
Incidence of Appropriate Shocks in Patients with Chronic Chagas Disease Regarding Ejection Fraction of Left Ventricle

| Ejection Fraction | Total | Normal | Mild | Moderate | Severe | P  |
|-------------------|-------|--------|------|----------|--------|----|
| N                 | %     | n      | %    | n        | %      |    |
| Total             | 63    | 100.0  | 12   | 19.0     | 5      | 7.9| 14 | 22.2 | 32 | 50.8 |
| Shock appropriate/inappropriate | | | | | | |
| No shock          | 38    | 60.3   | 7    | 58.3     | 3      | 60.0| 9  | 64.3 | 19 | 59.4 |
| Shock             | 25    | 39.7   | 5    | 41.7     | 2      | 40.0| 5  | 35.7 | 14 | 43.8 |
| Shock appropriate | | | | | | |
| No shock          | 40    | 63.5   | 8    | 66.7     | 3      | 60.0| 9  | 64.3 | 20 | 62.5 |
| Shock             | 23    | 36.5   | 4    | 33.3     | 2      | 40.0| 5  | 35.7 | 12 | 37.5 |
| Shock inappropriate | | | | | | |
| No shock          | 59    | 93.7   | 11   | 91.7     | 5      | 100.0|13 | 92.9 | 30 | 93.8 |
| Shock             | 4     | 6.3    | 1    | 8.3      | 0      | 0.0 | 1  | 7.1  | 2  | 6.3  |

P = 0.034), primary prevention (HR 0.29; 95% CI, 0.09–0.99; P = 0.048), lower education (HR = 2.51; 95% CI, 1.05–5.99; P = 0.038), and ejection fraction <30% (HR = 2.80; 95% CI, 1.09–7.18; P = 0.032) were predictors of poor prognosis (death; Table III). In the multivariate Cox model, ejection fraction <30% and low education were predictors of poor prognosis. The functional class IV increased the risk of death by 3.5 times but not at a significance level of P < 0.05 (Table IV). There were 36.5% of appropriate shocks, with the patient receiving an average of 3.61 ± 3.9 appropriate shocks. In the bivariate Kaplan-Meier analysis, ejection fraction (P = 0.992), functional class (P = 0.770), and the type of prevention (P = 0.342) were not predictors of appropriate shocks (Tables V–VII). The functional class I was predictor of inappropriate shock (P = 0.045) probably because these patients would better tolerate physical exercises and develop sinus tachycardia with heart rate over 200 bpm (Table VI).

**Discussion**

In this study, the annual mortality from all causes was 6.1% without occurrence of sudden death. An ejection fraction lower than 30% and
low education were poor prognostic factors. The annual mortality rate from all causes and the incidence of sudden death were lower in this study, compared with mortality in a similar series of patients with chronic Chagas disease receiving only antiarrhythmic medication. Rassi et al. studied 424 patients with Chagas disease during a mean follow-up of 7.9 years; they found a 62% rate of sudden death in patients without ICD. In the same study, the authors reported that the combination of nonsustained VT and ventricular dysfunction were associated with a 15-fold greater risk of death compared to patients without those markers. Sarabanda and Marin-Neto recently reported a similar annual mortality rate of 10.7% in a series of 28 patients after a mean follow-up of 38 ± 16 months, of which 78% of deaths were sudden. Mady et al., in a study of 104 patients with follow-up of 30 ± 24 months, found a 50% mortality rate, of which 64% was due to sudden cardiac death. Bestetti et al., in a study involving 74 patients with a mean follow-up of 18 ± 12 months, reported a 44% rate of sudden cardiac death. Scanavacca et al., in a study of 35 Chagas disease patients with sustained VT treated empirically with amiodarone, found an estimated probability of sudden death of 11% in 3 years. The above-mentioned were conducted among patients without ICD.

In this study, the efficacy of ICD in primary and secondary prevention of sudden death appears to have contributed to the lower annual mortality rate (6.1%) and nonoccurrence of sudden cardiac death. The use of amiodarone combined with β-blockers probably had a greater effect on the survival of the cohort, but this result did not have statistical significance. Similar to our study, Martinelli et al. found an annual mortality of 7.1% with no sudden death, despite a 50% incidence of appropriate shocks, in 116 patients with Chagas disease who received an ICD for secondary prevention with follow-up of 42 ± 32 months. The ICD Register Latin American Chagas disease, which included 89 patients for primary and secondary prevention of sudden cardiac death with a short follow-up period, showed a 6.7% rate of 1-year mortality, similar to our findings.

Cardinalli-Neto et al. showed a higher annual mortality rate (16.6%) and a 7% rate of sudden death in a recent report of a cohort of 90 patients with Chagas disease and ICD. In this investigation, 71% of Chagas disease patients received either antitachycardia pacing or shock as device-based therapy. Forty percent of patients in this cohort were using β-blockers and amiodarone. We believe that our lower incidence of shock and sudden death rates compared to this study are due to our patients’ more intense use of β-blockers associated with amiodarone (69.8%), an association known to decrease shock occurrence. Bestetti et al. showed, in a study involving 231 patients with heart failure due to Chagas’ disease, that the use of β-blocker was effective in improving patient survival (HR = 0.34; 95% CI, 0.23–0.51; P < 0.005).

The average age of our study was a decade younger than patients with ischemic heart disease and ICD. We believe that the low education contributes to a worse prognosis because less-educated patients have lesser understanding of their pathology, which often leads to their not strictly following medical guidelines. Low educational
level probably also contributes to an inadequate nutritional habit with high intake of sodium and carbohydrates and a low intake of proteins. Unfortunately, although ChHD was discovered over a hundred years ago, the epidemiological profile of ChHD patients in our country has changed little. These patients are still characterized by low income, low education, and poor living conditions.

The occurrence of ICD shocks in 36.5% of our cohort highlights the high risk of recurrence of fatal tachyarrhythmias in patients with chronic ChHD. We found no difference in the incidence of appropriate shocks when we divided the cohort by type of prevention, functional class, or ejection fraction, which indicates that arrhythmias occur even in patients with normal ejection fraction and who never had events (primary prevention).

Cardinalli-Neto et al. studied a population of 19 ChHD patients with an ejection fraction <35%, NYHA functional class II, and ICD for primary prevention, and found that four (21%) patients experienced 94 episodes of VF.

**Conclusions**

Based on long-term follow-up, the ICD was effective in preventing sudden cardiac death in patients with chronic ChHD. An ejection fraction <30% and low education were predictors of poor prognosis. The type of prevention, functional class, and ejection fraction were not predictors of appropriate shocks. A limitation of the study was its design, a retrospective and uncontrolled study. Also, our patients were not compared to patients with the same characteristics but without ICD, impeding quantifying the actual survival benefit.

**References**

1. Control of Chagas disease: Second Report of the WHO Expert Committee. Geneva, Switzerland, World Health Organization; 2002. WHO Technical Report Series 905.
2. Rocha MO, Ribeiro AL, Teixeira MM. Clinical management of chronic Chagas cardiomyopathy. Front Biosci 2003; 8:e44–e54.
3. Rassi A Jr, Rassi SG, Rassi A. Sudden death in Chagas’ disease. Arq Bras Cardiol 2001; 76:75–96.
4. Muratore CA, Batista Sa LA, Chiale PA, Eloy R, Tenorti MC, Escudero J, Lima AM, et al. Implantable cardioverter defibrillators and Chagas’ disease: Results of the ICD registry Latin America, Europace 2009; 11:164–168.
5. Duhiner S, Valero E, Pesce R, Zuelgaray JG, Mateos JC, Filho SG, Reyes W, et al. A Latin American registry of implantable cardioverter defibrillators: The ICD-LABOR study. Ann Noninvasive Electrocardiol 2005; 10:420–428.
6. Toro D, Muratore C, Aguinalga L, Batista L, Malan A, Greco O, Benchetrit C, et al. Predictors of all cause 1-year mortality in implantable cardioverter defibrillator patients with chronic Chagas’ cardiomyopathy. Pacing Clin Electrophysiol 2011; 34:1063–1069.
7. Cardinalli-Neto A, Bestetti RB, Cordeiro JA, Rodrigues VC. Predictors of all-cause mortality for patients with chronic Chagas’ heart disease receiving implantable cardioverter defibrillator therapy. J Cardiovasc Electrophysiol 2007; 18:1236–1240.
8. Scannavacca MF, de Brito FS, Maia I, Hachul D, Gizzi J, Lorga A, Rassi A Jr, et al. Brasileira de Cardiologia S. Guidelines for the evaluation and treatment of patients with cardiac arrhythmias. [Portuguese]. Arq Bras Cardiol 2002; 79(Suppl 5):1–50.
9. Martinelli Filho M, Zimerman LI, Lorga AM, Vasconcelos JTM, Rassi A Jr. Guidelines for implantable electronic cardiac devices of the Brazilian Society of Cardiology. Arq Bras Cardiol 2007; 89:e210–e238.
10. Hinkle LE Jr, Thaler HT. Clinical classification of cardiac deaths. Circulation 1982; 65:457–464.
11. The Antiarrhythmics Versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal in ventricular arrhythmias. N Engl J Med 1997; 337:1576–1583.
12. Kuck KH, Cappato R, Siebels J, Rüppel R. CASH Investigators. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: The Cardiac Arrest Study Hamburg (CASH). Circulation 2002; 102:748–754.
13. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, Mitchell LB, et al. CIDS Investigators. Canadian Implantable Defibrillator Study (CIDS): A randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation 2000; 101:1297–1302.
14. Mady C, Cardoso RH, Barreto AC, da Luz PL, Bellotti G, Pileggi F. Survival and predictors of survival in patients with congestive heart failure due to Chagas’ cardiomyopathy. Circulation 1994; 90:3098–3102.
15. Sterneck EB, Martinelli M, Sampaio R, Gerken LM, Teixeira RA, Scarpelli RA, Scannavacca M, et al. Sudden cardiac death in patients with Chagas heart disease and preserved left ventricular function. J Cardiovasc Electrophysiol 2006; 17:113–116.
16. Scannavacca MF, Sosa EA, Lee JJ, Bellotti G, Pileggi F. Empiric therapy with amiodarone in patients with chronic Chagas cardiomyopathy and sustained ventricular tachycardia. Arq Bras Cardiol 1990; 54:367–371.
17. Sarabanda AV, Marin-Neto JA. Predictors of mortality in patients with Chagas’ cardiomyopathy and ventricular tachycardia not treated with implantable cardioverter-defibrillators. Pacing Clin Electrophysiol 2011; 34:54–62.
18. Rassi A Jr, Rassi A, Little WC, Xavier SS, Rassi SG, Rassi AG, Rassi GG, et al. Development and validation of a risk score for predicting death in Chagas’ heart disease. N Engl J Med 2006; 355:799–808.
19. Bestetti RB, Dalbo CMR, Arruda CA, Correia Filho D, Freitas OC. Predictors of sudden cardiac death for patients with Chagas’ disease: A hospital-derived cohort study. Cardiology 1996; 87:481–487.
20. Bestetti RB, Ottaviano AP, Cardinalli-Neto A, Rocha BF, Theodoropoulos TAD, Cordeiro JA. Effects of B-Blockers on outcome of patients with Chagas’ cardiomyopathy with chronic heart failure. Int J Cardiol 2011; 151:205–208.
21. Martinelli M, Siqueira SF, Sternick EB, Rassi A Jr, Costa R, Ramires JAF, Kalil Filho R. Long-term follow-up of cardioverter-defibrillator for secondary prevention in Chagas’ heart disease. Am J Cardiol 2012; 23:1944–1946.
22. Cardinalli-Neto A, Nakazome MA, Grassi LV, Tavares BG, Bestetti RB. Implantable cardioverter-defibrillator therapy for prevention of sudden cardiac death in patients with severe Chagas cardiomyopathy. Int J Cardiol 2011; 150:94–95.
23. Connolly SJ, Dorian P, Roberts RS, Gent M, Baillien S, Fain ES, Thorpe K, et al. Comparison of B-blockers, amiodarone plus B-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators. J Am Med Assoc 2006; 295:165–171.