ORIGINAL ARTICLE

Ergometric Findings in Asymptomatic Chagasic Patients, With Normal ECG and Without Evident Heart Disease

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ABSTRACT

Background
Dysautonomia and QT interval dispersion are one of the earliest manifestations of Chagas disease which have proved to be predictors of increased morbi-mortality. New diagnostic technologies revealing earlier endothelial or dysautonomic disorders should provide better diagnostic and treatment strategies for the premature detection of patients with risk of developing chronic chagasic cardiomyopathy or sudden death.

Objectives
The aims of this study were:
1) To investigate clinical, electrocardiographic and ergometric characteristics in asymptomatic chagasic patients with normal electrocardiogram and no clinical evidence of the pathology. 2) To compare graded exercise testing results between chagasic patients and subjects with similar clinical characteristics but negative serological tests for Chagas.

Methods
This retrospective, observational study included 74 chagasic patients and 28 healthy subjects who underwent exercise testing during clinical check-up between March 2009 and September 2011.

Results
Chagasic patients often presented baseline heart rate ≤ 60 bpm (27.0% vs. 7.1%, p=0.02), lower maximal heart rate (129.5±22.8 vs. 145.2±16.5 bpm; p=0.002), prevalence of chronotropic incompetence, with maximum heart rate <80% pre-established value (47.3% vs. 14.3%; p=0.001) and higher rate of ventricular arrhythmias during exercise and recovery (25.7% vs. 0%; p=0.003).
While in the control group patients the QTc interval shortened normally during exercise, in most chagasic patients it was noticeably prolonged (Chagas group: 412.1 to 432.8 ms; p = 0.0005; control group: 412.4 to 385.8 ms; p<0.0001).

Conclusions
Asymptomatic chagasic patients without verifiable heart disease showed a high prevalence of dysautonomia, such as chronotropic incompetence and QTc interval prolongation during exercise. Stress testing is a noninvasive, reliable and relatively inexpensive diagnostic method that can contribute to the early diagnosis of dysautonomic and ventricular repolarization disorders and thus identify patients with Chagas disease who are at increased risk of arrhythmogenic sudden death.

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Key words > Chagas Disease - Electrocardiography - Primary Dysautonomia - QT Interval - Exercise Test

Abbreviations >

ABP	Blood pressure	**HR**	Heart rate
ECG	Electrocardiogram	**HRmax**	Maximun heart rate
GET	Graded ergometric test	**THRmax**	Total maximum heart rate

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BACKGROUND

Despite a century has elapsed since its discovery, Chagas disease is still one of the major causes of morbidity and mortality in Latin America, and in the last decades, due to migration of infected persons, has become a potential problem in Europe and the United States. (1) The World Health Organization estimates a world population of 12 million infected persons, 100 million at risk and an annual mortality of 50000 persons. (2) With some exceptions, Chagas disease evolves with: a) an acute phase that can be asymptomatic or course with a self-limited febrile syndrome lasting 4 to 8 weeks and b) a chronic phase consisting of two stages: a chronic period without evident pathology or an intermediate asymptomatic period, which can last 10 to 30 years or the whole lifetime, and a chronic symptomatic period with overt pathology, in which 10% of infected patients develop digestive and/or neurological pathologies and 25-30% of the patients present cardiac involvement, the most important and severe of which is cardiomyopathy, considered the main cause of mortality due to sudden or arrhythmogenic death, or functional impairment as a result of congestive heart failure. (3)

Inter-relating vascular, inflammatory, immunological and neurological factors have been postulated to develop and trigger the disease many years after its acute phase, so that in certain circumstances patients evolve from the chronic phase without evident disease to the chronic symptomatic phase of Chagas disease. (4, 5)

According to physiopathological analysis, Trypanososma cruzi has a neuroaminidase affecting cardiac function when it acts on the autonomic system conduction fiber membrane and myocardial and blood vessel endothelial cell membranes. (6) One of the earliest manifestations of Chagas disease is dysautonomia caused by impairment of the autonomic nervous system, which would be associated with antibodies acting against muscarinic receptors, first stimulating and then blocking them, with a clear acetylcholine-like effect. There is early appearance of anti-muscarinic antibodies once the parasite is lodged, having been detected in 30% of infected patients. (7-11)

Clinical evolution of Chagas disease is variable and unpredictable, so that detection of markers that help to identify patients at greater risk of sudden death or progression to the chronic symptomatic phase becomes a challenge. New diagnostic technologies enabling the early identification of endothelial or dysautonomic disorders should give rise to improved diagnostic and treatment strategies allowing the premature detection of patients at risk of evolving to chronic chagasic cardiomyopathy or suffering sudden death. The graded ergometric test (GET) is a noninvasive, reliable and relatively inexpensive procedure which in the methodology of Chagas disease study constitutes a Class IC indication in patients in the chronic phase of the disease without detectable cardiomyopathy assessed with current diagnostic methods. (12)

According to these observations, the aims of this study were:

a) To investigate clinical and ergometric signs of asymptomatic chagasic patients, with normal electrocardiogram (ECG) and no evident clinical pathology.
b) To compare GET clinical and ergometric data and the changes in electrocardiographic parameters in chagasic patients with those present in a group of subjects with similar clinical characteristics and negative Chagas serology.

METHODS

This observational, retrospective study included 102 patients who performed an ergometry test at our hospital between March 2009 and September 2011. The patients were distributed into two groups according to the serologic diagnosis of Chagas disease.

Chagas group: 74 patients with positive serology for Chagas disease, who presented normal ECG, chest X-ray and two-dimensional echocardiogram, and absence of heart disease or other organic pathology detectable with current available diagnostic methods.

Control group: 28 non-chagasic patients, selected from 100 consecutive ergometric tests, without history of coronary disease or evident clinical pathology and with ECG, chest X-ray and two-dimensional echocardiogram within normal limits.

All subjects included in the study were asymptomatic and performed a GET to be admitted to a gym, make non-competitive physical activity or fulfill a pre-employment health assessment. In the Chagas group patients, Chagas disease was diagnosed by the positive result of the three reactions that according to the National Institute of Parasitology Dr. Mario Fatala Chaben criteria are: indirect hemagglutinin reaction, indirect immunofluorescence test and the enzyme-linked immunosorbent assay method (Elisa). (12)

Patients with history of previous infarction or current coronary artery disease, valvulopathies, cardiomyopathies, supraventricular and ventricular arrhythmias, conduction disorders, thyroid disease, and medication and/or disorders affecting automatism, conduction and/or ventricular repolarization or basal ECG interpretation were excluded.

In each patient, the following demographic data were considered: age, gender, heart rate and blood pressure. Electrocardiogram, chest X rays and two-dimensional echocardiography performed the week before the ergometric test, were assessed.

The GET was peformed in an ergometric bicycle connected to a computerized system that acquires a 12-lead electrocardiographic recording at 25 mm/s at the end of each testing stage, both in exercise and recovery phases. In addition, heart rate and blood pressure were controlled. A continuous escalating protocol consisting of two phases was used: an active exercise phase with 3 min stages of progressive 150 kg loads and a recovery phase of three 1 min stages followed by two 3 min stages.

The GET was considered to be sufficient when heart rate (HR) during the exercise phase reached 85% of total maximum heart rate (THRmax) according to Robinson´s table, and was defined as chronotropic incompetence when maximum heart rate (HRmax) during exercise was less than 80% of predicted values. (13)

The number of patients presenting basal HR ≤ 60 beats per minute (bpm) or ≥ 100 bpm was considered as expression of dysautonomia. Blood pressure ≥ 190/100 mmHg at the end of maximum ergometric load was also taken into account to classify patients.

Delay in HR recovery was considered when in the second minute after exercise, HR had decreased less than 22 bpm. (14)

Using the computerized system that stores the electrocardiographic recording of each GET stage, two independent observers averaged the following ECG parameter values in milliseconds (ms) from V5 and V6 lead recordings of three consecutive cycles during basal, at the end of maximum attained load, and at the second minute of recovery: R-R (RR) interval; P-R (PR) interval; QRS duration (QRS); Q-T (QT) interval, measured from the beginning of QRS to the end of the T wave determined by the tangent method as the intersection point with the isoelectric baseline of the maximum down slope of the curve between the apex of the T wave and the U wave; the corrected QT interval (QTc), calculated according to Bazett´s formula; QTc-max ≥ 0.47 s and ST segment changes at 80 ms from the J point during GET.

Based on HRmax attained during the GET active exercise phase, patients in the Chagas group were distributed into two sub-groups:

With insufficient GET: 48 patients with HRmax < 85% THRmax during the exercise phase.

With sufficient GET: 26 patients where HR attained 85% of pre-established THRmax at maximum load

The main clinical, ergometric data and changes in electrocardiographic parameters during exercise and recovery GET phases were compared between chagasic and control group patients, and within the chagasic group, between patients with insufficient and sufficient GET.

Statistical analysis

Categorical variables are expressed as frequency and their percentage. Continuous variables are expressed as mean ± standard deviation and median (interquartile range) according to their distribution.

Discrete variable analysis was performed with the chi-square test and the partitioning chi-square test.

Continuous variables were analyzed with Student´s t test for two groups or Kruskal-Wallis test according to their distribution.

Intra-group comparison of continuous variables was performed with a paired t test. A p value < 0.05 was considered statistically significant.

RESULTS

One hundred and two patients with mean age of 47.6 ± 12.8 years were included in the study, 59 of which (57.8%) were men.

Table 1 shows the general clinical and ergometric characteristics of the patients in each group. No statistically significant differences in age and gender were found between the two groups.

The reason for early exercise termination was muscle fatigue. During GET, patients did not present symptoms and no ST segment and T wave modifications were observed.

Patients in the Chagas group frequently had basal HR ≤ 60 bpm (27.0% vs. 7.1%; p = 0.02) and HRmax attained during GET was lower (129.5 ± 22.8 bpm vs. 145.2 ± 16.5 bpm; p = 0.002).

Chagasic patients presented greater prevalence of THRmax ≤ 80% during GET (chronotropic incompetence) (47.3% vs. 14.3%; p = 0.003) and ventricular arrhythmia during exercise and recovery (25.7% vs. 0%; p = 0.003).

Table 2 shows electrocardiographic parameters and their changes during the ergometric test in each group. No statistically significant differences were found in basal electrocardiographic parameters.

During exercise, patients in the control group normally presented shortened QTc interval, while a significant number of patients in the Chagas group markedly prolonged it (Chagas group: 412.1 ± 18.5 ms to 432.8 ± 42.3 ms; p = 0.0005; control group: 412.4 ± 19.2 ms to 385.8 ± 19.3 ms.; p < 0.0001) (Figure 1).

In the Chagas group there was also a high prevalence of patients with QTc-max ≥ 0.47s (22.9% vs. 0%; p = 0.005).

In both groups there was a significant shortening of the PR interval. Patients in the Chagas group showed a tendency to widen the QRS, whereas this change was not seen in patients of the control group.

Table 3 shows that when chagasic patients were analyzed according to the HRmax attained during exercise, patients with insufficient GET had a lower basal HR (66.4 ± 15.3 bpm vs. 88.9 ± 13.8 bpm; p < 0.0001), higher prevalence of basal HR ≤ 60 bpm (41.7% vs. 0%; p = 0.0001), greater delayed HR recovery on the second minute after the exercise test (50% vs. 19.2%; p = 0.009) and a significant difference in the number of patients with prolonged QTc compared to normal shortening in patients with sufficient GET (419.7 ± 17.0 ms to 452.9 ± 27.2 ms, p < 0.0001 with insufficient GET, and 408.0 ± 18.1 ms to 395.4 ± 40.0 ms, p = 0.003 with sufficient GET).

DISCUSSION

During the chronic period without detectable chagasic cardiomyopathy, approximately 30% of infected patients present disorders of diverse magnitude, as dysautonomia, vascular endothelial dysfunction affecting myocardial microcirculation and late and regional inhomogeneous ventricular repolarization, evidenced by great dispersion of QT interval duration and QTc prolongation in the basal ECG. All these manifestations would be related with the presence of antimuscarinic antibodies and would be indicators of increased morbi-mortality, turning important its early detection with non-invasive and easily accessible methods. Several studies have shown that 95% of patients with antimuscarinic antibodies had dysautonomia symptoms and 50% presented QT interval dispersion > 65 ms. (9, 15, 16)

Table 1 results agree with previously mentioned studies (6, 11, 16), showing that a significant number of chagasic patients presented dysautonomia signs during the ergometric test: high prevalence of insufficient GET and basal HR ≤ 60 bpm, a significant lower increase of HRmax despite having attained similar ergometric loads than control group patients and mainly, the great percentage of patients with chronotropic incompetence during the active phase of the exercise. Frequent ventricular arrhythmia was also added to the unbalanced autonomic signs during GET in the Chagas group.

Chronotropic incompetence is defined as HR inability to increase in proportion to exercise intensity as shown by HRmax ≤ 80% THRmax. Chronotropic

Table 1. Clinical and ergometric characteristics in each group of patients

	Chagas group n = 74	Control group n = 28	p
Age (years)	47.9 ± 12,5	46.6 ± 13.8	0.65
Men	44 (59.5)	15 (53.6)	0.37
Insufficient GET	48 (64.8)	9 (32.1)	0.003
HRmax ≤ 80% THRmax	37 (47.3)	4 (14.3)	0.001
Basal HR (bpm)	74.3 ± 18.2	80.3 ± 11.5	0.08
Basal HR ≤ 60 bpm	20 (27.0)	2 (7.1)	0.02
Basal HR ≥ 100 bpm	10 (13.5)	3 (10.7)	0.70
HRmax	129.5 ± 22.8	145.2 ± 16.5	0.002
Basal DBP	76.3 ± 11.2	74.8 ± 11.1	0.55
Basal SBP	117.9 ± 17.4	118.4 ± 17.3	0.91
Maximum DBP	89.9 ± 10.1	89.6 ± 6.8	0.88
Maximum SBP	175.9 ± 18.8	174.5 ± 10.8	0.50
Maximum SBP ≥ 190 mm Hg	23 (31.1)	4 (14.3)	0.06
Maximum BP ≥ 190/95 mm Hg	16 (21.6)	4 (14.3)	0.29
Maximum load ≥ 900 kgm	16 (21.6)	8 (28.6)	0.46
Maximum load (kgm)	600 (600-750)	750 (600-900)	0.16
HR recovery delay at 2nd min	29 (39.2)	7 (25)	0.13
Ventricular arrhythmia during the test	19 (25.7)	0	0.003

GET: Graded ergometric test. HR: Heart rate. max: Maximum. bpm: Beats per minute. THRmax: Total maximum heart rate. BP: Blood pressure. DBP: Diastolic blood pressure. SBP: Systolic blood pressure. Data are expressed as n (%); mean ± standard deviation and median (interquartile range).

Table 2. Basal ECG and its changes during ergometry in patients of each group

	Chagas group n = 74	Control group n = 28	p
Basal PR	153.6 ± 15.3 mseg	149.1 ± 14.3 ms	0.17
PR- max	140.4 ± 21.0 ms#	129.1 ± 22.0 ms§	0.01
Basal QRS	79.4 ± 9.7 ms	77.6 ± 13.0 ms.	0.45
QRS max	81.6 ± 10.6 ms*	75.4 ± 12.6 ms.**	0.01
QRS max – basal difference	2.10 ± 10.4 ms	2.22 ± 12.6 ms.	0.04
Basal QTc	412.1 ± 18.5 ms	412.4 ± 19.2 ms.	0.95
QTc-max	432.8 ± 42.3 ms§	385.8 ± 19.3 ms#	< 0.0001
QTc-max ≥ basal	47 (63.5)	1 (3.5)	< 0.0001
QTc at 2nd min recovery ≥ basal	44 (59.4)	3 (10.7)	< 0.0001
QTc-max ≥ 0.47 s	17 (22.9)	0	0.005
QTc at 2nd min recovery	432.7 ± 32.7 ms	399.8 ± 24.9 ms	< 0.0001
QTc-max – basal difference	20.6 ± 48.8 ms	26.6 ± 18.3 ms.	< 0.0001
QTc at 2nd min recovery – basal difference	20.6 ± 39.8 ms	12.6 ± 21.1 ms	0.001

# p < 0.0001 vs. basal.
* p = 0.08 vs. basal.
§ p < 0.001 vs. basal.
** p = 0.36 vs. basal.

incompetence, considered the best indicator of dysautonomia, is attributed to lower sinus node sensitivity to sympathetic stimulation and circulating catecholamines due to underlying autonomic dysfunction, and has been shown to be an independent predictor of major cardiovascular events and increased all-cause mortality. (17, 18)

The most important finding of our study is shown in Table 2. During the exercise phase, ECG at end maximum load showed that while control group patients presented normal PR-max, QT-max and QTc-max interval shortening, probably due to adrenergic release, chagasic patients showed greater PR-max, QRS max interval duration and mainly a significant QTc-max prolongation, which became more notorious when compared with basal and control group recordings. It is noteworthy that almost 30% of the patients presented QTc-max ≥ 0.47 s, while none of the control group patients exhibited prolonged QTc-max.

Numerous studies have pointed out the presence of great dispersion in QT interval duration ≥ 65 ms in chagasic patients during the chronic period of the disease without evident cardiomyopathy, indicative of regional or localized myocardial fiber repolarization heterogeneity which would be associated with greater risk of complex ventricular tachyarrhythmias and increased morbi-mortality. (19-22)

However, other authors (23-26) have shown in non-chagasic populations that prolongation of longer duration QTc interval (≥ 458 ms in V5-V6 leads) would have greater importance, especially when it is ≥ 0.47 s, because it behaves as an independent predictor of sudden death. This could be an expression of localized delay in ventricular repolarization produced by the inhomogeneous prolongation of action potential duration as a consequence of temporal and regional dispersion of myocardial fiber refractory period, which when stimulated and increased by underlying autonomic unbalance favors gated reentry activity. These are the electrophysiological mechanisms participating in triggering complex ventricular arrhythmias and sudden death in Chagas disease, (27, 28)

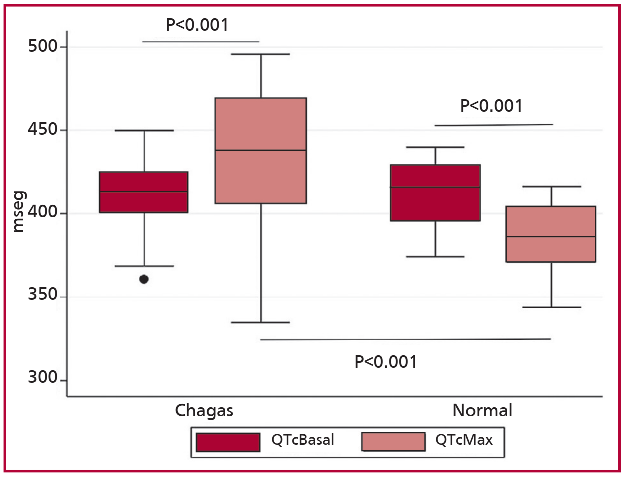

Fig. 1. QTc exercise changes in chagasic and in control group patients.

During GET, especially in chagasic patients with insufficient GET (see Table 3), a number of factors shown to be predictors of greater risk of sudden death can be detected, such as high prevalence of parameters indicating dysautonomia, delay in HR recovery in the second minute of exercise recovery together with the more significant prolongation of QTc-max interval compared to shortening in chagasic patients with sufficient PEG. The results would allow us to explain why dysautonomia has been associated to greater risk of sudden death in previous studies, even in early stages of Chagas disease. (7, 9, 19)

The delay in HR recovery in the second minute after exertion, which has been shown to be a predictor of increased mortality in the overall population, would also be attributable to dysautonomia by the autonomic unbalance between the interruption of sympathetic stimulation at the end of exertion and vagal response reactivation. (29)

The limitations of the study would be the reduced number of chagasic patients and lack of an adequate follow-up to test the predictive value of the significant QTc interval prolongation and evident dysautonomia signs during the ergometry, and to establish if these findings identify patients at greater risk of evolving to chronic, symptomatic chagasic cardiomyopathy.

Table 3. Comparison of clinical and ergometric data between chagasic patients with insufficient and sufficient GET.

	Insufficient GET n = 48 (64.9%)	Sufficient GET n = 26 (35.1%)	p
Age (years)	47.2 ± 11.6	49.2 ± 14.3	0.52
Men, n (%)	30 (62.5)	14 (53.8)	0.46
Basal HR	66.4 ±15.3	88.9 ± 13.8	< 0.0001
Basal HR ≤ 60 bpm	20 (41.7)	0	0.0001
Basal HR ≥ 100 bpm	2 (4.2)	8 (30.8)	0.001
HR recovery delay at 2nd min	24 (50.0)	5 (19.1)	0.009
Maximum BP ≥ 190/100 mm Hg	7 (14.6)	9 (34.6)	0.04
Basal PR	155.3 ± 16.3	150.7 ± 13.2	0.22
PR-max	149.4 ± 19.3	123.7 ± 11.9#	< 0.0001
Basal QRS	80.5 ± 8.9	77.4 ± 10.8	0.19
QRS max	83.8 ± 9.7*	78.6 ± 11.7**	0.07
QT-max	344.6 ± 34.0	265.1 ± 25.8	< 0.0001
Basal QTc	419.7 ± 17.0	408.0 ± 18.1	0.008
QTc-max	452.9 ± 27.2#	395.4 ± 40.0§	< 0.0001
QTc at 2nd min recovery	441.0 ± 30.5	417.3 ± 31.5	0.002
QTc-max ≥ basal	42 (87.5)	5 (19.1)	< 0.0001
QTc-max ≥ 0.47 s	15 (31.2)	2 (7.7)	0.02

HR: Heart rate. bpm: Beats per minute. BP: Blood pressure. Max: Maximum.
# p < 0.0001 vs. basal.
§ p = 0.003 vs. basal.
* p = 0.05 vs. basal.
** p = 0.63 vs. basal.

CONCLUSIONS

The results of our study show that asymptomatic chagasic patients without detectable cardiomyopathy present high prevalence of dysautonomia compatible signs during GET. Moreover, in a significant number of chagasic patients, autonomic unbalance was associated to marked QTc interval prolongation that expresses regional heterogeneity in myocardial fiber action potential duration and favors electrophysiological mechanisms triggering complex and sustained ventricular tachyarrhythmias

Thus, GET could become a useful diagnostic method to identify chagasic patients at greater risk of suffering arrhythmogenic sudden death. These findings require studies with larger number of patients and prolonged follow-up to accurately assess the increased risk of major events.

Conflicts of interest

None declared

RESUMEN

Hallazgos ergométricos en pacientes chagásicos, asintomáticos, con electrocardiograma normal y sin cardiopatía evidenciable

Introducción

Entre las manifestaciones más precoces de la enfermedad de Chagas se encuentran la disautonomía y la dispersión de los intervalos QT en el electrocardiograma, que han demostrado ser predictores de mayor morbimortalidad. Las nuevas tecnologías diagnósticas que posibilitan el hallazgo temprano de alteraciones endoteliales o disautonómicas deben originar mejores estrategias de diagnóstico y tratamiento que permitan la detección precoz de pacientes con riesgo de evolucionar a la miocardiopatía chagásica crónica o de sufrir muerte súbita.

Objetivos

1) Investigar los signos clínicos, electrocardiográficos y ergométricos de pacientes chagásicos asintomáticos, con electrocardiograma normal y sin patología clínica evidenciable.
2) Comparar los datos que presentan durante la prueba ergométrica graduada estos pacientes chagásicos con los de un grupo de características clínicas similares pero con serología negativa para Chagas.

Material y métodos

Estudio observacional, retrospectivo, en el que se incluyeron 74 pacientes chagásicos y 28 sujetos sanos en los que se efectuó una ergometría por control clínico entre marzo de 2009 y septiembre de 2011.

Resultados

Los pacientes chagásicos presentaron más a menudo frecuencia cardíaca basal ≤ 60 lpm (27,0% vs. 7,1%; p = 0,02), menor frecuencia cardíaca máxima (129,5 ± 22,8 lpm vs. 145,2 ± 16,5 lpm; p = 0,002), mayor incompetencia cronotrópica con frecuencia máxima < 80% que la preestablecida (47,3% vs. 14,3%; p = 0,001) y mayor frecuencia de arritmia ventricular durante el ejercicio y la recuperación (25,7% vs. 0%; p = 0,003).
Durante el ejercicio, mientras que en los pacientes del grupo control el intervalo QTc se acortó normalmente, en la mayoría de los pacientes del grupo Chagas se prolongó en forma notoria (grupo Chagas: 412,1 a 432,8 mseg, p = 0,0005; grupo control: 412,4 a 385,8 mseg, p < 0,0001).

Conclusiones

Los pacientes chagásicos asintomáticos sin cardiopatía demostrable presentaron durante la ergometría una alta prevalencia de signos de disautonomía, como la incompetencia cronotrópica y la prolongación del intervalo QTc durante el esfuerzo. La prueba ergométrica graduada es un método de diagnóstico incruento, confiable y de relativo bajo costo que puede contribuir al diagnóstico temprano de las alteraciones disautonómicas y de la repolarización ventricular y así identificar a los pacientes chagásicos con mayor riesgo de muerte súbita arritmogénica.

Palabras clave > Enfermedad de Chagas - Electrocardiografía - Disautonomías primarias - Intervalo QT - Prueba de esfuerzo

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