Electrocardiographic Characteristics in a Population with High Rates of Seropositivity for *Trypanosoma cruzi* Infection

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Abstract. This study was conducted in Posse, a rural community in Goiás, Brazil. Persons were recruited into the study through house-to-house sampling of all houses in the sampled area. Blood samples were collected for seropositivity assessments for *Trypanosoma cruzi* and an electrocardiogram was assessed using a portable system. The results demonstrate significant differences between seropositive and seronegative persons for electrocardiographic (ECG)–derived traits. Seropositive persons had substantially longer QRS and QT intervals than seronegative persons. The PR interval was significantly different between seropositive and seronegative persons. Conduction abnormalities were observed more frequently in seropositive than seronegative persons. Right bundle branch block, an ECG abnormality typical of Chagas disease, was observed in 15% of seropositive persons compared with less than 1% of seronegative persons. Results indicate that *T. cruzi* infection and subsequent Chagas disease will continue to be major health problems for the foreseeable future in this typical rural area of Brazil.

INTRODUCTION

Chagas disease is the leading cause of heart disease in Latin America, affecting approximately 17 million people.

*Trypanosoma cruzi*, the parasitic cause of Chagas disease, is transmitted to the human host by reduvid bugs that live in the walls and roofs of houses in many rural areas of Latin America.

There are no effective therapies for the chronic long-term phase of the disease and there are no vaccines or drugs to prevent infection with *T. cruzi*.

Substantial resources have been dedicated to eliminating the vector from household structures in Latin America. However, active transmission occurs in many areas, and between 100 and 120 million persons are considered to be at risk for infection with *T. cruzi*.

Approximately 300,000 persons are newly infected each year and approximately 60% of those infected with *T. cruzi* will experience a long-term chronic disease characterized by highly variable cardiac outcomes, and less frequently by mega-colon and/or mega-esophagus.

The presence of active transmission combined with the current lack of vaccines or effective prophylactic drugs means that Chagas disease will remain a significant health burden and major economic drain in South America for the foreseeable future. In addition, Chagas disease is an emerging health threat in the United States and Canada, particularly in regions with large South and Central American immigrant populations.

The cardiac form of Chagas disease is evidenced in electrocardiographic (ECG) data by conduction abnormalities that include bradyarrhythmias, premature ventricular contractions, and bundle branch blocks, particularly right bundle branch blocks. Case-control studies have found that right bundle branch block, left anterior hemiblock, and atrioventricular blocks occur at a much higher frequency in seropositive persons than in seronegative persons.

An elevated Q-T interval and T-wave axis deviation have both been implicated as predictive of mortality in patients with Chagas disease. Statistics indicate that more than half of those infected with *T. cruzi* can expect to progress to chronic Chagas disease and most will experience the cardiac form of the disease.

There are few large-scale studies that have assessed ECG-related variables in populations in areas endemic for Chagas disease (however, see the study by Maguire and others).

The purpose of the current study was to assess the epidemiology of cardiac disease as shown by ECG characteristics in a population with high rates of infection with *T. cruzi*.

MATERIALS AND METHODS

The study was conducted in Posse, a rural community in the state of Goiás, Brazil located approximately 350 km northeast of Brasilia, the capital of Brazil. The population consists primarily of subsistence farmers, most of whom were born in the municipality. The population is highly admixed and derived from European, African, and Amerindian ancestry.

Persons were recruited into the study through house-to-house sampling using a protocol that was reviewed and approved by the Institutional Review Boards of the University of Texas Health Science Center in San Antonio and the Rene Rachou Research Center of the Oswaldo Cruz Foundation in Belo Horizonte, Minas Gerais, Brazil. The sample is population based and includes all eligible adults in the sampling area who were willing to participate. The study was explained at each household and persons who elected to participate provided a consent form that was either signed or fingerprinted. A total of 1,389 persons were successfully recruited.

A 10-mL blood sample was collected into a red-top tube for assessment of seropositivity status. Samples were allowed to clot, and then were kept on wet ice until they were separated into serum and clot no more than eight hours after collection. Serum samples were then aliquotted and frozen in liquid nitrogen until transfer to the laboratories in Belo Horizonte and San Antonio on dry ice.

Serum samples from all persons were assessed by three standardized tests (enzyme-linked immunosorbent assay [ELISA], hemagglutination, and immunofluorescence) by the Laboratory of Cellular and Molecular Immunology at the Rene Rachou Research Center, FIOCRUZ. Persons were considered seropositive if two or more of these standardized
tests indicated seropositivity for *T. cruzi* infection. A total of 1,190 persons (86%) were typed with all three tests, and were determined to be positive if two or more tests showed positive results. The remaining persons were scored based on the results of two tests: 121 persons were scored as negative based on results of the hemagglutination and immunofluorescence tests, 3 persons were scored as positive on the basis of positive ELISA and immunofluorescence test results, and 75 persons were scored as positive on the basis of positive hemagglutination and immunofluorescence test results.

The ECGs were collected from all participants using the portable Marquette MAC5000 System (GE Medical Systems Information Technologies, Milwaukee, WI). In addition to the automated quantitative data output by the machine, qualitative ECG variables were verified by a clinical cardiologist experienced in the treatment of Chagas disease.

For the quantitative ECG traits, statistical analysis using a linear model was performed to test for differences between seropositive and seronegative persons. All analyses were performed simultaneously adjusting for the effects of several covariates including sex, age, age$^2$, sex × age, and sex × age$^2$. Results are provided both as the covariate-adjusted means for seropositive and seronegative persons and as standardized differences measured in standard deviation units. The latter index allows for easier comparison across variables and provides a measure of the biologic importance of a given statistical difference. Because the data set consists of large numbers of related persons, we explicitly allowed for kinship-based non-independence by performing all analyses conditional upon the known pedigree structure. Non-independence was modeled through a familiarity parameter that was treated as a nuisance parameter given that the focus of the current report is on the changes in mean effects induced by *T. cruzi* infection. Dichotomous discrete ECG variables such as bundle branch abnormalities were similarly analyzed using a probit regression model allowing for non-independence due to kinship. The program SOLAR,$^{31}$ which enables arbitrary modeling of mean effects in the presence of structured non-independence, was used for all statistical analyses.

RESULTS

Seropositivity and ECG measures were available for 1,389 persons. There were 690 males and 699 females. These persons were members of 110 families although almost all (1,193) can be placed into a single, large, extended family. The average age of the persons was 41.9 years. The rate of *T. cruzi* seropositivity was high in this population. There were 722 seropositive persons and 667 seronegative persons; 52% of the sampled persons were seropositive for *T. cruzi* infection.

A number of traits were determined from the ECG readings. Quantitative intervals were determined directly from the ECG. The quantitative intervals evaluated included the QRS interval, the QT interval, and the PR interval. The mean values for each interval in seropositive and seronegative persons are shown in Table 1. Also shown is the difference in standard deviation units between seropositive and seronegative persons.

These results show that there were significant differences between seropositive and seronegative persons for most of the quantitative ECG variables that were assessed in the population. All quantitative ECG-derived variables showed significant differences between seropositive and seronegative persons. Seropositive persons had substantially longer QRS and QT intervals than seronegative persons. The observed highly significant differences are of a magnitude approximately 0.4 of a standard deviation for these traits. Such a large standardized difference is quite striking. The PR interval was also significantly different in length between seropositive and seronegative persons. However, this increase is rather modest and represents a displacement of approximately 0.14 of a standard deviation unit. Seropositive persons also had significantly lower ventricular rates than persons seronegative for *T. cruzi* infection. This highly significant difference in ventricular rate represents a displacement of the seropositive mean approaching nearly a 0.75 of a standard deviation unit. Taken together, these results on a large population show dramatic differences in cardiovascular-related parameters between seropositive and seronegative persons.

We also assessed the frequency of a variety of qualitative Chagas disease-related traits in seropositive and seronegative persons. These traits are shown in Table 2. As is the case with the quantitative ECG measures, there were significant differences between persons who were seropositive for *T. cruzi* infection and uninfected persons.

Conduction abnormalities were more frequently observed in infected than uninfected persons. For example, right bundle branch block is an ECG characteristic that is typical of Chagas disease.$^7$ As expected, right bundle branch block is

<table>
<thead>
<tr>
<th>ECG trait</th>
<th>Frequency in seropositive persons</th>
<th>Frequency in seronegative persons</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right bundle branch block</td>
<td>0.0090</td>
<td>0.1524</td>
<td>$6.0 \times 10^{-20}$</td>
</tr>
<tr>
<td>Bifascicular block</td>
<td>0.0000</td>
<td>0.0526</td>
<td>$2.8 \times 10^{-9}$</td>
</tr>
<tr>
<td>Left anterior fascicular block</td>
<td>0.0045</td>
<td>0.0789</td>
<td>$8.6 \times 10^{-7}$</td>
</tr>
<tr>
<td>Marked sinus bradycardia</td>
<td>0.0150</td>
<td>0.0249</td>
<td>0.3874</td>
</tr>
<tr>
<td>Left axis deviation</td>
<td>0.0150</td>
<td>0.0540</td>
<td>0.0060</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>0.0525</td>
<td>0.0845</td>
<td>0.7128</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.0015</td>
<td>0.0069</td>
<td>0.2248</td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>0.1829</td>
<td>0.4349</td>
<td>$1.2 \times 10^{-9}$</td>
</tr>
</tbody>
</table>
much more frequent in seropositive persons than in seronegative persons, with less than 1% of seronegative persons having a right bundle branch block compared with 15% of seropositive persons having this branch block. This difference was highly significant \( (P = 6 \times 10^{-20}) \). Thus, right bundle branch block appears to be closely related to infection in this population.

Figure 1 shows the cumulative proportion of persons with right bundle branch block by age in males and females. There was no significant difference in the frequency of right bundle branch block between males and females in seronegative persons. However, in seropositive persons, right bundle branch block increases significantly with age, and also shows a substantial difference between males and females. Among seropositive persons, males are more likely to develop a right bundle branch block than females.

Other conduction abnormalities are altered by \( T. cruzi \) infection. As shown in Table 1, bifascicular block, left anterior fascicular block, and left axis deviation are present in seropositive persons at significantly higher frequencies than in seronegative persons. Significant differences in the frequencies of marked sinus bradycardia, left ventricular hypertrophy, and atrial fibrillation were not observed. However, for each of these abnormalities, infected persons showed nominally higher frequencies than uninfected persons. There was a substantial difference in the frequency of ECG abnormalities, with seropositive persons having a prevalence of approximately 43% versus only 18% in seronegative persons \( (P = 1 \times 10^{-9}) \). These results clearly demonstrate the effect of \( T. cruzi \) infection on sub-clinical heart abnormalities.

Figure 2 shows the plot of presence of any type of conduction block by age in seropositive and seronegative persons from the Posse population. Seropositive persons had much higher rates of conduction blocks at all ages. Although some conduction blocks are expected in uninfected persons, seropositive persons have higher prevalences of conduction blocks at all ages.

**DISCUSSION**

The study region in Posse is typical of many rural areas in central Brazil. This large-scale study of the local population provides insights into the implications of Chagas disease for local health services that surveys of cases and controls conducted in hospital settings cannot. The high rates of seropositivity in this rural area indicate that Chagas disease will be a continuing public health problem in the region for the foreseeable future. Despite intensive vector control efforts, Chagas disease will persist as a major consumer of health care resources because of the large population of persons who are already infected. Congenital transmission can result in new infections in regions with no vector-transmitted disease. Active transmission still occurs in many areas and congenital transmission also can cause infections. With the decreased emphasis on vector control in Brazil, it is possible that active transmission will recur in areas that were previously considered to be controlled.

The population variation in QT and QRS intervals may be informative in predicting the future health care needs in the region. Several investigators have noted the potential value of QT interval parameters for predicting outcome in Chagas disease. The QT and QRS intervals were significantly increased in seropositive persons in the Posse population. As previously reported, persons with ECG abnormalities predictive of a negative outcome in Chagas disease may be apparently healthy. Population level surveys conducted through general health clinics may be an excellent mechanism for identifying asymptomatic seropositive persons whose cardiac health should be monitored on a regular basis.

Epidemiologic studies of European populations that were
not exposed to *T. cruzi* infection showed that ECG abnormalities are more common in males than in females.\(^{36}\) That pattern was seen in the Posse population in seronegative persons. Interestingly, the divergence in prevalence of abnormalities between males and females was greater in seropositive persons. This finding may be reflective of increased physical labor by males in this agricultural population, which can put additional strain on the cardiovascular system. In particular, right bundle branch blocks are more frequent in seropositive persons than seronegative persons. The difference in ECG abnormalities between seropositive males and females reflects the general trend for increased rates of abnormalities in men.

In conclusion, population level surveys of seropositivity for *T. cruzi* infection and ECG variables are useful in predicting the future health care needs of local populations in Brazil. The epidemiologic data on seropositivity and ECG variables in the Posse population clearly indicate that Chagas disease will persist for a long time as a major public health burden. Despite the successes of the vector control programs in diminishing active transmission of *T. cruzi* when assessed at the national level, local populations in areas that are endemic for Chagas disease are still struggling with this devastating disease and will continue to do so for the foreseeable future.

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REFERENCES


