
Sudden Death in Chagas' Disease

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Sudden death is one of the most expressive phenomena of the natural history of Chagas' disease, affecting individuals in the most productive phases of their lives. In general, considering all evolutionary stages of the disease, we can say that sudden death is the major cause of death in this disease. It is worth noting that in 1912 the Brazilian Carlos Ribeiro Justiniano Chagas¹, the genial discoverer of the disease, reported the following: "We have numerous clinical observations of the cardiac form and a large number of autopsies that serve as the basis for factual interpretation. In the regions where the disease is common, the number of adult individuals with profound cardiac disorders is impressive... The immediate consequence of this fact is the great number of rapid deaths caused by the disease, and is really impressive in the statistics of lethality the great number of people dying suddenly due to cardiac syncope." Later, the author added² that a large number of families were shocked by the sudden death of one or several members, who died young and in apparent good health, in a phase of tolerance of the cardiac affection.

Chagas' disease is a major epidemiologic problem not just in Brazil. At this time it is considered the fourth disease of major social impact in Latin America, where it affects 16 to 18 million individuals. At least 80 million more individuals (approximately one quarter of the entire Latin American population) are at risk for acquiring the infection³. Despite all of this, systematized studies aiming to determine the real prevalence of sudden death in the chagasic population, its mechanisms, risk factors, and prevention are scarce. Therefore, an updated review about this complex, challenging, and important problem of public health is necessary.

Causes of death in Chagas' disease and frequency of sudden death

Death in Chagas' disease may result from cardiovas-

cular causes, which are the most common, and noncardiovascular causes. The determining mechanism of cardiovascular death may be either an arrhythmic event, often ventricular fibrillation and, less commonly, ventricular asystole, or a nonarrhythmic event such as pump failure (congestive heart failure), or even embolic phenomena (cerebral, pulmonary, mesenteric, etc). Noncardiovascular causes comprise complications of megaesophagus and megacolon.

In regard to the frequency of sudden death in Chagas' disease, data are conflicting, because they are under the influence of several factors, such as the concept of sudden death adopted, the population sample considered (field, office, or hospital) and its demographic characteristics (age, sex, race), the evolutionary stage of the disease, the degree of ventricular dysfunction of the patients in the studies, the type of treatment administered, and obviously, the time interval of patient's follow-up.

A satisfactory and consensual definition of sudden death does not exist. For some authors⁴⁻⁶, sudden death is the one that occurs naturally within seconds, minutes, or hours after onset of signs or symptoms, or both, seen by others and in an out of hospital environment, affecting apparently healthy individuals or those who at least seem so to people around them. For others^{7,8}, death occurring suddenly in patients with previous clinical manifestations of cardiovascular disease or any other illness should also be considered sudden death, and one classical example is the sudden death occurring after acute myocardial infarction⁹.

Aiming to differentiate and better characterize these two situations, some authors when referring to sudden death in ischemic heart disease¹⁰, and mainly in Chagas' disease¹¹⁻¹⁴, started to classify it as unexpected and expected, in order to consider just the first one as the true representative of this condition¹⁴. From our point of view, this differentiation has no clinical importance because, for prevention, its triggering mechanism is much more important than death expectancy. In Chagas' disease, whether the patient dies unexpectedly, with no signs or symptoms of the illness (unexpected sudden death), or the death is preceded by manifestations of the disease (expected sudden death), the final mechanism is usually the same, i.e., an arrhythmic event, most frequently ventricular fibrillation. In addition, in

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a retrospective more detailed investigation of chagasic patients with unexpected sudden death, Prata et al¹⁵ noticed previous cardiac symptoms (dyspnea, palpitations, seizures, and episodes of consciousness loss) in about 57% of the patients.

It is worth noting that from the qualitative point of view, gross and microscopic cardiac lesions of chagasic patients who died suddenly and who had no signs and or symptoms, of the disease, were very similar to those observed in patients with chronic Chagas' heart disease who died after a period of heart failure. Only from the quantitative point of view did differences occur, with lesions being less intense in chagasic patients who died suddenly¹⁶. Therefore, when we analyze the frequency of sudden death in Chagas' disease, we think that it is important to consider both events, the expected and the unexpected sudden deaths.

In regard to chronology of sudden death in Chagas' disease, we consider this the least relevant feature, because death almost always occurs instantaneously. Reports such as "He was all right, talking, and suddenly shouted 'My God' and died" or "As he/she did not wake up, I went to check and found him/her dead" or "He/she died suddenly, without saying a word", are common and reflect how fulminating the death is.

Supported by a wide literature review¹⁷⁻³², we have listed in table I the results of the major studies on causes of death and frequency of sudden death in different population subgroups of Chagas' disease. The careful analysis of these studies allowed the following conclusions: 1) sudden death, heart failure, and cerebral thromboembolism are the major causes of death in Chagas' disease; 2) the higher or lower frequency of a certain cause fundamentally depends on the characteristics of the population studied, with sudden death predominating in studies including only ambulatory patients^{18,20,21,24,26,32} or patients with ventricular arrhythmias^{27,30}, and pump failure predominating in those studies carried out in hospitalized patients with cardiac decompensation^{17,23,29}; and 3) even though death in chagasic patients is intrinsically associated with the degree of myocardial impairment, part of the cases of sudden death correspond to asymptomatic patients with mild electrocardiographic alterations and normal cardiac silhouette on X-ray^{19,20,28}.

Therefore, on the basis of all these studies and considering the different evolutionary stages of the disease, we may state that sudden death accounts for about 55 to 65% of the deaths in Chagas' disease, heart failure for 25 to 30%, and thromboembolic phenomena for the remaining 10 to 15%.

Clinical and epidemiological features

Sudden death in the chagasic patient occurs mainly between 30 and 50 years of age, being rarer after the sixth decade of life, and predominates in males^{13,33,34}. It usually happens during routine activities, physical exertion, or emotion, and is of the instantaneous type in around half of the cases. In the other half, death is preceded by premonito-

ry symptoms for seconds and, rarely, for minutes¹³. Unlike ischemic heart disease, whose sudden death has a peak frequency during the morning, in Chagas' disease, a vesperine predominance seems to occur (from 12 am to 6 pm)³⁵. In regard to the population affected, even though sudden death is more common in chagasic patients with complex ventricular arrhythmia or episodes of ventricular tachycardia, it may also be the first manifestation of the disease or its terminal event in patients with severe ventricular dysfunction and heart failure.

Anatomopathological characteristics

Despite the high prevalence of Chagas' disease in our country, systematized anatomopathological studies on chagasic patients with sudden death are scarce in the literature. In the few published studies^{16,36,37}, we observe that from the qualitative point of view, cardiac lesions are very similar whether sudden death has occurred unexpectedly or not. Quantitatively, however, alterations in hearts of chagasic patients with unexpected sudden death are a lot more discrete than those found in chagasic patients who died after a period of heart failure.

Grossly, in unexpected sudden death, the shape of the heart is normal or slightly elongated due to a larger increase in the left ventricle as compared with the right ventricle; cardiac weight and volume are mildly to moderately increased, and the cavities are discretely dilated. On the other hand, in the chagasic patient with previous manifestations of cardiac decompensation, the heart has a globoid or conical shape, much greater weight and volume, and the cardiac cavities are very dilated, particularly the ventricles³⁶.

From the microscopic point of view, the major lesions are focal or diffuse chronic inflammatory infiltration, mainly constituted by lymphomononuclear cells, the necrotic degenerative process, and fibrosis of substitution, which simultaneously affect the contractile myocardium, the specialized conducting tissue, and the intracardiac autonomic nervous system. Generally, these alterations are more discrete in chagasic patients with unexpected sudden death, as already pointed out, and the findings are similar to those of patients with the chronic form of Chagas' disease, who end up dying due to another mechanism^{16,37}.

Mechanisms of sudden death

Confirmation of the exact mechanism of sudden death in Chagas' disease is extremely difficult and complex. This results from lack of electrocardiographic recordings in patients with sudden death as the first manifestation of the disease, from the extremely reduced number of deaths during ambulatory electrocardiographic monitoring, and from the inefficacy or nonexistence of specialized centers for attending victims of cardiopulmonary arrest out of the hospital environment in Latin America. Therefore, all reports on the mechanisms of sudden death in Chagas' disease are mainly

Table I - Causes of death in different population subgroups of Chagas' disease

Authors	N° of patients	Characteristics of the population studied*	Follow-up	Deaths related to CD	Causes of death			
					SD	CHF	CS	Others
					n(%)			
Prata, 1959 ¹⁷	169	- Hospital population - Patients with decompensated HF	NR	82	31(38)	43(53)	-	8 [†] (9)
Lima & Rassi, 1962 ¹⁸	642	- Private patients - 100% with abnormal ECG (61% with VEs) - 47% with normal CS and 53% with enlarged CS (XR)	NR	57	40(70)	13(23)	4(7)	-
Porto, 1964 ¹⁹	503	- Private patients (endemic area) - Normal ECG in 39% of the patients and abnormal in 61% of the patients	Up to 5-6 years	96 [¶]	36(38)	53(55)	-	7 [†] (7)
Brasil, 1965 ²⁰	86	- Private patients - 50% with no apparent heart disease (subclinical form) and 50% with heart disease	10 years	25 ^{¶¶}	18(72)	6(24)	1(4)	-
Baruffa, 1974 ²¹	172	- Population of endemic area (Rio Grande do Sul State) - 23% in the indeterminate; 22% in the digestive form; 31% in the cardiac form, and 24% in the cardiodigestive form	NR	18	10(56)	8(44)	-	-
Macedo, 1976 ²²	840	- Population of endemic area - Clinical and epidemiological investigation	4 years	24	9(38)	14(58)	-	1 [§] (4)
Pugliese et al, 1976 ²³	160	- Patients with decompensated HF - Revision of medical records	Up to 2.5 years	96	10(10)	63(66)	1(1)	22 ^{††} (23)
Dias, 1982 ²⁴	268	- Pacientes with known acute phase	27 years	19	10(53)	5(26)	3(16)	1 [¶] (5)
Espinosa et al, 1985 ²⁵	104	- Ambulatory patients - 29% with normal ECG; 39% with abnormal ECG, Without CHF; and 32% with abnormal ECG and severe CHF	4.9 years	36 ^{¶¶}	15(42)	16(44)	5(14)	-
Coura et al, 1985 ²⁶	235	- Field patients - Chronic chagasic patients	Up to 10 years	41	31(76)	9(22)	1(2)	-
Santana, 1987 ²⁷	76	- Ambulatory patients (FC I or II) - 19.5% with normal ECG and 81.5% with abnormal ECG 57% with normal CS and 43 % with enlarged CS (RX)	5.2 years	14 ^{***}	10(71)	3(21)	1(7)	-
Acquatella et al, 1987 ²⁸	755	- Ambulatory patients - 48% with abnormal ECG, 12% borderline, and 40% abnormal - 79% asymptomatic patients; 13% with mild/mod symptoms and 8% with severe CHF	2.3 anos	48 ^{†††}	19(40)	19(40)	4(8)	6 [§] (12)
Carrasco et al, 1994 ²⁹	185	- Patients with abnormal ECG with no signs of CHF	6.4 years	33	12(36)	6(18)	12(36)	3 ^{**} (9)
	104	- Patients with abnormal ECG and CHF	2.3 years	67	14(21)	52(78)	1(1)	-
Silva, 1997 ³⁰	78	- Ambulatory or ward patients with NSVT on H - 85% in FC I ou II e 15% in FC III ou IV	4.6 years	21 ^{†††}	16(76)	2(9.5)	1(5)	2 ^{¶¶} (9.5)
Garzon, 1998 ³¹	987	Ambulatory or ward patients who underwent hemodynamic study	7 years	331	169(51)	147(44)	-	15 ^{††} (5)
Rassi Jr., 1999 ³²	444	Ambulatory patients (nonselected population)	9.1 years	111	74(67)	23(21)	-	14 ^{§§} (12)

CS- cardiac silhouette; CS- cerebral stroke; FC- functional class; CD- Chagas' disease; ECG - electrocardiogram; VEs - ventricular extrasystoles; H - Holter; HF - heart failure; CHF- congestive heart failure; mod - moderate; SD - sudden death; NR - not reported; P - patients; XR - chest X-ray; NSVT - nonsustained ventricular tachycardia. * At the moment of patient inclusion in the study: † unspecified causes; ‡ extracardiac causes; § complication of megacolon; † 1 Stoke-Adams, 7 shocks, and 14 pulmonary embolisms; ¶ complication of megacolon; # unknown causes; ** pulmonary thromboembolism; †† 1 mesenteric thromboembolism and 1 proarrhythmia; ††† thromboembolism; §§ other cardiovascular causes. †† Approximately 11% of the deaths occurred in patients with normal ECG, and 89% in patients with abnormal ECG. ¶¶ 20% of the deaths occurred in patients with no apparent heart disease, and 80% in patients with heart disease. ## 22% of the deaths occurred in patients with abnormal ECG and no CHF, and 78% in patients with abnormal ECG and severe CHF. *** All deaths occurred in patients with abnormal ECG; 93% of the deaths in patients with enlarged CS, and 86% in FC II patients. ††† 15% of the deaths occurred in asymptomatic patients, 25% in patients with mild/moderate symptoms, and 60% in patients with severe CHF. †††† Approximately 2/3 of the deaths occurred in FC I/II patients, and 1/3 in FC III/IV patients.

based on observations, hypotheses, or inference^{38,39}. Nevertheless, the essentially arrhythmogenic nature of chronic chagasic heart disease, which is mainly characterized by a high density and complexity of ventricular arrhythmias⁴⁰⁻⁴³, its fibrotic character, with akinetic or dyskinetic areas intermingled with preserved myocardial fibers^{44,45}, and the reentrant mechanism of sustained ventricular tachycardia in a large number of cases on programmed ventricular stimulation⁴⁶⁻⁴⁹, strongly suggest that ventricular fibrillation constitutes the terminal event in most cases of sudden death in Chagas' disease. Less frequently, a bradyarrhythmia (sinus

node dysfunction or total atrioventricular block) or electro-mechanical dissociation may be the cause of this event⁵⁰.

Mendoza et al³⁸, analyzing the Holter recording of 10 chagasic patients with ambulatory sudden death, identified ventricular fibrillation as the final event in 9 patients and bradyarrhythmia in only one. The precursor of ventricular fibrillation was *torsade de pointes* in 6 patients and sustained ventricular tachycardia in the 3 others. According to the authors, the high percentage of *torsade de pointes* may be explained by the coexistence in Chagas' heart disease of multiple abnormalities, such as disorders of conduction, sinus

node dysfunction, diffuse fibrosis, primary and secondary alterations of ventricular repolarization, high frequency of ventricular arrhythmias, particularly polymorphic and in runs, lesions of cardiac nerve plexuses, and ventricular dysfunction, which may lead to heart failure. The possibility of the proarrhythmic effect should also be remembered, because all patients with torsade de pointes were on class IA antiarrhythmic drugs (quinidine and disopyramide). In our material, the analysis of 13,843 Holter recordings revealed only one case of sudden death (chagasic patient), in whom the final event was also ventricular fibrillation. In addition, during the innumerable opportunities to monitor the cardiac rhythm in chagasic patients with in-hospital cardiopulmonary arrest, ventricular fibrillation was undoubtedly the most frequent arrhythmia observed. These data, even though referring to a selected sample, stress the importance of ventricular fibrillation in the genesis of sudden death in chronic Chagas' heart disease.

Exceptionally, other mechanisms may lead to sudden death in Chagas' disease⁵¹⁻⁵⁴, among which we can cite spontaneous ventricular rupture.

Interaction of structural, functional, and triggering factors

The classic biological model of sudden death proposed by Myerburg et al⁵⁵, establishing three fundamental factors for occurrence of ventricular fibrillation, which are the arrhythmogenic substrate, the triggering factors (ventricular extrasystoles), and some functional factors, may also be applied to chronic Chagas' heart disease. Therefore, structural myocardial abnormalities, such as foci of inflammation, areas of fibrosis, ventricular dilation, and akinetic or dyskinetic areas, generate unidirectional block and slow conduction in circumscribed ventricular regions, essential for the appearance of reentrant ventricular arrhythmias, which are the main triggering factor of sudden death in chronic Chagas' heart disease. However, as not all chagasic patients with ventricular arrhythmia die suddenly, the model is probably only completed when some functional factors participate, causing myocardial instability and thus favoring installation of fatal arrhythmias, such as ventricular fibrillation (fig. 1). Acute hemodynamic deterioration, hypoxemia, electrolytic disorders, the use of medications with a proarrhythmic potential, and mainly changes in the autonomic nervous system⁵⁶⁻⁵⁸ are examples of factors that may cause the arrhythmogenic substrate to be unstable. This is the reason why significant morphological differences are not found, from the qualitative point of view (grossly and microscopically), when comparing hearts of chagasic patients who died suddenly with hearts of chagasic patients dying during evolution of heart failure.

Identification of groups at risk

Mortality due to Chagas' disease is still very significant in several Latin American countries and is strictly rela-

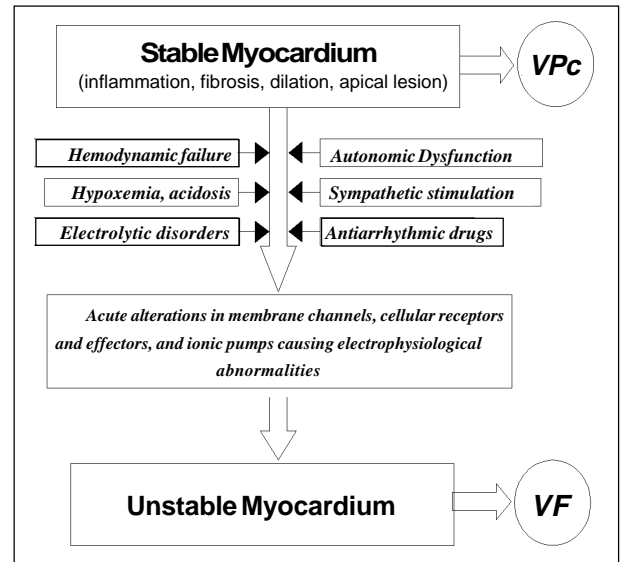


Fig. 1 – Instability of structurally abnormal myocardium through the interaction of different functional modulators, resulting in ventricular fibrillation. VPC - ventricular premature contraction; VF - ventricular fibrillation.

ted to the presence of heart disease. The risk of sudden death is obviously not the same for every chagasic patient; therefore, several authors^{25,27,29,30-32,50,59-72} have tried to identify factors predisposing certain patients to a higher risk of this catastrophic event. Therefore, variables, such as presyncope and syncope, ventricular dysfunction and heart failure, complex nonsustained and sustained ventricular arrhythmias, severe bradyarrhythmias (sinus node dysfunction and advanced atrioventricular blocks), and previous cardiac arrest have been identified as predictors of the risk of sudden death, at least in some studies. These risk predictors can be classified as major or minor predictors, as shown in table II. Other variables, such as simple ventricular arrhythmia on Holter^{27,29,68} and the complete right bundle-branch block⁵⁹, at least when isolated, do not negatively influence the prognosis of chronic chagasic heart disease.

Presyncope and syncope are common symptoms in chronic chagasic heart disease and may be caused either by brady- or tachyarrhythmias. Aiming to know the prevalence of these symptoms and to correlate them with the presence of cardiac arrhythmias, 143 chronic chagasic patients during outpatient visits were asked about the presence of symptoms and underwent 24-hour Holter monitoring so that their arrhythmias could be studied⁶⁴. Presyncope or syncope were reported by 20 (14%) patients, of whom 80% had episodes of nonsustained ventricular tachycardia and 30% had bradyarrhythmias (sinus node dysfunction or atrioventricular block), showing the high prevalence of severe arrhythmias in these situations. A study by Rassi et al⁶² comprised 45 chronic symptomatic chagasic patients, who underwent electrophysiological study because of presyncope (17 patients) or syncope (28 patients), and whose cause was not clarified by noninvasive methods. These authors evidenced induction of sustained ventricular tachycardia in 36% of the patients with syncope and in 6% of the patients with presyncope, and disorder of the sinus node or lesion of

Table II – Predictors of sudden death in chronic chagasic heart disease. ET – exercise test; SND – sinus node dysfunction; AVBs – atrioventricular blocks; VF – ventricular fibrillation; PVS – programmed ventricular stimulation; RBBB – right bundle-branch block; VT – ventricular tachycardia; HR – heart rate.

Major predictors:

- Ventricular dysfunction
- Nonsustained ventricular tachycardia* on Holter monitoring/ET
- Sustained ventricular tachycardias
- Patients who have recovered from cardiopulmonary arrest
- Severe bradyarrhythmias (SND, advanced AVBs)
- Syncope

Minor predictors:

- Late potentials (signal-average ECG)
- Presyncope

Variables with no prognostic value:

- Isolated ventricular extrasystole (Holter)
- Isolated RBBB
- Induction of polymorphic VT or VF on PVS

Variables to be investigated:

- HR Variability
- QT dispersion

* accompanied by ventricular dysfunction

His-Purkinje in 39% of the patients with syncope and in 41% of those with presyncope.

Martinelli et al⁶⁷ used noninvasive methods to study 53 consecutive patients with recurrent syncope of unknown mechanism and found abnormalities in 36 (68%) patients. Sustained ventricular tachycardia was induced in 15 (28%) patients, the HV interval was altered (greater than 70ms) in 11 (21%) patients, and 10 (19%) patients had both alterations, induced ventricular tachycardia and increased HV interval. On the basis of these results, the patients were treated with implantation of atrioventricular pacemakers antiarrhythmic drugs, and or, empirically or guided by electrophysiological study. During a mean follow-up of 85 months, 9 (17%) patients died suddenly, and 15 (28%) had recurrence of the syncope.

Complex ventricular arrhythmias, which are frequent in chronic Chagas' heart disease, also constitute major risk factors for sudden death, mainly when associated with impairment of ventricular function. Aiming to study the long-term prognosis of nonsustained ventricular tachycardia and ventricular dysfunction, 444 patients in our service underwent echocardiography and 24-hour Holter monitoring³². After a mean follow-up of 9 years, 132 patients had died (sudden death in 74 patients, congestive heart failure in 23 patients, other cardiovascular causes in 14 patients, noncardiovascular causes in 19 patients, and unknown mechanism in 2 patients). Classification of the patients in 4 subgroups according to the presence of nonsustained ventricular tachycardia and ventricular dysfunction revealed the poor prognosis for those with the two risk factors, an intermediate survival for those with only one of the risk factors, and a good prognosis for those with no ventricular tachycardia and no ventricular dysfunction.

Santana²⁷, in a longitudinal study comprising 76 chronic chagasic patients, reported an actuarial probability of 7-year survival of 48.0±10.8% in patients with nonsus-

tained ventricular tachycardia on Holter monitoring and of 29.5±12.9% in those patients with nonsustained ventricular tachycardia and cardiomegaly on the roentgen examination; on the other hand, the prognosis was good for those patients with simple ventricular arrhythmias. Similar results have been reported by other authors^{29,68}.

Rassi⁶⁰, following up patients with sustained ventricular tachycardia, reported a mortality of 93% in 8 years, with more than 70% of the deaths occurring in the first two years of follow-up. It is worth noting that sudden death accounted for 71% of the deaths in Santana's study and for 90% of the deaths in Rassi's study.

Presence of ventricular tachycardia during exercise testing also accounts for a higher risk of sudden death in chagasic patients. In the study by De Paola et al⁷¹, comprising 69 chagasic patients consecutively examined, after a mean 24-month follow-up, sudden death was observed in 16% of the 44 patients who had ventricular tachycardia during the exercise test; on the other hand, none of the 25 patients without ventricular tachycardia died suddenly.

In regard to the importance of functional class and ventricular dysfunction, Mady et al⁶⁹, in a 3-year follow-up of 104 chagasic male patients with heart failure, reported an excellent prognosis for functional class II patients (97% of survival), a reasonable prognosis for functional class III patients (58% of survival), and a very poor prognosis for functional class IV patients (only 16% of survival). Likewise, the 3-year survival probability was 100% when the ejection fraction was higher than 0.50, dropping to 70% in the patients with ejection fraction between 0.31 and 0.50, and decreasing to only 16% in those patients with ejection fraction equal to or lower than 0.30. However, in this study, the authors do not mention the causes of death.

Rassi et al⁵⁰, analyzing the natural history of total atrioventricular block, found a survival of only 33% in 147 untreated chagasic patients, who were followed up for a mean period of 3.6 years. In most of the cases (86%), death was sudden.

Two other methods of investigation, signal-averaged electrocardiography and programmed ventricular stimulation, have been used to identify high-risk patients. Signal-averaged electrocardiography allows the diagnosis of late potentials, which are considered noninvasive markers of electrophysiological substrate for reentrant ventricular arrhythmias. Moraes et al⁶⁶, studying the prevalence of late potentials in 192 patients with chronic Chagas' heart disease and their relation with sustained ventricular tachycardia, observed in the group with no bundle-branch block a higher prevalence of late potentials in the patients with sustained ventricular tachycardia, as compared with those without tachycardia (78% vs 31%, p<0.001). However, in the patients with bundle-branch block, this distinction could not be made (late potential present in 67% of the patients with sustained ventricular tachycardia and in 48% of the patients without tachycardia, p=0.07), confirming the lower usefulness of late potentials in chagasic patients with bundle-branch block. During a mean 40-month follow-up, 12

(21%) patients had recurrence of sustained ventricular tachycardia, 92% of whom had late potentials.

In the last few years, invasive electrophysiology⁶⁵ has appeared as an important method for assessing and managing patients at high risk for developing sudden death, particularly those recovering from cardiopulmonary arrest and those with recurrent episodes of sustained ventricular tachycardia. More recently, Silva³⁰ assessed the prognostic value of inducing ventricular tachycardia by programmed ventricular stimulation in 78 chagasic patients with nonsustained ventricular tachycardia on Holter, mean ejection fraction of 0.47 ± 0.18 , and no clinical history of sustained arrhythmias. Sustained monomorphic ventricular tachycardia was induced in 25 (32%) patients, who required treatment with class III antiarrhythmic drugs, 24 with amiodarone and only one with sotalol. After a mean follow-up of 56 months, the accumulated probability of survival (62% vs 24%) and the event-free proportion – cardiac death, spontaneous sustained ventricular tachycardia, and recurrence of syncope – were significantly higher in noninducible patients as compared with the inducible ones (50% vs 12%). On the other hand, induction of polymorphic ventricular tachycardia or ventricular fibrillation had no prognostic significance, and it may be an unspecific ventricular response. This fact has also been reported by Rassi et al⁶³.

Finally, technological advances have allowed the appearance of new methods of risk stratification, among which we cite the study of heart rate variability and the analysis of dispersion of the QT interval. These are noninvasive methods that assess the influence of the autonomic nervous system on the electrophysiological properties of the heart. As the sympathovagal balance is essential for maintaining myocardial electrical stability, changes in the balance between the parasympathetic and sympathetic autonomic activities may increase ventricular excitability and trigger fatal arrhythmias, such as ventricular fibrillation. Therefore, according to some experimental and clinical studies⁷³⁻⁷⁵, both reduction in variability of heart rate expressed by different parameters in time and frequency domain, and the increase in ventricular repolarization dispersion, which translates nonuniform recovery of ventricular excitability, were associated with a higher risk of developing ventricular tachyarrhythmias and sudden death, particularly after myocardial infarction. The frequent pathological involvement of the autonomic nervous system in Chagas' heart disease⁷⁶ turns these two new methods into promising tools for identifying patients at high risk for sudden death⁷⁷.

Relation between risk and total number of sudden death in Chagas' disease

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 chagasic individuals exist in Latin America, the annual rate of sudden death may be estimated in 0.17 to 0.19% (approximately 2/1,000). Therefore, to prevent two cases of sudden death in the chagasic popula-

tion, any intervention should also be applied to 998 more individuals who would not have any other event in a one-year period, making this strategy unnecessary when the cost-benefit relation is taken into account. If we consider that sudden death in the chagasic patient is closely related to the presence of heart disease, and that usually 20 to 30% of the chagasic patients develop some degree of cardiac impairment during the infection, the annual rate of sudden death in chagasic patients with heart disease increases to 0.56 to 0.94%. However, this rate is still not expressive and does not justify an intervention in an indiscriminate manner in all patients. Therefore, it is essential to identify subgroups at higher risk for sudden death, which may be obtained as some variables, such as ventricular dysfunction, complex ventricular arrhythmias, induction of ventricular tachycardia, and previous cardiopulmonary arrest, are recognized. As can be observed in figure 2, as subgroups at higher risk are identified, the absolute figure corresponding to sudden deaths progressively decreases. Individuals with heart disease and a high probability of sudden death may be identified, but they represent only a small part of the total number of sudden deaths observed in the chagasic population as a whole.

These data impose some limits on prevention of sudden death in Chagas' disease in an indiscriminate manner. As the risk of sudden death among chagasic individuals as a whole or among those with heart disease is not high, any intervention to large-scale prevention should be applied to a huge contingent of individuals who will never develop any event, in an attempt to benefit a minority that will have it. On the other hand, even though adopting therapeutical measures only in subgroups at high risk (patients with sustained ventricular tachycardia or recovering from cardiac arrest) may spare many lives among treated individuals (assuming an effective antiarrhythmic therapy exists), it has a small impact on reducing the total number of sudden deaths. Therefore, we believe that from the epidemiological point of view and considering the cost-benefit relation, we should focus on the subgroups at intermediate risk that have a reasonable number of fatal events, i.e., those chagasic individuals with some degree of myocardial impairment and associated complex ventricular arrhythmias.

Primary and secondary prevention of sudden death

The essentially arrhythmogenic nature of chronic Chagas' heart disease and evidence that certain types of arrhythmias, particularly complex ventricular arrhythmias, predispose to sudden death, have motivated several researchers to use different antiarrhythmic drugs with prophylactic aims. Therefore, therapeutical assays with drugs of the classes IA, IB, IC, and III were carried out⁷⁸⁻⁸⁷ and, in almost all of them, efficacy of the antiarrhythmic drugs on ventricular arrhythmias was observed. However, as suppression of ectopic ventricular beats does not necessarily imply a reduction in mortality⁸⁸⁻⁹⁰, when we choose to routinely admi-

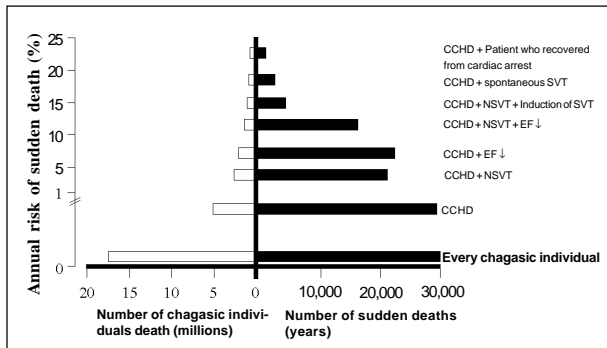


Fig. 2 – Relation between risk and absolute number of sudden deaths in different population subgroups with Chagas' disease. The annual risk of sudden death in the entire chagasic population, which comprises approximately 17 million individuals, is around 0.15 to 0.20%, accounting for and 30,000 deaths per year. With the inclusion of additional risk predictors, the chagasic population becomes more selective and the risk of sudden death increases gradually. However, this higher risk of sudden death in specific subgroups is accompanied by a progressive decrease in the total number of annual sudden deaths. Therefore, an inverse relation exists between the risk of sudden death and the total number of fatal events, making difficult the adoption of preventive measures in large scale. CCHD – chronic Chagas' heart disease; EF – ejection fraction; NSVT – nonsustained ventricular tachycardia; SVT – sustained ventricular tachycardia

nister antiarrhythmic drugs to chagasic patients with complex ventricular arrhythmias, we should know that it is possible to reduce the incidence of sudden death with the prophylactic treatment. Results of several prospective randomized studies⁹¹⁻⁹⁶ and two recent metaanalyses^{97,98} carried out in patients with other types of heart disease, such as ischemic and dilated (idiopathic) heart disease, show that amiodarone, unlike class I antiarrhythmic drugs, may prevent sudden death and also decrease total mortality in high-risk patients with complex ventricular arrhythmias or heart failure, or both. Extrapolating these data to chronic Chagas' heart disease, about which proper therapeutical assays are lacking, we believe that administration of amiodarone to chagasic patients with complex ventricular arrhythmias is totally justified, particularly when the arrhythmia in question is nonsustained ventricular tachycardia accompanied by ventricular dysfunction. In addition to reducing mortality, amiodarone has an extraordinary antiectopic efficacy^{82,84,85,87}, a low incidence of significant side effects^{99,100} and proarrhythmia¹⁰¹, particularly when administered in low doses, and, only exceptionally, does it change inotropism. Therefore, amiodarone may be used even in severe impairment of ventricular function, including the treatment of decompensated heart failure, which in chronic Chagas' heart disease is accompanied by complex ventricular arrhythmia in almost all cases⁴³. In chagasic patients with nonsustained ventricular tachycardia and preserved ventricular function, because the risk of sudden death seems to be lower, the most adequate management, currently, seems to be not to use prophylactic antiarrhythmic drugs. Another option would be the use of new noninvasive investigative methods, such as signal-averaged electrocardiography and heart rate variability for a better risk stratification in these cases.

In patients with sustained ventricular tachyarrhythmias, amiodarone is also the treatment of choice. Rassi¹⁰²

analyzed the actuarial curve of survival of 34 patients with sustained monomorphic ventricular tachycardia empirically treated with amiodarone isolated or associated with other antiarrhythmic drugs. He compared this curve with that of 42 untreated patients or patients who had used procainamide or quinidine, the only drugs available on the market at that time, and he observed a significantly higher survival in the group treated with amiodarone. After 1, 4, and 8 years of follow-up, survivals were respectively 87%, 65%, and 59% for the group of patients treated with amiodarone, and 57%, 22%, and 7% for the group of untreated patients or patients treated with class I antiarrhythmic drugs ($p < 0.01$, fig. 3A).

Scanavacca et al¹⁰³, following up 35 chagasic patients with sustained ventricular tachycardia empirically treated with amiodarone, also found good results with an estimated probability of sudden death of only 11% in 3 years, even though recurrence of arrhythmia had been relatively frequent, predominating in patients with severe ventricular dysfunction. These data support the defibrillating effect of amiodarone.

Sotalol, which has been more recently marketed in Brazil, has also been used for treating sustained ventricular tachycardia of chronic Chagas' heart disease¹⁰⁴. However, no studies exist assessing the effects of sotalol on reducing mortality.

Finally, ventricular tachycardia may be recurrent and refractory to medicamentous treatment in some cases. In these patients, the nonpharmacological treatment, such as percutaneous catheter ablation, surgical ablation, implantation of automatic cardioverter/defibrillator, or other surgical procedures may be attempted. The choice of treatment will be determined at first by the capacity for reproducing or not the clinical arrhythmia on the electrophysiological study, which is an examination always indicated in these situations. Inducing hemodynamically stable and well-tolerated sustained ventricular tachycardia allows the identification of the site of origin of tachycardia through different mapping techniques, and then the directed procedures, i.e., surgical or catheter ablation, may be chosen.

At first, surgical ablation should be considered when the ejection fraction is not significantly impaired, the surgical risk is low, and especially when associated surgical procedures, such as aneurysmectomy, are indicated. Magalhães et al¹⁰⁵ introduced the technique of interpapillary endomyocardial cryoablation with no previous electrophysiological mapping to be applied to patients with sustained ventricular tachycardia and akinesia or dyskinesia of the inferolateral region of the left ventricle, where the reentrant circuit of tachycardia is most commonly situated, according to observations in his group of work and those of Takehara et al¹⁰⁶. Initial results with this procedure proved efficacious in approximately 60% of the cases.

Catheter ablation may be performed in patients with depressed ventricular function, because the risk inherent to the procedure is lower. It is worth noting that reproduction of monomorphic sustained ventricular tachycardia in chronic Chagas' heart disease has been reported in 63 to 95% of the cases⁴⁶⁻⁴⁹. Reentry has been considered the major electrophysiological mechanism, and focal areas of fibrosis or

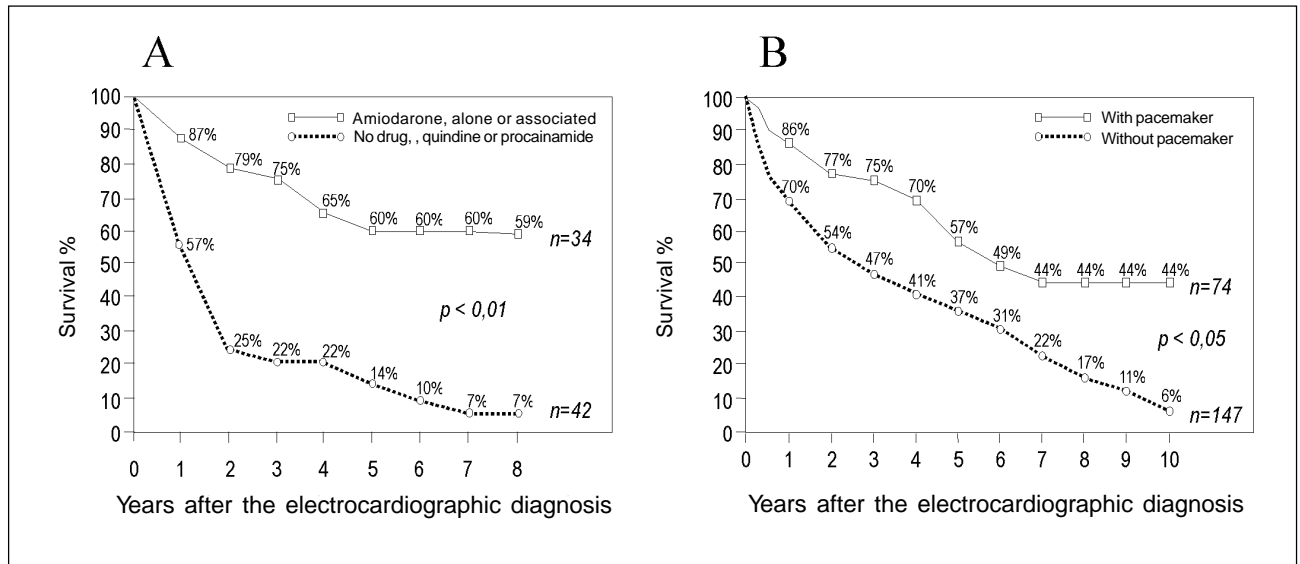


Fig. 3 – Actuarial curves of survival in chronic Chagas' heart disease. (A) Sustained ventricular tachycardia. (B) Total atrioventricular block.

perineurysmatic zones constitute the anatomical basis for the arrhythmogenic substrate.

The first successful ablation of chagasic ventricular tachycardia was reported in 1987 by Sosa et al¹⁰⁷. However, subsequent results using radiofrequency proved deceptive (unpublished data of several authors). This may be due to the fact that in chronic Chagas' heart disease the arrhythmogenic substrate is usually extensive, macroreentrant, and epimyocardial rather than subendocardial, making the conventional application of radiofrequency pulses in the subendocardial region ineffective.

In our institution, since 1991, 55 patients (49 chagasics), of whom 55% with recurrent and refractory sustained ventricular tachycardia, 23,5% with syncopal ventricular tachycardia, 14,5% with incessant ventricular tachycardia, and 2% with an implantable defibrillator and frequent shocks were treated with catheter ablation using electric energy of direct current. We obtained immediate success (no reinduction of tachycardia) in 74% of the mapeable tachycardias that were ablated. After a mean follow up of 42 months, 14 (25,5%) patients died (one during the procedure), 7 (12,5%) had recurrences, 11 (20%) were lost to follow-up, and 23 (42%) are alive and doing well. It is worth noting that except for one patient, all the others continue to use antiarrhythmic drugs..

More recently, Sosa et al^{109,110} reported the technique of epicardial mapping through pericardial puncture and epicardial application of radiofrequency performed in the hemodynamic laboratory, with encouraging results.

In regard to implantation of the automatic cardioverter/defibrillator¹¹¹, it is the treatment of choice for survivors of cardiac arrest with inducible ventricular fibrillation or symptomatic and intolerant sustained ventricular tachycardia during the electrophysiological study, or when one cannot reproduce the spontaneous arrhythmia, situations that make the mapping of the arrhythmogenic area impossible. Unsuccessful cases or cases refractory to the ablation techniques also constitute indications for using these devices.

The appearance of transvenous cardioverter/defibrillators¹¹², reducing morbidity and mortality related to their implantation, and the lower current cost of antiarrhythmic devices have allowed a wider use of these systems in our country. It is worth noting that the most modern devices may release several types of stimulation, such as antitachycardia, low-energy cardioversion, and high-energy defibrillation shocks, and may also function as an antibradycardia pacemaker. In addition, we have multiprogramming options for detecting tachycardia and the capacity for storing information regarding the interventions of the device.

The use of antiarrhythmic drugs after implantation of the automatic cardioverter/defibrillator is usually necessary to eliminate intermittent episodes of arrhythmias that may result in inadequate activation of the device, and also to slow an eventual tachycardia crisis, improving its hemodynamic tolerance and making its interruption through antitachycardia stimulation easy.

Among other surgical procedures, electrophysiology-oriented subendocardial resection, associated or not with cryoablation, is worth noting¹¹³. Nondirectional conventional ventricular aneurysmectomy is not recommended due to its low success index, because the origin of the ventricular tachycardia usually is not related to the site of the aneurysm, particularly when it is apical¹¹⁴.

Another measure that may help prevent chagasic sudden death is implantation of a definite cardiac pacemaker in every symptomatic or high-risk bradyarrhythmia. It improves the quality of life of symptomatic patients and increases survival, even in the presence of cardiomegaly and heart failure. Rassi¹⁰², analyzing the natural history of total atrioventricular block in 147 chagasic patients without pacemaker implantation, found survivals of 70%, 37%, and 6% after 1, 5, and 10 years of follow-up. On the other hand, in patients who underwent pacemaker implantation, of the VVI type, survival was significantly greater (86%, 57%, and

44%, respectively) (Fig. 3B). Sudden death accounted for 87% of the deaths of patients without pacemakers and 67% of the deaths of patients with pacemakers.

Final considerations

In conclusion, the symptomatic or asymptomatic chagasic patient with confirmed or suspected arrhythmia and, particularly with any degree of myocardial dysfunction, should be carefully assessed, at first with noninvasive me-

thods and, whenever necessary, complemented by invasive electrophysiological evaluation. If ventricular arrhythmia with prognostic significance is detected, its therapeutical control, at first medicamentous, should be pursued and reassessed, and the refractory cases should undergo special procedures. In the case of significant bradyarrhythmia, implantation of a definite cardiac pacemaker is mandatory. This is how we expect to reduce the number of sudden deaths, a common occurrence in chronic Chagas' heart disease, which affects people in the most productive phase of their lives.

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