Development of Chagas Cardiac Manifestations Among Texas Blood Donors

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Chagas disease, infection with the parasite *Trypanosoma cruzi*, has recently been identified as an important emerging parasitic disease in the United States. To describe the cardiac abnormalities in *T. cruzi*−positive blood donors in southeastern Texas, a pilot study of donors who had screened positive from 2007 to 2012 was performed. This one-time assessment included (1) a questionnaire to evaluate the source of infection, cardiac symptoms, and health co-morbidities; (2) electrocardiography; (3) echocardiography if electrocardiographic findings were abnormal; and (4) measurement of a high-sensitivity troponin T biomarker. Of those with confirmed infection, 41% (7 of 17) had electrocardiographic abnormalities consistent with Chagas cardiomyopathy. In addition, 36% (6 of 17) were suspected to be locally acquired cases. High-sensitivity troponin T serum levels increased with cardiac severity. In conclusion, cardiologists should consider Chagas disease in their differential diagnoses for patients who may have clinically compatible electrocardiographic changes or nonischemic cardiomyopathy, even if the patients have no histories of residing in Chagas-endemic countries. **(Am J Cardiol 2015;115:113−117)**

Chronic Chagas cardiomyopathy is the most common cause of nonischemic cardiomyopathy in Latin America.[1,2] Up to 30% of patients infected with *Trypanosoma cruzi* (*T. cruzi*) develop cardiomyopathy characterized by conduction abnormalities, arrhythmias, and left ventricular diastolic and/or systolic dysfunction.[3,4] Recent rare reports of locally acquired cases and an increase of identified cases due to blood donor screening have highlighted the importance of this disease in the United States.[5−8] Since blood donor screening began in 2007, approximately 2,000 donors have been identified nationally.[9] However, very little is known about the cardiac outcomes of this presumably healthy blood donor population. The aim of this study was to describe any possible cardiac abnormalities among southeastern Texas blood donors infected with the parasite *T. cruzi* that causes Chagas disease.

Methods

This study was reviewed and approved by the institutional review boards at Baylor College of Medicine and the Gulf Coast Regional Blood Center. The Gulf Coast Regional Blood Center serves the greater Houston area and >170 hospitals and health care institutions in the 26-county Texas Gulf Coast, Brazos Valley, and East Texas region. Blood donors who tested positive on 2 repeat tests (repeat reactive) on the Ortho *T. cruzi* enzyme-linked immunosorbent assay system (Ortho-Clinical Diagnostics, Raritan, New Jersey) and radioimmunoprecipitation assay testing (Quest Diagnostics, Madison, New Jersey) were invited to take part in this study through a mailed invitation letter from the blood center. Blood donation testing began at the blood center in 2007. Over the subsequent 5 years, 154 blood donors screened positive for *T. cruzi* infection. Of these, 30 responded to the invitation letter in the summer of 2013 and choose to take part in this study (20% participation rate). Of those who chose to take part, 17 were confirmed positive by radioimmunoprecipitation assay. The 13 donors who had screened positive but were negative on confirmatory testing served as a control group for the biomarker analysis. Mean time between testing to study assessment was 4 years (range 0.5 to 6).

Research participants took part in a one-time assessment, including (1) a questionnaire to evaluate co-morbidities, travel history, heart-related symptoms, and disease transmission exposures; (2) electrocardiography; (3) echocardiography if electrocardiographic findings were abnormal; and (4) measurement of a high-sensitivity troponin T biomarker. Participants underwent a resting 12-lead electrocardiography performed using a mobile GE Mac 800 machine (GE Healthcare, Waukesha, Wisconsin). Electrocardiograms (ECG) were categorized for Chagas disease severity using the expert panel review criteria derived from the Retrovirus Epidemiology Donor Study−II (REDS-II).[1] Using these criteria, patients were classified into 3 disease categories: (1)

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See page 116 for disclosure information.

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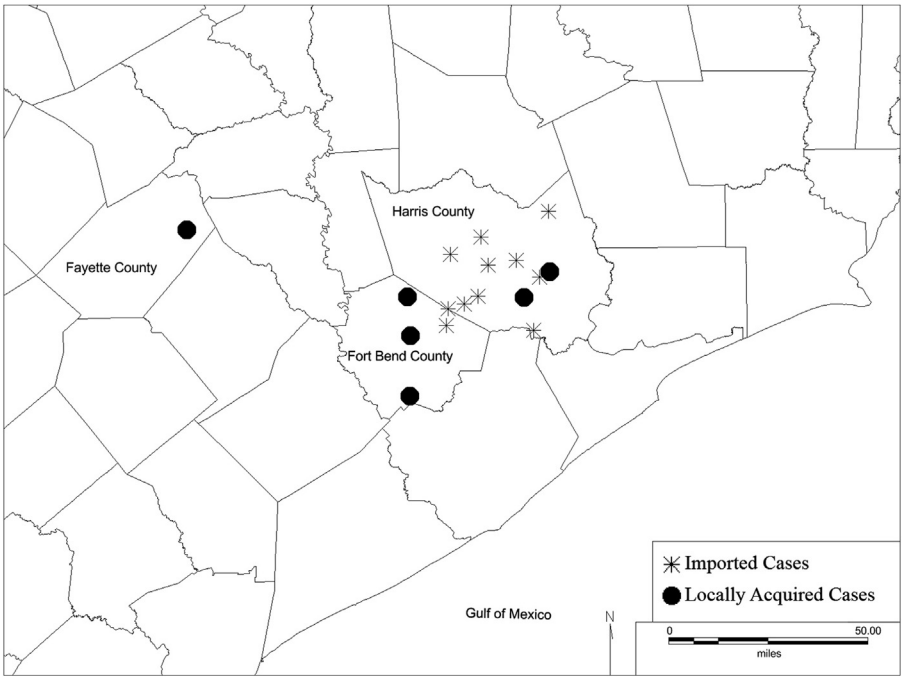

Figure 1. Location of the 17 confirmed *T. cruzi*–positive donors.

major typical ECG abnormalities consistent with Chagas cardiomyopathy, (2) minor ECG abnormalities possibly related to Chagas cardiomyopathy, and (3) indeterminate disease without any related abnormalities. Participants with either major or minor ECG abnormalities consistent with Chagas cardiomyopathy underwent echocardiography performed using a Philips iE33 ultrasound machine (Philips Healthcare, Andover, Massachusetts).

High-sensitivity troponin T (hsTnT) was measured using the Elecys highly-sensitive assay (Roche Diagnostics, Indianapolis, Indiana). HsTnT assays allow the detection of troponin T levels lower than the detection levels of earlier assays. HsTnT is a biomarker of subclinical myocardial injury and has been associated with increased risk for death, cardiovascular mortality, and heart failure in the general population.[10,11] The limit of blank for the hsTnT assay is 3.0 ng/L, and the limit of detection is 5.0 ng/L. A group of 13 false-positive blood donors served as a control group for this analysis. These 13 donors were confirmed to be negative for *T. cruzi* infection on 5 additional serologic tests (data not shown).

All statistics were analyzed using Stata version 12 (StataCorp LP, College Station, Texas). Descriptive statistics were performed to evaluate self-reported symptoms of participants by REDS-II Chagas disease severity grouping. Analysis of variance was performed to test for differences in hsTnT biomarker levels between the Chagas disease severity groups and a control group. MapInfo Professional (Pitney Bowes, Stamford, Connecticut) was used to map the location of the participants.

Results

We enrolled 17 blood donors with confirmed *T. cruzi* infection (Chagas disease) for a one-time assessment of cardiac health. The median age of our study population was 51 years (range 23 to 75), and the population was composed mostly of Hispanic (13 of 17) men (10 of 17). Thirty-six percent (6 of 17) were recognized as potential locally acquired infections. Those with evidence of locally acquired infection were mostly white (4 of 6) and male (4 of 6). One of the 6 participants was classified as a potential locally acquired case because of a report of regularly seeing the insect vector around the participant's Texas residence and recalling neither having ever been bitten nor seeing the insect vector in the participant's northern Mexico birth residence. The other 5 locally acquired cases were all in patients born in the United States, without significant histories of travel to endemic countries. Patients with locally acquired cases were more likely to reside in rural counties of southeastern Texas than those whose infections were likely acquired in endemic countries, who tended to reside in urban areas (Figure 1).

T. cruzi–infected donors rarely reported symptoms related to heart disease, which included dyspnea on exertion (2 of 17), heart racing while at rest (3 of 17), and pedal or ankle edema (3 of 17). Diabetes (1 of 17), hypertension (4 of 17), hypercholesterolemia (0 of 17), and history of coronary artery disease (1 of 17) were infrequently reported. In contrast, 41% (7 of 17) had abnormal ECG findings consistent with REDS-II criteria for Chagas cardiac disease (Table 1). Of those with abnormal ECG findings, 72% (5 of 7) had major ECG diagnostic abnormalities consistent with Chagas disease.[1] Additionally, 57% (4 of 7) of those with ECG abnormalities were potentially locally acquired cases. Of those with abnormal ECG results who underwent echocardiography, one individual (14%) had abnormal echocardiographic findings, with an ejection fraction of 40% and global left ventricular dysfunction.

HsTnT levels were detectable in 53% (9 of 17) of patients with confirmed *T. cruzi* positivity compared with 69% (9 of 13) of controls. Of those with detectable hsTnT levels,

Table 1
Co-morbidities, Electrocardiogram and Echocardiogram findings of *T. cruzi* positive donors

Age	Race	Gender	Locally Acquired?	Electrocardiogram	Echocardiogram	Relevant Co-Morbidities
23	White	Male	Yes	Normal	Not performed	Obesity
33	Hispanic	Male	No	Normal	Not performed	
38	Hispanic	Female	No	Normal	Not performed	
40	Hispanic	Male	No	Normal	Not performed	
45	Hispanic	Male	No	Possible lateral MI	Normal	
45	Hispanic	Male	No	Normal	Not performed	
46	Hispanic	Female	No	Normal	Not performed	
47	Hispanic	Female	No	Normal	Not performed	
51	Hispanic	Male	No	Normal	Not performed	
53	Hispanic	Female	No	SR, RBBB, LAD	Normal	
54	White	Female	Yes	Normal	Not performed	
58	Hispanic	Male	No	Non-specific IVCD	Global LV Hypokinesis; EF 40%	
61	Hispanic	Female	No	Normal	Not performed	
66	White	Male	Yes	LAFB	Normal	Diabetes; Hypertension
68	Hispanic	Female	Yes	LVH non-specific T wave abnormality	Normal	Hypertension
75	White	Male	Yes	SR with 1st degree AV block with inferior-posterior MI	Normal	Hypertension; Coronary Artery Disease
75	Hispanic	Male	Yes	Atrial paced with RBBB, LAFB, 1st degree AV block	Normal	Hypertension

EF = Ejection Fraction; IVCD = Intraventricular Conduction Delay; LAD = Left Axis Deviation; LAFB = Left Anterior Fascicular Block; LVH = Left Ventricular Hypertrophy; MI = Myocardial Infarction; RBBB = right bundle branch block; SB = Sinus Bradycardia; SR = Sinus Rhythm.

Figure 2. HsTnT serum biomarker values by Chagas disease status.

median values were significantly higher ($p < 0.03$) in *T. cruzi*−confirmed patients (median 13.0 ng/L) than in controls (7.0 ng/L), as seen in Figure 2. The control group had slightly higher prevalence of diabetes (3 of 13), hypertension (5 of 13), hypercholesterolemia (4 of 13), and history of coronary artery disease (1 of 13) than the Chagas group. Although the sample size was small, Chagas patients with major disease severity had higher hsTnT values (median 14.5 ng/L) compared with those with minor and indeterminate disease (median 8.0 ng/L).

After receipt of the letter from the blood center notifying the donor that he or she tested positive for *T. cruzi*, 71% (12 of 17) sought care from a doctor, with 58% (7 of 12) being referred to infectious disease specialists and 33% (4 of 12) being referred to cardiologists. Despite notification from the blood center of positive *T. cruzi* test results, only 25% (3 of 12) who sought care for their *T. cruzi* infection underwent electrocardiography, and only 1 patient was offered *T. cruzi* treatment before enrollment in this study.

Discussion

Our study of *T. cruzi*−positive individuals identified by blood bank screening has several important findings. First, 41% had ECG abnormalities consistent with Chagas cardiac involvement, and most of these abnormalities (72%) met major ECG diagnostic criteria supportive of Chagas disease. Importantly, we also discovered that 36% of participants were suspected to have acquired their infection in southeastern Texas. These patients were largely non-Hispanic whites with no histories of travel to endemic countries, and they do not fit within the demographics of the traditional high-risk groups for Chagas disease in the United States. Finally, those *T. cruzi*−infected patients with major diagnostic ECG abnormalities also had subclinical evidence of myocardial injury, as evidenced by elevated hsTnT levels.

Chagas disease is a source of major cardiovascular morbidity and mortality internationally. Although traditionally a disease affecting endemic regions in Latin America, there is increasing recognition that Chagas disease may be an important and underrecognized cause of morbidity and mortality in the United States.[12,13] A recent study of immigrant patients hospitalized with idiopathic dilated

cardiomyopathy in New York City demonstrated a 13% point prevalence of Chagas disease.[14] To our knowledge, there is no active surveillance in the United States of *T. cruzi* infection in the general population, other than blood donor screening, and patients with dilated cardiomyopathy are not routinely tested. Since blood donor screening began in 2007, approximately 2,000 radioimmunoprecipitation assay−confirmed *T. cruzi*−positive donors have been reported across the United States.[9] With a screening rate of 1 per 6,500 donors confirmed positive for Chagas disease in Texas, there is a high potential of a substantial disease burden that is going undiagnosed in the United States.[15]

In our study, we identified ECG abnormalities consistent with cardiac involvement in most patients with confirmed infection. After initial infection, it is estimated that 20% to 30% of patients will develop cardiac manifestations of Chagas disease, including abnormalities of the cardiac conduction system, arrhythmias, heart failure, thromboembolism, and sudden death.[2] It is estimated that patients with *T. cruzi* infection, new ECG abnormalities or evidence of cardiomyopathy may develop in 1.8% to 5% of patients per year.[1,16] Our study is the first study to conduct electrocardiography and assess for abnormalities in United States blood donors who are *T. cruzi* seropositive. Given the high prevalence of ECG abnormalities at baseline, our data suggest that patients who are identified to have *T. cruzi* infection through blood donor screening in the United States should undergo further cardiac testing, including baseline electrocardiography, and be assessed for treatment. Unfortunately, only a quarter of the patients were referred for cardiac testing after receiving the initial screening letter from the blood center, and only 1 was offered treatment.

Our study also highlights the changing demographics of *T. cruzi* infection in the United States and the potential for autochthonous infection. Of those with confirmed *T. cruzi* infection, 36% were most likely acquired in southeastern Texas. Texas is an area with well-established Chagas disease transmission, with reports of high seroprevalence among dogs, large ecologic niches for the vector triatomine insects, and locally acquired human infections recognized as early as 1955.[17−20] The prevalence in our study is substantially higher than a national blood donor study, which found 7.5% of *T. cruzi*−confirmed blood donors had evidence of locally acquired infection.[8] Importantly, the demographics of patients with presumed locally-acquired infection included nontraditional risk factors. Four patients were non-Hispanic Caucasians without histories of travel to endemic countries. Although the sample size was small, these findings have important implications in raising the level of suspicion for Chagas disease in patients presenting with dilated cardiomyopathy and ECG abnormalities consistent with Chagas disease, even in the absence of traditional risk factors for infection.

Finally, hsTnT was elevated in patients who were *T. cruzi* positive with major ECG abnormalities. HsTnT is a biomarker reflective of myocardial injury and is associated with increased risk for death and adverse cardiovascular outcomes, including heart failure, in the general population.[10,11] Clinically, it is critical to identify a cardiac biomarker that can appropriately serve as a diagnostic or prognostic indicator of severity of Chagas cardiomyopathy in *T. cruzi*−infected patients, as well as gauge the effectiveness of treatment in resolving cardiac disease. Other small studies have demonstrated that hsTnT may correlate with severity of Chagas cardiomyopathy,[21] but larger studies are needed in *T. cruzi*−infected populations to elucidate the potential role of hsTnT as a biomarker for Chagas, specifically in United States blood donors.

Although we were limited by a small sample size, we believe that this study has important health implications. The study raises awareness of Chagas disease in the United States and the need for further studies to identify the true burden of disease. Because our study included only presumably healthy blood donors, our study may not be representative of the general population of southeast Texas, and individuals with higher risk for Chagas disease, such as undocumented immigrants, impoverished individuals, and individuals with heart disease, may not be included. Future epidemiologic studies and vector surveillance programs are necessary to more accurately understand the true burden of disease.

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Disclosures

The authors have no conflicts of interest to disclose.

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