Infection With *Trypanosoma cruzi* and Progression to Cardiomyopathy

What is the Evidence and Is the Tide Finally Turning?

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Chagas disease, also known as American trypanosomiasis, has been haunting the American continent for centuries. Evidence of *Trypanosoma cruzi* has been traced back to mumified tissues from the Chinchorro Indians from the Atacama Desert almost 9000 years ago. However, the clinical description of the disease did not appear in the scientific literature until 1909, when Carlos Chagas brilliantly made the connection between the acute parasitic infection and the clinical manifestations. It seems perplexing that, after more than a century, we are just starting to pay attention to this devastating disorder, to the extent of identifying Chagas as the “most neglected of neglected diseases.” Some researchers have even gone so far as to suggest that Chagas disease may be the “new HIV/AIDS of the Americas,” opening a vivid debate among researchers. Regardless of the media attention spurred by a century, we are just starting to pay attention to this devastating disorder. Nonetheless, some light seems to be appearing at the end of this century-long tunnel.

*T. cruzi* is a complex parasite that has had almost 10 centuries to evolve. Strains differ in geographic endemic regions, for example, north of the Amazon and the Southern Cone regions, carrying different pathogenicity and clinical progression between *T. cruzi* I and II. However, this may be an oversimplification of the complexity of *T. cruzi* genetic variability because up to 6 different strains have been identified to date.

Recent studies assessing ECGs, chest x-rays, and 2-dimensional echocardiograms in a series of Colombian *T. cruzi*-infected individuals identified Tcl-TcIII and Tcl-TcIV strains, as well as the existence of the Tcl genotypes, demonstrating the presence of Ia and Id genotypes. Patients infected with Tcl demonstrated a higher prevalence of cardiac alterations than those infected with TcII. Recent substudies from the Benzimidazole Evaluation for Interrupting Trypanosomiasis (BENEFIT) trial show a striking difference in parasite load among patients infected with *T. cruzi* from Argentina, Brazil, and Colombia with early Chagas cardiomyopathy. The median parasite load in patients from Argentina and Colombia was 20 times higher than that observed in Brazilian patients. It is unknown whether a higher parasite load correlates with a faster progression to cardiomyopathy, but this seems intuitive.

Why do almost one third of patients infected with *T. cruzi* develop cardiomyopathy? Two main hypotheses have been proposed: parasite persistence and human host immune response to infection. In the acute phase, the host controls infection by multiple pathways. In the chronic phase, antigens that are elicited by the immune response are mediated by T cells, which play an important role in the pathological development. The balance between proinflammatory and anti-inflammatory cytokines may be critical in the chronic phase of the disease.

Studies on the specific role of cytokines in the immune response against *T. cruzi* indicate that large amounts of both Th1 and proinflammatory cytokines such as interferon-γ and tumor necrosis factor-α are related to cardiac disease. It is also known that these cytokines are regulated by anti-inflammatory cytokines such as...
as interleukin-10 and -5 observed in low concentrations. Genetic susceptibility to *T. cruzi* has also been studied in different regions and by several investigators. Recent studies indicate that the interferon-γ +874T/A genetic polymorphism may be involved in the susceptibility to but not in the progression of Chagas cardiomyopathy, linking inflammatory regulatory genes to the susceptibility to *T. cruzi* infection. Finally, autoantibodies directed to β₁ and β₂-adrenergoreceptors and muscarinic-2 receptors have been documented in asymptomatic carriers and have been used to predict progression to cardiomyopathy, but larger studies are needed to validate these markers.

What is our current knowledge of the progression of Chagas disease in asymptomatic seropositive blood donors? This is an important question today because a significant number of asymptomatic *T. cruzi* carriers have migrated to developed countries, of which the United States has the largest burden of infected individuals. In this issue of *Circulation*, Sabino and collaborators present contemporary data related to the 10-year incidence of Chagas cardiomyopathy among asymptomatic *T. cruzi*-seropositive blood donors. These investigators performed a retrospective cohort study that targeted initially healthy blood donors who were seropositive to *T. cruzi* and age-, sex-, and period-matched seronegative donors between 1996 to 2002 in 2 cities in Brazil. Between 2008 and 2010, all subjects underwent history and physical examinations, in addition to ECGs and 2-dimensional echocardiograms. They were analyzed blindly and outcomes were adjudicated. The mean follow-up between the index blood donation and outcome was ≈10 years for both seropositive and seronegative *T. cruzi* groups. Almost 500 patients were included in each group, and 24% were identified as having definite Chagas cardiomyopathy compared with only 5% of the *T. cruzi*-seronegative subjects. An interesting finding is that, after a mean of 10 years of follow-up, 26% of the *T. cruzi*-seropositive subjects developed left ventricular systolic dysfunction with an ejection fraction below 50% and 9% were classified as New York Heart Association class II or greater. Additionally, Chagas cardiomyopathy was associated with male sex, history of abnormal ECG, and the presence of an S₃ heart sound. This important contemporary information reveals that the annual incidence of Chagas cardiomyopathy is relatively low at 1.85% and is driven primarily by mild cardiomyopathy.

How does the present study influence or change our screening, risk-stratifying, or potential therapeutic strategies of asymptomatic *T. cruzi* carriers? First, this information needs to be interpreted with caution. The retrospective nature of this study is a limitation because there was no baseline cardiovascular evaluation, potentially resulting in an overestimation of the incidence of Chagas cardiomyopathy progression. Similarly, there was a 5% rate of false positives, highlighting the diagnostic difficulties encountered with Chagas cardiomyopathy. Last but not least, the authors fail to acknowledge that this information pertains to a Brazilian cohort and the *T. cruzi* strain in these cases is most likely TcII. As discussed, recent evidence obtained by real-time polymerase chain reaction at baseline from the BENEFIT trial indicates that patients with mild cardiomyopathy from Colombia and Argentina have a 20-fold higher parasite load compared with Brazilian patients. The TcII strain is the most prevalent in both Argentina and Brazil and TcI is most prevalent in Colombia, suggesting that other factors besides strain may play a role in determining both parasite load and pathogenicity. It remains unclear whether higher *T. cruzi* parasite load indeed accelerates both the progression and severity of the disease. The hope is that the BENEFIT trial will answer this vexing question and determine the effects of benznidazole on clinical cardiovascular outcomes.

The present data are an approximation of the annual incidence of progression to cardiomyopathy. The rate of progression may also be related to parasite load and other inflammatory and genetic markers. With this hypothesis in mind, the annual incidence may be estimated in the range of 1.5% to 4.0%. If 8 million people are infected, anywhere between 120 000 and 320 000 individuals a year would be expected to progress to Chagas cardiomyopathy. In the United States alone, this means between 4500 and 12 000 new cases annually if appropriately diagnosed. These estimates are bewildering because we still have no strong evidence that etiologic treatment halts the progression of cardiomyopathy.

But after 100 or more years of neglecting Chagas disease, the tide is turning. Studies like the present report, funded by the National Institutes of Health, and several ongoing clinical trials such as BENEFIT, the Study of Oral Posaconazole in the Treatment of Asymptomatic Chronic Chagas Disease (STOP-CHAGAS; NCT01377480), the Clinical Trial for the Treatment of Chronic Chagas Disease With Posaconazole and Benznidazole (CHAGASAZOL; NCT01162967), and other studies funded by the Canadian Institute of Health Research, Tropical Disease Research/World Health Organization, Drugs for neglected diseases and industry are ongoing and will provide answers for the role of etiologic treatment in the indeterminate early cardiomyopathy stages.

The authors of this report are to be commended for providing contemporary data on the incidence of developing Chagas cardiomyopathy in asymptomatic *T. cruzi* carriers. This information is important and relevant as we gain awareness of the importance of Chagas in different latitudes and prepare to confront the thousands of asymptomatic *T. cruzi* carriers who are nowadays spread around the world. As clinicians and scientists, we have an overdue responsibility for these patients and have to use all means possible to turn the tide to eliminate Chagas disease from our books.

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**References**


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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/127/10/1095

An erratum has been published regarding this article. Please see the attached page for:
/content/127/15/e552.full.pdf
In the article by Morillo, “Infection With Trypanosoma cruzi and Progression to Cardiomyopathy: What is the Evidence and Is the Tide Finally Turning,” which was published in the March 12, 2013 issue of the journal (*Circulation*. 2013;127:1095-1097), an error occurred.

On page 1096 in the first full paragraph, “…26% of the T cruzi–seronegative subjects…” should have read, “…26% of the T cruzi–seropositive subjects…”.

The error has been corrected in the current online version of the article. The authors regret the error.