Cardiac morbidity and mortality due to Chagas' disease: prospective electrocardiographic study of a Brazilian community

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ABSTRACT The evolution of Chagas' cardiomyopathy is poorly understood. We therefore examined the development of cardiac lesions in a rural Brazilian community for a period of 7 years. Initially, 42% of 1017 residents were seropositive for infection with *Trypanosoma cruzi*. Age-specific infection rates indicated that most had become infected before the age of 20 years. On follow-up, it appeared that those persons who developed cardiac lesions did so soon after infection, since the incidence of right bundle branch block and other ventricular conduction defects (VCDs) was also highest before age 20 years. The progressive nature of these lesions was demonstrated by frequent development of additional electrocardiographic abnormalities and high mortality among infected adults with VCDs. In contrast, mortality was low and approximately the same for seropositive and seronegative adults under 60 years who had normal electrocardiograms. Electrocardiography during the early asymptomatic stage of infection was able to distinguish persons with potentially lethal cardiac lesions from those with a benign prognosis.
Circulation 75, No. 6, 1140–1145, 1987.

CHAGAS' DISEASE remains a leading cause of heart disease in Latin America.[1] Symptoms of chronic cardiomyopathy appear years or decades after initial infection with the causative protozoan *Trypanosoma cruzi*.[2, 3] Once congestive heart failure or complete heart block supervenes, life expectancy is reduced to a few years.[4, 5] In some infected persons sudden death from arrhythmias is the first manifestation of illness.[6] However, population-based surveys in endemic areas indicate that the majority of persons have no clinical signs of cardiac disease, despite persistent infection.[6]

The evolution of cardiac lesions during the latent or "indeterminate" period between acute infection and the first symptoms is not fully understood.[3] Investigators have hypothesized that progressive myocardial damage occurs throughout this period,[3, 7] but reactivation of a dormant infection or inflammatory process has not been excluded.

There have been few longitudinal studies of the natural history of Chagas' disease,[5, 6, 8–13] and most have involved selected populations or did not specifically address the chronology of developing heart lesions. In 1974 we therefore began a prospective survey of an entire community in an endemic area of Brazil.[14, 15] This report describes the evolution of electrocardiographic (ECG) abnormalities over a 6 year period and the relationship between ECG findings and mortality after 7 years of observation.

Methods

Study population. In January 1974, there were 1051 persons living in the study area, a rural community of approximately 25 km^2 near the town of Castro Alves, Bahia, Brazil.[14] Of these, 1017 persons (97%) participated in the study between 1974 and 1980. A yearly census was carried out, and in January 1981, the survival status of each resident was ascertained by personal encounter or by interview of relatives and friends for those persons not contacted directly. Eyewitnesses were consulted to investigate the circumstances of each death, because autopsies could not be obtained and most deaths were unattended by medical personnel.

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The Harvard component, under the direction of Dr. Thomas H. Weller, was supported by a grant from the Wellcome Trust and by a grant (AI 16305-05) from the NIH. Its collaborative activities are under the aegis of the Pan American Health Organization.

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Received Jan. 5, 1987; accepted March 6, 1987.

During the study, residual insecticides were applied to the walls of houses for control of the local triatomine vector, *Panstrongylus megistus*. Periodic serologic surveys and searches of houses for triatomines indicated a progressive reduction in incidence of human infection and household infestation.[16] Medical assistance was provided to the population throughout the study.

The study was approved by the human studies committees of the Harvard School of Public Health and the Federal University of Bahia. Because of the high rate of illiteracy, all participants gave oral consent.

Serologic tests and electrocardiograms. Examinations were carried out in early 1974, 1977, and 1980. On each occasion, blood samples were obtained by venipuncture or fingerstick from all consenting persons, and electrocardiograms were obtained for those 10 years of age and older. A five-lead electrocardiogram and a 30 sec rhythm strip were recorded.[17] Electrocardiograms were coded according to a previously published modification of the Minnesota code[17] by two internists who were unaware of the serologic results.

Sera or eluates from blood dried on filter paper were tested for antibodies to *T. cruzi* by the indirect fluorescent antibody test (IFA), complement fixation test (CF), and enzyme-linked immunosorbent assay (ELISA).[14, 18, 19] CF and IFA were performed on samples in 1974 and 1977, and IFA and ELISA were performed in 1980. Concordance of these tests was greater than 98%. In cases of discrepancy, the tests were repeated, and if still discordant, priority was given to the results of IFA.

Analysis of data. Baseline prevalence rates were calculated from the results of serologic tests and electrocardiograms recorded in each person on entry into the study. Person-years of observation between serial electrocardiograms and from the first serologic test to death, loss to follow-up, or end of the study period were used as the denominator for calculating rates of ECG changes and mortality, respectively. Statistical analysis was performed with the use of programs for exact testing and internal estimation.[20]

Compliance. Initial serologic tests were performed on samples from 1017 (97%) of the 1051 residents of the area; 885 persons were examined in the first survey in 1974 and an additional 132 persons were examined in 1977 or 1980. At least one electrocardiogram was recorded for 861 (95%) of the 905 eligible persons who were 10 years of age or older by 1980. Of 706 of the persons 10 or more years old upon entry into the study, 455 (64%) had electrocardiograms recorded on three occasions, 121 (17%) had electrocardiograms recorded twice, and 130 (18%) had one electrocardiogram recorded. Of the 311 children less than 10 years old upon entry, 155 subsequently had electrocardiograms recorded after reaching the age of 10 years; two electrocardiograms were obtained from 54 of these and a single electrocardiogram from 101. Refusal, death, and inaccessibility after emigration from the area accounted for 19%, 7%, and 74% of missed ECG examinations, respectively.

In January 1981, the survival status of all but one of the persons in whom electrocardiograms were obtained was determined. All 155 children whose first electrocardiograms were recorded only after reaching age 10 years were alive in 1981, but they were not included in the study of mortality.

Results

Prevalence of infection and disease. When first examined, 431 (42%) of the 1017 participants had serologic evidence of infection with *T. cruzi*. No child under the age of 1 year was seropositive. Rates of seropositivity rose with increasing age to approximately 60% among persons 20 years old, remained at this level among persons 20 to 54 years old, and then declined among older persons.[14]

Table 1 summarizes the prevalence rates of ECG findings for persons 10 years of age and older on entry into the study. Most striking was the presence of right bundle branch block (RBBB) in 13.5% of seropositive persons, a rate 15 times greater than in seronegative persons.

Incidence of infection and disease. Eleven persons "seroconverted" during the study and were analyzed separately. One 25-year-old woman with a previously normal electrocardiogram developed RBBB with anterior fasicular block (AFB) within 3 years of seroconversion. A 52-year-old hypertensive woman with left ventricular hypertrophy and strain developed incomplete left bundle branch block within 6 years of seroconversion. All seroconvertors survived until the end of the study. No person with a positive serologic test became seronegative.

During the 6 years of observation, the incidence rate of ventricular conduction defects (VCDs) was significantly greater for seropositive persons than for those who were seronegative. Most new VCDs were noted in seropositive persons under the age of 20 years, while no new VCDs were observed in seronegative persons less than 60 years of age (tables 2 and 3). Seventeen percent of seropositive children already had RBBB and/or AFB when first examined upon reaching 10 years of age (table 2). Ten- to fourteen-year-olds had the highest incidence rate of new VCDs among seropo-

TABLE 1
Prevalence rates of certain ECG findings on entry to the study

	Seronegative (n = 355)		Seropositive (n = 371)	
Finding	n	Percent with finding	n	Percent with finding
Normal electrocardiogram[A]	265	79.1	243	65.5
RBBB[A,B]	3	0.9	50	13.5
AFB without RBBB	6	1.8	13	3.5
1° AVB	1	0.3	5	1.1
VEs	18	5.4	27	7.5

Only persons 10 years of age or older at the time of entry are included. Other ECG findings are detailed in Maguire et al.,[15] who describe the findings of the 1974 cross-sectional study.

1° AVB = first-degree atrioventricular block; VEs = ventricular estrasystoles.

[A]$p < .001$ by chi-square and exact test for seronegative vs seropositive. $p > .10$ for other findings.

[B]For the seropositive group, includes 21 RBBB with fascicular block. RBBB includes incomplete RBBB (QRS duration ≥ 0.10 sec).

TABLE 2
ECG findings in children with previous serologic tests

Finding	Seronegative (n = 114) n	Seronegative (n = 114) Percent with finding	Seropositive (n = 41) n	Seropositive (n = 41) Percent with finding
Normal ECG[A]	112	98.2	32	78.0
RBBB[A,B]	0	0	6	14.6
AFB without RBBB	0	0	1	2.4
1° AVB	1	0.9	0	0
Right-axis deviation	1	0.9	2	4.9

Children were less than 10 years old when first tested serologically. Subsequently their first electrocardiograms were taken after reaching the age of 10 years.

1° AVB = first-degree atrioventricular block.

[A]$p < .001$ by exact test for seronegative vs seropositive. $p > .10$ for other findings.

[B]Includes RBBB with AFB in four persons.

TABLE 4
Development of ventricular extrasystoles

Age (years)	Seronegative, rate per 1000 person-years (n = 295)[A]		Seropositive, without VCDs, rate per 1000 person-years (n = 251)[A]		Seropositive, with VCDs, rate per 1000 person-years (n = 46)[A]	
10–19	3.3	(2; 612)	3.1	(1; 327)	23.8	(1; 42)
20–39	6.8	(3; 441)	18.9	(10; 528)	88.2	(9;102)
40–59	10.6	(3; 282)	18.7	(6; 321)	60.6	(4; 66)
≥60	46.8	(8; 171)	87.7	(10; 114)	95.2	(2; 21)
Total	10.6	(16;1506)	20.9	(27;1290)	69.3	(16;231)

In each age group below 60 years, the rate for seropositive persons with VCDs was at least three times greater than either the rate for seronegative persons or the rate for seropositive persons without VCDs ($p < .05$ for each group). In all age groups, the rate for seropositive persons without VCDs was less than three times the rate for seronegative persons ($p > .05$ for each group).

[A]Numbers in parentheses are the number of persons with new ventricular extrasystoles and the number of person-years of observation.

sitive persons with previously normal electrocardiograms (table 3).

Seropositive persons with VCDs frequently acquired additional ECG abnormalities. Seropositive persons with AFB on a previous tracing had an incidence rate of RBBB of 43.5 per 1000 person-years (table 3). Complete atrioventricular block and atrial fibrillation occurred only in seropositive persons with RBBB and AFB on prior electrocardiograms (in two persons 23 and 43 years old, respectively; the former received a permanent pacemaker shortly after diagnosis). Seropositive persons with VCDs were also at increased risk of developing ventricular extrasystoles (table 4). Between the ages of 20 and 60 years, multiform and paired ventricular extrasystoles occurred more often among seropositive persons with RBBB and AFB on prior electrocardiograms (seven occurrences in 219 person-years) than among seropositive persons without VCDs (four occurrences in 937 person-years) (relative risk 7.5; 95% confidence limits 2.7 to 21.2). Such complex ventricular extrasystoles were not detected in seronegative persons under the age of 60 years. The risk of developing supraventricular extrasystoles, T wave changes, and small increases in duration of QRS complexes was slightly but not significantly increased for seropositive persons when VCDs were present.

TABLE 3
Development of VCDs in seropositive persons

Age (years)	Persons with normal QRS complex on prior electrocardiogram (n = 263): Rate of developing RBBB per 1000 person-years[A,B]		Persons with normal QRS complex on prior electrocardiogram (n = 263): Rate of developing isolated AFB per 1000 person-years[B]		Rate of developing RBBB per 1000 person-years in persons with isolated AFB on prior electrocardiogram (n = 13)[B]	
10–14	19.2	(3; 156)	6.4	(1; 156)	0	(0; 3)
15–19	0	(0; 171)	0	(0; 171)	111.1	(1; 9)
20–39	3.5	(2; 559)	0	(0; 559)	30.3	(1;33)
40–59	2.8	(1; 354)	0	(0; 354)	47.7	(1;21)
≥60	0	(0; 135)	7.4	(1; 135)	0	(0; 3)
Total	4.4	(6;1375)	1.5	(2;1375)	43.5	(3;69)

In the seronegative group, five persons developed new VCDs (left BBB in one, AFB in four) during 1569 person-years of observation. All five were over the age of 60 years.

[A]Includes RBBB with AFB in four persons.

[B]Numbers in parentheses are the number of persons with the new finding and number of person-years of observation.

For persons with a normal electrocardiogram on entry, the electrocardiogram remained normal in 80% (153/192) of those seropositive in contrast to 90% (194/215) of those who were seronegative. No changes in the electrocardiogram were detected for 46.4% (26/56) of seropositive persons who had VCDs initially. In no case did RBBB or fasicular block revert to normal.

Mortality. Seropositivity was associated with an increased mortality among persons 20 to 59 years old (estimate of risk ratio 1.8; 95% confidence limits 0.8 to 4.2; $p = .09$) (table 5). In this age group, the risk of death was strongly related to initial ECG status (table 6). Seropositive persons whose initial electrocardiograms showed RBBB, especially in combination with fasicular block or ventricular extrasystoles, had a significantly higher mortality rate than seropositive persons with a normal electrocardiogram. In contrast, mortality rates were the same for seropositive and ser-

TABLE 5
Mortality for persons 10 years or older on entry into the study

Age (years)	Mortality per 1000 person-years				Relative risk†	95% confidence limits	p value
	Seronegative[A]		Seropositive[A]				
10–19	1.2	(1; 857)	1.4	(1; 695)	1.2	0.1–19.6	.44
20–39	4.9	(3; 611)	5.1	(5; 988)	1.2	0.3–4.7	.38
40–59	10.0	(4; 400)	17.6	(10; 568)	2.3	0.8–7.3	.07
60–79	22.5	(5; 222)	18.2	(4; 220)	0.9	0.2–3.2	.43
≥80	162.8	(7; 43)	0	(0; 8)	—	—	—
Total	9.4	(20;2133)	8.1	(20;2479)	1.2	0.6–2.4	.27

One seropositive person was lost to follow-up and five seronegative persons who seroconverted are excluded.

Relative risk = estimate of the rate ratio (mortality of seropositive group ÷ mortality of seronegative group) calculated from age-stratified data (10 year strata).[20]

[A]Numbers in parentheses are the number of deaths and the number of person-years of observation.

onegative persons whose initial electrocardiograms were normal. Multiform or paired ventricular extrasystoles were registered on at least one electrocardiogram in 75% of those with RBBB who died. Tall precordial R waves, isolated AFB, and isolated extrasystoles were associated with a slightly increased mortality in both the seropositive and seronegative groups.

A total of 40 deaths occurred during the study, and in most cases the cause could only be surmised. However, of the eight seropositive persons with RBBB who died, five had symptoms suggesting chronic congestive heart failure, and three were observed to die suddenly during exertion despite having appeared well previously. The circumstances of death were more varied in the seronegative group and in the seropositive group without RBBB. Malignancy was diagnosed or suspected in three persons in each group, including an esophageal carcinoma found at autopsy of a seropositive man with Chagas' megaesophagus. Accidents and violence (three persons), febrile illnesses (five persons), unexplained abdominal pain (five persons), and symptoms of congestive heart failure (five persons) were also commonly reported.

Discussion

In contrast to previous impressions of a long latent period, these age-specific data suggest that myocardial damage begins early in the course of chronic *T. cruzi* infection and is progressive in a subpopulation of those infected. Most residents of the area had acquired infection before the age of 20 years, as indicated by baseline prevalence rates of seropositivity.[14] The incidence rate of RBBB and of AFB peaked in seropositive children and adolescents, indicating a shorter incubation period for development of chronic Chagas' cardiomyopathy than generally recognized.[2, 9] The risk of progressive ECG changes and of mortality was greatest for young and middle-aged seropositive adults who had VCDs on the initial electrocardiogram. In contrast, seropositive adults under the age of 60 years with normal electro-

TABLE 6
Mortality according to seroreactivity to *T. cruzi* and ECG findings for persons 20 to 59 years old on entry into the study

Group	n	Mortality per 1000 person-years[A]	Relative risk	95% confidence limits	p value
Seropositive, normal electrocardiogram	140	3.2 (3;949)	1.0		
Seronegative, normal electrocardiogram	116	3.9 (3;771)	1.1	0.2–5.4	0.45
Seropositive, RBBB[B]	38	33.5 (8;239)	7.3	2.5–20.6	0.0001
Seropositive, VEs[B]	25	39.2 (6;153)	7.6	2.5–23.5	0.0002
Seropositive, RBBB and VEs	9	116.3 (5; 43)	12.7	4.1–39.4	<0.0001

Relative risk = estimate of the rate ratio (mortality of group ÷ mortality of seropositive group with normal electrocardiogram) calculated from age-stratified data (10 year strata)[20]; VEs = ventricular extrasystoles.

[A]Numbers in parentheses are the number of deaths, and the number of person-years of observation.

[B]Includes nine persons with both RBBB and VEs.

cardiograms developed few ECG changes and experienced mortality rates similar to those of seronegative persons.

The host-parasite factors that determine the outcome of infection in different persons have not been identified. Immune mechanisms, rather than destruction of cells by parasites, appear to be responsible for the chronic cardiomyopathy.[3] In fatal cases, there is diffuse inflammation of the myocardium and fibrosis of both the myocardium and the conducting system.[21] In contrast, the hearts of asymptomatic infected persons are normal or have only small foci of inflammation or fibrosis.[3]

Although we and others have demonstrated a favorable prognosis for seropositive adults with normal electrocardiograms,[5, 13, 22] echocardiography, electrophysiologic testing, and other sensitive techniques expose subtle abnormalities in many such persons.[23, 24] These abnormalities are thought to represent residual foci of fibrosis or autonomic denervation from the acute stage of infection.[3] The prognostic significance of these lesions has been debated, but our data suggest that they tend to remain subclinical. Clearly, the common practice of denying employment to all seropositive persons is unwarranted since the majority will not develop chronic heart disease.

Seropositive persons with conduction defects are at high risk for developing progressive myocarditis, although years may elapse before the appearance of symptoms.[2, 7] These persons should be examined regularly for potentially treatable complications such as congestive failure or complete heart block. Those with ventricular extrasystoles in combination with conduction defects, even on a short ECG tracing, are at high risk of sudden death and should be considered for antiarrhythmic therapy.[25] Unfortunately, appropriate medical care is not yet available for many persons exposed to Chagas' disease.

The high incidence of VCDs in seropositive children and adolescents observed in this study differs from the age distribution reported in Venezuela. Puigbó et al.[9] were unable to document RBBB in infected persons under the age of 15 years, and they and Moleiro et al.[11] found that the incidence of VCDs peaked in infected adults. These differences may reflect strain differences in the pathogenicity of the infecting parasites,[26] or in age-related patterns of exposure to the parasite. Like our study, the Venezuelan studies showed the progressive course of cardiac disease in infected persons who develop VCDs.[9, 11]

T. cruzi infects an estimated six million persons in Brazil,[1] and approximately one-third are under the age of 20 years.[14] Our data indicate that at least 10% of these or 200,000 persons will develop RBBB by age 20 years. Because antiparasitic drugs have little effect on chronic infection, we anticipate that over one-half of those with RBBB will die from Chagas' heart disease by the age 60 years. At present, the best hope of eliminating the mortality associated with Chagas' disease lies in measures to interrupt transmission of the parasite. The demonstrated success of vector control measures in reducing the incidence of infection among children has led to the institution of widespread control programs in Brazil and other affected countries.[1]

We thank Dr. Reinaldo Rosa, mayor, and the citizens of Castro Alves for invaluable local assistance; the Faculdade de Medicina, Universidade Federal da Bahia (UFBa), for providing laboratory facilities and administrative support; Dr. Eduardo Mota, UFBa, Srs. Antonio Celso Batista, Tomé de Silva Oliveira, Tomás Campos, and José Pedrosa of Fundação Oswaldo Cruz, and Drs. Tacito M. Muniz and J.T. França of the Superintendency of Public Health Campaigns (SUCAM) for assistance with field work; Sras. Vera Menezes, Tereza Maisk de Paiva, and Roberto Magalhães for laboratory work; Drs. Walter Willett and George Hutchison of the Harvard School of Public Health (HSPH) for helpful suggestions; Dr. Mark Boyer and members of the faculty and staff of the Department of Tropical Public Health, HSPH, for logistical assistance and support; and Miss Lynn Sayers for preparing the manuscript.

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Circulation. 1987;75:1140-1145
doi: 10.1161/01.CIR.75.6.1140
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539