Chagas' Heart Disease: Evolutive Evaluation of Electrocardiographic and Echocardiographic Parameters in Patients with the Indeterminate Form

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Objective - *To identify and associate potential electrocardiographic and echocardiographic changes in patients with the indeterminate form of Chagas' disease during long-term follow-up.*

Methods - *One hundred sixty patients underwent standard electrocardiography and two-dimensional guided M-mode echocardiography for left ventricular ejection fraction determination. Patients were followed up for 98.6±30.4 months, undergoing repeat electrocardiographic studies at 6-month intervals and echocardiographic studies at 12-month intervals.*

Results - *Based on the electrocardiographic findings, the patients were divided into group I, 125 patients (78.6%) with normal electrocardiograms throughout follow-up, and group II, 34 patients (21.3%) who developed electrocardiographic changes. Group II was further divided into group IIA (9 patients, 5.6%) with permanent electrocardiographic changes, group IIB (14 patients, 8.8%) with transitory electrocardiographic changes, and group IIC (11 patients, 6.9%) with changes appearing only on the final electrocardiogram. Left ventricular ejection fractions remained normal in the entire population studied and did not differ among groups.*

Conclusion - *The indeterminate form of Chagas' disease clearly represents a benign condition with a favorable long-term prognosis. Although some patients develop electrocardiographic changes, left ventricular systolic function is well preserved.*

Key words: Chagas' heart disease, electrocardiographic changes, ejection fraction

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Chagas' disease is an important public health disorder in Latin America. It is an infectious disease caused by the protozoan parasite, *Trypanosoma cruzi*, which is transmitted zoonotically. Infection may occur following skin contact with the excrement of different strains of *Triatoma* insects, which serve as a vector. The parasite can multiply and transform within the *Triatoma* insect following ingestion via blood meal from an infected host. Chagas' disease is a chronic disease characterized by cardiovascular and gastrointestinal involvement. After an often-unrecognized acute phase followed by a generally undetected and lengthy latent period, cardiac symptoms and dysfunction of the esophagus, the colon, or both may develop.

Data from the World Health Organization state that 25% of the population in Latin American countries, approximately 90 million people, are exposed to this disease. As a consequence, it is estimated that as many as 16 million people are infected [1].

In Brazil, the endemic area is estimated to be around 3.6 million km^2, the largest in South America [2,3]. According to published data, 5 to 6 million people in this region are infected [2,3]. Studies in endemic areas show that 25 to 35% of the infected population manifests cardiac symptoms, with severe myocardial damage in 10%. As many as 6000 cardiac deaths are reported each year [4].

However, it has been known since Carlos Chagas' pioneering studies [5] that up to 60% of infected patients have no evidence suggesting cardiovascular or gastrointestinal involvement. These individuals are thought to have what is known as the indeterminate form of the disease. The long-term outcome in these patients has not been clearly determined. Although longitudinal follow-up studies have demonstrated the development of electrocardiographic changes in some [6,7], these changes do not seem to modify the prognosis. As a result, survival in this group of patients appears comparable to that of the general population [3,8-11]. The reason for the lack of a detectable impact of these ongoing

electrocardiographic changes on patient prognosis (i.e. the favorable prognosis) is unclear [7]. We hypothesized that these changes are not accompanied by myocardial dysfunction.

The objective of this study was to prospectively evaluate patients with the indeterminate form of Chagas' disease and relate the likely appearance of electrocardiographic changes during follow-up to potential changes in left ventricular function.

Methods

We studied 160 patients with the indeterminate form of Chagas' disease from 1979 until 1994, encompassing a mean follow-up interval of 98.6±30.4 months. The population included 98 women and 62 men, ranging in age from 17 to 61 years, with a mean age of 36.5±8.8 years. A diagnosis of the indeterminate form was made in asymptomatic patients based on the presence of two positive serologic tests for Chagas' disease in combination with a normal electrocardiogram and chest radiograph with no evidence of cardiac enlargement. Barium studies of the esophagus and the colon in such patients are also normal [12,13].

Subjects represented individuals from the general population in whom serologic tests were performed prior to blood donation. They came from endemic areas and were living in São Paulo. To assure that they were not reinfected after enrollment, none of them returned to their former homes. This study was approved by the Ethics Committee at our institution. All patients were educated about the objectives of the study and provided written informed consent.

Clinical follow-up was performed at a 3-month interval, and the same cardiologist always conducted the outpatient visits. Standard electrocardiograms were performed at six-month intervals and were analyzed independently by two cardiologists. Determinations of electrocardiographic changes were based on internationally recognized criteria [14].

Annual M-mode two-dimensional guided echocardiography was performed with 2.5 to 3.5 MHz transducers and standard equipment. Tracings were recorded on strip chart paper at 50 $m.s^{-1}$. Left ventricular internal dimensions at end-systole and end-diastole were obtained with the help of simultaneous electrocardiographic registration, according to the recommendations of the American Society of Echocardiography [15]. End-systolic and end-diastolic volumes, and the corresponding ejection fraction, were calculated based on the cube method for left ventricular volume determination [16].

$LVEF_3$, the ejection fraction corresponding to the echocardiogram obtained at the end of the study, was compared with the $LVEF_1$ obtained during enrollment. In addition to the annual studies, a supplemental echocardiogram was obtained, and the $LVEF_2$ was determined, whenever an electrocardiographic change was detected.

Statistical analysis of the data was performed using the analysis of variance for repeated measures. An a value of 0.05 was chosen to establish significant differences. Statistical calculations were made using SAS software [17].

Results

Only one patient was excluded from the study because of having suffered an acute myocardial infarction 104 months following enrollment. A total obstruction of the anterior descending coronary artery was demonstrated angiographically before successful thrombolysis.

Based on electrocardiographic changes, the remaining 159 patients were classified into two groups: group I and group II. Group I corresponded to 125 patients (78.6%) without changes on follow-up electrocardiograms. It included 78 women, ranging from 20 to 57 years in age, with a mean age of 36.0±8.3 years. Group II consisted of 34 patients (21.3%) with electrocardiographic changes that developed during the follow-up interval. It included 20 women, ranging from 17 to 61 years, with a mean age of 38.2±10.4 years. The total period of follow-up in group I averaged 97.5±28.5 months (range: 48 to 175 months) and in group II averaged 102.8±36.8 months (range: 48 to 177 months).

Group II was further divided into three additional subgroups: group IIA, 9 patients (5.6%), with permanent electrocardiographic changes; group IIB, 14 patients (8.8%), with transitory electrocardiographic changes; and group IIC, 11 patients (6.9%) in whom the electrocardiographic changes appeared only at the final evaluation period. The types of electrocardiographic alteration are summarized in Table I.

Table II depicts mean ages within subgroups. As can be seen, group IIA and group IIC patients were older than group IIB and group I patients (p=0.0008).

Table III shows the ejection fractions determined via echocardiography for the entire population studied. These ejection fractions did not significantly change during follow-up, either in group I or in any of the three group II subgroups. Initial ($LVEF_{1)}$ and final ($LVEF_3$) ejection fractions were similar between group I and group II patients. Furthermore, ejection fractions determined in group II patients close to the appearance of an electrocardiographic change ($LVEF_2$) did not statistically differ from those obtained either at the beginning or end of the study.

Discussion

The results of the present study indicate that only a portion of patients with the indeterminate form of Chagas' disease develop significant electrocardiographic changes. Furthermore, these changes do not appear to be accompanied by corresponding left ventricular dysfunction.

Previous longitudinal studies of such patients have revealed percentages of electrocardiographic changes ranging from 23% to 38% during long-term follow-up [7,8]. Thus, our present results, showing electrocardiographic abnormalities in up to 21% of the studied subjects, are in accordance with the literature. However, it has to be emphasized that electrocardiographic abnormalities that could have been clearly attributed to Chagas' disease existed in only 15 of 34 group II patients. This was particularly the case in those who developed conduction defects like an isolated right bundle-branch

Table I - Electrocardiographic changes observed during follow-up

	Electrocardiographic changes	Nº patients (%)
Group IIA	Isolated right bundle-branch block	2 (1.2)
	Right bundle-branch block associated to left anterior fascicular block	1 (0.6)
	Left bundle-branch block	1 (0.6)
	Complete atrioventricular block	1 (0.6)
	Anteroseptal electrically inactive area	1 (0.6)
	Isolated supraventricular extrasystoles	1 (0.6)
	Displacement of QRS axis to the left without left anterior fascicular block	1 (0.6)
	T wave changes	1 (0.6)
Group IIB	T wave changes	3 (1.8)
	Junctional rhythm	3 (1.8)
	Isolated supraventricular extrasystoles	1 (0.6)
	Isolated ventricular extrasystoles	1 (0.6)
	Ventricular bigeminism	1 (0.6)
	Wandering pacemaker	1 (0.6)
	Acute atrial fibrillation	1 (0.6)
	First degree atrioventricular block	1 (0.6)
	Incomplete right bundle branch block	1 (0.6)
	Displacement of QRS axis to the left without left anterior fascicular block	1 (0.6)
Group IIC	T wave changes	5 (3.0)
	Isolated ventricular extrasystoles	3 (1.8)
	Ventricular bigeminism	1 (0.6)
	Right bundle-branch block	1 (0.6)
	Inferior electrically inactive area	1 (0.6)

Table II - Mean ages of patients with indeterminate form of Chagas' disease by group

Group	Nº of patients	Age (years)
I	125	36.0±8.3
IIA	9	46.4±4.5*
IIB	14	32.4±8.7
IIC	11	39.1±11.3*
		* p = 0.0008

*p = 0.0008; significant increase compared with group I and group IIB.

Table III - Evolutive echocardiographic ejection fraction

Group	Nº of patients	$LVEF_1$*	$LVEF_2$	$LVEF_3$*
I	125	0.73±0.05	-	0.74±0.04
IIA	9	0.73±0.03	0.71±0.08	0.73±0.07
IIB	14	0.72±0.04	0.73±0.06	0.72±0.08
IIC	11	0.73±0.04	0.71±0.03	0.71±0.03
	-	p=0.6886	p=0.7474	p=0.0601

*p=0.6698

$LVEF_1$- initial left ventricular ejection fraction; $LVEF_2$- left ventricular ejection fraction determined close to the appearance of an ECG change; $LVEF_3$- final left ventricular ejection fraction.

block, right bundle- branch block accompanied by left anterior divisional block, left bundle-branch block, eventual high-degree atrioventricular blockade, or all of these. Despite this, all electrocardiographic abnormalities were taken into account in the present analysis, including the nonspecific ones commonly reported in the general population [3,6,8,11,18-28]. This likely led to an overestimate of the frequency of electrocardiographic changes herein reported.

Echocardiographic data on indeterminate form patients are numerous, but sometimes conflicting, due to a generalized lack of strict criteria used to characterize this latent form of the disease. Many reports include patients with only minor electrocardiographic changes, which likely represent mild, but true, myocardial damage [29,30]. This may explain some earlier reports of either segmental [30] or diffuse impairment of left ventricular contractility [32,33].

However, data are lacking on long-term echocardiographic function in patients with the indeterminate form of the disease. To the best of our knowledge, the sole study published in this regard documented the development of global left ventricular systolic dysfunction in a small number of patients with previously documented diastolic dysfunction [34]. To date, the presence of diastolic dysfunction does not rule out the diagnosis of the indeterminate form of Chagas' disease, which is based solely on electrocardiographic criteria, as already stated. Indeed, it is conceivable that diastolic dysfunction could represent the initial stage of myocardial damage, and antedate global left ventricular systolic dysfunction. Unfortunately, diastolic properties were not systematically evaluated in our study from the beginning. However, the most recent echocardiograms performed in our patients did not show changes in diastolic function (data not shown), indicating that diastole was not initially impaired. As a consequence, this may explain the lack of evolving systolic dysfunction in our patients in contrast with the findings in the previously reported study.

Interestingly, patients with permanent electrocardiographic changes or changes observed only at the final evaluation, were older than those with or without transitory abnormalities. Whether or not the changes observed on the final electrocardiographic examination represent permanent

or only transitory changes awaits further evaluation. It is likely, however, that because these changes developed late, and in older subjects, they may be permanent. Nevertheless, the time-related appearance of electrocardiographic abnormalities suggests that the evolution of the indeterminate form of Chagas' disease is influenced by patient age.

On the other hand, the present results clearly suggest that patients with the indeterminate form of Chagas' disease, in general, have a very good prognosis. The factors related to this favorable outcome have yet to be determined, but a normal ejection fraction despite electrocardiographic changes may be relevant in this regard.

Unfortunately, it is a common practice in our country to perform serological tests for Chagas' disease as part of the clinical evaluation for employment admission. Subjects with positive results are often relegated and have difficulty getting hired, even when applying for bureaucratic jobs. We hope that the present results will contribute to a better understanding of this form of Chagas' disease and reverse this situation. Our view is that these subjects should be advised not to exclude themselves from normal daily activities and that they are fully able to apply for and to perform all kinds of jobs, including those requiring muscle strength.

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