Update on Chagas Heart Disease on the First Centennial of Its Discovery

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Introductory Note

In 1909 Carlos Chagas discovered a new parasite, the \textit{Trypanosoma cruzi} (\textit{T. cruzi}) and described, in greater detail, its cycle of transmission (vector, hosts) and the acute clinical manifestations of the first human case of the disease that bears his name.\textsuperscript{1} A few years later, the main clinical form of this new morbid entity—Chagas heart disease—was fully characterized.\textsuperscript{2} Paleoparasitology studies allowing the recovery of \textit{T. cruzi} DNA from human mummies indicate that Chagas disease already afflicted mankind as early as 9000 years ago.\textsuperscript{3} Of note, in 2009, we also celebrated the bicentennial of the birth of Charles Darwin, who may have contracted Chagas disease during his expedition to South America, as suggested by his vivid description of suffering the triatomine sting and by some of his late life symptoms.\textsuperscript{4}

Recent Trends in Epidemiology

Several epidemiological trends have been observed for Chagas disease over the last decades. There has been a clear decline in the number of patients estimated to harbor the \textit{T. cruzi}, from the 16-18 millions in the 1990s to 8-10 million persons nowadays. It is also estimated that the incidence of new cases of the infection steadily declined from 700 000/year in 1983 to 200 000/year in 2000 and to 50 000/year currently.\textsuperscript{5} Nevertheless, Chagas disease still constitutes the third largest parasitic disease burden globally, after malaria and schistosomiasis.

The overall decline in the prevalence and incidence of chronically infected people is the result of several factors, the most important of which is related to effective control of vectorial transmission. A major achievement in this context is illustrated by the success of the Southern Cone Countries Initiative, launched since 1991 in Argentina, Brazil, Bolivia, Chile, Paraguay, and Uruguay, and covering an area responsible for roughly 60\% of the global prevalence of \textit{T. cruzi} infection.\textsuperscript{6} This initiative, based on the spraying of infested dwellings with pyrethroid insecticides, resulted in successful interruption of parasite transmission by \textit{Triatome infestans} (a major domiciliary vector species) in Uruguay in 1997, Chile in 1999, and Brazil in 2006. Partial interruption of vectorial transmission has also been achieved in Argentina, Bolivia, and Paraguay. Other initiatives are ongoing in Central American (against \textit{Rhodnius prolixus} and \textit{Triatoma dimidiata}) and in Andean Countries, with results still pending.\textsuperscript{6}

Transmission of Chagas disease has also been curtailed through rigorous and wide-ranging screening for \textit{T. cruzi} infection among blood and organ donors. For instance, in Brazil, blood banks increased serological control from 13\% in 1980 to 99\% in 2006. In the same period, the overall proportion of blood donor candidates infected with \textit{T. cruzi} decreased tenfold, from 4\% to 0.4\%.\textsuperscript{5,6}

Although these control measures had raised the hope of complete elimination of Chagas disease by 2010, it is now clear that eradication, meaning the definitive interruption of the transmission, will remain an elusive goal, unless control and entomological surveillance actions continue to be undertaken for many years.\textsuperscript{5} In addition, it is now evident that the infection by the \textit{T. cruzi} evolved from its primitive enzootic form to a widespread anthrozoanosis, and the parasite is now disseminated across many sylvatic ecotopes that are being progressively disrupted by humans in regions such as the Amazon and the Chaco.
deleterious consequences of deforestation in the Amazon region, the recrudescence of \textit{T cruzi} acute infection is potentially a major one.\textsuperscript{7} For example, more than 400 acute cases have been recently reported, most of them from microepidemic outbreaks following oral transmission. This route of infection, with 100 new cases reported annually, usually carries a higher mortality rate, presumably due to a more prominent parasite load. The problem is compounded by the demonstration of at least 8 secondary vector species potentially capable of invading human dwellings, in Brazil and Mexico, and the detection of vector resistance against the current pyrethroid insecticides in some Argentine and Bolivian regions.\textsuperscript{5} Also, there is evidence to substantiate the hypothesis that the parasite continues to be introduced into the peri-urban communities, such as that described in Arequipa, Peru.\textsuperscript{8}

The increasing number of patients with Chagas disease recently detected in non-endemic areas, such as North America and several regions of Europe, Asia, and Oceania, due to growing population migratory moves is another contemporary issue.\textsuperscript{9} The disease's tendency toward ubiquitousness is exemplified by serological surveys, with estimates that 80 000 to 120 000 chronically infected \textit{T cruzi} individuals are now living in the United States. Because of that, the Food and Drug Administration is currently recommending universal screening of blood donors for \textit{T cruzi}. In Spain, where over one million immigrants from Latin America have settled, services specialized in tropical medicine and international health problems are currently facing the need to diagnose and treat individuals with Chagas disease.\textsuperscript{10}

Despite the unquestionable accomplishment represented by some of the epidemiological trends just discussed, and because of the challenges remaining to be adequately addressed, prevention of \textit{T cruzi} infection is mandatory, especially at the primary (protecting people at risk of becoming infected) and secondary level (implementing trypanocidal therapy at early stages of the disease to avoid organ damage and to interrupt the epidemiologic chain of the disease), both in endemic and non-endemic countries.\textsuperscript{11} Thus, recognizing the potential for Chagas disease transmission through transfusion, organ transplantation and vertical routes in non-endemic countries, and identifying and providing care for people already infected has become a truly global concern. For instance, although the risk of congenital disease has usually been considered low, it is by no means negligible, since data from endemic areas show that 1\%-10\% of neonates may become infected.

### Current Insights Into the Pathogenesis and Pathophysiology of Chronic Chagas Cardiomyopathy

Chronic Chagas heart disease (CHD), the most serious manifestation of Chagas disease, is an inflammatory form of dilated cardiomyopathy that leads to extensive cardiac fibrosis and progressive impairment of ventricular contractile function. Several mechanisms may contribute to the pathogenesis of CHD, as recently reviewed.\textsuperscript{12}

- Striking neuronal depopulation accompanied by abnormal autonomic cardiac regulation has been shown by several independent pathologic studies. Due to the dysautonomia, chagasic patients are deprived of the tonic inhibitory action normally exerted by the parasympathetic system on the sinus node, and also lack the vagally mediated mechanism to respond with the quick onset of bradycardia or tachycardia to transient changes in blood pressure or venous return. Although at early stages of disease sympathetic denervation has also been shown at the sinus node and myocardial regions, based on a strikingly predominant parasympathetic impairment, the neurogenic theory postulated that a long-lasting autonomic imbalance would lead to a catecholamine-induced cardiomyopathy.\textsuperscript{13} However, several conceptual obstacles have challenged this theory, including the subtleness and variability of the intensity of cardiac denervation in CHD patients and the lack of correlation between parasympathetic denervation and the extent of myocardial dysfunction.\textsuperscript{12} Nevertheless, neurogenic alterations may contribute to trigger malignant arrhythmia and sudden death, and to disturb the coronary microcirculatory control.

- Several coronary microvascular abnormalities, including increased platelet activity, microthrombi, spasm, and endothelial dysfunction have been reported in animal models of \textit{T cruzi} infection and in human CHD studies.\textsuperscript{12} Abnormal reactivity to vasodilator and vasoconstrictor stimuli has been reported in the epicardial coronary arteries of CHD patients. These disturbances may be related to inflammation and endothelial cell damage directly caused by \textit{T cruzi} or by immune effector cells; they may also lead to ischemic myocardial damage and fibrosis and are likely to participate in the genesis of angina-like symptoms, electrocardiographic changes, and perfusion defects described in chagasic patients with angiographically normal coronary arteries. These microvascular disturbances have also been postulated to cause low-pressure perfusion and ischemia in watershed zones between the main coronary arteries, thus leading to formation of the characteristic aneurysmatic lesions at two principal
sites: the apex and the basal posterior wall of the left ventricle.

– According to recent reviews, a consensus is emerging that parasite persistence and parasite-driven immune deleterious responses play a pivotal role in the pathogenesis of CHD.12,14-16 The evidence supporting this concept comes from multiple aspects: a) in recent years more sensitive methods of parasite detection, such as immunohistochemistry and polymerase chain reaction (PCR), have demonstrated a clear topographic correlation of T cruzi antigens or parasite DNA and inflammatory changes in chronic lesions; b) reduction of parasite burden through etiologic treatment attenuates organ damage in humans and animals experimentally infected with T cruzi; conversely, immunosuppressive treatments/situations usually aggravate the inflammatory response; and c) re-infection or continued exposure to active transmission increases parasite load and disease severity both in experimental models and in human cases.

– It is indisputable that autoimmunity exists in Chagas disease. However, its role in the pathogenesis of chronic myocardial damage is more controversial. Data supporting either molecular mimicry or polyclonal activation as directly involved in the pathogenesis of myocardial lesions ascribed to T cruzi infection are sparse and inconclusive.14 Nevertheless, it is logical to conclude that the antiparasitic immune response may work as a double-edged sword when not properly modulated.17

– It is also a plausible hypothesis that the nature and intensity of the host immune response in controlling parasites in specific tissues plays the most important role in determining why some individuals develop organ damage (30%-40%) while the majority of them remain throughout life with the so-called indeterminate form of chronic disease (ie, without clinical manifestations of disease).

– A variety of structural and functional cardiovascular changes occur in patients with chronic CHD, because of 3 key pathological processes: inflammation, cell death, and fibrosis. Inflammatory infiltrates consist predominantly of CD8+ lymphocytes. Myocardial cells usually undergo myocytolysis and contraction band necrosis, being replaced with fibrotic tissue. The conduction system and the intramural cardiac neurons and fibers are also frequent targets of T cruzi. Tissue damage results from the rupture of infected cells releasing trypomastigotes, the local production of some proinflammatory cytokines, and other cytotoxic mechanisms involving CD8+ T cells and, less frequently, CD4+ T cells. Intact amastigote parasites are rarely found in chronically infected patients by using standard histological techniques, but T cruzi antigen fragments and parasite DNA are readily detected with more sensitive methods (PCR or immunohistochemistry). Focal or diffuse areas of myocellular hypertrophy usually coexist with marked reparative fibrosis, with replacement and dense interstitial accumulation of collagen fibers. All areas of the heart, including the conduction system, may be involved. This explains the frequent occurrence of atrioventricular and intraventricular blocks, as well as of sinus node dysfunction in patients with CHD. Also, the slow but incessant destruction of cardiac fibers, with hypertrophy of the remaining myocytes, and intermingled fibrotic areas set the stage for the typical regional and global impairment of ventricular systolic function and the triggering of malignant arrhythmias.

Overview of Clinical Features and Diagnosis of Chagas Heart Disease

Cardiac abnormalities may be detected in all phases or forms of Chagas disease. The etiology is established by at least 2 positive serological tests, usually ELISA, immunofluorescence, or hemagglutination, which detect circulating antibodies against the T cruzi. Infection may also be confirmed by parasitological methods such as xenodiagnosis or PCR-based techniques, which detect circulating T cruzi materials. However, these methods are not yet widely available for clinical purposes.

In the acute phase, symptoms and signs are usually mild and the electrocardiogram may show low-voltage, diffuse ST-T changes and first-degree atrioventricular block; chest x-ray shows variable degrees of cardiomegaly; serologic tests for T cruzi infection are usually negative during the first weeks, but the diagnosis may be made upon detection of circulating parasites by a variety of methods. The diagnosis of acute phase due to blood transfusion requires a high level of awareness, especially in non-endemic areas. This notion is also pertinent to the increasing problem of recognizing reactivation of Chagas’ disease in immunocompromised chronic patients.

In the chronic phase, it is not uncommon for patients with marked ECG abnormalities to be asymptomatic physical laborers or capable to perform strenuous physical activities. Exertional dyspnea, palpitations, dizziness, syncope, chest pain, fatigue, and edema are the commonest symptoms of CHD. They are the expression of three major syndromes that may co-exist in the same
patient: heart failure, cardiac dysrhythmia and thromboembolism (systemic and pulmonary).

ECG abnormalities include various conduction disturbances, ST-T changes, low QRS voltage, pathologic Q-waves, and ventricular ectopic beats. The association of right bundle branch block and left anterior hemiblock is a very typical finding in chronic CHD.

Various imaging methods can be used to show the peculiar and striking segmental wall motion abnormalities in both ventricles. The most characteristic lesion is the apical aneurysm, but dysynergy at the posterior-lateral wall is the lesion most frequently associated with the development of sustained ventricular tachycardia. The aneurysms are also sources of thromboembolic complications, both in the pulmonary and systemic circulations.

Global ventricular systolic dysfunction occurs in more advanced cases, unchaining congestive heart failure, usually with prominent signs of systemic congestion (hepatomegaly, neck vein distension, anasarca). This peculiar feature of CHD is possibly linked to early severe damage of the right ventricle (RV), a chamber frequently neglected in the clinical and echocardiographic evaluation of cardiac performance, but more readily assessed with radionuclide angiography.

Sudden cardiac death can occur even in previously asymptomatic patients, and is the most common cause of mortality in CHD. It is usually associated with ventricular tachycardia and/or ventricular fibrillation or, more rarely, with complete atrioventricular (AV) block or sinus node dysfunction. Holter monitoring shows episodes of non-sustained ventricular tachycardia in nearly 40% of patients with wall motion abnormalities and New York Heart Association (NYHA) functional class I/II and in 90% of those with heart failure (NYHA III/IV), an incidence that is higher than that of other cardiomyopathies.

Patients with CHD and chest pain may present a difficult diagnostic problem, particularly in non-endemic countries, because the disease often masquerades as an ischemic syndrome, since they can present marked ST-T changes, abnormal Q-waves, and show various types of myocardial perfusion defects when evaluated with myocardial scintigraphy. Since coronary angiography is usually normal, those disturbances have been postulated to be due to derangements at the microvascular level.

**Principles Involved in Management of Patients With Chagas Heart Disease**

Treatment of clinical manifestations of CHD is mostly dependent on measures that have been demonstrated to improve survival and/or quality of life in patients with other etiologies for heart failure or rhythm disturbances. However, the empirical translation to patients with CHD of the therapeutic interventions proven to be effective in other settings may not be appropriate, because of the inherent pathophysiological characteristics observed in this disease. Thus, the empirical approach, widely adopted as it is, is not evidence-based on studies specifically conducted in patients with CHD.

Clinical treatment of congestive heart failure is based on sodium intake restriction, diuretics (high daily doses usually required), digitalis, angiotensin-converting-enzyme inhibitors, and spironolactone (because of the inclusion of some CHD patients in the RALES trial and the belief that this drug could attenuate the fibrotic process). The use of beta-blockers has been hindered by bradycardia and conduction disturbances, but when tolerated (usually with lower doses) may favorably impact the clinical course of the disease. Cardiac transplantation is now a valid alternative for selected patients with intractable heart failure. Notwithstanding the danger of reactivation of the infection (usually avoided through the use of low-intensity immunosuppression to prevent rejection, and/or pre-treatment with trypanocidal agents), recent results of cardiac transplantation in patients with CHD have been comparable to the best ones achieved with other etiologies of heart failure.

Amiodarone is recommended as first-choice treatment for patients with complex ventricular dysrhythmia, particularly when there is significant myocardial dysfunction. It is not uncommon for ventricular tachycardia to co-exist with advanced conduction disturbances at various cardiac levels, and pacemaker implantation may be required in those settings. The use of implantable cardioverter defibrillation is empirically advocated for selected patients surviving cardiac arrest, or who have refractory and hemodynamically unstable sustained ventricular tachyarrhythmias. However, those patients still require concomitant use of amiodarone, and may not ultimately benefit from the device because of too frequent delivery of shocks triggered by the high-density of VT runs.

Multisite pacing and cardiac resynchronization are probably being overused for treating patients with CHD, without any supporting evidence of benefit. There are several concerns about the use of cardiac resynchronization therapy in CHD: dysynergy caused by extensive fibrosis is likely to hamper resynchronizing; also, QRS prolongation is frequently related
to right bundle branch block, and the effect of resynchronization in this setting has not been well established.

Because of the high incidence of thromboembolic phenomena in CHD, oral anticoagulants are recommended for patients with atrial fibrillation, previous embolism, and apical aneurysm with thrombus, even in the absence of controlled clinical trials demonstrating their efficacy. However, poor social and economic factors may limit the implementation of this therapy, because of the increased risk of bleeding.

Stem cell therapy is currently investigational in patients with CHD, after preliminary preclinical studies in murine models suggested a potential benefit and several observational reports in humans.

Etiological treatment in established CHD is now under scientific scrutiny by the BENznidazole Evaluation For Interrupting Trypanosomiasis (BENEFIT) project. As of July 24, 2009 the BENEFIT trial has enrolled nearly 1700 patients in Argentina, Bolivia, Brazil, and Colombia, who were double-blindly randomized to treatment with benznidazole or placebo and will be followed for a mean period of 5 years.

Conclusions

Although significant advances occurred in most fields dealing with understanding and controlling Chagas disease, much work remains to be done after one century. In particular research efforts are definitely necessary, to ensure more effective and steady scientific progress toward the achievement of better knowledge of pathophysiological aspects and their clinical and prognostic consequences. For instance, instead of further reports on autonomic derangements in additional small groups of patients with Chagas disease (something that had been performed through systematic investigation carried out starting in the late 1960s), investigators should try to answer the crucial question whether or not cardiac dysautonomia has a prognostic impact for those patients. Another example of perfunctory research is that aiming to develop additional strong and independent prognostic factors. Finally, new and more effective chemotherapeutic agents against the T cruzi are awaited, now that its genomics have been revealed and more potential targets for trypanocidal therapy have been devised. Initiatives in this direction seem now feasible, as a morbid entity formerly confined to South America may become a global public health issue.

REFERENCES
