ORIGINAL ARTÍCLE

C-Reactive Protein and Interleukin-6 Serum Levels Increase as Chagas Disease Progresses Towards Cardiac Failure

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Introduction and objectives. Chagas disease is the most common cause of myocarditis in Latin America, including Venezuela. Some 25% of patients progress to chronic chagasic cardiomyopathy, which is characterized by heart failure and arrhythmias. The serum levels of C-reactive protein (CRP) and interleukin-6 (IL-6) have prognostic value in non-chagasic cardiopathy. The goal of this study was to investigate the relationship between the serum levels of CRP and IL-6 and the developmental stage of Chagas disease.

Patients and methods. The study included 64 Chagas disease patients (34 female and 30 male; age 62.2 [1.7] years) and 20 healthy individuals (10 of each sex; age 50.4 [2.7] years). Clinical investigations included echocardiography and measurement of CRP and IL-6 serum levels using ELISAs. Chagas disease patients were graded according to Carrasco et al 1994 classification. Patients with ischemic cardiopathy, liver disease, autoimmune disease, a systemic inflammatory condition, immunosuppression, cancer, pericarditis, or endocarditis were excluded.

Results. Multiple regression analysis demonstrated an association between Chagas disease developmental stage and the serum IL-6 level. The serum CRP level increased during only the most advanced phase of the disease. In addition, a high left ventricular mass index was associated with a high IL-6 level and male sex.

Conclusions. IL-6 and CRP serum levels could be of prognostic value in assessing Chagas disease progression because there are significant correlations between elevated levels and the deterioration of cardiac function.

Key words: *Chagasic cardiomyopathy. C-reactive protein. Interleukin-6.*

Las concentraciones séricas de interleucina-6 y proteína C reactiva se incrementan a medida que la enfermedad de Chagas evoluciona hacia el deterioro de la función cardíaca

Introducción y objetivos. La enfermedad de Chagas (EC) es la causa de miocarditis más común en América Latina y Venezuela. El 25% de los pacientes evoluciona hacia una miocardiopatía chagásica crónica (MCC), caracterizada por insuficiencia cardíaca y arritmias. La proteína C reactiva (PCR) y la interleucina-6 (IL-6) tienen valor pronóstico en las cardiopatías no chagásicas. En este estudio se ha determinado la relación entre las concentraciones de PCR e IL-6 y la fase evolutiva de la EC.

Pacientes y método. Se incluyó a 64 pacientes con EC (34 mujeres y 30 varones; edad: 62,2 ± 1,7 años) y a 20 individuos sanos (10 de cada sexo; edad: 50,4 ± 2,7 años); en todos ellos se realizaron una valoración clínica, una ecocardiografía y la determinación de las concentraciones séricas de PCR e IL-6 mediante ELISA. Los pacientes fueron clasificados según Carrasco et al (1994). Se excluyó a los pacientes con cardiopatía isquémica, hepatopatías, enfermedades autoinmunitarias, procesos inflamatorios, neoplasias, inmunodepresión, pericarditis y endocarditis.

Resultados. El análisis de regresión múltiple mostró una asociación entre la fase evolutiva de la EC y las concentraciones de IL-6, mientras que los valores elevados de PCR sólo estuvieron asociados con la fase más avanzada de la EC. Adicionalmente, se observó un mayor índice de masa del ventrículo izquierdo asociado con valores elevados de IL-6 y el sexo masculino.

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ABBREVIATIONS

CCC: chronic Chagas cardiomyopathy.
CRP: C-reactive protein.
ELISA: enzyme-linked immunoassay.
IL: interleukin.
LVMI: left ventricular mass index.

Conclusiones. Los valores de IL-6 están correlacionadas con la fase evolutiva y los de PCR con las formas más graves de la EC; ambos podrían ser considerados marcadores pronósticos de la MCC.

Palabras clave: *Miocardiopatía chagásica. Proteína C reactiva. Interleucina-6.*

INTRODUCTION

Chagas disease, or American trypanosomiasis, is a parasitic tissue and blood infection caused by a flagellate protozoan known as *Trypanosoma cruzi* and transmitted to humans and other mammals by hematophagous, hemipterous insects from the *Triatominae* subfamily.[1]

Chagas disease is the most common tropical disease and cause of myocarditis in Venezuela and Latin America. Ninety million people are presently at risk for the disease and 24.7 million are already infected. Among the latter it is estimated that 25% (6.2 million) will develop a chronic Chagas cardiomyopathy (CCC) characterized by congestive heart failure, complex cardiac arrhythmia, occupational disability, and sudden death.[2,3] The condition affects the poorest strata of rural communities, with poverty a risk factor for contracting the disease and developing complications. In Venezuela, the prevalence of Chagas disease in rural areas ranges from 3% to 8.3%,[4] with 936 deaths due to CCC reported in 1996.[5]

In recent years, inflammation has been shown to play a key role in both the genesis of CCC and the progression of the disease. During the first week of the acute phase, this response is characterized by polyclonal B-cell activation, followed by immunodepression at 6 weeks, accompanied by maximum parasitemia[6]; the main immunodepressive defect is a lack of interleukin-2 (IL-2) production and a reduction in the expression of its membrane receptors.[7]

The acute cellular and humoral response is not capable of eliminating the intracellular parasite and therefore, *T cruzi* will persist in the myocardium. Interferon-gamma is thought to be a protective lymphokine against *T cruzi* infection, with an effect mediated by the release of free radicals, including nitric oxide. Interferon-gamma concentrations are regulated by IL-4, IL-10, and transforming growth factor-beta (TGF-beta), inhibiting the activity of TH1 cells and thus disrupting the control of intracellular *T cruzi* infection. Tumor necrosis factor-alpha (TNF-alpha) has been implicated in resistance to parasitic infection; however, it has also been related to tissue damage.[8]

Inflammation plays a key role as Chagas disease progresses toward CCC. The inflammatory cells, which are indirectly activated, result in increased synthesis of acute phase reactants, which are sensitive markers and can have prognostic value regarding the progression of the disease.[3] C-reactive protein (CRP) and IL-6 are considered to be potential markers of myocardial injury induced by *T cruzi*.[6]

C-reactive protein has been associated with acute coronary syndromes and with the evolution of patients following an acute myocardial infarction. A number of studies have demonstrated the predictive value of serum CRP concentrations and have related CRP levels with future atherothrombotic events, including coronary events, infarctions, and progression of peripheral vascular disease.[9] Serum CRP concentrations have also been shown to increase in children infected with *T cruzi* during the acute phase,[10,11] but not in the chronic phase[11,12] of Chagas disease.

IL-6 is a key inflammatory factor, with secretion activated by CRP, and has been implicated in the pathogenesis and progression of cardiovascular diseases.[13] The presence of elevated circulating concentrations of IL-6 in patients with heart failure, and serum levels of this marker correlate with the severity of left ventricular dysfunction. Likewise, increased IL-6 expression in cardiac tissue has been associated with progression of heart failure.[13]

T cruzi infection in experimental animal models results in elevated serum and tissue IL-6 values[14] induced during the progressive phase of the parasitemia, namely, the acute period of Chagas disease[15]; the transialidase enzyme of *T cruzi* is the highest inducer of IL-6 secretion.[16] The relationship between IL-6 and the development of CCC is still not clear, and the results of animal studies are contradictory.[14,16]

Only 25% of patients with Chagas disease develop CCC.[2,3] A crucial aspect in the treatment of these patients would be the availability of biochemical markers able to predict disease progression. The present research analyzes CRP and IL-6 concentrations in patients with Chagas disease in order to correlate them with the progression of cardiac involvement.

PATIENTS AND METHODS

A cross-sectional analytical study was conducted in patients previously diagnosed with Chagas disease who came to the Chagas outpatient clinic at the Centro

Cardiovascular Regional ASCARDIO and the Escuela de Medicina Pablo Acosta Ortiz (Universidad Centroccidental Lisandro Alvarado) in Barquisimeto, Estado Lara, Venezuela.

The nonprobabilistic sample was composed of 64 nonconsecutive patients of both sexes. Chagas disease was confirmed by 3 serological tests: direct agglutination, immunofluorescence, and enzyme-linked immunoassay (ELISA), according to previously established protocols,[17] and patients with 2 or more positive assays were accepted as positive.

The patients were classified according to the 3 phases proposed by Carrasco et al (1994):[18] Phase I (n=24), asymptomatic patients with no electrocardiographic or echocardiographic evidence of cardiac involvement; Phase II (n=20), asymptomatic patients with electrocardiographic or echocardiographic evidence of cardiac involvement; and Phase III (n=20), patients with heart failure.

The exclusion criteria were: *a*) patients with acute or chronic ischemic heart disease defined as a confirmed history of anterior or recent myocardial infarction, history of angina pectoris and/or positive stress test or stress echocardiogram for ischemia, or cardiac catheterization indicative of coronary artery disease; *b*) patients with acute or chronic liver disease; *c*) patients with acute or chronic inflammatory processes (e.g., rheumatoid arthritis, collagen disease, vasculitis, or cancer) and acute or chronic infections (e.g., endocarditis, pneumonia, and/or tuberculosis); *d*) patients who are immunosuppressed or receiving corticoid therapy; *e*) patients with non-Chagas acute or recurrent pericarditis; and *f*) patients with primary valve disease due to disorders that are congenital or secondary to infectious processes (e.g., rheumatic fever and/or endocarditis).

The study also included a control group of 20 individuals over age 18 with no history or serological evidence of Chagas disease or other heart condition.

In keeping with the standards of the Centro Cardiovascular Regional ASCARDIO Institutional Review Board, which are based on the Declaration of Helsinki amended in 1996, all patients underwent a clinical history, chest x-ray, echocardiogram, hematological testing, and blood biochemistry. Serum CRP and IL-6 concentrations were determined using commercial ELISA kits (VITRO 250, Johnson & Johnson, for CRP and Diaclone Research, for IL-6).

Statistical Analysis

After determining the respective descriptive statistics for characterizing the final sample, the multiple linear regression models used to relate the IL-6 and CRP values to the phase of Chagas disease were considered. The Kolmogorov-Smirnov test showed that the distribution of the levels of the mediators cited was not Gaussian and therefore, logarithmic transformation of the levels of these mediators prior to inclusion in the respective models was performed. The following variables were included in the regression analysis: Chagas disease phase, sex, age, heart failure, hypertension, diabetes mellitus, and dyslipidemia.

The following equation was used for each model:

$$Y=\beta_0+\beta_1X_1+\beta_2X_2+\beta_3X_3+\ldots+\beta_nX_n$$

in which Y (IL-6 or CRP values) was correlated to each variable combination; β_n represents the regression coefficients, subindices 1 to n, each respective variable being analyzed; subscript 0, the independent term or baseline value (intercept) and X_n, the value of each variable. The variable values (X_n) were determined as follows: dichotomous variables, such as sex or presence of the diseases mentioned above, were considered dummy variables and assigned values of 1 (male sex, presence of each particular disease) or 0 (female sex, absence of each disease). Since age is a numeric value with approximately normal distribution, it was used without transformations. The progressive phases of Chagas heart disease were also included in the regression models as dummy variables, with 0 and 1 used to represent the absence or presence of a particular phase. The control group included individuals without Chagas disease. Backward elimination was used to exclude variables with no significant effect.

Results are expressed as mean ± standard error or 95% confidence interval (95% CI). Statistical significance was set at P=.05. Statistix 1.0 and Prism 3.0 were used for the statistical analysis.

RESULTS

The average age of the participants was 50.4±2.7 years for the population of healthy volunteers and 62.2±1.7 years for seropositive patients. The average age of patients according to phase of Chagas disease was as follows: Phase I, 56.9±3.0; Phase II, 62.7±2.7, and Phase III, 68.3±2.2 years, respectively, with a significant difference observed in Phase II and III patients versus the control group and Phase I patients (Table 1). The multiple regression analysis (see below) found no correlation between age and status of Chagas disease progression.

Distribution according to sex was similar in both study groups, with a significant decrease in the proportion of women as the disease progressed and a higher proportion of men in Chagas Phases II and III (Table 1). However, the multiple regression analysis (see below) did not disclose any correlation between sex and the phase of Chagas disease.

In the means calculated for the echocardiographic parameters (Table 2), in particular, left ventricular end-diastolic diameter, left ventricular end-systolic

TABLE 1. **Age, Sex, and Serum Interleukin-6 and C-Reactive Protein Values in Healthy Individuals and in Phases I, II, and III Patients With Chagas Disease***

Experimental Groups	Age, years	Sex		IL-6 (% pg/mL)	CRP (mg/dL)
		Men	Women		
Control	50.4±2.7	10	10	0.8±0.1	0.2±0.05
Phase I	56.9±3.0	6	18	3.3±0.7	0.1±0.06
Phase II	62.7±2.7	11	9	3.8±1.2	0.5±0.3
Phase III	68.3±2.2	13	7	11.2±3.8	4.0±1.4

*IL-6 indicates interleukin-6; CRP, C-reactive protein.

TABLE 2. **Echocardiographic Parameters in Patients With Chagas Disease According to Stage***

Echocardiographic Parameter	Phase of Chagas Disease		
	Phase I	Phase II	Phase III
LVEDD, mm	49.0±0.8	51.2±0.8	60.1±1.33†
LVESD, mm	31.9±0.8	35.5±1.3	44.4±1.2t
Shortening, %	30.9±1.6	29.0±1.6	28.1±2.1
LVEDV, mL	99.2±3.9	140.5±5.5	195.0±13.1t
LVESV, mL	44.0±4.6	50.2±4.0	104.2±10.6t
EF, %	62.3±1.6	56.1±2.2	38.0±3.2†
LA, mm	32.7±0.7	32.3±1.0	44.5±1.3†
RV, mm	14.0±0.7	14.9±1.0	18.6±1.4†
LVM, g	265.9±18.5	329.3±29.7	427.5±29.6t
LVMI, g/m^2 SC	111.8±4.6	130.0±11.2	244.3±14.1†

*LA indicates diastolic diameter of the left atrium; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; EF, ejection fraction; LVMI, left ventricular mass index; LVM, left ventricular mass; RV, right ventricular diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.
†P<.05 with respect to Phases I and II.

diameter, left atrial diastolic diameter, right ventricular diastolic diameter which indicate chamber dilation, significant quantitative increases were confirmed with respect to the degree of the disease (P<.05). An assessment of left ventricular end-diastolic volume and left ventricular end-systolic volume showed a significant increase (P<.05) as the disease progressed. The ejection fraction was inversely proportionate to the phase of disease progression; the parameters measuring dilation and cardiac remodeling (e.g., left ventricular mass and left ventricular mass index, LVMI), showed similar alterations, with direct changes according to the phase of the disease, which were only significant in the most advanced phase.

Mean absolute CRP values in the study group showed a significant progressive increase (P<.005) in Phase I (0.1±0.06 mg/dL), Phase II (0.5±0.3 mg/dL), and Phase III (4.0±1.4 mg/dL), respectively, with a substantial, significant difference in serum values between patients with Phase III Chagas disease and those with Phases I or II. The control group expressed similar mean values (0.19±0.05) to those of Phase I patients (Table 1).

Mean IL-6 values for the controls and Chagas patients showed that lower values in the control group (0.8±0.1 pg/mL); conversely, patients with Chagas disease showed significant serum IL-6 increases (P<.05) according to the phase, with values of 3.3±0.7, 3.8±1.2, and 11.2±3.8 pg/mL for Phases I, II, and III, respectively (Table 1).

Multiple regression analysis relating Chagas phase to serum IL-6 concentrations (analyzing the variables of age, sex, diabetes mellitus, hypertension, heart failure, and dyslipidemia), confirmed the hypothesis that IL-6 values show a significant correlation to disease phase (Table 3). Backward elimination of nonsignificant variables yielded an intercept with a coefficient of –0.4 (95% CI, –0.6 to –0.3) and P=.0003, Phase I showed a coefficient of 0.7 (95% CI, –0.4 to –0.9) and P<.0001, Phase II showed a coefficient of 0.8 (95% CI, –0.5 to –0.9) and P<.0001, Phase III showed a coefficient of 1.2 (95% CI, –0.9 to –1.3) and P<.0001. C-reactive protein correlated only to Chagas Phase III (Table 4), obtaining intercept values of –1.2 (95% CI, –1.5 to –1.1) and P<.0001, for Phase III of 1 (95% CI, 0.5-1.2) and P=.0001.

Finally, a multiple regression analysis was performed between values for the functional variables obtained from echocardiographic studies and serum IL-6 and CRP values, taking into consideration the intervening variables. The results showed that LVMI was associated with male sex, Phase III disease, and IL-6 values (Table 5 and Figure).

Although the simple correlation analyses showed a positive correlation between IL-6 or CRP and LVMI, a negative correlation between IL-6 or CRP and the ejection fraction, as well as between IL-6 and BMI, the multiple regression analysis did not confirm these results.

DISCUSSION

In the control groups and in patients with Chagas disease, a similarity was observed with regard to the sex of the individuals, thus supporting the validity of the sample; nevertheless, there was a predominance of men in the more advanced phases of the disease (Table 1). However, the multiple regression analysis found no

TABLE 3. **Relationship Between the Phase of Chagas Disease and Interleukin-6 Values. Multiple Linear Regression Analysis***

Variable	Coefficient	95% CI	*P*
Intercept	–0.409	–0.924 to 0.106	.124
Age, years	0.001	–0.008 to 0.0105	.764
Male	–0.128	–0.366 to 0.110	.295
Diabetes mellitus	–0.136	–0.549 to 0.278	.523
Hypertension	–0.118	–0.348 to 0.113	.321
Congestive heart failure	0.111	–0.420 to 0.642	.684
Dyslipidemia	0.284	–0.003 to 0.570	.056
Phase I	0.690	0.358 to 1.024	.0001
Phase II	0.761	0.421 to 1.101	<.0001
Phase III	1.114	0.562 to 1.665	.0002

*Logarithmic transformation was used to normalize the data; only significant variables remaining after backwards elimination are shown.

TABLE 4. **Relationship Between the Phase of Chagas Disease and CRP Values. Multiple Linear Regression Analysis***

Variable	Coefficient	95% CI	*P*
Intercept	–1.141	–2.107 to –0.174	.024
Age, years	–0.002	–0.002 to –0.01	.782
Male	0.093	–0.35 to 0.54	.684
Diabetes mellitus	–0.037	–0.81 to 0.74	.925
Hypertension	–0.002	–0.44 to 0.43	.994
Dyslipidemia	–0.063	–0.60 to 0.48	.820
Phase I	–0.100	–0.73 to 0.53	.756
Phase II	–0.014	–0.65 to 0.62	.966
Phase III	1.620	0.59 to 2.66	.003

*Logarithmic transformation was used to normalize the data; only significant variables remaining after backwards elimination are shown.

TABLE 5. **Multiple Regression Analysis Between Left Ventricular Mass Index and Interleukin-6 Values***

Variable	Coefficient	95% CI	*P*
Intercept	94.51	76.2-112.78	<.001
IL-6 (log)	42.41	15.47-69.35	.0031
Male	36.41	14.75-58.07	.0017
Phase III of Chagas disease	92.62	66.40-118.84	<.001

*Only significant variables remaining after backwards elimination are shown. Adjusted r^2=0.66; n=64.

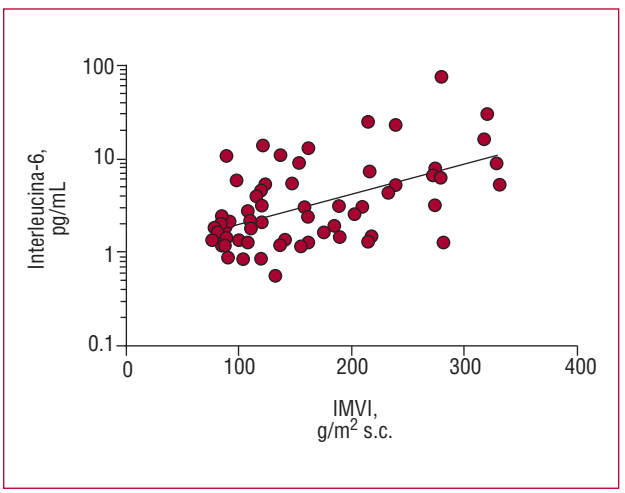

Figure. Relationship between left ventricular mass index (LVMI) and serum interleukin-6 (IL-6) concentrations in patients with Chagas disease.
IL-6 values are shown in logarithmic scale, with the line representing the antilogarithm of the points that defined the linear regression obtained when plotting the line of logarithmic values of IL-6 based on the dependent variable.

correlation between Chagas phases and either age or sex. Male sex in Chagas cardiomyopathy is a factor of poor prognosis, with a higher overall mortality among men between age 30 and 59, a finding that has been related to a higher frequency of electrocardiographic abnormalities.[19]

The controls and the patients with Phase I disease had basically the same characteristics in terms of age, whereas the patients with Phases II and III showed significant differences when compared to both the control group and Phase I group. Studies show that the onset of the clinical symptoms of Chagas disease occurs around age 40, with an estimated average of 6 to 12 years elapsing before the patient reaches Phase II and an identical period occurring in most cases until Phase III is reached.[20]

Various authors support the theory that the chronic inflammatory mechanisms of Chagas cardiomyopathy are due to autoimmune processes in the host. The cells involved in the autoimmune process are modulators of CRP and interleukin production, which could trigger the cascade of focal or generalized inflammatory responses.[21]

An assessment of plasma CRP concentrations in patients with Chagas disease according to phase and in the controls showed a clear, significant increase among Phase III patients. This difference suggests that inflammatory changes are present and active during the more advanced stage of the disease. The presence of inflammatory foci and myocyte necrosis due to lymphocyte migration has been described in Chagas disease, even in the presence of a low degree of parasitism.[22] The inflammatory foci may be the result of microcirculation changes, which cause ischemic alterations followed by fibrosis and myocardial remodeling.[23]

Serum CRP concentrations increase during the acute phase of Chagas disease[10,11]; however, elevated values in

the chronic stage[11,12] have not been reported, something apparently not consistent with the findings observed in this research. Nevertheless, the investigations cited were conducted with individuals in an indeterminate stage of Chagas disease, which would correspond to Phases I and II of our study, in which we were unable to find statistically significant CRP increases.

T cruzi infection in experimental animal models leads to elevated serum and tissue IL-6,[14] which is induced during the increasing stage of parasitemia in the acute period of Chagas disease.[15] It has been postulated that the main inducer of IL-6 in *T cruzi* infection is the enzyme transialidase of the parasite itself.[16] The relationship between IL-6 and the development of CCC is still unclear and contradictory; for instance, transgenic mice that do not express IL-6 present greater parasitemia and die earlier than wild strains.[14] On the other hand, animals sensitized with *T cruzi* transialidase and therefore, with elevated IL-6 values are also more susceptible to invasion by the parasite.[16] In the present study, multiple regression analysis showed that the IL-6 values were associated with the progressive phases of Chagas disease, indicating that the values of this cytokine might increase as the disease progresses, thus contributing to the progression of the myocardial damage.

Sato et al (1999)[24] showed that IL-6 has a negative ionotropic effect which induces a hypocontractile state in the myocardium. These investigators have also shown that plasma IL-6 concentrations are higher in the decompensated stage of heart failure syndrome compared to the recovery stage.

Petretta et al (2000)[25] correlated IL-6 concentrations to the functional class of patients with heart failure syndrome and found that IL-6 concentrations were progressively higher with a higher functional class (NYHA). This study concludes that IL-6 determination provides a more accurate indication of hemodynamic deterioration among patients with heart failure.

Lastly, the multiple regression analysis revealed that plasma IL-6 concentrations are related to the echocardiographic parameter LVMI and to male sex. Left ventricular mass index reflects the cellular remodeling that leads to chamber dilation and, secondarily, to ejection alterations. The relationship between IL-6 and higher LVMI in male patients could help explain the worse prognosis of these patients in Chagas disease.

CONCLUSIONS

Elevated IL-6 concentrations were related to the phase of Chagas disease, indicating that once these patients have progressed beyond the acute phase, they experience a chronic inflammatory process, which becomes more severe with progression to Phase III status. This suggests an increase in the cell injury that leads to deterioration of cardiac function, with men being more prone to cell injury mediated by this pathophysiological mechanism. C-reactive protein elevation appears to occur later and be related to progression toward Phase III and functionally to heart failure, which would reflect recurrence of the acute inflammatory process. According to the data obtained from the statistical analyses regarding the concentrations of these plasma proteins and the phase of the disease, IL-6 could be used in the future as a prognostic marker in patients with this disease. However, the type of design used does not allow us to state that the markers precede disease progression; a long-term prospective cohort study with a consecutive sample would, therefore, be needed. The implications of these findings may suggest that new guidelines should be established for the stratification of patients with Chagas disease and guide therapeutic strategies that might change the prognosis and survival of these patients.

REFERENCES

1. Rassi A, Tranchesi J, Tranchesi B. Doença de Chagas. In: Veronesi A, editor. Doenças infecciosas parasitarias. Río de Janeiro: Guanabara Koogan, 1991. p. 674-705.
2. Moncayo A. Chagas' disease: current epidemiological trends after the interruption of vectorial and transfusional transmission in the southern cone countries. Mem Inst Oswaldo Cruz. 2003; 98:577-91.
3. Marin Neto JA, Simoes MV, Sarabanda AV. Chagas' heart disease. Arq Bras Cardiol. 1999;72:247-80.
4. OPS/OMS Venezuela. Análisis preliminar de la situación de salud de Venezuela. OPS/OMS Representación para Venezuela, Aruba y Antillas Holandesa, 2002 [17 screens]. Available from: http://www.ops-oms.org.ve/site/venezuela/ven-sit-salud-nuevo.htm
5. Ministerio de Sanidad y Asistencia Social, República de Venezuela. Caracas: Anuario Epidemiológico y Estadística Vital; 1996. p. 294-6.
6. Cardoni RL. Inflammatory response to acute *Trypanosoma cruzi* infection. Medicina (Buenos Aires). 1997;57:227-34.
7. Briceno L, Mosca W. Defective production of interleukin 2 in patients with Chagas' disease. Purified IL-2 augments in vitro response in patients with chagasic cardiomyopathy. Mem Inst Oswaldo Cruz. 1996;91:601-7.
8. Laucella SA, Rottenberg ME, de Titto EH. Role of cytokines in resistance and pathology in *Trypanosoma cruzi* infection. Rev Argent Microbiol. 1996;28:99-109.
9. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest. 2003;111:1805-12.
10. Medrano NM, Luz MR, Cabello PH, Tapia GT, Van Leuven F, Araujo-Jorge TC. Acute Chagas' disease: plasma levels of alpha-2-macroglobulin and C-reactive protein in children under 13 years in a high endemic area of Bolivia. J Trop Pediatr. 1996;42:68-74.
11. Medrano-Mercado N, Luz MR, Torrico F, Tapia G, van Leuven F, Araujo-Jorge TC. Acute-phase proteins and serologic profiles of chagasic children from an endemic area in Bolivia. Am J Trop Med Hyg. 1996;54:154-61.
12. Cetron MS, Basilio FP, Moraes AP, Sousa AQ, Paes JN, Kahn SJ, et al. Humoral and cellular immune response of adults from

northeastern Brazil with chronic *Trypanosoma cruzi* infection: depressed cellular immune response to *T. cruzi* antigen among Chagas' disease patients with symptomatic versus indeterminate infection. Am J Trop Med Hyg. 1993;49:370-82.
13. Kanda T, Takahashi T. Interleukin-6 and cardiovascular diseases. Jpn Heart J. 2004;45:183-93.
14. Gao W, Pereira MA. Interleukin-6 is required for parasite specific response and host resistance to *Trypanosoma cruzi*. Int J Parasitol. 2002;32:167-70.
15. Truyens C, Angelo-Barrios A, Torrico F, Van Damme J, Heremans H, Carlier Y. Interleukin-6 (IL-6) production in mice infected with *Trypanosoma cruzi*: effect of its paradoxical increase by anti-IL-6 monoclonal antibody treatment on infection and acute-phase and humoral immune responses. Infect Immun. 1994;62: 692-6.
16. Saavedra E, Herrera M, Gao W, Uemura H, Pereira MA. The *Trypanosoma cruzi* trans-sialidase, through its COOH-terminal tandem repeat, upregulates interleukin 6 secretion in normal human intestinal microvascular endothelial cells and peripheral blood mononuclear cells. J Exp Med. 1999;190:1825-36.
17. Añez N, González N, Crisante G, Rojas A, Premoli G, Ramírez JL, et al. Curso Taller: Pruebas confirmatorias en el diagnóstico de la enfermedad de Chagas. XVIII Jornadas José Witremundo Torrealba. San Carlos, Venezuela, 1999.
18. Carrasco HA, Parada H, Guerrero L, Duque M, Durán D, Molina C. Prognostic implications of clinical, electrocardiographic and hemodynamic findings in chronic Chagas' disease. Int J Cardiol. 1994;43:27-38.
19. Basquiera AL, Sembaj A, Aguerri AM, Omelianiuk M, Guzmán S, Moreno Barral J, et al. Risk progression to chronic Chagas cardiomyopathy: influence of male sex and of parasitaemia detected by polymerase chain reaction. Heart. 2003;89:1186-90.
20. Acquatella H, Catalioti F, Gómez-Mancebo JR, Davalos V, Villalobos L. Long-term control of Chagas disease in Venezuela: effects on serologic findings, electrocardiographic abnormalities and clinical outcome. Circulation. 1987;76:556-62.
21. Milei J, Stornino R, Jorg M, Chiale P, Schetjman D, Sterin-Borda E, et al. Patogenia. En: Storino R, Milei J, editores. Enfermedad de Chagas. Buenos Aires: Editorial Doyma Argentina S.A.; 1994. p. 103-28.
22. Cunha-Neto E, Kalil J. Autoimmunity in Chagas' heart disease. Sao Paulo Med J. 1995;113:757-66.
23. Rossi MA. Microvascular changes as a cause of chronic cardiomyopathy in Chagas' disease. Am Heart J. 1990;120:233-6.
24. Sato Y, Takatsu Y, Kataoka K, Yamada T, Taniguchi R, Sasayama S, et al. Serial circulating concentrations of C-reactive protein, interleukin (IL)-4, and IL-6 in patients with acute left heart decompensation. Clin Cardiol. 1999;22:811-3.
25. Petretta M, Condorelli GL, Spinelli L, Scopacasa F, De Caterina M, Leosco D, et al. Circulating levels of cytokines and their site of production in patients with mild to severe chronic heart failure. Am Heart J. 2000;140:E28.