

## Mechanisms Responsible for Myocardial Damage Progression in Chronic Chagas Disease

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The mechanisms leading to the progression of chronic Chagas heart disease are still unknown. The hypotheses proposed for explaining the pathogenesis of this endemic disease include the persistence of the parasite in the hearts of infected patients,<sup>1</sup> the development of an autoimmune response,<sup>2</sup> and cardiotoxicity caused by catecholamines.<sup>3</sup> Recent studies have consistently and unequivocally shown the persistence of the parasite in the blood and myocardial tissue of patients with chronic Chagas disease. This is true of patients in the indeterminate, arrhythmic and congestive stages.<sup>1</sup> However, the survival of these patients does not appear to be determined exclusively by the presence of the parasite. Patients from different South American countries (in non-endemic zones) who were serologically positive for *Trypanosoma cruzi* and active infection but who had normal left ventricular cineangiography showed 100% survival at 16 years of follow-up.<sup>4</sup> However, the presence of segmental myocardial damage (apical aneurysm) or left ventricular systolic dysfunction was accompanied by a mortality of nearly 60% at four years of follow-up (Figure).<sup>5</sup> A number of clinical studies have investigated whether eradication of the parasite with specific treatment modifies the course of chronic Chagas disease, but while the results have been mildly encouraging they have also been somewhat contradictory.<sup>6</sup>

Over the last 10 years, a number of randomized, double-blind trials have been undertaken to investigate the effects of benznidazole in patients with indeterminate and chronic disease. Follow-up was for 3-4 years. The aims of these studies were related to the reduction of the parasitic load (conversion to seronegativity or a

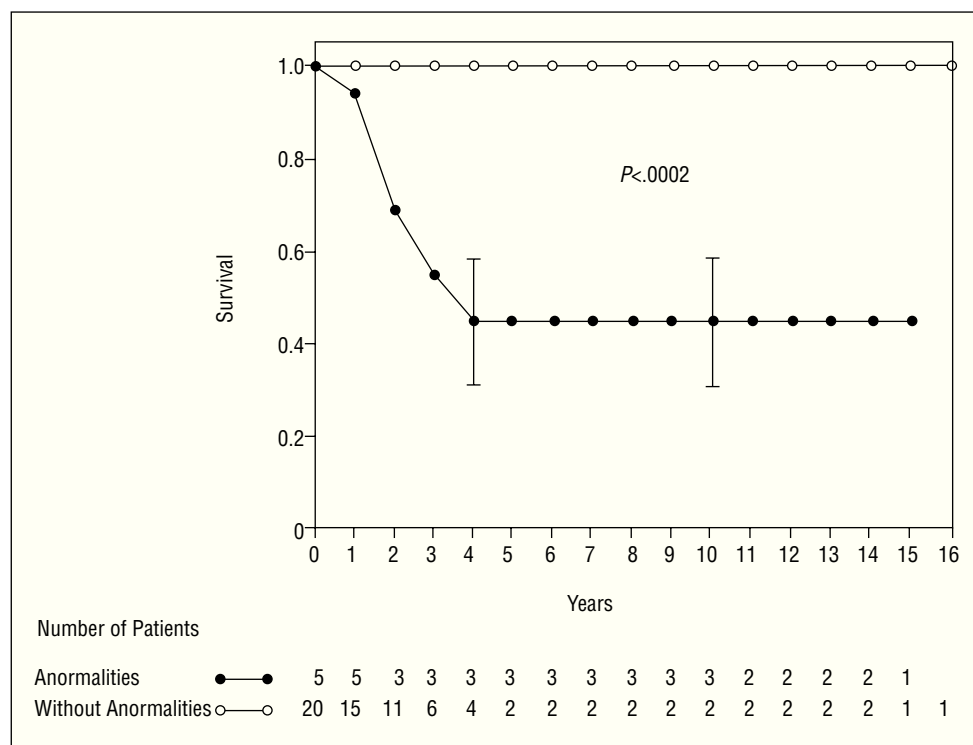
reduction in the rate of positive xenodiagnostic test results). Generally, drop out rates were high and discrepancies were encountered between the results of conventional serological and ELISA seroconversion tests. Positive xenodiagnoses spontaneously became negative in nearly half of the patients tested. Other randomized studies have investigated the efficacy of itroconazole and allopurinol, the main aim being to "normalize" the electrocardiogram (ECG). The normalization criteria were, among others, the disappearance of ventricular or supraventricular extrasystoles, and modifications of the electrical axis. However, methodological problems and the intrinsic weakness of the criteria used to assess the parasitic load and progression of the disease means no treatment can be recommended over any other.<sup>6</sup>

The paper by Viotti et al<sup>7</sup> in this issue of the REVISTA ESPAÑOLA DE CARDIOLOGÍA analyses the indicators of progression of Chagas disease in its earliest stages, i.e., the indeterminate stage, and the stage when heart disease is manifest but heart failure has not yet occurred. The study involved 856 patients, all seropositive for *T. cruzi*, who were stratified into three groups: group I, patients with normal heart as assessed by echocardiogram (731); group II, patients with heart disease but no ventricular enlargement (35 patients), and group III, patients with heart disease and ventricular enlargement (90 patients). The main aim of the work was to determine the factors indicating likely progression from a lower to a higher clinical severity group. The variables considered to influence this progression were specific treatment with benznidazole, ventricular conduction abnormalities, and changes in the heart rhythm or systolic and diastolic ventricular diameters. The results were examined by Cox multivariate analysis and risk of progression scores determined. The main finding, as Table 1 clearly shows, was that progression depends on the initial damage to the heart (in group I, 4.6% of patients progressed to a higher group, while 39% of patients in group III so progressed;  $P < .0001$ ).

It should be noted that specific treatment with benznidazole was the only indicator associated with a

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**Figure.** Survival of *T. cruzi* seropositive patients according to left cineventriculography findings. The survival of patients with normal cineventriculography (○) was 100% at 16 years of follow-up. Patients with segmental abnormalities and/or ventricular dysfunction, however, showed a mortality of nearly 60% at 4 years of follow-up (●). Reproduced and adapted with the permission of Hagar and Rahimtoola.<sup>5</sup>

delay in heart disease progression. This finding could be of great importance - so one must be careful to ask whether it could simply be the result of the experimental design and statistical treatment. Certainly the study suffers from the following limitations: *a)* stratification was performed after treatment was complete; *b)* the sample is characterized by a marked predominance of patients (90%) with either no or only minimal heart damage; and *c)* Figure 2, which shows the changes in clinical group in accordance with etiological treatment, does not include curves for each of the 3 clinical groups resulting from stratification. Finally, the results of this study should be analyzed within the context of other recent investigations in which the quantification of myocardial damage (post-treatment) was also undertaken with two-dimensional echocardiography.<sup>8</sup>

Electrocardiographic abnormalities in asymptomatic patients with chronic Chagas disease do not necessarily indicate myocardial damage. Patients can be found with no damage, with segmental damage, and with diffuse damage plus left ventricular dysfunction. Therefore, methods have to be used that allow the evaluation of regional motility and the degree of left ventricular dysfunction.<sup>9</sup> In an observational study in which patients were not stratified before treatment, Lauria-Pires et al<sup>8</sup> examined the effectiveness of benznidazole and nifurtimox in terms of parasite eradication and prevention of progression in patients with chronic Chagas disease. The former was assessed by serological methods, parasite DNA amplification and xenodiagnostic meth-

ods, the latter by a series of ECG, Holter monitoring and two-dimensional echocardiography. Follow-up was for 10 years. The infection remained active in all treated patients and 93.7% of non-treated patients. The ECG results showed greater changes in the treated patients, and no significant differences were found between the 2 groups in terms of echocardiographic findings. The authors concluded that specific treatment against the parasite should not be embarked upon since it did not modify the natural history of the disease.

The results of Viotti et al<sup>7</sup> and Lauria-Pires et al,<sup>8</sup> whose investigations were similarly designed and made use of similar methodologies, are obviously contradictory, and no definitive conclusions can be drawn on the beneficial effects of anti-parasite treatment. The basic problem is the absence of any stratification of heart disease before the start of therapy. Thus, a prospective, randomized, placebo-controlled study is required to determine the true effects of specific treatment in groups of patients with similar clinical characteristics and comparable myocardial damage. Without such a trial, results are likely to continue being contradictory.

Contrary to that suggested by the hypothesis of parasite persistence in the heart, patients with Chagas disease seem to benefit from medication that does not act on the parasite. Different studies have shown that medication designed to prevent neurohormonal activation can lead to improved survival and quality of life.<sup>10</sup> In addition, in Chagas heart disease the myocardial damage is characterized by segmental abnormalities (apical aneurysm) from the acute phase. In the ar-

rhythmic and congestive phases, myocardial damage is diffuse and the ventricular cavity enlarged. In other words, cardiac remodeling is also present in chagasic cardiomyopathy. Since abnormalities in the parasympathetic control of the heart rate, neurohormonal activation, and antibodies to muscarinic and adrenergic receptors are detected late, cardiac remodeling as an adaptive response to initial myocardial damage might explain the natural history of the disease and the benefits of non-specific treatment.<sup>11,12</sup>

In summary, 2 therapeutic strategies exist whose aim is to favorably influence the inexorable progression of myocardial damage in Chagas disease: one is to try to eradicate the parasite, the other to prevent cardiac remodeling and neurohormonal activation. Both require further investigation via adequately designed studies with sufficient statistical power to respond to the basic question regarding the pathogenesis of chronic Chagas heart disease: is the mechanism that leads to progression based on the persistence of the parasite or on cardiac remodeling and neurohormonal activation?

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