Implantable cardioverter defibrillators and Chagas’ disease: results of the ICD Registry Latin America

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Aims
Chagas’ disease is an endemic parasitic affliction in Latin America. It is frequently associated with ventricular tachyarrhythmia and sudden death. The aim of this study is to assess the evolution of patients with Chagas’ disease treated with an implantable cardioverter defibrillator (ICD).

Methods and results
Eighty-nine chagasic patients with ICD were included for analysis from the Medtronic ICD Registry Latin America. At implant, mean age was 59 ± 10 years, and 72% were male. Eighty-one patients (91%) had secondary prevention indications. Mean left ventricular ejection fraction was 40 ± 11%, and mean follow-up was 12 ± 7 months. During follow-up, six patients died (6.7%); three due to congestive heart failure, one due to sudden death, and two due to non-cardiac cause. Hospitalization occurred in seven patients. Thirty-eight patients (42%) received appropriate ICD therapies. A total of 737 episodes were detected by the ICD. The mean period between ICD implantation and the first appropriate therapy was 104 days. Electrical storms were observed in 14 of the 89 patients (15.7%). Inappropriate therapies were observed in seven patients.

Conclusion
This registry confirms that ICD therapy provides protection by effectively terminating life-threatening arrhythmias in patients with Chagas’ disease. This is especially so when patients receive the device for secondary prevention.

Keywords
Defibrillators • Chagas’ disease • Sudden death • Ventricular arrhythmias • ICD

Introduction
Chagas’ disease is an endemic disease in Latin America caused by an unicellular parasite, the Trypanosoma cruzi. Almost 18 million people are infected,1 and ~25% of them develop chronic myocardial disease after years or decades. The intermediate phase may last for two to three decades, and only the manifestation of the disease is the immunological reaction. The main causes of death are congestive heart failure and sudden cardiac death2,3 due to dilated cardiomyopathy. Although malignant ventricular arrhythmias are thought to be the main cause of sudden death, bradyarrhythmias and thrombo-embolic events also account for some of the sudden death.4,5 Chagas’ disease has become a worldwide problem, given the new patterns of immigration. Physicians around the world should become aware of its existence and how to recognize and treat it.6

Implantable cardioverter defibrillators (ICDs) are a first-line tool for primary and secondary prevention of sudden death.7–11 However, the efficacy and safety in treating patients with Chagas’ disease have been assessed in few studies.12–14

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The aim of this retrospective study is to summarize our experience in patients with Chagas’ disease and life-threatening ventricular arrhythmias implanted with ICDs and to classify the type of spontaneous ventricular tachyarrhythmia presented and the respective therapy provided by the device.

Methods

Patient population
The Medtronic ICD Registry was introduced in Latin America to collect data on the pathological conditions, leading to the indication of ICDs in the region. This registry includes data from patients living in Puerto Rico and the Caribbean, Mexico, and South America implanted with a Medtronic ICD. Between January 2005 and August 2007, 307 consecutive patients were included in the registry. Eighty-nine patients (17.5%) were diagnosed as having Chagas’ disease. This disease was diagnosed according to the criteria proposed by each institution (at least to have one positive serological test for Chagas’ disease: indirect haemaglutination, complement fixation, or ELISA indirect immunofluorescence). Patients with other concomitant diseases, which could induce heart disease by itself, were ruled out from this analysis. The study complies with the Declaration of Helsinki, and the protocol was approved by the local Ethics Committee. Informed consent for ICD implantation was obtained from all patients, and procedures were performed according to each institutional guidelines.

Demographic data, ECG, two-dimensional echocardiogram, and concomitant treatment were reported in all patients.

Implantable cardioverter defibrillators
Single- (20%) or dual-chamber (80%) Medtronic ICDs (Medtronic, Minneapolis, MN, USA) were implanted. All devices had storage capability to help in the retrospective analysis of intracardiac electrograms. Heart rate cutoff criteria for the detection of ventricular tachyarrhythmias and therapies were programmed and activated according to the treating physician’s discretion.

Evaluation of events and implantable cardioverter-defibrillator therapies
Follow-up visits were scheduled at 6-month intervals or in the case of multiple shocks or an adverse event that required ICD follow-up. Stored data were analysed to classify tachyarrhythmia. The electrograms were analysed according to the following criteria. Ventricular fibrillation (VF) was defined as ventricular arrhythmia with a cycle length of 240 ms or less. Ventricular tachycardia (VT) was defined as regular morphology (monomorphic) or irregular (polymorphic) ventricular arrhythmia, with a cycle length of >240 ms. Appropriate intervention was defined as an ICD shock or anti-tachycardia overdrive pacing delivered in response to ventricular tachyarrhythmia. Inappropriate intervention was defined as those triggered by a rapid ventricular rate due to supraventricular tachyarrhythmias, sinus tachycardia, or devices malfunction. All stored electrogrograms were classified as appropriate or inappropriate by three experienced electrophysiologists. Disagreement was resolved by consensus. Electrical storm was defined as the occurrence of VT or VF, resulting in device intervention three or more times within a 24 h period.

Statistical analysis
Baseline descriptive statistics are presented as mean ± SD for continuous variables and numbers with percentages for categorical variables. Differences between categorical variables were evaluated by Fisher’s exact test or chi² test. A probability value of <0.05 was considered statistically significant.

Results
The clinical characteristics of the study population are summarized in Table 1. Seventy-two per cent of the patients were male; mean age at the time of implant was of 59 ± 10 years. Seventy-two percent of the patients presented with heart failure New York Heart Association functional class I/II. Mean left ventricular ejection fraction (LVEF) was 40 ± 11%, and mean left ventricular end-diastolic diameter was 61 ± 7 mm. Biventricular pacemaker with ability to defibrillate (CRT-D) was implanted in eight patients.

At the time of hospital discharge, 40 patients received concomitant anti-arrhythmic drugs, including amiodarone (n = 38) or class 1 drugs (n = 2, propafenone) to prevent ventricular arrhythmias. Others drugs used were β-blockers (n = 27, 30%) and angiotensin-converting enzyme inhibitors (n = 23, 26%).

At the time of the last follow-up (mean 12 ± 7 months), 71 patients (80%) received anti-arrhythmic drugs, including amiodarone (n = 70) and propafenone (n = 1). In addition, 56 patients were treated with β-blockers (63%).

The main clinical indication for ICD implant was secondary prevention (n = 81; 91%). Twenty patients had a history of sustained VT with haemodynamic deterioration; 47 patients sustained monomorphic VT without haemodynamic deterioration; 2 patients had unexplained syncope; and 12 had a history of aborted cardiac arrest. Eight patients received the ICD for primary prevention of sudden death.

After a mean follow-up of 12 ± 7 months (range 1–30), six patients died (6.7%). Three patients died due to congestive heart failure, one due to sudden death, and two due to non-cardiac cause. Thirty-eight patients (42%) received one or more appropriate ICD therapies, in whom the ICD terminated VF/flutter (2 patients) or VT (36 patients).

During follow-up, only seven patients were hospitalized (three due to atrial fibrillation, two due to ventricular tachyarrhythmia and electrical storm, and two due to decompensate heart failure).

### Table 1 Clinical demographic data

<table>
<thead>
<tr>
<th>Age (mean, SD) (range)</th>
<th>59 ± 10 (18–80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n, male/female</td>
<td>78/11</td>
</tr>
<tr>
<td>NYHA functional class I/II/III/IV, n (%)</td>
<td>11/53/20/5</td>
</tr>
<tr>
<td>(12/60/22/6)</td>
<td></td>
</tr>
<tr>
<td>LVEF (%) (mean, SD) (range)</td>
<td>40 ± 11 (16–73)</td>
</tr>
<tr>
<td>(61 ± 7 (40–77))</td>
<td></td>
</tr>
<tr>
<td>LVEDD (mm) (mean, SD) (range)</td>
<td>61 ± 7 (40–77)</td>
</tr>
<tr>
<td>Indication</td>
<td></td>
</tr>
<tr>
<td>Primary prevention, n (%)</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Secondary prevention, n (%)</td>
<td>81 (91)</td>
</tr>
<tr>
<td>Sustained ventricular tachycardia, n (%)</td>
<td>67 (82.5)</td>
</tr>
<tr>
<td>Aborted sudden death, n (%)</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Syncope, n (%)</td>
<td>2 (2.5)</td>
</tr>
</tbody>
</table>

Baseline characteristics of 89 patients with Chagas’ disease implanted with an ICD. SD, standard deviation; n, number; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter.
A total of 737 episodes of ventricular tachyarrhythmia in 38 patients (19.4 episodes/patient, range 1–250 episodes) were detected. Implantable cardioverter defibrillator shocks were delivered in 35 episodes, anti-tachycardia pacing (ATP) in 554, and both in 107. Shock therapy was observed in 22 patients (in 10 patients following unsuccessful ATP). Mean cycle length of ventricular arrhythmias was $380 \pm 69$ ms (range 210–630). Three episodes were classified as VF ($230 \pm 17$ ms), two as polymorphic VT ($270 \pm 14$ ms), and 732 as monomorphic VT ($381 \pm 68$ ms). The total number of episodes and the different cycle lengths are shown in Figure 1. Seventy-six per cent of the episodes were terminated by ATP, 17.9% with shock, and 5.6% spontaneously (Figure 2). No patient with ICD for primary prevention indication received appropriate therapy.}

Appropriate ICD intervention rates were similar in patients presenting with sudden death (50%), VT with haemodynamic deterioration (50%) or without haemodynamic deterioration (47%), or unexplained syncope (50%).

Forty-four of the 89 patients had LVEF $>40\%$, whereas 8 (18.1%) suffered from ventricular tachyarrhythmias, who required ICD treatment. In contrast, 30 of the 45 patients (66%) with LVEF $<40\%$ received ICD therapies ($P = 0.0001$).

Time to first appropriate intervention (ATP or shock) was 104 days (range 2–832).

Electrical storm was observed in 14 patients (15.7%). The interval between ICD implant and electrical storm was 3–480 days (average 105 days). The VT storm episode was the reason for the first delivered therapy in three of these patients. The mortality rate in patients with electrical storm was 7.1%, while those without electrical storm had a mortality rate of 6.6% ($P = \text{ns}$).

Seven patients (8%) experienced inappropriate therapy during follow-up. All of them due to atrial fibrillation with rapid ventricular response.

**Discussion**

This large observational registry reports the clinical impact of ICD therapy in patients with Chagas’ disease treated for the prevention of sudden death.

The mortality rate in our study was 6.7% during the first year. There were discrepancies in the mortality rate between Chagas’ disease patients with ICDs in previous studies. Cardinalli-Neto et al. published their experience with 46 Chagas’ disease patients implanted with an ICD. During a mean follow-up time of 587 ± 439 days, no patient died during the study period. Cardinalli-Neto et al. also recently reported the largest single-centre experience in Chagas’ disease patients, 90 patients received an ICD for secondary prevention. During a mean follow-up of 756 ± 581 days, 31 of 90 patients (34%) died. The total mortality rates were 18, 27, 40, 50, and 73% after 1, 2, 3, 4, and 5 years, respectively.

One of the major findings was that a large number of patients had at least one episode of ventricular tachyarrhythmia that required ICD therapy in a relatively short follow-up. This high incidence of ICD therapies is in agreement with data from other series of patients reported previously. In our cohort, VT was by far the most frequent event detected by the ICD regardless of implant indication. In contrast to our findings, Cardinalli-Neto et al. observed that a substantial number of patients presented with VF instead. This difference may be explained in part because they included 91% of the patients with aborted sudden death and in our registry only 15% had aborted cardiac arrest.

Patients with Chagas’ cardiomyopathy seem to be more prone to develop arrhythmic events in the first month after implant. In our registry, the mean time to first appropriate therapy was 104 days. This is in accordance with a prior report from Rabinovich et al., who showed a high percentage of appropriate shocks in the early period after device implantation (6 months) in a chagasic population.

Anti-arrhythmic drugs were used very frequently during follow-up due to arrhythmic recurrences (VT/VF) that required shocks from the ICD.

One-third of our patient population (37%), which received ICD therapies, presented electrical storms. This fact reflects that 15.7% of the total population of our study (14 of 89 patients) experienced electrical storms. Prior studies in patients with ICDs in different clinical populations reported a similar incidence of electrical storms that varied between 10 and 18.3%. In concordance...
with those studies, we did not observe a greater mortality rate in patients suffering from electrical storm. The mortality rate in patients with electrical storm was 7.1%, whereas those without electrical storm had a mortality rate of 6.6% (P = ns).

We ignore the precise reason for this very high incidence in patients with Chagas’ disease. It is possible that the high ventricular ectopic density usually seen in this population could be the trigger for sustained arrhythmias. Additionally, modulating factors such as the neurovegetative imbalance observed in carriers of this disease may facilitate the electrophysiological substrate for triggering ventricular arrhythmias.

The most frequent complication observed during follow-up was inappropriate shocks. Inappropriate therapy occurred in 8% of the patients due to spurious shocks over supraventricular arrhythmias. This percentage is lower than previously reported in the setting of non-ischaemic cardiomyopathy. It is highly likely that the high percentage of patients with dual-chamber devices (80%) could contribute to a lower incidence of inappropriate therapies. The use of anti-arrhythmic drugs during follow-up could also contribute to the same observation (amiodarone 80% and β-blockers 63%).

According to the international guidelines, patients with sustained VT without a haemodynamic compromise and an LVEF >0.40 may not have a definite indication to ICD therapy. In our study, 44 of the 89 patients had LVEF >40%, whereas 8 (18.1%) suffered from ventricular tachyarrhythmias who required ICD treatment. In contrast, 30 of the 45 patients (66%) with LVEF <40% received ICD therapies (P = 0.0001). No patients with primary indication for ICD implantation received therapy.

No randomized clinical trials had evaluated primary prevention of sudden cardiac death in patients with Chagas’ disease.

Non-sustained VT is an independent predictor of total mortality in Chagas’ cardiomyopathy. Silva et al. found that Chagas’ patients with non-sustained VT had a significant association between induced sustained VT and sudden cardiac death.

In comparison with standard medical therapy and amiodarone, ICD therapy has shown to improve survival in patients with depressed left ventricular function. No patients with Chagas’ cardiomyopathy were included in induced prevention trials. We could speculate that ICD therapy may represent a benefit to prevent sudden death in patients with Chagas’ cardiomyopathy and low ejection fraction. As previously reported by Rassi, the urgent need for a randomized trial in Chagas’ disease is imperative in order to clarify our understanding in this pandemic Latin American affliction.

**Limitations**

There are several limitations to consider when interpreting the results of this registry.

This is an observational study of 71 collaborative medical institutions, with possible bias in patient selection. This registry included only Medtronic devices. The mean follow-up was short (12 months). As Chagas’ disease is a slowly progressive disease, it is possible that more appropriate and inappropriate therapies and even other complications may be observed during a longer follow-up.

**Conclusions**

This registry confirms that ICD therapy provides protection by effectively terminating life-threatening arrhythmias in patients with Chagas’ disease. This is especially so when patients receive the device for secondary prevention purposes.

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**Conflict of interest:** C.A.M. has conducted research and given lectures for Medtronic. R.G. and J.M. are employed by Medtronic.

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