Sudden Cardiac Death in Chagas Disease

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Abstract

Chagas disease remains a major epidemiologic problem in endemic countries. The most dramatic course of the disease is represented by sudden cardiac death. Some of these deaths could be preventable, if efforts are directed towards identifying high-risk patients. Implantable cardioverter-defibrillators are an effective treatment for the prevention of sudden cardiac arrhythmic death, however; its costs are the major limitation for their widespread use in the endemic region. This review will cover some of the most relevant aspects of sudden cardiac death in Chagas disease.

Key words: Chagas Disease; Sudden Death; Ventricular Tachycardia

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Epidemiology

Sudden death is a non-traumatic, unexpected fatal event occurring within 1 hour of the onset of symptoms in an apparently healthy subject. If death was not witnessed, a recent definition includes the one that occurs in someone in good health 24 hours before the event.1 Sudden cardiac death (SCD) is the predominant mode of death in Chagas cardiomyopathy, followed by death associated with heart failure with an annual mortality rate varying from 0.2% to 19.2%.²

Epidemiological data about sudden death in Chagas disease rates are conflicting, because they are under the influence of several factors, such as the definitions used to determine sudden death, populations under study and demographic characteristics. It is also influenced by the stage of the disease, the degree of ventricular dysfunction, the type of treatment administered, and obviously, the follow-up of a given population.

Mainly, there are two different ways of dying unexpectedly in Chagas disease: (i) Patients with no signs or symptoms of the illness (unexpected sudden death), and (ii) patients in whom death is preceded by manifestations of the disease (expected sudden death).

There was a reduction of transmission of the disease in South America that has led to a 70% reduction in the incidence of Chagas disease in the whole region (Latin America): the number of incident cases decreased from an estimated 700,000 new cases per year in the whole region in 1983 to 41,200 new cases per year in 2006. Moreover, the annual number of deaths dropped from more than 45,000 to 12,500.³ However, the real incidence of sudden death in Chagas disease remains unknown.

Braggion-Santos et al retrospectively reviewed 4501 autopsy reports between 2006 and 2010, to identify cases of SCD in Brazil. Forty-nine patients (5.5%) had diagnosis of Chagas disease, including those with previously known Chagas cardiomyopathy (ChCM) and those with positive serology at the time of the autopsy.

The proportion of patients with Chagas disease decreased from 2006 to 2010 (12 patients: 7.1% in 2006, 13 patients: 7.0% in 2007, 11 patients: 5.8% in 2008; five patients: 3.0% in 2009, eight patients: 4.3% in 2010), but the difference over the years did not reach statistical significance (p = 0.14).³

It is difficult to know if this work represents the reality of Latin America as a region because Brazil is considered as having a high prevalence of human infection (1.9 million infected individuals in 2005), with ChCM still having a very important role in cardiovascular mortality in this country, especially in cases of sudden death.⁴

According to unofficial statistics, around 50,000 deaths due to Chagas disease occur every year, 60% of which are sudden. As 16 to 18 million infected individuals live in Latin America, the annual rate of sudden death may be estimated in 0.17 to 0.19%.⁵

SCD in Chagas disease is closely related to the presence of heart disease; between 20 and 30% of Chagas disease patients will develop some degree of cardiac disease during the infection and the annual rate of sudden death in Chagas disease patients with demonstrated heart disease increases from 0.56 to 0.94%.⁶ However; it may be possible to discriminate a sub-group at higher risk of SCD (left ventricular dysfunction, complex ventricular arrhythmias, etc).
Pathophysiology

Sudden death in patients with Chagas disease occurs predominantly in males between 30 and 50 years of age. It usually happens during routine activities, physical exertion, or emotion. In contrast with ischemic heart disease, the circadian variation reveals that deaths occur predominantly during the evening between 12 am to 6 pm.6

Confirmation of the exact mechanism of sudden death in Chagas disease is extremely difficult and complex. All reports on the mechanisms of sudden death in Chagas disease are mainly based on observations, hypotheses and inferences.7, 8

A patient with Chagas disease can suddenly die due to arrhythmic causes or due to non-arrhythmic causes. Non-arrhythmic causes are not uncommon and include: massive pulmonary embolism, cardio-embolic stroke or rupture of a left ventricular apical aneurysm. In the vast majority of cases, therefore, SCD in patients with Chagas disease is essentially an arrhythmic phenomenon (both brady and tachyarrhythmia phenomena).

Nearly 95% of patients who died suddenly had an abnormal 12-lead electrocardiogram: ventricular premature contractions are observed in 79% of patients, and conduction disorders are also frequently observed: right bundle branch block is seen in the vast majority of patients and anterior fascicular block is seen in 58% of patients.9

When the pacemaker was not yet available to the community, the most common cause of sudden cardiac death was sudden paroxysmal 3rd degree AV block. Currently, AV block only exceptionally may be a cause of sudden cardiac death in Chagas disease patients due to accessible pacemakers to this population.10

Some authors have found in studies analyzing Holter recordings, a high prevalence of ventricular fibrillation as the cause of death. But the most compelling evidence was found in patients who have received ICD therapy (stored EGMs). Cardinalli Neto et al showed in 46 consecutive Chagas disease patients with an ICD implanted, 84% patients received any ICD therapy (shocks or anti-tachycardia pacing). Ventricular fibrillation was the cause of first shock in 12 patients (32%), ventricular tachycardia in 11 (29%), and ventricular tachycardia not responding to anti-tachycardia pacing degenerating into ventricular fibrillation in nine (24%).11 Thus, patients with chronic ChCM who survived cardiac arrest have a peculiar arrhythmogenic profile characterized by frequent episodes of ventricular fibrillation.

Our group published a series of 148 Chagas patients with ICDs. During an average of 18 months follow up, 42.5% presented appropriate ICD therapies and 10.2% of the patients died.12 The cause of death was labeled as cardiac in 20% all of them (mostly heart failure progression), non-cardiac deaths occurred in seven (46.6%; stroke in three patients, pneumonia in three patients, and Dengue in one patient), and SCD in 26.6%. Probably these patients are highly selected and represent a group with higher risk than patients with asymptomatic forms of Chagas disease. But there is no doubt that the arrhythmic death remains the main cause of sudden death in Chagas disease. For the development of any sustained arrhythmia some circumstances are generally present, such as a fixed substrate, a trigger and finally a modulating condition.

In the heart of a patient with Chagas disease there are macroscopic and microscopic changes, the presence of segmental wall motion abnormalities, particularly the left ventricular apical aneurysm, reflects the underlying myocardial substrate.13 Premature ventricular complexes and non-sustained VT are common findings in Holter recordings and may play a role triggering ventricular arrhythmia. Patients with Chagas disease may have also an increased parasympathetic tone. It may explain the circadian behavior of the arrhythmia and modulate ventricular arrhythmias. An increased number of premature ventricular contractions can be seen in patients with Chagas disease affected by autonomic dysfunction.14

In summary the structural changes in the left ventricle associated with changes in the cardiac autonomic nervous system can contribute for triggering sudden cardiac death in patients with ChCM.

Predictors of mortality

There are several prognostic factors in ChCM associated with higher mortality that have been assessed in different populations. There are clinical factors and factors derived from complementary studies. Due to the multiple factors associated with poor prognosis, the optimal strategy to combine prognostic determinants to better stratify risk of death is the best way to assess the risk of the Chagas disease patient.

Clinical Factors

Male gender seems to be associated with an adverse prognosis in Chagas disease. Male patients are more commonly affected with ChCM and was associated with increased mortality in some prospective studies.15, 16, 17

Functional capacity as evaluated by NYHA functional class is the most consistent marker of poor prognosis in all heart conditions. ChCM is not the exception. NYHA functional class III and IV provide independent and additional prognostic information to the left ventricular ejection fraction2 to prognosticate worse evolution.

Syncpe as a marker of increased mortality is the assumption that the underlying cause of syncpe is malignant ventricular tachycardia. However, there are many other causes for syncpe, and it does not appear to be an independent predictor of death.

ECG markers

The role of the ECG in the management of patients with Chagas disease is very important. ECG evaluation is essential to assess the risk of adverse outcomes and also to determine the presence of cardiac involvement. An abnormal ECG has been associated with increased mortality in Chagas disease. The most common findings are right bundle branch block and left anterior fascicular block. The following findings are associated with poor prognosis17, 18, 19:

1. Right bundle branch block
2. ST-segment elevation
3. Atrial fibrillation
4. Increased heart rate
5. Premature ventricular contractions on resting ECG
6. Pathological Q waves
7. Low QRS voltage
8. QT dispersion or maximal-corrected QT interval were associated with adverse outcomes in some series20
9. The presence of surface fragmented QRS (QfQRS) is a marker of arrhythmias in patients with ischemic heart disease, cardiomyopathies and ion channel diseases.21

Our group studied patients with ChCM and ICD with the aim to evaluate the role of QfQRS as a marker of arrhythmias.22 We included 98 patients from 14 centers in Latin America; the mean follow up was 33±20 months. QfQRS was found in 56 of the patients (59.6%). Location of the fragmentation was inferior.
in 57.1%, lateral 35.7% and anterior 44.6%. Predictors of appropriate therapy in the multivariate model were increased age (p=0.01), secondary prevention indication for the ICD (p=0.01) and ventricular pacing >50% of the time (p=0.004). The presence of fQRS did not identify patients at higher risk of presenting appropriate therapies delivered by the ICD (p=0.87); regardless of QRS interval duration.

Despite the fact that our study was not originally designed to answer why fQRS was not found to be a marker of arrhythmia, the above mentioned physiopathological reasons may help to explain the disparity with the results of studies in other clinical scenarios.

**Holter monitoring**

Non-sustained Ventricular Tachycardia (NSVT) on ambulatory ECG monitoring has been demonstrated to indicate worse evolution in patients with ChCM. In addition, the combination of NSVT and left ventricular dysfunction was associated with a 15-fold increased risk of death compared with patients without both risk markers. Rassi et al showed the prevalence of cardiac arrhythmias on Holter monitoring. They included 143 ChCM patients who underwent 24-hour Holter monitoring so that their arrhythmias could be quantified. Presyncope or syncope were reported by 14% patients, of whom 80% had episodes of NSVT and 30% had bradyarrhythmias.

**Exercise Test**

Exercise-induced ventricular tachycardia (sustained and NSVT) has been significantly associated to sudden cardiac death in short and long-term follow-ups. Pedroza et al showed a high prevalence of exercise induced ventricular arrhythmia in clinically stable chagasic patients, representing about 43%, 1% of the cohort. During a 9.9 years follow-up, the patients with exercise-induced ventricular arrhythmia presented worse prognosis, especially those with cardiomegaly on x ray.

**Echocardiogram**

Echocardiography is one of the most useful diagnostic tests for initial evaluation and follow-up of patients with chronic Chagas disease. Different prognostic echocardiographic parameters have been described, most of them related to left ventricular function. Some studies have found that left ventricular systolic dimension and ejection fraction were independent prognostic markers of mortality. Left ventricular function (LVEF) is the most common independent predictor of death in many studies. We recently published that age more than 65 years and LVEF less than 30% were independent predictors of all-cause mortality in patient with ChCM and ICD implanted. However, it is important to note that sustained VT, the main cause of sudden death in Chagas disease patients, may occur also in patients with preserved left ventricular function.

Some studies have found that right ventricular dysfunction was a powerful predictor of death, adding incremental prognostic value to NYHA functional class and LVEF. There are several demographic, clinical and noninvasive variables that have been tested. Given the high variety of variables, risk scores have been designed in order to facilitate the screening of risk.

Viotti et al published the first score in 2005. The authors demonstrated that age, left ventricular systolic diameter, intraventricular conduction abnormalities, sustained VT and treatment with benznidazole were predictors of heart disease progression. These variables were used to build a clinical risk score. The scores assigned to each variable are shown in Table 1. The maximum risk score on this scale is 10; a score of 0 represents no risk. The risk of progression is plotted in Figure 1. Some issues about this score need to be clarified. The score predicts risk progression, but it does not predict death or sudden death. In Viotti series there was significant loss of follow-up (26%) and this may alter the predictive power of the score. Finally there was not a control group to validate the score.

In 2006, Rassi et al published another score tested in 424 patients and validated in 1053 patients with Chagas disease. The scores assigned to each variable are shown in Table 2. Arisk score derived by the combination of points attributed to each of these features accurately classified patients into a low (0-6 points), medium (7-11) or high-risk (12-20) group. The risk of cardiovascular mortality at 5 and 10 years is depicted in Figure 2. The C statistic in the development cohort was 0.84 (95% CI 0.79 -0.89). This means a great power of score discrimination. It is useful to remember that the score's variables were also strong predictors of the risk of death from cardiovascular causes and sudden death from cardiac causes, except for male sex, which was of borderline significance for the prediction of death from cardiovascular causes, and low QRS voltage, which was of borderline significance for the prediction of sudden death from cardiac causes.

Recently, Ribeiro et al. developed another simple risk score testing the value of a wide QRS complex in predicting risk of death in patients with Chagas disease. Three independent prognostic factors were identified: LVEF <50%, ventricular tachycardia at either Holter monitoring or stress testing and prolonged (>150 ms) filtered QRS complex. Each score's variable add an extra point. Patient with 0-1 point had 1% probability of death; patients with 2 points had 20% probability of death and with 3 points, 50% probability. It is important to note that established risk factors for Chagas disease, such as NYHA class, were not selected in the final model and the use of signal-averaged ECG is not used in many centers, which limits the routine use of this score.

| Table 1. The scores assigned to each variable in Viotti’s score (Modified from reference 27) |
| Variable | Point s |
| Age older than 50 years | 2 |
| Systolic diameter more than 40 mm | 3 |
| Intraventricular conduction disorders | 2 |
| Sustained ventricular tachycardia | 3 |
| Benznidazole treatment | -2 |

| Table 2. The scores assigned to each variable in Rassi’s Score (Modified from reference 16) |
| Variable | Points |
| New York Heart Association class III or IV | 5 |
| Cardiomegaly (chest x-ray) | 5 |
| Segmental or global wall motion abnormality (echo) | 3 |
| Non-sustained ventricular tachycardia (24-h Holter) | 3 |
| Low QRS voltage (ECG) | 2 |
| Male sex | 2 |
A considerable limitation of all risk-prediction models is that they were developed considering all-cause mortality as the end point. Sudden cardiac death, however, is the most common mode of death in Chagas disease. There is no prediction model for sudden death. Sudden death, but not death from progressive heart failure, is preventable by the implantation of cardioverter-defibrillators and the development of a risk score specifically designed to recognize the risk of sudden death would be of great clinical value.

**Treatment**

**Anti-arrhythmic treatment**

Amiodarone is widely used as an antiarrhythmic agent in patients with Chagas disease. A classic study from Rosenbaum et al showed that amiodarone is the most effective antiarrhythmic drug in ChCM and is well tolerated (30). Due to its toxicity, amiodarone should not be used in patients with mild disease or good prognosis. Monomorphic simple premature ventricular ectopy seems to have no impact on the prognosis of Chagas disease and do not require specific treatment. There are controversies surrounding the use of antiarrhythmic therapy in complex ventricular ectopy in patients with reduced LVEF. In symptomatic patients without ventricular dysfunction, antiarrhythmic treatment can be individualized. When ventricular ectopy and NSVT are present in patients with left ventricular dysfunction, amiodarone is a safe drug to use. In spite of an absence of strong evidence that amiodarone improves the prognosis of these patients, its effects on the long-term reduction in the density of the arrhythmias and on the control of symptoms is well known.

**Implantable cardioverter-defibrillator**

The mechanisms most frequently involved in sudden death in ChCM are malignant ventricular arrhythmias, VT degenerating into VF and VF not preceded by VT as described above. The ICD has become the main therapeutic strategy for preventing sudden death in different heart diseases. The usefulness of ICDs among patients with ChCM has been evaluated in previous observational studies; however, no large randomized controlled trials have examined the efficacy and safety of treatment with ICDs in ChCM yet. The treatment of ventricular arrhythmias in Chagas disease patients using ICD implantation is empirical, based on extrapolated recommendations for heart disease of other etiologies.

Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities recommended ICD implantation in ChCM patients for primary and secondary prevention of sudden cardiac death. The Brazilian Ministry of Health recommends that ICDs should be implanted in the following 3 situations:

1. Resuscitation from cardiac arrest due to documented sustained VT or VF due to a non-reversible cause, with LVEF less than or equal to 35% or structural heart disease.
2. Spontaneous VT due to a non-reversible cause, with LVEF less than or equal to 35% or the presence of structural heart disease.
3. Syncope of unknown origin, with inducible, hemodynamically unstable or clinically relevant VT or VF, with LVEF less than or equal to 35% or the presence of structural heart disease.

A few prospective, observational studies and prospective, non-randomized studies have examined a limited number of Chagas disease patients. Studies of ICD implantation in patients with ChCM have aimed to evaluate its efficacy and safety and to identify predictors of appropriate therapy. As an example, Cardinali-Neto et al recently reported the largest single center experience on ICD implantation in Chagas disease patients. They analyzed 90 patients receiving 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. The number of shocks per patient by day 30 was found to be the only independent predictor of all-cause mortality.

Muratore et al analyzed data from 89 patients with ChCM implanted with ICD, 91% of them due to secondary prevention. After a mean follow-up of 12 months, the total mortality was 6.7%. A total of 737 episodes of ventricular tachyarrhythmias in 38 patients were detected. ICD shocks were delivered in 35 episodes (4.8%), antitachycardia pacing in 554 (75.1%), and both in 107 (13.1%). Appropriate ICD intervention rates were similar in patients presenting with sudden death (50%), VT with hemodynamic deterioration (50%) or without hemodynamic deterioration (47%), or unexplained syncpe (50%).

Several studies have compared the results of ICD implantation in patients with ChCM and patients with other etiologies to determine commonalities and differences between these populations. The use of ICDs appears to provide effective protection for Chagas patients and constitutes a safe procedure with low frequencies of inappropriate therapy and complications, despite having been assessed in only few prospective and retrospective observational studies that examined limited numbers of patients.

**Resynchronization therapy in Chagas disease**

Cardiac resynchronization therapy (CRT) has become an established treatment for patients with moderate to severe heart failure, wide QRS complex, optimized heart failure treatment, and evidence of ventricular dyssynchrony.
Randomized controlled clinical trials have shown that CRT improves NYHA functional class, exercise capacity, quality of life, and hemodynamics and reduces morbidity and mortality. The speculation of which patients may benefit from CRT is mostly based on the results of clinical trials. No patients with ChCM were included in these large trials. Only a few papers with small numbers of patients using cardiac resynchronization (CRT) have been published to date. Alves Fagundes et al recently reported their experience on CRT implantation in Chagas disease patients. They analyzed 19 patients within a mean follow up of 24.7 ± 20 months. The LVEF improved from 28% ± 5% to 32.2% ± 11% and the NYHA functional class decreased from 3.5 ± 0.5 to 2.5 ± 0.8. No differences were found when compared with ischemic or idiopathic dilated cardiomyopathy patients. More recently, Araujo et al. published an article dealing with CRT in patients with heart failure secondary to ChCM. The authors enrolled 72 patients in class III/IV, 100% on beta-blocker therapy, 70% on angiotensin converting enzyme inhibitor/angiotensin receptor blocker, 47% with left bundle branch block, mean QRS duration 148.1 ± 17.5 ms, mean left ventricular systolic diameter 66.2 ± 7.6 mm, and mean LVEF 27.3 ± 7.7%. After a mean follow-up of 47 months, only 13% were in class III/IV, there was an 81% increase in the LVEF, and a 12% decrease in the left ventricular systolic diameter. Importantly, this is the largest cohort of patients with CHF secondary to Chagas cardiomyopathy receiving CRT reported so far.

It seems reasonable to indicate CRT to patients with refractory heart failure secondary to ChCM with a clinical picture similar to that found in non-Chagas disease heart failure patients. However, before making solid statements not based on solid evidence, ongoing trials using CRT in ChCM should be waited, as promising results are expected. One consideration should be given to the high prevalence of right bundle branch block (RBBB) in ChCM. In some studies, PR prolongation associated with RBBB has shown similar response to CRT than those with LBBB, so extrapolating from those studies would be an option until more data on CRT in ChCM becomes available. One should take into account that RBBB associated with left anterior fascicular block (a common finding in ChCM) has shown poor response to conventional CRT.

Cell therapy in patients with Chagas disease

Heart transplantation is the only available option for patients with heart failure that failed optimum pharmacological and electrical treatment. There are several limitations to performing heart transplantation in patients with Chagas disease, not only because its high costs and the scarcity of donated organs, but also because the need of immunosuppressive agents after transplantation that may reactivate latent infections. The discovery of stem cells capable of differentiating into specialized cell types has opened new avenues for the treatment of heart failure due to ChCM. This therapy is able to ameliorate heart disease caused by chronic infection with Trypanosoma cruzi, repairing the heart tissue damaged by the pathological process using the patient’s own cells. Vilas-Boas et al published the first report on this topic in 2006. The efficacy of the therapy was evaluated in 28 patients in whom 50 mL of bone marrow aspirate was collected from each patient by multiple punctures of the two iliac crests. A significant improvement in several parameters during a 60 day follow-up also suggested a potential benefit of the therapy. These included improvements in NYHA functional class, the Minnesota quality of life questionnaire , the distance walked in six minutes, and the LVEF (20.1 ± 6.8% to 23.0 ± 9.0%, P = 0.02). Trainini et al showed their experience in five patients with cell therapy in chagasic patients with heart failure NYHA III/IV. At 17.2 ± 8.8 months, 4 patients were alive and with NYHA I (<0.005). One patient died suddenly after 17 months of follow up. An increase of the LVEF was observed (27.6% ± 5.9% to 36.6% ± 2.3%; P< 0.05). Although information is limited, cell therapy in patients with Chagas disease can be useful for some kind of highly selected patients.

Heart transplantation

Indications for heart transplantation in patients with chronic heart failure secondary to ChCM is debatable and somewhat difficult to implement, in comparison to non-Chagas disease patients. There have been many concerns with regards to the usefulness of heart transplantation in Chagas disease patients due to the lack of proper indications for the procedure, the pathogenesis of the disease, the adequate immunosuppressive protocol, Trypanosoma cruzi infection reactivation, and long-term results. Survival rates from studies following patients with severe chronic heart failure due to several etiologies indicated that patients with ChCM and severe heart failure have a 1 year survival rate of 40% to 70%, depending on the series. Another study showed 1-year survival probability is 20% in patients with NYHA IV and a LVEF, 30%. More recently, Dib et al found that patients with Chagas disease heart failure listed for heart transplantation on isotropic support have an annual probability of mortality of 100%.

Declarations of Interest

The authors declare no conflicts of interest.

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