Chapter 8

Sudden Death Circadian Rhythm in Chagasic Patients Compared to Non-Chagasic Patients

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Additional information is available at the end of the chapter

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Abstract

Chagas disease (Ch) affects 8–10 million people in Latin America. Sudden death is the major cause of death in patients with Ch. Objective: To compare the circadian rhythm of sudden death in Ch vs. non-Ch patients. Methods: Retrospective analysis of all the cases of sudden death (SD) is recorded in our department, including autopsied patients from 1963 until 2011. Pattern of death of 266 patients (116 Ch and 146 non-Ch), 56.7% men, average age 54, 6 years old, divided into four groups: Group A: Ch with SD (n = 38), Group B: non-Ch with SD (n = 58), Group C: Ch with non-SD (n = 81), and Group D: non-Ch with non-SD (n = 89). Results: 44.7% (17/38) of sudden deaths in Group A (Ch) occurred between 6 am and 5:59 pm, while for Group B (not Ch) 70.7% (41/58) died in that time ($p < 0.005$). Between 6 pm and 5:59 am occurred 55.3% (21/38) of the SD in Group A (Ch) compared with 29.3% (17/58) in Group B ($p < 0.005$). Conclusions: Circadian rhythm of SD in patient with Ch differs from those patients with non-CH. In CH patients, SD occurs predominantly during the night compared with non-Ch SD that occurs predominantly during the morning.

Keywords: sudden death, cardiomyopathy, circadian rhythm, Chagas disease

1. Introduction

The Chagas disease is a malady caused by the *Trypanosoma cruzi* protozoan, and it represents an endemic disease in Latin America, affecting 8–10 million of patients, most of them being poor [1–2]. It is estimated that 400,000 infected persons live in nonendemic countries, mainly in the United States and Europe [3, 4]. A recent meta-analysis of European studies that, in aggregate, screened 10,000 Latin American immigrants found a positive serological test prevalence of 4.2% [5]. Based on published seroprevalence in Latin American immigrant populations (1.31%), it was

estimated that approximately 300,000 individuals with *T. cruzi* infection live in the United States, with 30,000–45,000 cardiomyopathy cases and 63–315 congenital infections annually [6].

The sudden death circadian variation has been demonstrated in two large-scale studies, the Framingham Heart Study [7] and the Massachusetts Death Certificate Study [8]. Both studies show a peak of sudden deaths between 7 and 11 am with a lower incidence during sleep, which is similar to the rate of ischemic and arrhythmic events [9, 10]. The sudden death is the main cause of death in those patients with the Chagas disease, being responsible of the 55–65% of their deaths [11]. Lopes et al. [12] demonstrated that there is a sudden death circadian rhythm in Chagasic patients. In this study, 50 cases of Chagasic sudden death, along with 473 cases of nonsudden natural death, were compared in several centers. To the best of our knowledge, this is the first report that compares the rhythm of the sudden and nonsudden death of Chagasic patients vs. non-Chagasic patients with cases within a same center.

2. Material and methods

A retrospective study of a consecutive series of sudden death cases, registered within our department between 1963 and 2011, including the ECG records, Holter records from sudden death victims, autopsies, and the Death report by the relatives. The Chagas disease diagnosis was performed through serological studies, or a necroscopic study was performed in the cases of autopsies.

The date and time of death were collected from necropsy protocols and/or emergency clinical histories, as well as data obtained from relatives and witnesses.

Sudden cardiac death (SCD) is generally defined as a sudden and unexpected pulseless event, but noncardiac conditions need to be excluded before the occurrence of a primary cardiac event can be confirmed [13]. A case of established SCD is an unexpected death without obvious extracardiac cause, occurring with a rapid witnessed collapse, or if unwitnessed, occurring within 1 h after the onset of symptoms [13]. A probable SCD is an unexpected death without obvious extracardiac cause that occurred within the previous 24 h [13]. In any situation, the death should not occur in the setting of a prior terminal condition, such as a malignancy that is not in remission or end-stage chronic obstructive lung disease [13]. In our study, we included both established and probable SCD.

A total of 266 cases were analyzed; 56.7% of the subjects were male with an average age of 54.6 years, which were divided into four groups: Group A: Chagasic patients with sudden death, n = 38; Group B: non-Chagasic patients with sudden death, n = 58; Group C: Chagasic patients with non-sudden death, n = 89; and Group D: non-Chagasic patients with non-sudden death, n = 81.

The results were assessed using exploratory data analysis (EDA) and comparison of ratio differential. As the statistic validation rule, a p-value <0.05 was considered as statistically significant.

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3. Results

A total number of cases per hour of sudden death in patients with and without Ch are shown in **Figure 1**. **Figure 2** shows the number of cases per hour of nonsudden death in patients with and without Ch. After analyzing the data divided into 12-h periods (day and night), significant differences were observed. **Figure 3** shows the percentages of cases from the SD groups occurring during night and day. Forty four point seven per cent (44.7%) (17/38) of the sudden deaths in Group A (Ch) occurred between 6 am and 5:59 pm, while for Group B (non-Ch), 70.7% (41/58) of the patients died within that time ($p < 0.005$). Between 6 pm and 5:59 am, 55.3% (21/38) of the deaths of Group A (Ch) occurred in that time compared to 29.3% (17/58) from Group B ($p < 0.005$). **Figure 4** shows the data of nonsudden death cases. 49.4% (40/81) of Group C (Ch non-SD) died between 6 am and 5:59 pm compared to 59.6% (53/89) of Group D (non-Ch, non-SD), (p not significant), while between 6 pm and 5:59 am, 50.6% of Group C (Ch, non-SD) cases died compared to 40.4% (36/53) of Group D (non-Ch, non-SD) (p was not significant).

In order to perform a more detailed analysis, the percentages of cases were grouped within 3-h periods: (6–8, 9–11, 12–14, 15–17, 18–20, 21–23, 24–2, 3–5). **Figure 5** shows the circadian rhythm of sudden death in Chagasic patients (Group A) compared to the non-Chagasic patients (Group B). Within these periods, a higher death percentage in the Chagasic group is observed within the 21–23 h interval (34 vs. 3%, $p = 0.0001$), while the non-Chagasic arm presented a higher percentage of cases within the 9–11 h range (43 vs. 3%, $p < 0.0001$), of 24 to 21 2 h (10 vs. 0% $p < 0.005$), and from 3 to 5 h (7 vs. 0%, $p < 0.005$). The difference of the other analyzed periods was not significant. When comparing the number of cases of non-sudden

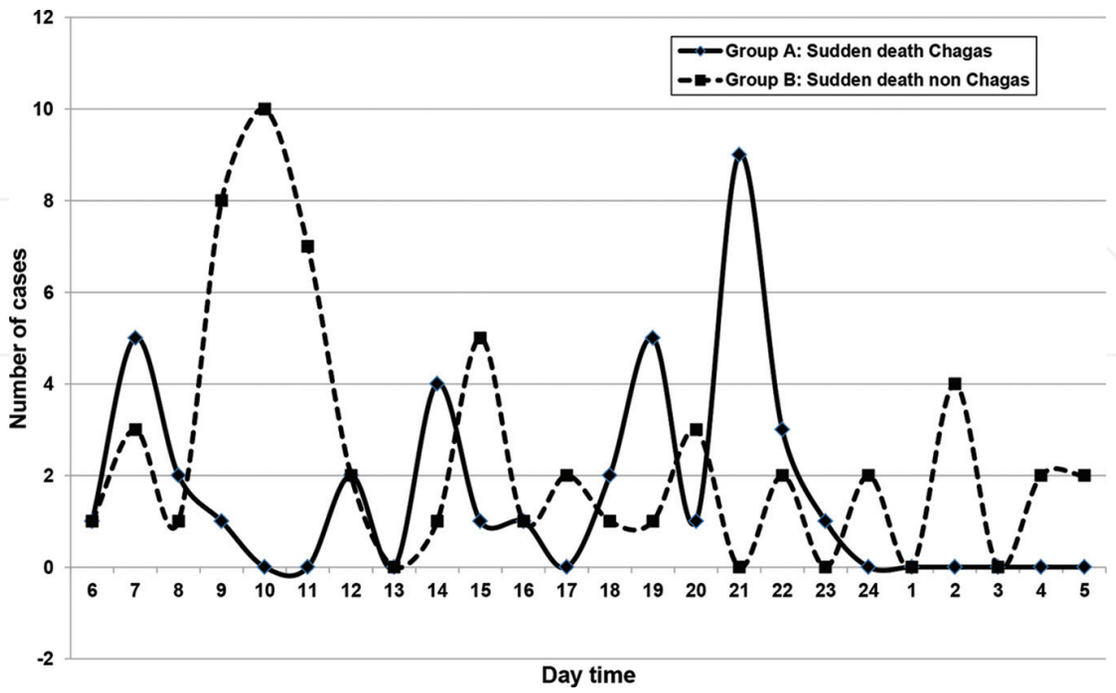

Figure 1. Sudden death of circadian rhythm.

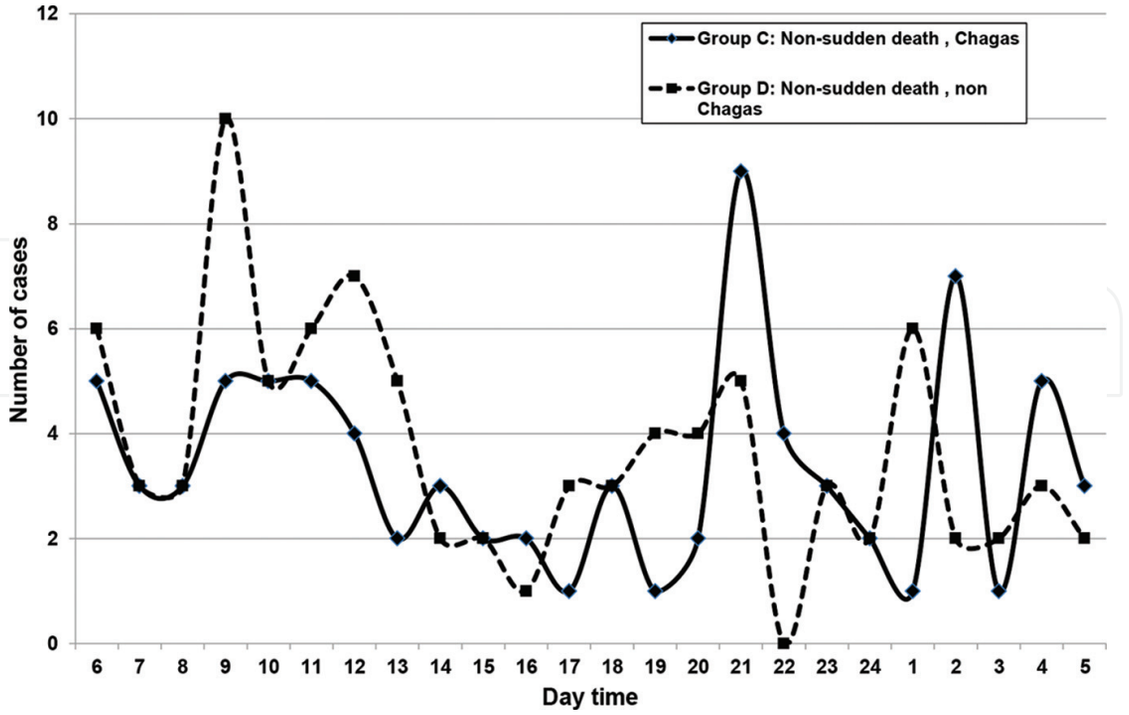

Figure 2. Circadian rhythm of nonsudden death.

	Group A Chagas SD n=38		Group B Non-Chagas SD n=58		Dif %	P-value
	Cases	%	Cases	%		
6:00 am - - 5:59 pm	17	44.7	41	70.7	26%	0.0048
6:00 pm - - 5:59 am	21	55.3	17	29.3		

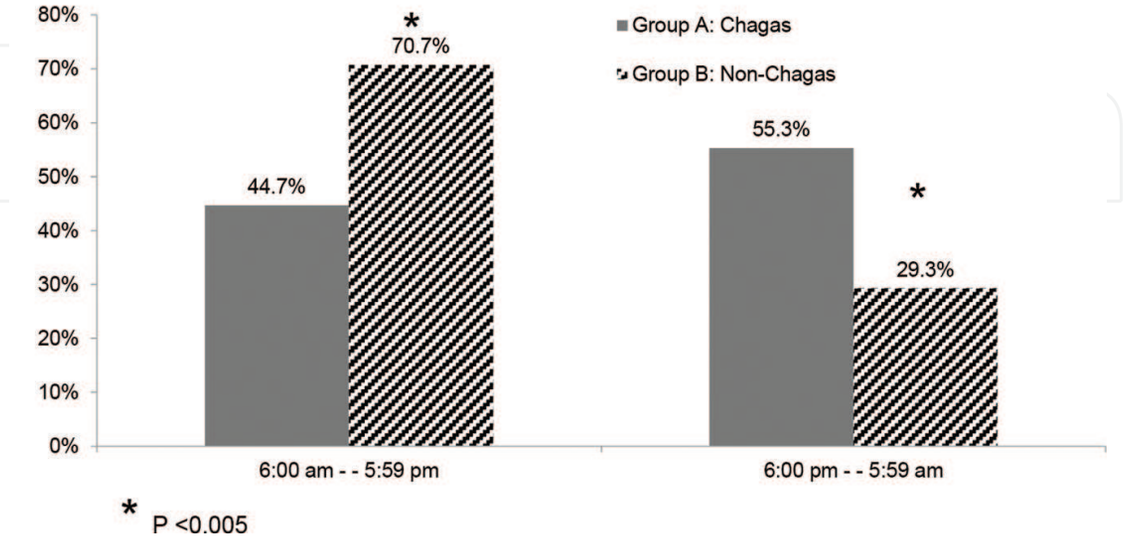

Figure 3. Comparison of 12-h periods of sudden death of Chagasic and non-Chagasic patients.

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	Group C Chagas, non-sudden death, n=81		Group D Non-Chagas, non-sudden death, n=86		Dif %	P-value
	Cases	%	Cases	%		
6:00 am - - 5:59 pm	40	49.4	53	59.6	12%	0.054
6:00 pm - - 5:59 am	41	50.6	36	40.4		

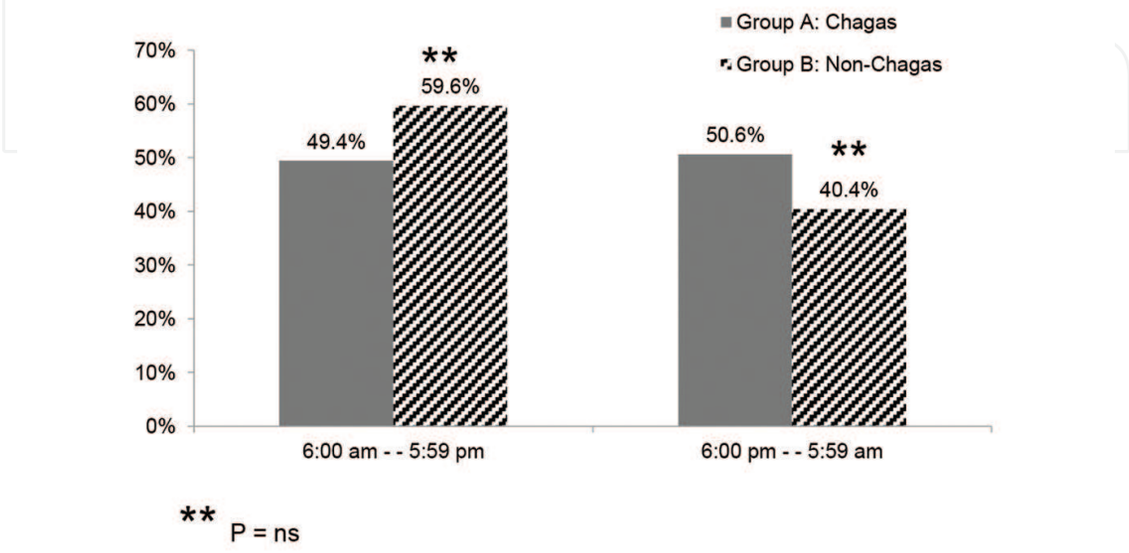
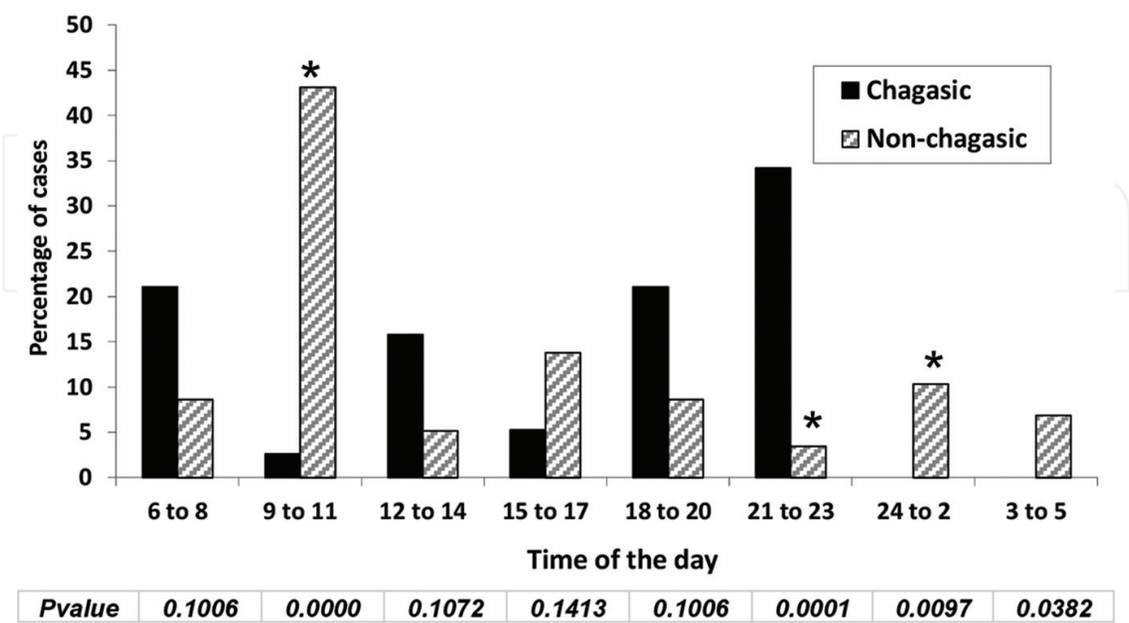


Figure 4. Comparison of 12-h periods of nonsudden death in Chagasic vs. non-Chagasic patients.



Pvalue	*0.1006*	*0.0000*	*0.1072*	*0.1413*	*0.1006*	*0.0001*	*0.0097*	*0.0382*

Figure 5. Sudden death circadian rhythm in Chagasic patients compared to non-Chagasic patients.

deaths in Chagasic patients vs. non-Chagasic patients, a significant difference in any of the analyzed ranges was not observed.

4. Discussion

The sudden death is the primary cause of death in patients suffering from Chagas disease, representing around 60% of the total cases [11], hence the importance of its study. Our study clearly evidenced that in Chagasic patients, the higher percentage of cases of sudden death occurred during the nighttime (**Figures 1**, **3**, and **5**). When we analyzed the non-sudden death results, no difference between the Chagasic and non-Chagasic arms was observed (**Figures 2 and 4**). Our results agree with those of Lopes et al. [8], who demonstrated a sudden death predominance in Chagasic patients during the nighttime. On the other hand, our study also agrees with previous studies in the non-Chagasic population in the United States, which were a predominance of sudden death cases occurred in the morning [7, 8]. The importance of our study lies in two milestones:

(1) This study represents the largest series reported to date comparing the sudden death circadian rhythm in Chagasic and non-Chagasic patients. (2) The fact that this study represents a series where all included patients belonged to the same center within a Latin American country, allowing a better group comparison.

The potential mechanisms for the sudden death circadian variation in the general population are not entirely clear, especially since due to the interaction among them, it is difficult to independently determine the importance of each factor. The proposed mechanisms include:

a. Autonomic nervous system alterations.

It is being proposed that both the sympathetic nervous system and the parasympathetic system may stimulate the circadian variation. Using the frequency domain, it has been demonstrated an unfavorable variability profile of the heart rate in the morning time. [14–17] This may be caused by both the sympathetic tone endogen variations and the increasing level of physical activity [15–17]. The use of beta-blockers reduces or removes the morning peak of ischemic and arrhythmic events [18–22], which supports the hypothesis of increasing adrenergic tone, since this same effect is not achieved via antiarrhythmic non-beta blockers medication [23]. Generally, the HRV indexes significantly decrease during the daytime and increase during the night [24–30].On the other hand, the variations of autonomic tone and parasympathetic-sympathetic balance have been proposed as the cause, which have been analyzed through heart rate variations (HRV) [31–35].

b. Morning variations of the electrophysical properties.

In both invasive electrophysiological studies [28] and non-invasive studies using permanent pacemaker telemetry [15, 31], circadian variation of the ventricular refractory has been demonstrated, being the last lower during the morning time and higher during sleep.

This variation does not seem to be related to the potassium or circulating catecholamine levels [31]; on the other hand, it would be aligned with the variations of the maximum QT interval [33].

c. Circadian variation of ischemic episodes.

A peak in the morning and in the afternoon of ischemia-related conditions, such as the myocardial infraction [22, 34, 35], anginal crisis [36–38], and strokes, [39, 40] has been reported. These episodes have been related to morning variations of the endothelial function [41] and of thrombogenesis biochemical markers [42–46]. Durgan et al. [47] demonstrated that there is a relation between the date time and the tolerance to reperfusion-ischemia in cardiomyocytes of isolated mice, being the lowest tolerance during the morning time.

The factors that may bias for the circadian rhythm to be different in patients with Chagas disease are not clear; however, several hypotheses have been posed:

1. The autonomic balance of Chagasic patients, which has been evidenced by several authors [48–50]. Cardiac autonomic dysfunction, characterized mainly by parasympathetic depression, is present in human and experimental Chagas disease, even in patients with minor ECG alterations [51].
2. The endothelial dysfunction [52].
3. The presence of antibodies against the adrenergic receivers may reduce the morning adrenergic activity, hence, suppressing the morning peak [53].

Abello et al. [54], when analyzing 22 Chagasic patients with third-generation implantable defibrillators, demonstrated a ventricular tachycardia circadian rhythm pattern, characterized by a frequency peak between noon and 18:00 h with a nadir between 24:00 and 6:00 h, which would be in line with our results.

5. Conclusion

The sudden death circadian rhythm in Chagasic patients significantly differs from that of the non-Chagasic patients, showing a greater prevalence during the nighttime. Further studies are needed in order to analyze both the prognostic implications and the therapeutic ones.

6. Limitations

Regarding the certainty of the time of death, the study limitation is common to that of all sudden death studies, since the time of death, which is mostly reported by a witness, decreasing the accuracy of the data. In most of the times, we ignored the personal history of the patients (previous pathology, concomitant treatment, etc.) because the death occurred suddenly. Also,

we do not have previous data from other complementary explorations such as echocardiogram, stress test, and so on in much of the cases.

Conflict of interest

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