Sudden Death is Uncommon in Chronic Chagas Disease without Evident Heart Disease

La muerte súbita no es frecuente en la enfermedad de Chagas crónica sin cardiopatía demostrable

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In 2012, our group published a systematic review (1) in this Journal, analyzing the available updated evidence about the incidence of sudden death (SD) in the indeterminate phase of Chagas disease.

On that occasion, a bibliographic search in Pubmed and SciELO was performed until March 2011 using the following keywords: "Chagas" and "follow-up Studies [MeSH] or prognos*[Text Word] or predict*[Text Word] or course*[Text Word]". This search provided 1,058 articles, 19 of which complied with the initial search criteria, and only 15 included enough data to constitute a group of asymptomatic indeterminate chagasic patients with normal ECG.

The 15 selected studies included 9,382 chagasic patients, 6,487 with normal and 2,895 with abnormal ECG. The analysis reported the death of 60 patients with normal ECG (0.92%) and 529 with abnormal ECG (18.27%) (OR 23.95; CI 95% 18.27-31.38; p < 0.0001). Four studies which included 1,025 control non-chagasic patients reported 60 deaths (5.85%). However, the ECG was analyzed in only one of these studies where 8 out of 337 control patients with negative serology and normal ECG died (2.43%). The loglin model (2-6) was fitted to the data and the null hypothesis revealed that: 1) mortality of asymptomatic patients with normal ECG was not different from that in the control group with normal ECG (p=0.38); and 2) both chagasic and seronegative patients with abnormal ECG exhibited increased mortality (p <0.0001) compared with patients with normal ECG. Regarding the risk of sudden death, five studies separately reported this type of death. Table 1 (also published in the original article) details the relative risk of SD in patients with normal or abnormal ECG. That systematic review showed that SD is uncommon for indeterminate Chagas disease, and that these patients present the same risk of the general population.

The publication of this article was followed by several comments. In a letter to the editor (7), Shapachnik disagrees with the term "indeterminate form" of Chagas disease and proposes to replace it with "chronic phase without evident heart disease" (by ECG, X-ray, Holter and echocardiography) according to the term used by the 2010 SAC Council Consensus of Chagas Disease (8); he also advocates carrying out sophisticated complementary studies on these patients. This Consensus proposes several studies on this group of patients (indeterminate form or chronic phase without evident heart disease), and assigns class of recommendation and level of evidence to each of them: lab tests, ECG (class I recommendation, level of evidence A), chest X-ray (I, A), stress test (I, C), 24-hour Holter (I, C), echocardiography (I, C), exploration of autonomic nervous system (I, C; by active postural maneuver, hyperventilation test, Valsalva maneuver, tilt test, and anti-muscarinic receptor antibodies), exploration of the endothelium (I, C; by thrombomodulin and brachial echo-Doppler), SPECT (IIb, C), MRI with gadolinium (IIb, C), signal-averaged ECG (IIb, B) and "analysis of fibrosis" (IIb,C).

In turn, Yanovsky, in his letter to the editor (9), refers to an article published by Pinto Díaz et al. (10) Although in that article the authors do not report the cause of death of patients with Chagas disease and normal ECG, Yanovsky attributes it to Chagas disease.

Over the past 5 years, several reviews and meta-analyses have been published on sudden death in the indeterminate phase of Chagas disease.

In a review published in 2018, (11) Perez-Molina et al. continue to use the term "indeterminate form of Chagas" and refer that this stage of the disease has a good prognosis. They argue that, although the most sophisticated complementary methods find subtle anomalies in these patients, the prognostic implication of those findings is not yet clear. (11) Moreover, Nunes et al. in a recent review published as the

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Source	Chagasic patients		Seronegative patients	
	Normal ECG	Abnormal ECG	Normal ECG	Abnormal ECG
Porto (2)	0.00925926	0.06666667	No data	No data
Pinto (3)	0.02375449	0.07346189	No data	No data
Maguire (4)	0.00312826	0.02380952	No data	No data
Mota (5)	0.00202429	0.01038462	0.0243161	0.01190476
Manzullo (6)	0.0000231	0.00094545	No data	No data
Total	0.00763788	0.03505363	0.00243161	0.01190476

Table 1. Relative risk of sudden death in the indeterminate form of Chagas diseas

American Heart Association Scientific Statement, attribute a very good prognosis to the indeterminate form of Chagas disease, with mortality comparable to that of the general population provided ECG remains normal. (12) Rassi et al. (13) also conclude that patients with the indeterminate form of Chagas disease present the same mortality rate as the general population, and point out that although modern methods find anomalies in these patients, they are mild and do not present an evident prognostic implication. In addition, they question the cause of these abnormalities, as it is unclear whether the underlying pathology is a consequence of acute myocarditis at the onset of the disease or is due to an inflammatory balance between the host and the parasite. (13) While Pereira Nunes et al. (14) find that SD may occur in early stages of the disease, they argue that patients with the indeterminate form of Chagas disease have a life expectancy similar to that of the general population and believe -as other authors- that the prognostic value of the abnormalities found in the most sophisticated complementary methods is not clear.

The "Recommendations for imaging in patients with Chagas disease" -a document endorsed by the American Society of Echocardiography, the Inter-American Society of Echocardiography, and the Brazilian Society of Cardiology, published in the Journal of the American Society of Echocardiography in 2018 (15)- conclude that sophisticated complementary methods are not indicated for chagasic patients with normal ECG, chest X-ray and echocardiography, based on the concept that the indeterminate phase of Chagas disease presents the same mortality rate as the general population. (15) Malik et al. attribute an excellent prognosis to this phase, with mortality rates similar to those of the general population. (16)

In an opinion article published in 2016, Pereira Junior et al (17) and Giménez and Mitelman (18) list many of the subtle cardiac alterations that can be detected in the early stages of the disease. However, the prognostic significance of these alterations is not clearly defined, and no conclusive robust evidence or necropsy studies support an increase of mortality rate in the indeterminate phase of Chagas disease. Linetzki et al. argue that although positive serology for Chagas is associated with a higher risk of death in patients with heart failure, there is little evidence suggesting lower survival in asymptomatic chagasic patients. (19) Cucunubba et al. (20) state that mortality is increased in patients with asymptomatic Chagas disease. However, the asymptomatic group included individuals with "minimal ECG damage"; therefore, this group comprised patients who do not correspond to the indeterminate stage of the disease due to ECG-demonstrable electrical alterations.

Capuani et al. (21) published a retrospective study which analyzed medical records of blood donors who referred to be asymptomatic in the pre-donor questionnaire. They divided the population into two groups (seropositive and seronegative for Chagas disease in the usual screening of potential donors), and found an excess risk of death in the seropositive group. However, no ECG was performed on patients in this study, making it impossible to classify them as belonging to the indeterminate form of Chagas disease, as patients with chagasic cardiomyopathy may not present symptoms despite having abnormal ECG and/or echocardiography. Similarly, the main Brazilian guidelines (22) and publications (23) maintain the concept of indeterminate form as described above.

Rabelo et al. (24) studied the extension of myocardial fibrosis evaluated using delayed-enhancement MRI in chagasic patients, and found that the presence and extension of fibrosis in the indeterminate form of Chagas disease was similar to that of the chronic cardiac phase with normal ejection fraction (defined as ECG alterations with normal echocardiography). In both groups, the amount of fibrosis was significantly lower than in the group of patients with chronic cardiac phase and reduced ejection fraction. This has been interpreted as reflecting a certain benignity manifested by fibrosis sequelae in these patients, in whom SD is uncommon. (24)

CONCLUSION

After analyzing the literature published since 2011, we still consider that asymptomatic chagasic patients should be studied first with ECG, chest X-ray, echocardiography and eventually, 24-hour Holter. If these studies turn out to be normal, the patient's risk of death is the same as that of the general population and can therefore be recommended to lead a normal life as far as his/her work and sports activities are concerned. However, we should bear in mind that these patients must be periodically monitored due to the risk of disease progression, which implies an increased risk of death. Therefore, the old distinction between infected and sick would be a euphemism. (25)

We also believe that there is no strong evidence or autopsy supporting the routine use of more sophisticated diagnostic methods (stress test, autonomic studies, nuclear medicine studies, magnetic resonance imaging, etc.) in these patients. However, medical science is constantly evolving. The concept of myocardial histological structure in patients with the indeterminate form of Chagas disease has been done on the basis of necropsy studies of chagasic patients who died from accidental causes. For obvious reasons, recent ECG or echocardiography were not available for these patients and their classification as indeterminate was not easy. Today, non-invasive complementary methods -such as cardiac MRI- are available to detect the presence of anatomical lesions. In order to understand the true significance of results by applying new methods, a comprehensive data collection is necessary, combining classical and studied methods (ECG, X-ray, Holter and echocardiography) with modern approaches and necropsies.

This should be a collaborative effort, with data collection throughout the country, coordinated by the Argentine Federation of Cardiology (FAC) and the Argentine Society of Cardiology (SAC) Chagas Disease Councils. In this regard, the National Registry of Chagas Disease of the Argentine Federation of Cardiology RENECH study, is an outstanding example. (26) Only after carrying out this type of studies will we have solid scientific evidence to make correct recommendations; until then we must be cautious, use only the certainties available, and avoid recommendations on speculations or anecdotal cases without necropsy verification. In conclusion, sudden death is uncommon in the indeterminate form of Chagas disease.

Conflicts of interest
None declared.

(See authors' conflicts of interest forms on the website/Supplementary material)

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