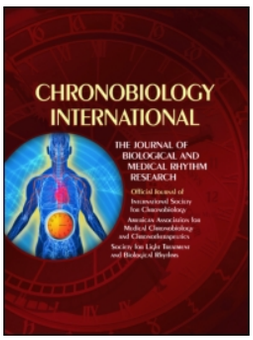

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Chronobiology International

The Journal of Biological and Medical Rhythm Research

ISSN: 0742-0528 (Print) 1525-6073 (Online) Journal homepage: http://www.tandfonline.com/loi/icbi20

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To cite this article: Juan Marques, Iván Mendoza, Claudia Suárez, Federico Moleiro, Iván Mendoza-Britto & Maria Marques-Mejías (2017): Sudden death circadian rhythm in Chagasic patients compared to non-Chagasic patients, Chronobiology International, DOI: 10.1080/07420528.2017.1293086

To link to this article: http://dx.doi.org/10.1080/07420528.2017.1293086

Published online: 07 Mar 2017.

CHRONOBIOLOGY INTERNATIONAL
http://dx.doi.org/10.1080/07420528.2017.1293086

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Sudden death circadian rhythm in Chagasic patients compared to non-Chagasic patients

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ABSTRACT

Chagas disease (Ch) affects 8–10 million people in Latin America, most of them are poor. Sudden death (SD) is the major cause of death in patients with Ch. To the best of our knowledge, the present report covers the largest reported series comparing the SD of Ch versus non-Ch patients *Objective*: To compare the circadian rhythm of SD in Ch versus non-Ch patients. *Methods*: Retrospective analysis of all the cases of SD recorded in our department, including autopsied patients from 1963 until 2011. The pattern of SD of 262 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 = 89), and Group D: non-Ch with non SD (n = 81). For the statistical analysis, proportion comparison was used. *Results*: 44.7% (17/38) of SDs in Group A (Ch) occurred between 6 a.m. and 5:59 p.m., while for Group B (not Ch) 70.7% (41 /58) died in that time ($p < 0.005$). 55.3% (21/38) of the SD in Group A (Ch) occurred between 6 p.m. and 5:59 a.m. compared with 29.3% (17/58) in Group B ($p < 0, 005$). *Conclusions*: Circadian rhythm of SD in patient with Ch differs from those with non-Ch. In Ch patients, SD occurs predominantly during the night compared with non-Ch SD that occurs predominantly during the day especially during the morning.

ARTICLE HISTORY
Received 4 January 2017
Revised 1 February 2017
Accepted 6 February 2017

KEYWORDS
Cardiomyopathy; Chagas disease; circadian rhythm; sudden death

Introduction

The Chagas disease is a malady caused by the *Trypanosoma cruzi* protozoan, and represents an endemic disease in Latin America, affecting 8–10 million of patients, most of them are poor (Organización Panamericana de la Salud, 2006; Rassi et al., 2010;). The sudden death circadian variation has been demonstrated in two large-scale studies: the Framingham Heart Study (Muller et al., 1989) and the Massachusetts Death Certificate Study (Willich et al., 1987). Both studies show a peak of sudden deaths between 7 and 11 a.m. with a lower incidence during sleep, which is similar to the rate of ischemic and arrhythmic events (Willich et al., 1992; Guo & Stein, 2003). The sudden death is the main cause of death in patients with the Chagas disease, being responsible of the 55–65% of their deaths (Rassi et al., 2001). Lopes et al. (1993) 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 non-sudden 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 non-sudden death of Chagasic patients versus non-Chagasic patients with cases within a same center.

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, in the cases of autopsies, a necroscopic study.

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.

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SCD (sudden cardiac death) 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 (Fishman et al., 2010). 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 hour after the onset of symptoms (Fishman et al., 2010). A probable SCD is an unexpected death without obvious extracardiac cause that occurred within the previous 24 hours (Fishman et al., 2010). 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 (Fishman et al., 2010). 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; 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.

Results

After analyzing the data divided in 12-hour periods (day and night), significant differences were observed. Figure 1 shows the percentages of cases from the SD groups occurring during night and day. In total, 44.7% (17/38) of the sudden deaths in Group A (Ch) occurred between 6 a.m. and 5:59 p.m., while for Group B (non-Ch) 70.7% (41/58) of the patients died within that time (p < 0.005). 55.3% (21/38) of the deaths of the Group A (Ch) occurred between 6 p.m. and 5:59 a.m., as compared to 29.3% (17/58) from Group B (p < 0.005). Figure 2 shows the data of non-sudden death cases. In total, 49.4% (40/81) of the Group C (Ch non-SD) died between 6 a.m. and 5:59 p.m., as compared to 59.6% (53/89) from Group D (non-Ch, non-SD), (p not significant), while 50.6% of the Group C (Ch, non-SD) cases died between 6 p.m. and 5:59 a.m., as compared

	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		

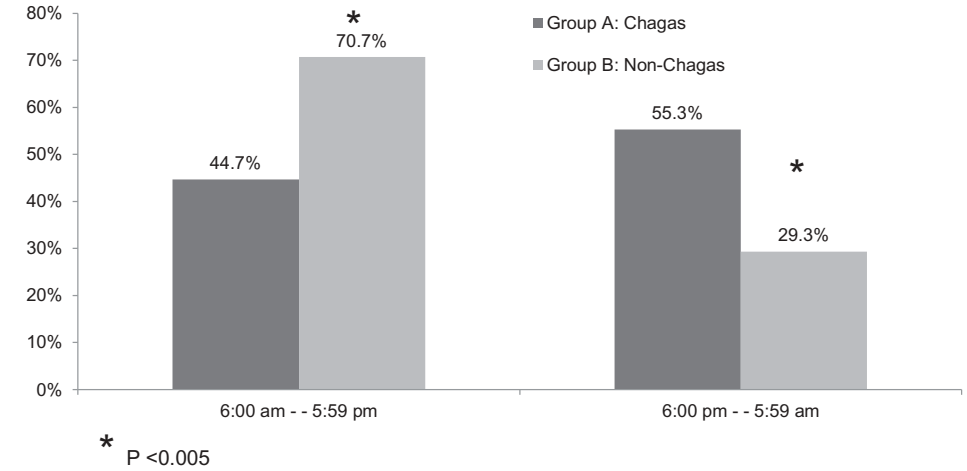


Figure 1. Comparison of the percentages of cases from the SD groups occurring during night and day. Fifty-five percent (55%) of sudden deaths of Chagasic patients happened between 6 p.m. and 5:59 a.m., while only 29.3% of the sudden death cases in non-Chagasic patients occurred within this period (p = 0.00478).

	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		

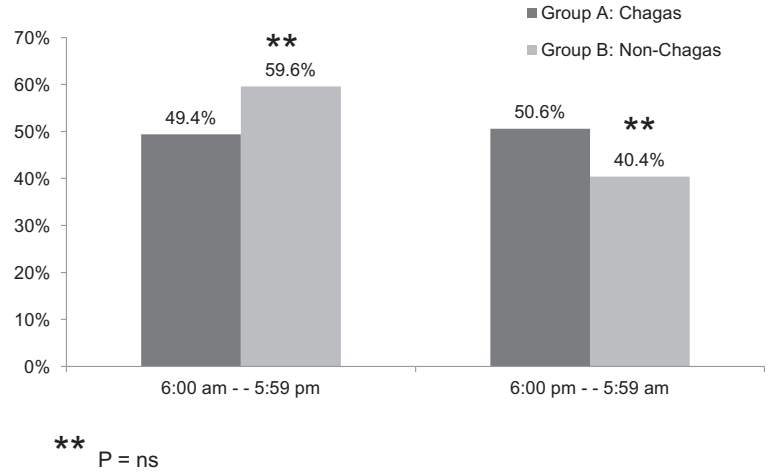


Figure 2. Comparison of the percentages of cases of non-sudden death occurring during night and day. No significant differences between the Chagasic and non-Chagasic patients were observed.

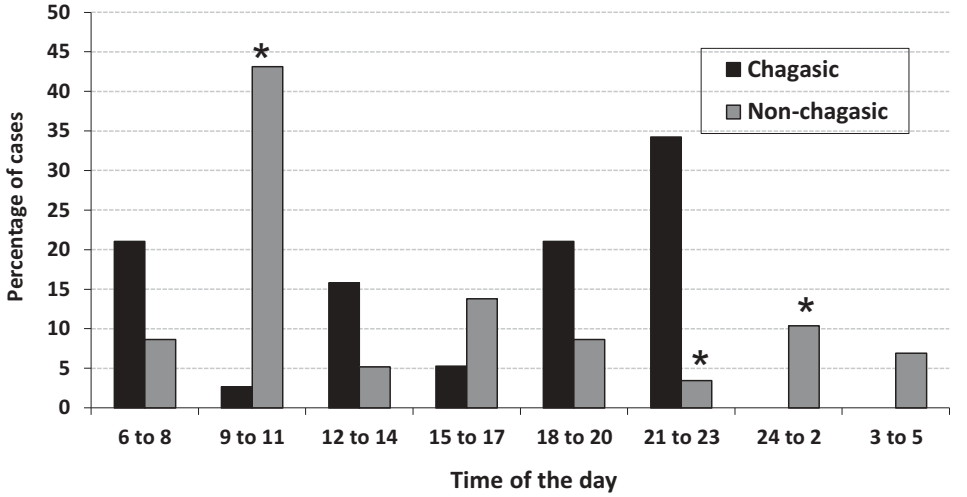
to 40.4% (36/53) from Group D (non-Ch, non-SD) (p was not significant).

In order to perform a more detailed analysis, the percentages of cases were grouped within 3-hour periods: (6–8, 9–11, 12–14, 15–17, 18–20, 21–23, 24–2, 3–5). Figure 3 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% versus 3%, $p = 0.0001$), while the non-Chagasic arm presented a higher percentage of cases within the 9–11 h range (43% versus 3%, $p < 0.0001$), of 24–2 h (10% versus 0% $p < 0.005$), and from 3 to 5 h (7% versus 0%, $p < 0.005$). The difference of the other analyzed periods was not significant. When comparing the number of cases of non-sudden deaths in Chagasic patients versus non-Chagasic patients, a significant difference in any of the analyzed ranges was not observed.

Discussion

The sudden death is the primary cause of death in patients suffering from Chagas disease, representing around 60% of the total cases (Rassi et al., 2001), and 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 night time (Figures 1, 3, and 5). When we analyzed the non-sudden death results, no difference between the Chagasic and non-Chagasic arms was observed (Figure 2). Our results agree with those of Lopes et al. ((1993), who demonstrated a sudden death predominance in Chagasic patients during the night time. On the other hand, our study also agrees with previous studies in the non-Chagasic population in the United States, where a predominance of sudden death cases occurred in the morning (Willich et al., 1987; Muller et al., 1989). The importance of our study lies in two milestones:

(1) This study presents the largest series reported to date comparing the sudden death circadian rhythm in Chagasic and non-Chagasic patients. (2) Due to the fact that all included patients belonged to the same center, a better group comparison was performed.



Pvalue	0.1006	0.0000	0.1072	0.1413	0.1006	0.0001	0.0097	0.0382

Figure 3. Sudden death circadian rhythm analyzed within 3-hour periods, comparing the Chagasic with non-Chagasic patients. (*) indicates significant difference ($p < 0.001$) between Ch and non-Ch patients. The highest statistical significance was observed in the 9–11 h range ($p < 0.00001$) and in the 21–23 h range ($p = 0.0001$).

(2) 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 proposed that both the sympathetic nervous system and the parasympathetic system may stimulate the circadian variation. Using the frequency domain, an unfavorable variability profile of the heart rate in the morning time has been demonstrated (Hohnloser and Klingenheben, 1994; Huikuri et al., 1995; Klingenheben et al., 1995; Nakagawa et al., 1994). This may be caused by both the sympathetic tone endogen variations and the increasing level of physical activity (Huikuri et al., 1995; Klingenheben et al., 1995; Nakagawa et al., 1994). The use of beta blockers reduces or removes the morning peak of ischemic and arrhythmic events (Aronow et al., 1995; Behrens et al., 1997; Kupari et al., 1990; Muller et al., 1985; Peters et al., 1989), which supports the hypothesis of increasing adrenergic tone, since this same effect is not achieved via antiarrhythmic non-beta blockers medication (Peters et al., 1994). Generally, the heart rate variation (HRV) indexes significantly decrease during the day time and increase during the night (De Scalzi et al., 1984; Furlan et al., 1990; Haseroth et al., 2001; Korpelainen et al., 1997; Lombardi et al., 1992; Massin et al., 2000; Yamasaki et al., 1996). On the other hand, the variations of autonomic tone and parasympathetic-sympathetic balance have been proposed as the cause, which has been analyzed through HRVs (Behar et al., 1993; Cannon et al., 1997; Cinca et al., 1986; Kong et al., 1995; Molnar et al., 1996).

B. Morning variations of the electrophysical properties

In both the invasive electrophysiological studies (Cinca et al., 1986) and non-invasive studies using permanent pacemaker telemetry (Huikuri et al., 1995; Kong et al., 1995), 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 catecholamines levels (Kong et al., 1995). On the other hand, it would be aligned with the variations of the maximum QT interval (Molnar et al., 1996).

C. Circadian variation of ischemic episodes

A peak in the morning and in the afternoon of ischemia-related conditions such as the myocardial infraction (Behar et al., 1993; Cannon et al., 1997; Muller et al., 1985), anginal crisis (Behar et al., 1991; Hausmann et al., 1990; Hausmann et al., 1991), and strokes (Argentino et al., 1990; Wroe et al., 1992) has been reported. These episodes have been related to morning variations of the endothelial function (el-Tamimi et al., 1995) and of thrombogenesis biochemical markers (Angleton et al., 1989; Bridges et al., 1993; Kurnik, 1995; Ogawa et al., 1989; Sakata et al., 1992). Durgan et al. (2010) demonstrated that there is a relation between the date and 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 has been evidenced by several authors (Carrasco Guerra et al., 1997; Junqueira, 1991; Ribeiro et al., 2001). Cardiac autonomic dysfunction, characterized mainly by parasympathetic depression, is present in human and experimental Chagas disease, even in patients with minor ECG alterations (Vasconcelos & Junqueira-Júnior, 2012).
(2) The endothelial dysfunction (Torres et al., 1995). (3) The presence of antibodies against the adrenergic receivers may reduce the morning adrenergic activity, hence suppressing the morning peak (Chiale et al., 2001).

Abello et al. (2007) analyzed 22 Chagasic patients with third-generation implantable defibrillators, and 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.

Conclusion

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

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 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, etc., in much of the cases.

Conflict of Interest

Juan Marques, Medical Director of MSD Venezuela.

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