

## Serum Troponin T in Patients With Chronic Chagas Disease

Ana L. Basquiera, Ricardo Capra, Mirtha Omelianiuk, Marcos Amuchástegui, Roberto J. Madoery, and Óscar A. Salomone

Hospital Privado Centro Médico de Córdoba, Córdoba, Argentina.

High serum levels of T troponin (TnT) have been described in patients with nonischemic myocardial pathologies as markers of myocardial damage. We aimed to determine whether a highly sensitive TnT assay could identify patients with early stage chronic Chagas disease cardiopathy. We studied 39 outpatients with a serologic diagnosis of Chagas disease by clinical examination, electrocardiogram and echocardiogram. Among all patients, 15 had no cardiac lesions, 15 showed only typical electrocardiographic changes, and nine had echocardiographic alterations. All TnT determinations were negative except in one patient in the latter group (1 out of 9; 11.11%). This patient had the lowest ejection fraction (29%) and had a left ventricular diastolic diameter of 77 mm. Thus, in the present study troponin T levels were not associated with early signs of myocardial damage in Chagas disease.

**Key words:** *Chagas disease. Troponin. Myocardial pathy.*

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### Concentraciones séricas de troponina T en pacientes con enfermedad de Chagas crónica

Se ha descrito la presencia de concentraciones séricas elevadas de troponina T (TnT) en pacientes con miocardiopatía no isquémica y se ha postulado que estas proteínas puedan ser marcadores de daño miocárdico. El objetivo del presente estudio fue determinar si las concentraciones séricas elevadas de TnT se asocian a una lesión temprana en la miocardiopatía chagásica. Estudiamos a 39 pacientes con serología positiva para enfermedad de Chagas, en los que se llevaron a cabo: evaluación clínica, electrocardiograma, ecocardiograma y medición sérica de TnT (límite de detección, 0,01 ng/ml). Del total, 15 pacientes no presentaban lesión cardíaca, 15 tenían sólo alteraciones electrocardiográficas típicas y en nueve se observó una disminución de la fracción de eyección o dilatación ventricular izquierda. Todas las determinaciones de TnT fueron negativas, excepto en un paciente del último grupo, que presentaba el mayor grado de disfunción ventricular izquierda. En este grupo de pacientes, la TnT no sirvió como marcador de la afección temprana por enfermedad de Chagas crónica.

**Palabras clave:** *Enfermedad de Chagas. Troponina. Miocardiopatía.*

## INTRODUCTION

Chagas disease is caused by the protozoan parasite *Trypanosoma cruzi* and is widespread in Central and Latin America. It is estimated that 16-18 million people are currently infected by *Trypanosoma cruzi* and 100 million are at risk of contracting the infection.<sup>1</sup> Chagas disease has two stages, an acute phase immediately following acquisition of the infection, and a chronic phase that may last several years and irreversibly affect various organs, such as the heart, esophagus and colon,

as well as the peripheral nervous system.<sup>1</sup> Most patients go through an asymptomatic period, called indeterminate, during the chronic stage of the disease. Only 20%-30% go on to develop the cardiac alterations characteristic of chronic chagasic cardiomyopathy (CCC), which gradually leads to heart failure, atrioventricular conduction block, or sudden death.<sup>2</sup> Nevertheless, histological changes consistent with myocardial injury are present over the entire course of the disease.<sup>3</sup> It would be very useful to have markers of progression in the population experiencing the indeterminate period, but to date, it is still not possible to predict this transition.<sup>2</sup>

Cardiac troponins are proteins found in heart and skeletal muscle that regulate the speed and power of muscle contraction. Troponin T (TnT) is a biochemical marker of myocardial lesion with high specificity and sensitivity in ischemic heart disease.<sup>4,5</sup> Increased serum

Correspondence: A.L. Basquiera.  
Hospital Privado Centro Médico de Córdoba.  
Naciones Unidas 346. 5016 Córdoba. Argentina.  
E-mail: [anabasquiera@arnet.com.ar](mailto:anabasquiera@arnet.com.ar)

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TnT values have been found in patients with heart failure of various etiologies,<sup>6</sup> and its persistence seems to be associated with decreased survival in patients with idiopathic dilated cardiomyopathy.<sup>7</sup>

The clinical value of serum TnT concentrations has not been assessed in chronic Chagas disease. The aim of this study was to determine whether elevated serum TnT values are associated with the presence of characteristic lesions of chagasic cardiomyopathy.

## PATIENTS AND METHOD

### Population

We studied 39 consecutive patients with positive serology for Chagas disease attended in the Cardiology Service of the Hospital de Privado de Córdoba in Argentina. All patients were clinically stable, none had been hospitalized for heart failure in the three months prior to inclusion in the study, and all were assessed on an outpatient basis. Diagnosis of Chagas disease was established according to the results of the following serological tests: enzyme-linked immunosorbent assay, indirect hemagglutination test (positive  $\geq 1/28$ ) and indirect immunofluorescence test (positive  $\geq 1/32$ ).

The following exclusion criteria were applied: history of ischemic heart disease, primary valve disease, use of cardiotoxic drugs, chronic renal insufficiency and surgery of any type in the previous 30 days. All patients underwent a clinical examination, 12-lead electrocardiography and bidimensional Doppler echocardiography. Patients were divided into three groups:<sup>8</sup> indeterminate (IND) group, with no cardiac lesions; CCC-A group, with electrocardiographic alterations alone (sinus bradycardia  $< 50$  bpm, first-degree atrioventricular [AV] block, left anterior hemiblock, incomplete or complete right bundle branch block, permanent pacemaker, or combinations of these factors), and CCC-B group, with echocardiographic alterations, defined as left ventricular ejection fraction  $< 50\%$  and/or left ventricular diameter at end diastole equal to or greater than 56 mm. All patients gave informed consent for participation in the study.

### Troponin T determination

TnT determination was performed in serum obtained from venous blood, using a third-generation analytic method with electrochemiluminescent detection (Roche Diagnostic), in an Elecsys 2010 automatic analyzer (Hitachi). The test includes two specific monoclonal antibodies against human TnT. Values over 0.01 ng/mL were considered positive.

### Statistical analysis

Data are expressed as mean  $\pm$  standard deviation (SD), or as number and percentage. Baseline characteristics between groups were compared by ANOVA and the Turkey-Kramer multiple comparison procedure, or by the  $\chi^2$  test with  $2 \times 3$  contingency tables, when appropriate. Significance was set at a  $P < .05$ . All data analyses were performed using the StatsDirect Statistical Software, version 2.2.3 (StatsDirect Ltd, England, 2002).

## RESULTS

Among the 39 patients studied, 15 showed no abnormality in the various studies performed (IND group). Of the remaining patients, 15 presented only characteristic electrocardiography alterations (CCC-A), and 9 showed alterations in left ventricular dimensions or contractility (CCC-B). Patient characteristics are summarized in Table 1. The most frequent electrocardiographic alterations in the CCC-A and CCC-B groups were complete right bundle branch block alone (40% and 11.11%, respectively) or combined with left anterior hemiblock (20% and 22.22%, respectively). The remaining patients presented sinus bradycardia ( $n=5$ ), sinus bradycardia plus first-degree AV block ( $n=2$ ), sinus bradycardia plus first-degree AV block and complete right bundle branch block ( $n=2$ ), incomplete right bundle branch block ( $n=4$ ) and permanent pacemaker ( $n=3$ ).

Only one patient (from the CCC-B group) in the series presented an abnormal troponin T value consi-

TABLE 1. Characteristics of the 39 patients with chronic Chagas disease

Variable	IND (n=15)	CCC-A (n=15)	CCC-B (n=9)	P
Age, years	56.27 $\pm$ 7.35	60.93 $\pm$ 11.28	61.22 $\pm$ 17.95	.4833
Sex, men/women	2/13	8/7	6/3	.0171 <sup>a</sup>
Abnormal electrocardiograms, %	0	100	88.89	$< .0001^a$
Left ventricular diameter at diastole, mm	41.2 $\pm$ 7.19	44.16 $\pm$ 6.39	56.2 $\pm$ 11.19	.0003 <sup>b</sup>
Left ventricular ejection fraction, %	67 $\pm$ 8.23	62.4 $\pm$ 8.23	49.67 $\pm$ 17.1	.0021 <sup>b</sup>
Troponin T, positive, %	0	0	11.11	.1808 <sup>a</sup>

<sup>a</sup>IND significant differences as compared to CCC-A and CCC-B. <sup>b</sup>CCC-B significant differences as compared to IND and CCC-A

IND indicates indeterminate; CCC, chronic chagasic cardiomyopathy.

Values are expressed as mean  $\pm$  SD.

dered to be positive (0.029 ng/mL). All the other determinations were negative. The patient with the abnormal TnT value, classified as New York Heart Association functional class III, had the lowest left ventricular ejection fraction value (29%) and the largest left ventricular diameter at diastole (77 mm) of all the patients studied. Because of the low percentage of positive determinations, test results could not be expressed in terms of sensitivity and specificity.

## DISCUSSION

In various studies carried out in patients with chronic heart failure using second generation assays for TnT determination, increased values were found in patients with acute left-ventricular dysfunction (mean ejection fraction 19%; range 14%-28%)<sup>9</sup> and in patients hospitalized for non-chagasic heart failure.<sup>10</sup> For both TnT and troponin I, correlations were found with severity of heart failure and decreased ejection fraction.<sup>10,11</sup>

As in other types of heart disease, the slow progression of chagasic cardiomyopathy involves a process of myocardial remodeling. Histologically, however, it differs from other cardiomyopathies in certain aspects. In chagasic heart disease, there is a higher, denser accumulation of extracellular collagen surrounding the muscle fiber groups, and moderate to severe chronic inflammatory infiltrate is more frequent and follows a multifocal pattern. The presence of microvascular alterations, such as capillary and arteriolar dilation, can lead to local ischemia and fibrosis.<sup>12-14</sup> Moreover, apoptosis of the cardiac muscle fibers does not occur as frequently as in other cardiomyopathies,<sup>15</sup> and it has been suggested that the main mechanism of cell death may be necrosis.<sup>16</sup> All these histologic markers are present, though at different levels of intensity, in all phases of the chronic stage of Chagas disease, even in the indeterminate.<sup>12,13</sup> Since TnT is a cytosolic enzyme that is released with cell membrane damage,<sup>4</sup> its serum values would be expected to be increased at any phase of the chronic period. Nevertheless, in our study using a highly sensitive test, only one patient with advanced chagasic cardiomyopathy presented elevated TnT concentrations.

In conclusion, serum TnT concentration appears to have little value as an early marker of myocardial lesion in patients with positive serology for Chagas disease.

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