

# ORIGINAL ARTICLE

## Chagas disease, a risk factor for high blood pressure

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### Abstract

**Background.** Chagas disease is a parasite infection caused by the protozoan *Trypanosoma cruzi*. Its most common complications is chronic Chagas heart disease but impairments of the systemic vasculature also has been observed. Although the different mechanisms that regulate blood pressure are disrupted, to our knowledge data on the association of hypertension and chronic Chagas disease are scarce. In this regard we evaluate whether Chagas disease constitutes a high blood pressure risk factor. **Materials and methods.** We recruited 200 individuals, half of them with positive serology for *T. cruzi*. They were subjected to a complete clinical examination. **Results.** The mean age of sampled individuals was  $46.7 \pm 12.3$ , and the mean of systolic and diastolic blood pressure were  $124 \pm 12$  mmHg and  $82 \pm 10$  mmHg, respectively. There were no between-group differences regarding age, sex distribution or body mass index. Chagas disease contributed significantly to high blood pressure (OR = 4, 95% CI 1.8323–7.0864,  $p = 0.0002$ ). **Conclusion.** Our results reveal an important association between Chagas disease and high blood pressure, which should be contemplated by physicians in order to promote preventive cardiovascular actions in patients with Chagas disease.

**Key Words:** Association, blood pressure, Chagas disease, hypertension, risk factor, vascular disease

### Introduction

Chagas disease is a chronic zoonosis caused by the protozoan *Trypanosoma cruzi*, with a worldwide distribution affecting at least 8–10 million people throughout South and Central America, USA and Europe. The disease evolves from a frequently oligo-symptomatic acute phase lasting a few weeks, which is the indeterminate form of chronic Chagas disease, characterized by circulating antibodies against *T. cruzi*, no electrocardiographic changes and normal radiological examination of the chest, esophagus and colon. The asymptomatic period of chronic infection lasts for many years, but 30–40% of patients subsequently develop chronic Chagas heart disease (CCHD) that may cause approximately 50,000 deaths annually (1). It has been observed in animal models and in humans that *T. cruzi* also induces vascular lesions mediated principally by an increase

of the plasma levels of thromboxane  $A_2$  and endothelin-1, which cause vasoconstrictions and platelet aggregation (2–4). Both endothelin-1 and thromboxane  $A_2$  are implied in the pathogenic of arterial hypertension (5,6). Essential hypertension is the most common chronic asymptomatic disease in adults and it is the leading cause of attributable mortality. Its prevalence depends on the population studied, but it is estimated that about 27% of the worldwide population > 20 years old suffer of hypertension (7). Several reports mentioned that the frequency of hypertension in patients with Chagas disease is similar to that described in general populations; however, despite the proven vascular involvement in Chagas disease, to our knowledge data on the association of hypertension and chronic Chagas disease are scarce. In this regard, we evaluate whether Chagas disease constitutes a high blood pressure risk factor.

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## Materials and methods

The study received ethical approval from the Ethics Review Board of Universidad Nacional del Litoral. Informed consent was obtained from all patients.

### Sample population

We performed a case-control study including 100 non-chagasic individuals and 100 patients with positive serology for *T. cruzi* (enzyme-linked immunosorbent assay, indirect hemagglutination and indirect immunofluorescence) with no history of other cardiac diseases, renal disturbances, thyroid disease or any other systemic complaints, as well as treatment with anti-*T. cruzi* compounds or immunosuppressive drugs. Patients with dyslipidemia, diabetes and high intake of alcohol (defined by the World Health Organization as the daily intake of more than 70 g in men and 50 g in women) were also excluded. All the individuals were subjected to a complete clinical examination. Patient with Chagas disease then were categorized into three groups according to the CCHD classification (8): (i) CCHD stage I, i.e. normal radiological studies, ECG and ECHO, (ii) CCHD stage II, i.e. with ECG alterations like left anterior divisional block, right bundle branch block, total atrioventricular block, left or right bundle branch block, complex ventricular arrhythmias, and block of the anterosuperior division of the left branch; and (iii) CCHD stage III, showing dilated cardiomyopathy by ECHO. Patients in the CCHD stage III group were unaware of being infected with *T. cruzi* until they were admitted to the hospital because of heart failure. All individuals were recruited at the Clinical Service of the Iturraspe Hospital, Santa Fe, Argentina.

### Blood pressure assessment

The blood pressure assessment and the diagnosis of new cases of hypertension were done according to the recommendations of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. High blood pressure category included those patients with medical history of hypertension or individuals with pre-hypertensive values of blood pressure.

### Statistical analysis

Data were analyzed with MedCalc version 12.2.1. The data are expressed as means  $\pm$  SD or median and interquartile range. Normal distributions of the continuous variables were tested by Kolmogorov-Smirnov method. Chi-square test or Fisher's exact were used for categorical variables. A multiple binary logistic regression models were used to assess the impact of variables that were associated with high blood pressure. Confounders and independent risk

factors were included in the final logistic regression model. A  $p$ -value  $< 0.05$  was considered significant.

## Results

The mean age of sampled individuals was  $46.7 \pm 12.3$ , 60% were women, and the mean of systolic and diastolic blood pressures were  $124 \pm 12$  and  $82 \pm 10$  mmHg, respectively. Systolic and diastolic blood pressures were barely correlated with age ( $r = 0.2$ ,  $p < 0.01$ ). There were no between-group differences regarding age, sex distribution or body mass index (BMI). The incidence of high blood pressure was higher in the patients with Chagas disease compared with the control group, showing a clear association between Chagas disease and high blood pressure ( $p = 0.02$ ). Male gender and overweight were also associated with hypertension ( $p = 0.05$ ). The characteristics of the patients in each group are summarized in Table I.

According to the Storino classification, 39% of the patients with Chagas disease were CCHD stage I, 34% CCHD II and 27% CCHD stage III. There were no between-group differences regarding sex distribution or BMI, but patients from the CCHD stage III group were older than the others ( $p < 0.05$ ), and presented increased levels of systolic blood pressure [analysis of variance  $F$ -ratio: 9.02,  $p < 0.001$  (Student-Newman-Keuls test for all pairwise comparisons,  $p < 0.05$ )]. Hypertension was associated with heart failure due to Chagas disease ( $p = 0.02$ ).

Concerning the electrocardiographic alterations in patients with Chagas disease, left anterior divisional block with right bundle branch block ( $n = 12$ ), right bundle branch block ( $n = 7$ ) and atrial fibrillation associated with right bundle branch block ( $n = 7$ ) were the majors findings in CCHD II and CCHD III groups. Four patients from the CCHD II group presented sinus bradycardia, whereas two individuals from the CCHD III group have third degree atrioventricular block requiring pacemaker implantation. With regard to the subgroup of individuals with hypertension, eight individuals presented a positive Sokolow Index compatible with left ventricular hypertrophy. On the other hand, among the non-chagasic individuals, three patients presented isolated ventricular extrasystoles and two right bundle branch block. Only three patients with hypertension showed a positive Sokolow Index.

In relation to the echocardiogram pathological findings, two individuals from the CCHD II group presented concentric ventricular hypertrophy and four had apical septal hypokinesis without diastolic or systolic disturbance. Among the CCHD III group, most of the patient ( $n = 13$ ) presented globally dilated cardiomyopathy with reduced ejection fraction, seven had left atrial enlargement and abnormal left ventricular relaxation with diastolic heart failure, and

Table I. Characteristics of sampled individuals.

	Non-chagasic patients, <i>n</i> = 100	Patients with Chagas disease, <i>n</i> = 100	<i>p</i>
Age	51.6 ± 6.2	53.7 ± 11.4	NS
Gender ( <i>n</i> )			
Male	42	38	NS
Female	58	62	
Systolic blood pressure	121.3 ± 8.4	127.5 ± 13.3	0.0001 <sup>a</sup>
Diastolic blood pressure	82.1 ± 9.5	82.7 ± 9.7	NS
High blood pressure ( <i>n</i> )			0.02 <sup>b</sup>
Pre-hypertension	21	17	
Hypertension	13	34	
Serum lipids, mmol/L			NS
Total cholesterol	3.99 ± 0.6	4.13 ± 0.51	
HDL-cholesterol	1.2 ± 0.03	1.15 ± 0.06	
LDL-cholesterol	2.17 ± 0.51	2.38 ± 0.73	
Triglycerides	1.29 ± 0.17	1.33 ± 0.21	
BMI ( <i>n</i> )			NS
Normal	87	89	
Overweight	13	11	

Quantitative variables are expressed as means ± SD. <sup>a</sup>Patients with Chagas disease presented higher levels of systolic blood pressure. <sup>b</sup>The incidence of high blood pressure was higher in the patients with Chagas disease compared with the control group. NS, not significant; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index.

five had concentric ventricular hypertrophy with diastolic disturbance. Regarding the non-chagasic patient with hypertension group, three patients with electrocardiographic disturbances compatible with left ventricular hypertrophy showed this finding by echocardiogram.

As expected, overall association between hypertension with concentric ventricular hypertrophy was statically significant ( $p = 0.04$ ).

Considering age, sex, BMI, alcohol consumption, cigarette smoking and Chagas disease, we perform a multiple binary logistic regression model to assess the impact of variables that were associated with high blood pressure. Despite male gender and overweight were associated with hypertension ( $p = 0.05$ ), the Wald criterion demonstrated that only the variables age and Chagas disease made a significant contribution to prediction of high blood pressure (OR = 1, 95% CI 1.02–1.12,  $p = 0.002$  and OR = 3.4, 95% CI 1.75–6.84,  $p = 0.0003$ , respectively), with an area under the receiver operating characteristic curve of 0.76 (95% CI 0.69–0.82,  $p = 0.03$ ).

## Discussion

It is well known that *T. cruzi* infection promotes impairments of the systemic vasculature, particularly the microvasculature. In animal models, it was observed that the *T. cruzi* infection of the endothelium is usually associated with platelet-fibrin aggregates, and with the expression of pro-inflammatory cytokines, which leads to the presence of atherosclerosis (2,8). It has been previously reported that

*T. cruzi* triggers increased plasma levels of thromboxane  $A_2$  and endothelin-1 in mice and chronic chagasic patients (2,4,8,9), which might result in vascular injury and hypertension (5,6,10,11). However, a previous Argentinian study by Palmero et al. (12) found that patients with Chagas disease had lower pressure levels in comparison to the general population, regardless of the presence of heart failure, and our results describes an important association between Chagas disease and hypertension. An equal incidence of hypertension in Chagas disease has been reported as in the general population (13–16); however, our prevalence of high blood pressure is higher, similar to that recently described by Pompilio et al. (17).

In conclusion our results reveal an important association between high blood pressure and Chagas disease, whichs make a significant contribution to prediction of hypertension (OR = 3.4, 95% CI 1.75–6.84,  $p = 0.0003$ ). Although longitudinal studies are needed to ascertain this, physicians should contemplate whether *T. cruzi* infection induces the development of hypertension, in order to promote preventive cardiovascular actions in patients with Chagas disease.

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