Limited Myocardial Contractile Reserve and Chronotropic Incompetence in Patients With Chronic Chagas’ Disease
Assessment by Dobutamine Stress Echocardiography

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OBJECTIVES
To determine whether dobutamine stimulation in patients with Chagas’ disease may uncover abnormal contractile responses as seen in ischemic myocardium.

BACKGROUND
Segmental left ventricular (LV) dysfunction in the absence of coronary atherosclerosis is frequently seen in patients with chronic Chagas’ heart disease. Myocardial ischemia and coronary microcirculation abnormalities have been found in animal models and in humans with Chagas’ disease. In addition, chagasic sera may contain autoantibodies against human beta-adrenergic receptors.

METHODS
Two groups of patients with Chagas’ disease were studied by echocardiography: group 1 (n = 12) without and group 2 (n = 14) with LV segmental wall motion abnormalities (mostly apical aneurysm). Ten normal subjects served as control subjects. We performed qualitative assessment of wall motion and quantitative evaluation of LV cavity under baseline conditions and after dobutamine stimulation.

RESULTS
Patients with Chagas’ disease exhibited a blunted inotropic and chronotropic response to dobutamine stimulation. After dobutamine, fractional area change in Chagas’ group 1 (54.7 ± 6.6%; SD) and in group 2 (35.1 ± 12.1%) were significantly lower than control group (66.7 ± 2.5%; p < 0.001). In addition, in 6 of 14 group 2 patients, dobutamine induced a biphasic response with improvement at low dose and deterioration at peak dose, as seen in patients with coronary artery disease. Although the three groups had similar basal mean heart rates and attained a similar mean peak dobutamine doses, both groups of patients with Chagas’ disease had a significantly blunted mean heart rate effect after dobutamine (p < 0.0001).

CONCLUSIONS
Thus, dobutamine stimulation unmasks a chronotropic incompetence and a blunted myocardial contractile response in chagasic patients, even in those with no overt manifestation of heart disease. (J Am Coll Cardiol 1999;33:522–9) © 1999 by the American College of Cardiology

About 16 to 18 million individuals in Latin America (1) are thought to have chronic Chagas’ disease (positive serologic test result) of whom 25% manifest cardiac involvement (2). Approximately half of the patients with symptomatic Chagas’ disease have a left ventricular (LV) apical aneurysm or other segmental LV wall motion abnormalities, or both (in particular of the posteroinferior wall) (3–5) whose origin is poorly understood (6–8). Patients with Chagas’ disease invariably exhibit normal angiographic appearance of the coronary arteries (2–8). Recent experimental animal work (6,9,10) and clinical studies (11) have demonstrated that myocardial ischemia induced by abnormal coronary microvasculature function may play an important role in the pathophysiology of the disease, and we theorized that it could impose a limitation in global contractile ventricular reserve. In addition, sera of patients with Chagas’ disease contain autoantibodies against both beta1 and beta2 adrenergic receptor subtypes with a theoretical gradual blockade of myocardial neurotransmitter receptors impairing both inotropic and chronotropic effects (12,13).

In parallel, developments in pharmacologic stress testing have established dobutamine echocardiography as a useful method to detect myocardial ischemia in patients exhibiting limited coronary flow reserve typically due to obstructive coronary artery disease (14,15). Dobutamine is primarily a beta1 adrenoreceptor agonist with mild beta2 and alpha1...
adrenoreceptor stimulant activity. To our knowledge, the clinical effect of dobutamine stimulation in chagasic patients has not been described previously. Thus, this study was designed to investigate whether dobutamine echocardiography may uncover a limited contractile or impaired chronotropic reserve in patients with chronic Chagas’ heart disease based on the hypothesis of abnormal coronary microcirculation (i.e., in the absence of epicardial coronary artery disease) and myocardial adrenergic dysfunction.

METHODS

Study patients. We prospectively studied 28 consecutive patients with chronic Chagas’ heart disease between October 1993 and February 1996, among 466 subjects referred to the Echocardiography Laboratory of the Centro Médico and Hospital Universitario de Caracas to undergo stress echocardiography. Two patients were excluded for analysis, one because of the presence of aortic stenosis and another because of chronic atrial fibrillation. In the remaining 26 patients, the clinical presentation included palpitations in 8, transient cerebrovascular embolic episodes in 3, atypical chest pain in 3, and 1 had an episode of congestive heart failure. The diagnosis of Chagas’ disease was based on epidemiology, positive serologic findings by two tests and characteristic electrocardiographic and/or clinical findings (4). Ten other Chagas’ seronegative subjects who were found to have a normal dobutamine test result, five of whom underwent coronary angiography that was normal, constituted the control group. All patients and subjects underwent a complete physical examination, electrocardiogram (ECG), chest X-rays, serum sampling, two-dimensional and Doppler echocardiographic study. None had evidence of heart failure on physical or radiologic examination. We excluded patients with unstable angina or myocardial infarction, history of ventricular tachycardia or fibrillation, sick sinus syndrome, complete heart block, valvular heart disease, obstructive lung disease, arterial hypertension, diabetes mellitus, pregnancy, alcoholism or subjects with an age of <18 or >70 years. The study protocol was approved by the Ethics Committee of Centro Médico de Caracas. Informed consent was obtained in all subjects.

The Chagas’ patient population (n = 26) was classified according to the presence of normal (group 1, n = 12) or abnormal (group 2, n = 14) wall motion on the baseline echocardiogram. Coronary arteriography was normal in all patients in whom it was performed (n = 10) among those in group 2. Three of these patients refused to undergo cardiac catheterization and one patient died before angiography could be performed. We did not obtain coronary angiography in group 1 subjects (without wall motion abnormalities). Within group 2 patients, six were being treated with either enalapril or captopril, two each were receiving low dose amiodarone or digoxin and one each was receiving warfarin or long-term aspirin therapy. No patients were receiving beta-adrenergic blockers or calcium antagonists. Eighteen patients were receiving no treatment.

Study protocol. Dobutamine stress echocardiography was carried out via a standard protocol (15) starting with a dose of 5 µg/kg per minute administered IV, increased every 3 min to 10, 20, 30, and 40 (in control subjects), up to 50 µg/kg per minute in the patient groups. No patient received atropine. Heart rate (HR), blood pressure, arrhythmias and ECG changes were monitored. The standard parasternal long- and short-axis views and apical four- and two-chamber LV apical views were obtained with a 2.5-MHz transducer with the patient lying in a left lateral decubitus position. Images were recorded on VHS 0.5-in. videotape during the last minute of every dose. An echocardiographic system (Hewlett-Packard Sonos 1500 or 2500) was employed. Analysis of myocardial response was performed from selected LV images digitized and stored in cine-loop format or in optical disk. The selected images were acquired at end-exhalation to minimize respiratory interference. The test was stopped if the patient developed ventricular or atrial tachycardia, hypotension (<90 mm Hg) or hypertension (systolic ≥200 mm Hg), angina, achievement of 85% of the maximal predicted HR, a maximum dobutamine dose of ≥40 µg/kg per minute, and/or development or worsening in wall motion abnormality. After the conclusion of the study, patients were monitored for 10 more minutes. Image acquisition in all patients and subjects was performed by the same cardiac sonographer.

Qualitative analysis of LV systolic wall motion. We employed the LV wall motion model of 16 segment proposed by the American Society of Echocardiography (16). Each segment was evaluated by two independent observers employing the following scoring system: 1 for normal, 2 for hypokinetic, 3 for akinetic and 4 for dyskinetic (or aneurysm). Hyperdynamic LV wall motion obtained at peak dobutamine dose was also scored as 1. The mean wall motion score index was obtained by summing the grades of each segment and dividing by the total number of segments analyzed. An idealized normal dobutamine response score index would be 1 at baseline and 1 at peak dose. Contractile reserve was noted to be present both when hyperkinesis developed as well as when a segment with baseline abnormal wall motion improved resulting in a reduction in wall motion score. Other types of contractile responses to dobutamine infusion would be worsening in segmental LV function resulting in an increased score, as seen due to myocardial ischemia and a biphasic response consisting of

**Abbreviations and Acronyms**

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ECG</td>
<td>electrocardiogram or electrocardiographic</td>
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<tr>
<td>EDA</td>
<td>end-diastolic left ventricular cavity area</td>
</tr>
<tr>
<td>ESA</td>
<td>end-systolic left ventricular cavity area</td>
</tr>
<tr>
<td>HR</td>
<td>heart rate</td>
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<td>LV</td>
<td>left ventricle or left ventricular</td>
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improved segmental function at low dose dobutamine followed by worsening at high dose as seen in hibernating ischemic myocardium (17). The echocardiographic studies and segmental responses were graded by three of us. Disagreements were resolved by an observer (J.E.P.) unaware of the patients’ clinical history or findings.

Quantitative analysis of LV cavity areas. Quantitative analysis of the LV cavity areas was carried out from the two-chamber apical view at end diastole (EDA) and at end systole (ESA) (both at baseline and at peak dobutamine dose). We have described previously that the apical aneurysm involvement in most patients with Chagas’ heart disease is more extensively displayed employing this view (4). In the four-chamber apical view, the systolic motion of the Chagasic aneurysm tends to be, in some patients, off-line from the LV long axis resulting in apical tangential views.

LV echocardiographic images depicting distinct endocardial definition were digitized (ECG-R wave triggered, 60 frames, 30-ms interval) using a cine-loop dual split-screen format to measure end diastole and end systole. All cavity area measurements were performed by careful advancing of the digital images frame by frame. End diastole was defined as the frame immediately before the opening of the mitral valve leaflets. LV fractional area change (percent) was obtained by the following: (EDA-ESA)/EDA \times 100. Only supraventricular conducted beats were digitized for analysis. In the case of premature ventricular contractions, the beat immediately after the postextrasystolic beat was utilized for measurements. Each LV cavity area measurement was expressed as the mean value measured by two independent observers (I.S., H.A.). Each beat was measured three or more times by each observer. Interobserver variability for the measurement of LV cavity areas in a given frame ranged between 0.9% and 1.8% for end diastole and between 1.5% and 1.6% for end systole.

**Statistical analysis.** Continuous variables were expressed as mean ± SD. Changes in HR, blood pressure, score indexes, EDA, ESA, fractional area change, before and at peak dobutamine doses were compared by two-way repeated measures analysis of variance. Analysis of HR changes at each increasing dobutamine dose had the dobutamine variable nested by clinical group. Fisher exact test was performed to compare categorical variables. Results of the dobutamine test in predicting future cardiovascular events were performed by Fisher exact test (Yates’ correction), multiple regression analysis and by the Cox proportional hazard rate method (STATISTICA v 4.5, StatSoft, Inc., Tulsa, Oklahoma). The null hypothesis was rejected at the 95% confidence level considering a p value <0.05 as significant.

**RESULTS**

**Clinical data.** There were no significant differences among groups 1, 2 and control with respect to gender (p = 0.40) or mean age (p = 0.16), although control subjects were somewhat older than patients in both Chagas’ groups (Table 1). All subjects from group 1 and one patient from group 2 were asymptomatic. Within group 2, 10 of 14 patients were in class I and three patients were in class II New York Heart Association functional status. Eleven of 12 patients from group 1 had normal ECGs, whereas in only 4 of 14 of group 2 subjects, the ECG was normal (p < 0.001). Other significant ECG abnormalities included ST-T segment elevation on precordial leads present only in group 2 patients (p = 0.003) and right bundle branch block (p = 0.044) (Table 1).

**Baseline echocardiography.** By definition, all subjects from Chagas’ group 1 had normal resting LV wall motion pattern. The baseline echocardiographic LV segmental wall motion abnormalities in group 2 patients included apical aneurysm in 10 patients, apical akinesis in 3, akinesis or hypokinesis of the posteroinferior wall in 9, akinesis or
hypokinesis of the posterior septum in 4 and 2 that exhibited generalized hypokinesis. Three of 10 patients with an apical wall motion abnormality had normal ECGs.

**HR response and blood pressure during dobutamine infusion.** The mean peak dobutamine dose achieved for the three patient groups was 38 ± 10 μg/kg per minute. As shown in Table 2, although the three patient groups had no significant differences in mean HR at baseline (p = 0.442) and in the peak dobutamine dose attained (p = 0.072), there was a highly significant difference in the mean HR reached at peak dobutamine dose (p < 0.0001). Although the control group attained a maximum mean HR of 137 ± 6 beats/min, both Chagas’ groups reached a significantly lower mean peak HR; group 1 of 130 ± 13 beats/min and group 2 of 102 ± 23 beats/min (p < 0.0003, each against control). There were also significant differences in achieving the age-corrected maximum predicted HR during stress (p = 0.002) (Table 2).

Analysis of the HR response to each dobutamine dose increase from 5, 10, 20, 30, 40 and 50 μg/kg per minute showed significant differences among the three groups (p < 0.0004), consisting of a blunted HR response to dobutamine by both Chagas’ groups (Fig. 1). The difference persisted when group 1 was compared against group 1 (p = 0.0002) or when group 2 was compared against the control group (p = 0.001). In addition, the significant blunted HR response existed even by excluding from analysis six patients from group 2 having a biphasic contractile response, among the three groups (p < 0.001) or between the control group and group 2 (p < 0.003).

There were no significant differences in mean baseline systolic and diastolic blood pressure and in systolic and diastolic blood pressure at peak dobutamine infusion among the three groups (Table 2).

**Qualitative analysis of LV wall motion.** Although subjects from the control group and patients from group 1 showed uniform increase in wall motion pattern after dobutamine, the contractile response of group 2 was complex. Analysis of 224 LV segments in these 14 (group 2) patients at a low-dose dobutamine (5 or 10 μg/kg per minute) demonstrated no change in the extent of motion in 175 segments, improved function of 46 segments and worsening function of 3 segments. At peak dobutamine infusion, the function of 75 LV segments remained unchanged, while 130 segments improved and 19 segments worsened.

Of interest, 16 of these 19 LV wall segments that were characterized by worsening in function exhibited a biphasic response (18) denoted by improved wall thickening and endocardial motion during low-dose dobutamine dose with deterioration at peak dose. This biphasic response to dobutamine infusion occurred at the midposterior or posteroinferior wall segments in five patients, and at the apicoanterolateral wall in one patient. Patients exhibiting a biphasic response had a significant decrease in mean score wall motion index from a baseline value of 2.13 ± 0.20 to
1.86 ± 0.20 at low-dose dobutamine (p = 0.03), increasing not significantly to 2.05 ± 0.19 at peak dobutamine (p = 0.10). The abnormal apical segments (i.e., akinetic or aneurysmal) remained unchanged throughout.

Quantitative analysis of LV cavity areas. Significant differences existed either at baseline and at peak dobutamine dose in LV mean EDA, ESA, and in fractional area change percent among the three groups (Table 2, Fig. 2). The Chagas' group 2 had larger LV areas and decreased fractional area change percent. As a result of dobutamine infusion, a significant decrease in mean LV ESA and an increase in fractional area change percent occurred in the control group but not in groups 1 and 2 (Tables 2 and 3).

Thus, although group 1 Chagas' patients had no overt heart disease, they had a significantly reduced fractional area change percent at peak dobutamine infusion (p = 0.006) as compared with responses of the control group (Fig. 2, C).

Dobutamine side effects and ventricular arrhythmias. Besides awareness of heart beating, the procedure was well tolerated in most subjects. Premature ventricular contractions were present at baseline in none of group 1 and in seven group 2 patients (50%). These were uniform in six, bigeminy in two, and transient idioventricular rhythm in one. During the dobutamine infusion, 17% of group 1 patients had occasional premature ventricular contractions at doses of ≥40 μg/kg per minute. Two patients in group 2 had occasional ventricular triplets at dobutamine doses of 20 and 30 μg/kg per minute, and one patient had a single 6-beat run of ventricular tachycardia at a peak dose of 50 μg/kg per minute. There were no ECG ST or T wave changes as a result of the dobutamine infusion. One patient experienced transient asymptomatic hypotension at the end of the test. No patient developed angina or heart failure.

Reasons for test interruption. No patient with Chagas' disease reached his or her respective target HR. The test was stopped in 21 of 26 (81%) Chagas' patients because a maximum dobutamine dose of ≥40 μg/kg per minute was achieved. Six patients had biphasic responses that occurred at dobutamine doses of 40 μg/kg per minute in three, at 30 μg/kg per minute in one, and at 20 μg/kg per minute in two.

Clinical follow-up. Mean follow-up of all Chagas' subjects until December 1997 (30 ± 14 months; range, 1 to 50) yielded six cardiovascular events in group 2 patients: three fatal (sudden death) and three nonfatal (syncope, peripheral embolism and heart failure due to atrial fibrillation). Significant variables predictable of adverse events included the following: increase in HR at peak dobutamine dose of only ≥35 beats/min (p = 0.0001), attaining of age-corrected maximum of HR of only ≤60% (p = 0.0056), basal fractional area change ≤40% (p = 0.0147) and presence of aneurysm (p = 0.02). Variables such as age ≥50 years, male sex, basal or peak dobutamine wall motion score indexes, fractional area change percent at peak dobutamine and ischemic or biphasic responses were nonsignificant. The most significant Cox model for event prediction was the combination of increase in HR at peak dobutamine dose of only ≥35 beats/min and a basal fractional area change of ≤40% (p = 0.00052). Event-free survival at 29 months was 75% for all subjects with Chagas' disease.

DISCUSSION

Results of this study demonstrate that patients with chronic Chagas' heart disease exhibit chronotropic incompetence and a blunted contractile response to dobutamine stimulation, even among patients (group 1) having only abnormal...
serologic findings without overt heart disease and with normal LV wall motion at baseline. Furthermore, patients with LV apical wall motion abnormalities (group 2) frequently exhibit a biphasic response to dobutamine consistent with viable but eventually ischemic myocardium (mainly in the posteroinferior walls) despite normal coronary anatomy by angiography in all patients in whom it was performed. The possible mechanisms mediating this abnormal biphasic response to dobutamine (19) are complex and may include induced myocardial ischemia (6), beta-adrenoreceptor dysfunction (12,13,20,21) and variable extent of structural myocardial damage (i.e., increased collagen content) due to Chagas’ heart disease (22).

Limited inotropic reserve. As compared with control subjects, in whom peak dose dobutamine was accompanied by fractional area change up to 67%, Chagas’ group 1 patients exhibited a significantly blunted fractional area change response to only about 50%, similar to that previously observed in patients with coronary artery disease and baseline wall motion abnormalities or those developing an ischemic response to dobutamine (23). In group 2 Chagas’ patients, the inotropic reserve was even more blunted reaching fractional area change values approximately 30% at peak dobutamine infusion.

The hypothesis of presumed myocardial ischemia in chronic Chagas’ heart disease is based clinically on suggestive ECG changes (3), on symptoms including acute myocardial infarction with normal coronary arteries (24), on a high proportion of segmental wall motion abnormalities (4,5) and on experimental data derived from tissue cultures (25,26) and living animals (6,9). As dobutamine echocardiography may unmask viable ischemic myocardium (17), results of dobutamine infusion in Chagas’ patients should help to elucidate the pathophysiology of the responses and assist with management strategies.

Results of this study are consistent with the hypothesis that patients with chronic Chagas’ disease are afflicted with impaired coronary microcirculatory reserve (6–8), as they exhibited normal coronary arteries by angiography. We have demonstrated previously that patients with chronic Chagas’

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**Table 3. Comparison Between Control Group vs Chagas’ Groups of Left Ventricular Areas and Fractional Areas Changes at Baseline and at Peak Dobutamine Dose**

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<th>Control Group vs</th>
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<th>Group 2</th>
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<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
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<tr>
<td>End diastolic</td>
<td>0.561</td>
<td>0.034</td>
<td></td>
</tr>
<tr>
<td>End systolic</td>
<td>0.557</td>
<td>&lt; 0.001</td>
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<tr>
<td>Fractional area change</td>
<td>0.90</td>
<td>0.043</td>
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<tr>
<td><strong>Dobutamine</strong></td>
<td></td>
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<tr>
<td>End diastolic</td>
<td>0.463</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td>End systolic</td>
<td>0.006</td>
<td>&lt; 0.001</td>
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</tr>
<tr>
<td>Fractional area change</td>
<td>0.006</td>
<td>&lt; 0.001</td>
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EDA and ESA = mean left ventricular end-diastolic and end-systolic areas; FAC = denotes fractional area change.
Heart disease may exhibit an abnormal endothelium-dependent coronary vasoreactivity (11). An intracoronary infusion of acetylcholine induced a paradoxical decrease in coronary blood flow and a significantly blunted coronary vasodilator response to adenosine. The contribution of other endothelium-derived constrictive factors observed experimentally should also be considered (9,26). Recently, increased endothelin (ET-1) release from Trypanosoma cruzi-infected human umbilical vein endothelial cells (26) has been reported.

In addition, uniform ultrastructural alterations in myocardi um are observed even in chagasic asymptomatic individuals that may also contribute to abnormalities in contractile function (22). These pathologic findings include mitochondrial, nuclear, cell membrane irregularities, and dilatation and filling of the T-tubule system with a glycoprotein-like substance.

**Chronotropic incompetence.** Both Chagas’ groups were unable to increase HR in response to high doses of dobutamine. Autoantibodies against both beta-adrenergic receptor subtypes (β₁ and β₂) have been detected in human chagasic sera (12,13,21). Because the cardiac chronotropic effect of dobutamine is mainly due to its β₁ adrenoreceptor stimulation, recent studies suggest an interaction between antibodies to *T. cruzi* and the receptors. Antibodies detected in sera from chagasic patients showed molecular mimicry recognizing both the second extracellular loop of the human β₁ adrenergic receptor and the carboxy-terminal part of the ribosomal PO protein of *T. cruzi* (13). These antibodies have been shown to exert a positive chronotropic effect in experiments in vitro in cardiomyocytes from neonatal rats. More recently it has been shown that IgG fractions of sera from patients with chronic Chagas’ disease are able to decrease the HR of isolated rabbit hearts (27). A possible role of chagasic autoantibodies in our series is only speculative as we did not estimate its presence. Clinically, patients with Chagas’ disease have been shown to exhibit impaired chronotropic response during dynamic exercise (28,29). Our observations of a blunted chronotropic response to dobutamine are consistent with reduced beta-adrenergic receptor sensitivity or down-regulation, as seen in other dilated cardiomyopathies.

**Safety.** Ventricular ectopic activity before and during dobutamine infusion was common in patients with segmental wall motion abnormalities. Only 2 of 26 patients develop additional arrhythmias at dobutamine doses of ≥30 μg/kg per minute. Thus, this dose seems to be safe in this patient population while allowing detection of most of the segmental wall motion abnormalities found. As no patient experienced angina pectoris or showed additional ECG changes, these signs were not useful in this patient population as markers to stop the test.

**Clinical significance.** A blunted cardiac response to adrenergic stimulation in Chagas’ disease supports a role for dysfunctional sympathetic activity in these patients. Responses to dobutamine infusion in conjunction with echocardiography, differentiating viable from irreversibly injured myocardial tissue, may improve the classification of these patients for the purpose of better defined prognosis and management.

**Limitations.** The finding of a limited chronotropic response at peak dobutamine and decreased basal fractional area change ≤40% as a predictor of outcome in patients with chronic Chagas’ disease should be tested in a larger study. We assessed LV area changes only from the two-chamber apical view where commonly the extent of the apical aneurysm is displayed more extensively. It may be possible that analysis of other views might lead to different estimations of LV area changes. Nevertheless, global contractility was evaluated semiquantitatively by the score system. We intended, but were unable to perform coronary angiography in all patients, including group 1 patients in whom it was not justified as these patients were mostly asymptomatic. Finally, we cannot assume that our observations are applicable to Chagas’ patients in whom the disease is far advanced.

**Conclusions.** Patients with early stages of Chagas’ disease (only serologic evidence of Chagas’ disease but without segmental LV dysfunction; group 1) as well as those with baseline LV segmental wall motion abnormalities exhibit blunted myocardial contractile response to dobutamine infusion, chronotropic incompetence and a biphasic isotropic response (i.e., similar to that seen in ischemic myocardium) to dobutamine despite normal angiographic appearance of the coronary arteries.

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**REFERENCES**