

Progression of Baseline Electrocardiogram Abnormalities in Chagas Patients Undergoing Antitrypanosomal Treatment

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Background. The objective of the study was to better understand the impact of antitrypanosomal treatment on the evolution of Chagas-related, prognostically important electrocardiogram (ECG) abnormalities.

Methods. Initial and posttreatment ECGs were obtained in a prospective cohort of Chagas patients treated with nifurtimox or benznidazole and compared to an untreated cohort. Electrocardiogram disease progression was compared in those with and without baseline abnormalities pre- and posttherapy.

Results. Fifty-nine patients were recruited in the treatment arm and followed for an average of 3.9 years. There were no differences between ECG groups with regards to follow-up, age, baseline ejection fraction, or therapy. In the treated cohort, 0 of 30 patients with normal ECGs developed an abnormal ECG compared with 7 of 29 patients with baseline ECG abnormalities who developed new ECG abnormalities ($P = .005$). In an untreated cohort of 30 patients, 3 of 7 with normal ECGs developed an abnormality compared with 14 of 23 patients with baseline abnormalities ($P = .67$). Untreated patients had a higher likelihood of developing new EKG abnormalities (56.7% vs 11.9%, $P < .001$) despite shorter follow-up, and in a multivariate analysis adjusting for baseline EKG status across both treated and untreated cohorts, treated patients were still less likely to have progression of their EKG disease (odds ratio = 0.13, $P < .001$). The corrected QT (QTc) interval was not significantly affected by either study medication (415 vs 421 ms, initial vs posttreatment QTc; $P = .06$).

Conclusions. Over an average follow-up of 3.9 years, treated patients with normal baseline ECGs did not have significant changes during a course of treatment; however, those with baseline abnormal ECGs had significant progression of their conduction system disease despite treatment, and those without treatment also experienced a progression of ECG disease. These preliminary results suggest that Chagas patients with normal ejection fraction and normal ECG may benefit the most from antitrypanosomal treatment.

Keywords. Chagas disease; chagas cardiomyopathy; electrocardiogram.

Chagas disease (CD) is a vector-borne illness arising from infection with the protozoan *Trypanosoma cruzi*, and it affects 6–7 million people worldwide, including an estimated 300 000 in the United States [1, 2]. Of those infected, 30%–40% progress from an indeterminate, asymptomatic form of serologic positivity to clinically expressed disease, including a cardiomyopathy marked by patchy fibrosis, systolic and diastolic dysfunction, apical aneurysm, thromboembolism, cardiomegaly, microvascular damage, and both tachyarrhythmias and

bradyarrhythmias [3–5]. A recent systematic review determined a prevalence of ECG abnormalities of 40.1% in people with CD from endemic regions, compared with 24% in the general population without CD. Right bundle branch block (RBBB) (odds ratio [OR] = 4.6), left anterior fascicular block (LAFB) (OR = 1.6), and combined RBBB/LAFB (OR = 3.34) were all significantly more likely in people with CD [6]. Moreover, ECG change is a potential harbinger of progression to more severe cardiomyopathy [7, 8]. Research suggests that antitrypanosomal treatment does not extend lifespan or improve heart function in those patients who have progressed to heart failure [9], but antiparasitic treatment before this stage may be beneficial [3, 10–12], because parasite load appears to correlate with the development of Chagas cardiomyopathy (CC) [13, 14]. Using characteristic ECG changes as a marker of early CD, we analyzed the largest single cohort of treated CD patients with normal heart function in the United States; the objective was to determine whether antitrypanosomal treatment altered the course of Chagas-related ECG changes over time in patients with and without baseline ECG abnormalities.

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METHODS

Study Cohort

The Center of Excellence for Chagas Disease (CECD) at Olive View-UCLA Medical Center provides community-based screening and subsequent clinical care for *T cruzi* infection in northern Los Angeles, California. Based at a safety-net county hospital, the CECD is the sole center in the United States that provides comprehensive, systematic care for an immigrant population at high risk for CD. From 2008 to 2014, the CECD conducted a systematic screening of 4755 Latin American immigrant adults aged 18–60 via initial enzyme-linked immunosorbent assay-based testing followed by confirmatory testing with a radioimmune precipitation assay or immunofluorescence antibody assay in partnership with the Centers for Disease Control and Prevention (CDC) [15]. Before this screening program, 12 patients with confirmed positive *T cruzi* infection had been identified at Olive View Medical Center and were enrolled in the treatment program. Antitrypanosomal therapy with nifurtimox or benznidazole was provided on a limited basis to a select group of patients, who were followed as a prospective cohort with regularly scheduled visits to identify changes in cardiac function, ECG, basic laboratory testing, and medication side effects.

Patients were deemed suitable candidates for treatment if they were positive on both screening and confirmatory tests and were adults 18–60 years of age able to give consent and attend follow-up visits every 2 weeks at minimum. Patients with active New York Heart Association class III-IV heart failure or left ventricular ejection fraction (LVEF) <35% were excluded from therapy, as were patients aged >60 years or with significant renal or hepatic dysfunction. Depending on drug availability, patients were initiated on either 8–10 mg/kg nifurtimox divided into 3 daily doses initially with a goal treatment period of 12 weeks minimum based on CDC recommendations at the time or 5 mg/kg benznidazole per day for 60 days [9, 16]. Patients with severe medication reactions underwent treatment suspension, dose reduction, or medication switch at the discretion of the treating CECD physician and in consultation with CDC partners. Untreated confirmed positive patients were included in the study as a control group provided they had greater than 2 months of EKG follow-up. The untreated cohort consisted of patients who declined to be treated or who had contraindications precluding treatment. Screening, treatment, and follow-up research were approved and reviewed on an annual basis by the institutional review board at the Education and Research Institute at Olive View-UCLA Medical Center.

Data Collection and Analysis

Electrocardiogram and echocardiography were performed at baseline (before treatment) and at the conclusion of therapy, with the final ECG conducted on the day of

treatment discontinuation. Electrocardiograms were reviewed by a board-certified cardiologist blinded to treatment assignment, outcome, and LVEF. An “abnormal ECG” was defined as any ECG finding (eg, including sinus bradycardia <50 beats per minute or axis deviation) other than normal sinus rhythm with a normal axis. Electrocardiogram disease progression was further defined based on a development possibly attributable to CD: (1) new bundle branch block; (2) change in underlying rhythm; (3) shift in QRS axis; or (4) development of frequent premature ventricular complexes (PVCs)—defined as >1 PVC during a 10-second period. These 4 parameters were chosen given their prior associations with CD and represent a more conservative and specific subset of ECG findings than used in other studies of CD and ECG [17–19]. The corrected QT (QTc) was calculated by measuring the longest QT on the 12-lead ECG and dividing that value by the square root of the preceding R-R interval (Bazett’s formula). Left ventricular ejection fraction was calculated from transthoracic echocardiography using the biplane Simpson’s method of disks [20].

Baseline covariates were presented as mean \pm standard deviation and compared using the Student *t* test or Fisher’s exact test. Electrocardiogram disease progression was compared in those with and without baseline ECG abnormalities pre- and posttherapy using Fisher’s exact test. The association of LVEF and baseline ECG abnormalities was assessed using Pearson’s correlation. Changes to a patient’s baseline QTc interval were compared based on treatment status or baseline ECG using a paired *t* test. A 2-tailed alpha <.05 was considered significant. All analyses were performed using STATA, version 14.1 (StataCorp, College Station, TX).

RESULTS

Fifty-nine patients from the treated cohort and 30 patients from the untreated cohort were included. Eighteen patients underwent treatment with benznidazole and 41 with nifurtimox. Three patients crossed over from nifurtimox to benznidazole and 1 patient crossed from benznidazole to nifurtimox due to adverse reactions. Five patients did not complete a full course of therapy with either drug. Patients were followed for an average of 3.9 years, and there were no differences between the 2 treatment groups with regards to length of follow-up, age, or drug used (Table 1). The untreated cohort was significantly older and had significantly lower ejection fraction (EF) at baseline compared with the treated cohort. Approximately half of the treated cohort (29 of 59) had ECG abnormalities at baseline. The most common baseline ECG abnormalities were sinus bradycardia (15), RBBB (5), and LAFB (4) (Table 2).

In the treatment cohort, 0 of 30 patients with normal ECGs developed an abnormal ECG during the study period compared with 7 of 29 patients with baseline ECG findings who developed new ECG abnormalities ($P = .005$) (Figure 1). No patients with

Table 1. Baseline Characteristics^a

Treated Cohort	Normal Baseline ECG (n = 30)	Abnormal Baseline ECG (n = 29)	P Value
Age (mean, years)	41	43	.47
Nifurtimox treatment	17	17	
Benznidazole treatment	13	12	
Treatment duration (days)	115 ± 29	92 ± 9	.47
ECG follow-up (months)	45 ± 5	48 ± 5	.71
Baseline LVEF	59% ± 2%	56% ± 1%	.27
LVEF at study conclusion	57% ± 1%	56% ± 1%	.46
Untreated Cohort	Normal Baseline ECG (n = 7)	Abnormal Baseline ECG (n = 23)	P Value
Age (mean, years)	53	57	.56
ECG follow-up (months)	34 ± 5	24 ± 4	.15
Baseline LVEF	35% ± 6%	33% ± 3%	.77
Baseline heart rate (bpm)	70 ± 7	74 ± 3	.59
Combined groups	Treated (n = 59)	Untreated (n = 30)	P Value
Age (mean, years)	42	56	<.001
ECG follow-up (months)	46 ± 3	26 ± 3	<.001
Baseline LVEF	56% ± 6%	34% ± 3%	<.001
Baseline heart rate (bpm)	66 ± 12	73 ± 16	.03

Abbreviations: bpm, beats per minute; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; SD, standard deviation.

^aValues are presented as means ± SD unless otherwise specified.

baseline ECG abnormalities regressed to a normal ECG, and there was no correlation between treatment discontinuation/crossover and the development of ECG findings. Of those who developed new ECG changes, 3 developed new-onset bradycardia, 2 developed RBBB, and 2 developed PVCs.

In the untreated cohort, 3 of 7 with normal ECGs developed an abnormal ECG compared with 14 of 23 patients with baseline ECG abnormalities who developed new ECG abnormalities ($P = .67$). Of those who developed new ECG changes, 9 developed an indication for a pacemaker, 2 developed atrial fibrillation, 2 developed PVCs, and 1 developed LAFB. Overall, untreated patients had a higher likelihood of developing ECG abnormalities compared with their treated counterparts (56.7% vs 11.9%, $P < .001$) despite a significantly shorter follow-up period (26 vs 46 months, $P < .001$). In a multivariate analysis adjusting for baseline EKG status, treated patients were

less likely have progression of their EKG disease (OR = 0.13, $P < .001$).

Treated subjects had normal mean baseline QTc intervals (414 ± 31 ms) that did not change significantly over the course of treatment with either medication (posttreatment, 420 ± 25 ms; $P = .06$). Ejection fraction was also normal at baseline in the treated cohort (mean $56\% \pm 2\%$) without significant change during treatment course ($P = .50$), as were mean baseline and posttreatment heart rates. There was no significant association between LVEF and baseline ECG abnormalities ($P = .98$) in the treated cohort. The average EF was lower in the untreated cohort ($34\% \pm 14\%$), but again this was not statistically associated with baseline ECG abnormalities ($P = .77$).

DISCUSSION

In the largest single-center US cohort of treated CD patients, those with baseline ECG abnormalities developed new ECG changes despite antitrypanosomal therapy, whereas those without baseline ECG changes remained normal over the same time frame. Untreated patients had progression of their ECG disease regardless of baseline ECG status and at a significantly higher rate compared with treated patients, although there were significant important differences at baseline, including advanced age and deteriorated EF. In addition, neither nifurtimox nor benznidazole caused significant QTc prolongation compared with baseline or beyond the normal range. Although these results should be considered preliminary, our study suggests that baseline ECG changes in CD may be a harbinger of extensive disease before the onset of echocardiographic systolic failure, consistent with prior studies showing that ECG abnormalities tend

Table 2. Baseline ECG Abnormalities: Treated Cohort

Abnormality	Count
Right bundle branch block (RBBB)	5
Incomplete right bundle branch block	2
Left bundle branch block	0
Incomplete left bundle branch block	1
Left anterior fascicular block	4
Left posterior fascicular block	2
Combined RBBB + hemiblock	3
Frequent premature ventricular complex	2
Sinus bradycardia	15
Repolarization abnormalities	4

Abbreviations: ECG, electrocardiogram; RBBB, right bundle branch block.

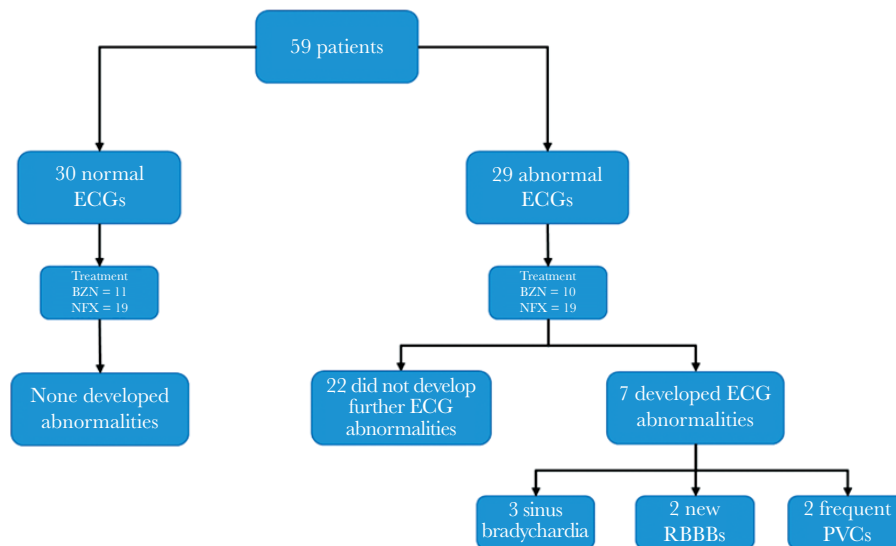


Figure 1. ECG changes in treated cohort.

to precede the development of Chagasic cardiomyopathy (CC) [10, 18, 21–23].

The protozoan *T. cruzi* likely causes both direct damage and reactive inflammation leading to myocardial fibrosis, systolic and diastolic dysfunction, scar-related ventricular arrhythmias, microvasculopathy, cellular damage, fibrosis of the conduction system, and autoimmunity [14, 24–26]. The point at which irreversible damage has occurred is still unclear. The largest randomized trial to date, the BENEFIT trial, showed that anti-trypanosomal therapy with benznidazole for 60 days in CC did not significantly reverse myocardial damage to the point where either EF or major outcomes improved [9].

Our small study raises the possibility of extending those findings to patients with both normal ECGs and ECG abnormalities, although a larger cohort should be studied to confirm these results. Chagas disease is associated with specific ECG patterns related to the pathological mechanism of disease. Prior studies have shown that certain findings, such as incomplete left bundle branch block, are no more prevalent in CD than in comparable patients with non-CD cardiomyopathy, but that, regardless of EF, the presence of RBBB, and in particular a combination of RBBB and LAFB, is strongly associated with the presence of CD [6, 15, 17]. In the BENEFIT trial, baseline ECG abnormalities were present in >90% of patients with CC, including >50% of patients with RBBB [9].

These ECG changes may hypothetically presage CC and signal a threshold of cardiac damage beyond which patients do not derive benefit from anti-trypanosomal therapy, although prior research is conflicting. Among a cohort of 111 children with normal baseline ECGs treated with 5 mg/kg benznidazole per day for 60 days, 18.6% developed new ECG abnormalities over 8 years of follow-up; compared with untreated children with

CD, there was no significant difference in the incidence of new ECG abnormalities [27]. These results contrast with our own, which suggest that there is a difference between treated patients with and without baseline ECG abnormalities; however, in the above-mentioned study, there was significant crossover from the untreated to the treated group during the assessment period, limiting the total number analyzed, and there was a limited ability to assess persistent parasitemia after treatment. Differences in the case definition of ECG abnormalities, with our definition including a narrower, more specific range of ECG findings, as well as age, duration of infection, and geographic differences may also explain these contrasting findings.

On the other hand, a smaller study of 43 CD patients treated with itraconazole in Chile revealed that 10.9% of patients with normal ECGs developed new ECG abnormalities over a 20-year period, compared with a historical rate of 9.7% per year in a separate cohort of untreated CD patients; and only 1 patient with an abnormal baseline ECG converted to a normal one over the 2 decades of follow-up [28]. A larger study of 310 treated and untreated CD patients with normal ECGs at baseline found a significant difference in the rate of new ECG changes over 20 years between untreated patients and those treated with benznidazole (53.19% vs 20.02%, $P < .0001$) [29]. Together with our research, these papers support consideration and further study of a strategy targeting early treatment before the development of cardiac disease as manifested by either baseline ECG changes or structural heart changes.

Our study has a number of limitations. Despite being the largest US cohort of treated CD patients, the sample size of treated patients ($n = 59$) is nonetheless too small to justify generalization, and these results should be considered preliminary and hypothesis-generating. This was an observational study,

which is not adequate to measure pharmacological efficacy. Only a few covariates were available for analysis, which, along with the small sample size, limited our ability to control for confounding or perform multivariate analysis, and we did not have follow-up titer data with which to correlate our findings. In addition, there are limited ECG criteria for assessing the probability of CD-attributable ECG abnormalities, leading to possible misclassification. However, prior research suggests the number of ECG alterations correlates with elevation of N-terminal probrain natriuretic peptide (NT-proBNP) levels suggestive of heart failure [8]. Furthermore, CD is associated with particular ECG patterns, especially the combination of RBBB and LAFB. The prevalence of ECG alterations is much higher among individuals with CD than seronegative individuals, and within *T cruzi*-positive individuals, is associated with age and male gender [30]. The development of a range of ECG abnormalities, including RBBB, LAFB, and first-degree atrioventricular block, has been reported among CD patients with a normal baseline ECG [6, 15, 31].

CONCLUSIONS

In conclusion, in this small cohort study, the presence of significant baseline ECG abnormalities was associated with the development of further conduction system disease despite antitrypanosomal treatment, whereas no such abnormalities developed in patients with a normal ECG at baseline who underwent treatment. Future therapeutic trials in patients with normal systolic function should provide subgroup analyses based on baseline ECG findings.

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