Decreased Cardiopulmonary Baroreflex Sensitivity in Chagas’ Heart Disease

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Abstract—No study has been performed on reflexes originating from receptors in the heart that might be involved in the pathological lesions of Chagas’ heart disease. Our study was undertaken to analyze the role of cardiopulmonary reflex on cardiovascular control in Chagas’ disease. We studied 14 patients with Chagas’ disease without heart failure and 12 healthy matched volunteers. Central venous pressure, arterial blood pressure, heart rate, forearm blood flow, and forearm vascular resistance were recorded during deactivation of cardiopulmonary receptors. By reducing central venous pressure by applying −10 and −15 mm Hg of negative pressure to the lower body, we observed (a) a similar decrease of central venous pressure in both groups; (b) a marked increase in forearm vascular resistance in the control group but no increase in the Chagas’ group; and (c) no significant changes in blood pressure and heart rate. To analyze cardiopulmonary and arterial receptors, we applied −40 mm Hg of lower-body negative pressure. As a consequence, (a) central venous pressure decreased similarly in both groups; (b) blood pressure was maintained in the control group, whereas in patients with Chagas’ disease, a decrease in systolic and mean arterial pressure occurred; (c) heart rate increased in both groups; and (d) forearm vascular resistance increased significantly and similarly in both groups. Unloading of receptors with low levels of lower-body negative pressure did not increase forearm vascular resistance in patients with Chagas’ disease, which suggests that the reflex mediated by cardiopulmonary receptors is impaired in patients with Chagas’ disease without heart failure. Overall control of circulation appears to be compromised because patients did not maintain blood pressure under high levels of lower-body negative pressure. (Hypertension. 2000;36:1035-1039.)

Key Words: baroreflex ■ heart rate ■ autonomic nervous system ■ cardiovascular diseases ■ baroreceptors

Evidence is mounting that cardiopulmonary receptors modulate the reflex control of the circulation, providing tonic restraint of the sympathetic efferent activity to the peripheral vessels and to the heart. The receptors respond to cardiac filling pressure changes by activating reflexes that modify regional vascular resistance and alter the distribution of cardiac output.1 The cardiopulmonary baroreflex is impaired in some pathological states, such as arterial hypertension, neurocardiogenic syncope, ventricular hypertrophy, and heart failure, playing an important role in the autonomic dysfunction observed in these situations.2

Chagas’ disease, or American trypanosomiasis, is caused by the hemoflagellate Trypanosoma cruzi and is an important cause of heart disease in South and Central America. The pathological involvement of the heart in the chronic phase of Chagas’ disease is characterized by the presence of inflammatory infiltrates, focus of myocarditis, pericarditis, and periganglitis, associated with focal fibrosis, with a variable intensity.3 Several anatomopathology studies in experimental models and in human beings have shown conspicuous autonomic denervation in Chagas’ disease. Therefore, Chagas’ heart disease can be considered a natural model of intrinsic cardiac nervous system denervation.4 Physiological studies and pharmacological tests have demonstrated impairment in the parasympathetic and sympathetic control of the sinus node in chronic Chagas’ disease. This alteration was observed in different clinical manifestations of Chagas’ disease, such as the latent form, cardiac involvement with or without heart failure, and digestive “mega” syndromes.5 However, no study was performed on the reflex that originated in receptors localized in the heart that potentially might be involved in the pathological lesions observed in Chagas’ heart disease. Therefore, the purpose of this study was to determine whether cardiopulmonary baroreflex is compromised in Chagas’ heart disease by recording the reflex responses of circulation during the unloading of the cardiopulmonary baroreceptors. Accordingly, the systemic hemodynamic as well as the forearm blood flow (FBF) and resistance responses to decreases in venous return obtained with incremental negative pressure applied to the lower body were analyzed in patients with Chagas’ heart disease without heart failure.
TABLE 1. Baseline Values in Control and Chagas’ Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group</th>
<th>Chagas’ Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body surface index, g/m²</td>
<td>24.8±0.4</td>
<td>24.9±1.1</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>128.9±2.8</td>
<td>124.8±3.4</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>71.5±2.1</td>
<td>69.4±2.3</td>
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<tr>
<td>Mean blood pressure, mm Hg</td>
<td>91.3±2.2</td>
<td>88.4±2.7</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>65.1±1.9</td>
<td>61.9±3.2</td>
</tr>
<tr>
<td>CVP, mm Hg</td>
<td>7.4±1.5</td>
<td>6.6±1.0</td>
</tr>
<tr>
<td>FBF, mL/100 mL tissue per minute</td>
<td>2.6±0.3</td>
<td>2.5±0.3</td>
</tr>
<tr>
<td>FVR, units</td>
<td>41.3±3.9</td>
<td>42.6±4.1</td>
</tr>
</tbody>
</table>

Methods

Subjects
Fourteen patients with Chagas’ disease (5 men and 9 women) 41.5±1.5 years of age (mean±SEM) and 13 healthy volunteers (5 men and 8 women) 40.8±1.8 years of age (mean±SEM) were studied. On the basis of medical history and physical examination, all subjects were free of cardiovascular or other systemic disease, and none was receiving medication. Patients with Chagas’ disease had positive serological reactions to Chagas’ disease and were from different endemic regions of the disease. All subjects showed normal standard ECG, but all patients with Chagas’ disease exhibited 2 cardiac rhythm disturbances considered to be prevalent in Chagas’ heart disease (bradycardia, first-degree or second-degree atrial-ventricular heart blocks, complete or incomplete right bundle-branch block, left anterior fascicular block, ventricular and supraventricular arrhythmias). The left ventricular ejection fraction measured by Doppler echocardiography was 60% in all patients with Chagas’ disease. Written informed consent was obtained from all subjects before the study, and the Medical Ethics Committee of the University of São Paulo, Medical School, São Paulo, Brazil, approved the study protocol.

Experimental Protocol
On the morning of the experiments, the patients were taken to the Hemodynamic Laboratory for a central venous catheterization. A polyethylene catheter (Intracath, 16 gauge/24 in) was inserted percutaneously through an antecubital vein of the left arm and advanced under fluoroscopic vision in or near the right atrium. The catheter was kept patent by continuous drip (2 mL/h) of heparinized saline (2 U/mL). After that, the patients were brought to the Laboratory of Clinical Investigation of the Hypertension Unit. The subjects were positioned supine in a lower-body negative pressure (LBNP) chamber (Bioengineering Department, Heart Institute, University of São Paulo), with the chamber enclosing the subject’s legs with an airtight seal at the level of the iliac crests. The research laboratory was noise free, and lights were dimmed. Room temperature was controlled at 22°C, and the temperature of the LBNP chamber was constant throughout the study. All subjects rested for ≥30 minutes after being monitored and before data collection. The hemodynamic variables were continuously registered during a 3-minute baseline period and during the sequential application of LBNP at −10, −15, and −40 mm Hg. Each stimulus was applied for 3 minutes, and the stimuli were separated by a 10-minute interval.

Hemodynamic Measurements
Central venous pressure (CVP), arterial blood pressure, heart rate, and FBF were recorded simultaneously on a Gould strip-chart recorder (RS 3800, Gould Inc, Recording Systems Division) and on a computer (Gateway 2000 4DX2-66V) with a system for data analyses, CODAS (Computer Operated Data Acquisition Software: AT-CODAS; DATAQ, Instruments).

The CVP (mm Hg) was determined by connecting the central venous catheter to a Gould P23 D transducer, with zero reference estimated to the subjects’ midaxillary level in the fourth intercostal space. The arterial blood pressure was measured by a digital photoplethysmograph device capable of providing accurate beat-to-beat systolic and diastolic values (Finapress, Omeda 2300, Monitoring Systems). The heart rate was calculated from the analysis of the peak systolic interval of the arterial pressure curves obtained with Finapress. The FBF (mL/100 mL forearm volume per minute) was measured in the right arm by venous occlusion plethysmography, with a double-stranded mercury-in-Silastic strain gauge designed by Whitney. Briefly, the strain gauge was placed 5 cm distal the antecubital crease, and the arm was supported 10 cm above the heart level. The venous occlusion pressure was 35 to 40 mm Hg, and circulation to the hands was arrested by inflating a wrist cuff to the suprasystolic pressure (200 mm Hg) for 1 minute before limb blood

Figure 1. Reflex responses (Δ%) of FBF during different levels of LBNP in 13 normal volunteers (control) and in 14 patients with Chagas’ disease.

Entries are mean ± SE

* = significantly different (p< 0.05) from baseline values

# = significantly different (p< 0.05) between Chagas’ vs Control group
flow determination. Each FBF determination comprised 12 separated measurements performed at 10-second intervals (a 3-minute period). The FBF for each LBNP stage and baseline was calculated as the mean of all curves registered during the 3-minute registration period. Forearm vascular resistance (FVR) was calculated as mean arterial pressure/FBF and expressed as resistance units (U).

Statistical Analyses
All data were processed with SAS System software. Fisher’s exact test or χ² for categoric variables were used to compare baseline characteristics. Multiple ANOVA was used to test for group differences for baseline and continuous variables. Values of P<0.05 were considered significant. Results are presented as mean±SEM.

Results
Baseline Values
Baseline hemodynamic parameters of control and Chagas’ groups are shown in Table 1. The values of systolic, diastolic, and mean arterial blood pressures, heart rate, CVP, FBF, and FVR were similar in both groups at baseline.

Reflex Responses
LBNP at −10 and −15 mm Hg
In response to −10 and −15 mm Hg of LBNP, the decrease of CVP was similar in both groups (−2.4±0.2 versus −3.4±0.2 mm Hg at −10 LBNP and −3.5±0.3 versus −4.3±0.1 mm Hg at −15 LBNP, respectively for control and Chagas’ groups). The systolic, diastolic, and mean arterial pressure and heart rate did not change significantly compared with the baseline values in both groups (Table 2). The FBF in the control group showed a significant decrease that was proportional to the intensity of LBNP (−13.5±4.9% and −18.9±4.7%, respectively, at −10 and −15 LBNP). In contrast, in the Chagas’ group, the FBF did not decrease and even exhibited a tendency to increase compared with baseline (3.1±5.9% and 10.8±10.3%, respectively, at −10 and −15 LBNP) (Figure 1). The FVR increased significantly in the control group and proportionally to the intensity of LBNP (22.5±6.9% and 33.6±8.7, respectively, at −10 and −15 LBNP), whereas in the Chagas’ group, no significant changes were registered (3.9±5.9% and 0.9±6.7%, respectively, at −10 and −15 LBNP) (Figure 2).

LBNP at −40 mm Hg
Also at this level of LBNP, the CVP decreased similarly in both groups (−6.0±0.5 versus −6.3±0.1 mm Hg, respectively, to control and Chagas’ groups). However, the changes of arterial blood pressure were different in both groups. The values presented in Table 2 (mean of 3 minutes of LBNP application) demonstrated that in the control group the systolic and mean arterial pressures were similar to baseline values, but the diastolic blood pressure and heart rate had a significant increase. Otherwise, the Chagas’ group exhibited a significant fall in systolic and mean arterial pressure despite the fact that heart rate increased significantly, similar to the control group. The diastolic blood pressure also did not exhibit the increase observed in the control group. A separate analysis of the blood pressure and heart rate responses during the first 30 seconds of application of −40 mm Hg LBNP (data not shown) demonstrated that the control group exhibited an initial decrease in systolic blood pressure (−20 mm Hg) that was totally recovered, associated with a significant increase in the heart rate (15.1±2.8%). The Chagas’ group showed a similar initial fall in systolic blood pressure (−20 mm Hg), but although the heart rate had a significant increase (13.6±3.8%), the systolic blood pressure exhibited only a partial recovery, maintaining a lower level during the application of LBNP. In contrast to LBNP at −10 and −15 mm Hg, LBNP at −40 mm Hg produced a significant and similar decrease in the FBF in both groups (−24.7±6.3% versus −26.8±6.0%, respectively, for control and Chagas’ groups) (Figure 1). Also, the FVR increase was similar in both groups (55.8±11.2% versus 43.4±11.8%, respectively, for control and Chagas’ groups) (Figure 2).

![Figure 2. Reflex responses (Δ%)](image)

Entries are mean ± SE
* = significantly different (p<0.05) from baseline values
# = significantly different (p<0.05) between Chagas’ vs Control group

Figure 2. Reflex responses (Δ%) in FVR during different levels of LBNP in 13 normal volunteers (control) and in 14 patients with Chagas’ disease.

| TABLE 2. Cardiovascular Changes (ΔPercentile) in Control and Chagas’ Groups |
|-----------------------------|-----------------------------|-----------------------------|
| Variable                    | −10 mm Hg LBNP              | −15 mm Hg LBNP              | −40 mm Hg LBNP              |
| Systolic blood pressure, mm Hg | 0.1±1                       | −0.9±0.8                    | 0.5±0.8                     | −1.6±1.2                   | −0.6±1.3                    | −7±2.6*                     |
| Diastolic blood pressure, mm Hg | 0.5±0.7                     | 0.3±0.7                     | 0.5±0.7                     | 0.3±0.7                    | 7.4±1.4*                    | 1.1±2                       |
| Mean blood pressure, mm Hg  | 2.0±0.6                     | −0.2±0.8                    | 1±0.5                      | −0.6±1                    | 2.3±1.2                    | −3.9±2*                     |
| Heart rate, bpm             | 2.4±1.3                     | 0.8±0.9                     | 2.9±0.8                    | −0.3±1.6                  | 15.1±2.8*                   | 13.6±4*                     |
| FBF, mL/100 L per minute    | −13.8±5*                    | 3.1±6                       | −18.9±5*                   | 10.8±10                   | −24.7±6*                    | −26.8±6*                    |
| FVR, units                  | 22.5±7*                     | 3.9±6                       | 33.6±8*                    | 0.9±6.7                   | 55.8±11*                    | 43.4±12*                    |

Values are mean±SEM.
*Significantly different (P<0.05) from baseline values.
†Significantly different (P<0.05) between Chagas’ vs control groups.
Discussion

The main finding of this study is that the cardiopulmonary reflex control of FVR is impaired in patients with Chagas’ heart disease without heart failure. The similar decrease of the CVP at −10 and −15 mm Hg of LBNP indicates that the unloading of the receptors was equivalent in both groups. The fact that the decrease in the FBF and the increase in the FVR at −10 and −15 mm Hg were observed in the control group without significant changes in arterial blood pressure and heart rate suggests that the vascular responses were mainly due to the cardiopulmonary reflex. These data are in agreement with previous reports showing that the application of LBNP up to −20 mm Hg did not change the arterial blood pressure and consequently did not engage the arterial baroreceptors.1,7 However, on the basis of recent data, we cannot completely exclude the participation of the arterial reflexes in the vascular responses induced by low levels of LBNP. It has been demonstrated that nonhypotensive hypovolemia decreases the diameter and the hemodynamic response of the carotid artery8,9 and the area of the aortic pulse.10 Although the mechanical engagement of arterial baroreflex may be enrolled in our study, at this level of LBNP the cardiopulmonary baroreflex appears to exert the major influence. Therefore, the absence of the FVR to low levels of LBNP in the Chagas’ group suggest that cardiopulmonary reflex is depressed in these patients.

In this study, we were not able to determine which part of the cardiopulmonary reflex pathway is compromised. On the basis of clinical and Doppler echocardiography data, the patients with Chagas’ disease exhibited no heart failure. However, the ECGs of all patients exhibited alterations that are considered prevalent in the cardiac form of Chagas’ disease and are associated with a certain level of cardiac involvement by the disease.11 We can speculate that the cardiac involvement of Chagas’ disease (focus of myocarditis and fibrosis, pericarditis, periganglitis) also enrolls cardiac receptors, their afferent fibers, or both.3,4 It has been reported that patients who undergo heart transplantation, a cardiadenervated group, have deficient cardiopulmonary reflex control of FVR.12 Therefore, alterations at the level of the receptor/afferent fibers could play an important major role in the depressed cardiopulmonary reflex control presently observed.

We cannot rule out the participation of the central nervous system in the abnormal cardiopulmonary reflex control in Chagas’ disease. However, the involvement of the central nervous system in Chagas’ disease is rare and not intense, except in reactivation of T Cruzi infection in immunocompromised patients.13 Moreover, the normal response of FVR at intense levels of LBNP, −40 mm Hg, suggests that the sympathetic efferent fibers responsible for the vascular innervation are not impaired in Chagas’ disease. It is important to remember that no grossly anatomic lesions were described in the vessels of patients with Chagas’ disease.5

The hemodynamic responses of −40 mm Hg of LBNP in the control group were similar to those described previously.7 The mean arterial pressure was maintained close to the baseline values, with a small decrease in the systolic blood pressure and a significant increase in diastolic blood pressure associated with a significant increase in the heart rate. Although the Chagas’ patients showed no clinical symptoms or signs of low cardiac output during intense volume unloading, they exhibited a small but significant decrease in both systolic and mean arterial pressures associated with a blunted increase in the diastolic blood pressure. It is important to note that although the blood pressure behaved differently in both groups, the heart rate increased by the same degree. The behavior of arterial blood pressure of patients with Chagas’ disease during stress testing and the Valsalva maneuver was not different from the control.3 However, with the use of a passive postural stress test (tilt test), it was possible to demonstrate that patients with Chagas’ disease had a compromised control of blood pressure, such as a decrease in systolic blood pressure and a blunted increase in diastolic blood pressure.14,15 Regarding the control of heart rate, an impairment in heart rate control in Chagas’ disease was demonstrated in other functional studies.14,16,17 Besides the anatopathological demonstration of cardiac denervation,4 a recent study that used cardiac scanning with 123I-labeled metaiodobenzylguanidine has identified in vivo regional sympathetic denervation in patients with Chagas’ disease.18 A similar observation was reported in patients with diabetes associated with the functional autonomic involvement of the disease and with a worse prognosis of the disease.19

The normal response of FVR at −40 mm Hg LBNP in patients with Chagas’ disease indicates that when both arterial and cardiopulmonary receptors are unloaded, the reflex control of FVR is preserved. Previous studies with patients with cardiac transplantation12 and heart failure20,21 demonstrated a defect on reflex control of FBF and resistance during application of low and high levels of LBNP. In these studies, the reflex modulated by cardiopulmonary receptors was considered compromised, although the arterial baroreceptor reflex might also be simultaneously enrolled. Because the increase in vascular resistance depends on an increase in sympathetic nerve activity,22,23 it appears that the sympathetic innervation of this vascular bed is not compromised in Chagas’ disease. In fact, a study of patients with heart failure24 demonstrated a defect in the sympathetic nerve activity control when cardiopulmonary receptors were unloaded with LBNP and a normal baroreflex response during hypotension produced by administration of sodium nitroprusside, which indicates a more selective defect of the sympathetic control by the cardiopulmonary reflex. In our study, the incapacity of patients with Chagas’ disease to maintain normal arterial blood pressure at high levels of LBNP suggests the existence of an overall deficient control of cardiovascular control in Chagas’ heart disease, which deserves further study. Indeed, during −40 mm Hg LBNP, there is a clear fall in blood pressure in patients with Chagas’ disease. However, the increase in heart rate and FVR was similar to that in control subjects. The fact that the stimulus to the arterial baroreceptors was greater but the response, that is, tachycardia and increased FVR, was not appropriately increased suggests an impairment of the arterial baroreflex in patients with Chagas’ disease.

Nevertheless, our findings suggest that the impairment of the cardiopulmonary reflex may be enrolled as a cofactor in
the constellation of autonomic nervous alterations associated with Chagas’ disease and could influence the evolution from the latent form of the disease to different clinical manifestations of Chagas’ chronic disease and sudden death.5,25–27

Acknowledgment
This study was supported by fund E.J. Zerbini, FAPESP.

References


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_Hypertension_. 2000;36:1035-1039
doi: 10.1161/01.HYP.36.6.1035

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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