Pharmacological Stress in Chagas Disease: A Doppler-Echo Study

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SUMMARY
In normal subjects, myocardial velocities assessed with Doppler tissue imaging (DTI) increase by a mean of 140% during dobutamine stress echocardiography.

Objectives
The purpose of this study was to investigate whether dobutamine stress echo associated with left ventricular (LV) DTI could demonstrate incipient cardiomyopathy in patients with Chagas disease without evidence of heart disease assessed by conventional tests. We evaluated 39 patients (14 men and 25 women) with a mean age of 44 years (range 29 to 67 years), who were serologically positive for Chagas disease without obvious heart disease (group A). Heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured. Chest X-rays and ECG’s were performed. The following parameters were measured with Doppler-echocardiography: left ventricular diastolic (LVDD) and systolic (LVSD) diameters, fractional shortening (FS), segmental wall motion and LV area fractional shortening (AFS), E and A velocities (m/sec) and mitral flow E/A ratio. Myocardial velocities (Vm), diastolic Em velocity (myocardial velocity during early filling), Am (myocardial velocity during atrial contraction), Sm systolic velocity and the Em/Am ratio were measured with DTI in the basal segment of the anterolateral wall and the mid segment of the lower septum. Dobutamine was administered up to a dose of 40 gammas/kg/min and measurements were repeated with the maximum dose. These results were compared to those obtained in 15 normal subjects (group B).

Results
Post dobutamine, HR increased from 65 beats per minute (bpm) to 120 bpm in group A (p<0.001) and from 74 to 151 bpm in group B (p<0.001). Maximum HR attained was lower in group A than in group B; i.e., 120 vs. 151 bpm (p<0.01). Wall motion was normal in 38 patients (group A). Post dobutamine, the increase in Vm compared to baseline Vm were, in group A: Em 9% (NS), Am 6.6% (NS) and Sm 15% (NS) and in group B: Em 46% (p<0.05), Am 72% (p<0.01) and Sm 108% (p<0.01). Post dobutamine, FS and AFS were significantly increased in both groups.

Statistical Analysis
The Wilcoxon test was used (Kiwistat 2001) and a p value <0.05 was considered significant.

Conclusions
Patients with Chagas disease exhibited chronotropic impairment and a lesser increase in Vm post stress than normal subjects. The scarce increase in Vm with dobutamine could suggest the presence of an incipient cardiomyopathy.

Key words
Chagas Disease - Echocardiography, Doppler - Dobutamine - Echocardiography, stress - Chagas cardiomyopathy

Abbreviations
Am Myocardial velocity during atrial contraction
LVDD Left ventricular diastolic diameter
DTI Doppler tissue imaging
LVSD Left ventricular systolic diameter
Em Diastolic myocardial velocity during early filling
FS Fractional shortening
FSA Fractional shortening area
HR Heart rate
bpm Beats per minute
Sm Systolic myocardial velocity
DBP Diastolic blood pressure
SBP Systolic blood pressure
V Velocity
Mv Myocardial velocity

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INTRODUCTION

Chagas disease is an infectious disease caused by *Trypanosoma cruzi*. The number of people infected in Latin American countries is estimated in approximately 20 million, which has a major social and economic impact. (1, 2) Heart disease in Chagas disease is the mechanism responsible for the high morbi-mortality rate in this population. According to the WHO, Chagas-Mazza disease is the most frequent tropical disease in Latin America. Between 20% and 30% of the infected subjects who underwent the acute phase evolved to chagasic heart disease and 10% of them have the dilated form. (3)

The acute phase of the disease is followed by an asymptomatic period of variable duration, between 20 to 30 years, called intermediate, sub-acute or latent stage, characterized by being asymptomatic or oligosymptomatic.(4)

The mechanisms implicated in the pathogenesis of chagasic myocardopathy are: a) neurogenic, b) inflammatory (direct parasite lesion and/or immunologic impairments) and c) micro circulatory abnormalities. Of these mechanisms, the immune seems to be the most important pathogenic factor. Hence, antibodies against beta adrenergic receptors 1 and 2 that gradually block the receptors and provoke a decrease in the response to catecholamines have been described in the serum of patients with Chagas disease.(5)

Patients with Chagas disease that undergo the intermediate stage and that do not show heart disease have been included in the present study.

With the aim of assessing the presence of incipient myocardial lesion in patients with Chagas disease and normal baseline ventricular function, the parietal motility and variations of the tissue myocardial velocities (Mv) under the effect of stress with dobutamine.

Mv modifications obtained by post dobutamine Doppler tissue imaging (DTI) in patients with Chagas disease have not been described yet. Acquatella et al, using dobutamine echo stress observed chronotropic and inotropic incompetence in patients with Chagas disease with and without cardiac disease.(6)

Determination of Mv by DTI has shown that it is useful to assess the segmental ventricular wall contractility as it provides data on the shortening velocity of the fiber and represents more accurately the elastic properties and myocardial contractile force. (7)

The studies by Yamada et al showed a 140% average increase in the tissue Mv after the dobutamine echo stress in normal subjects. (8)

MATERIAL AND METHODS

Population

Thirty nine patients were included prospectively: 14 male and 25 female, average age 44 ± 11 years (range: 29 to 67 years) with positive serum for Chagas disease (immune-fluorescence, complement fixation and hematoglutination), without cardiac compromise (group A). The control group included 15 normal subjects, of similar age, that were assessed for diagnosis of coronary disease with negative results (group B). Both groups were assessed by clinical exam, thorax x-Ray, electrocardiogram and echocardiogram to rule out heart disease.

Inclusion criteria: patients with serum positive for Chagas disease, absence of clinical-radiological signs of heart disease and normal echocardiogram.

Exclusion criteria: patients with poor echocardiographic window, history of diabetes, high blood pressure, coronary artery disease, myocardial infarction sequelae, dilated cardiomyopathy, hypertrophic cardiomyopathy and restrictive cardiomyopathy, heart valve disease and systemic or metabolic diseases with myocardial repercussions.

Clinical parameters: Heart rate, diastolic, and systolic blood pressure were assessed.

Echocardiography

Left ventricular wall motion quantification

A bidimensional echocardiogram was performed to all the patients using Ving Med CFM 800 echo-Doppler ultrasound machine with a 2.5 MHz mechanic annular array transducer. A continued recording of the images was videotaped.

Patients were studied in left lateral position as from the apical views of 4 and 2 chambers, and left parasternal in its short and long axes. The ventricular diameters and parietal widths were measured; the shortening fraction (SF) and the left ventricle fractional shortening area (FSA) were determined (end of diastole area –end of systole area/end of diastole area x 100).

Qualitative left ventricular wall motion analysis

The left ventricular wall motion was assessed according to the 16 segments model proposed by the American Society of Echocardiography (9). Each segment’s motility was assessed by two independent observers, using the following echocardiography score: 1 normal, 2 hypokinesia, 3 akinesia, and 4 dyskinesia. The left ventricular wall motion score index was obtained by the addition of the scores in each one of the segments divided by the total number of assessed segments.

Echo-Doppler and DTI

From the apical 4-chambers view, the following parameters were obtained with Doppler tissue images at the spectral curve of the transmittal flow: peak E wave velocity (early filling wave) and peak A wave velocity (atrial filling wave) in m/sec and the E/A ratio.

For the obtention of DTI the Nyquist limit, the gain and the wall filter were reduced to 20 cm/sec. Em diastolic Mv (myocardial velocity during early filling), Am (myocardial velocity during atrial contraction) and systolic Sm were measured in m/sec with a sample volume of 0.5 cm length, positioned at the central portion of the IV segments: later basal wall and midseptal, from the apical 4-chambers view.

Single and average values were obtained for each of the Mv: Em, Am and Sm recorded at the laterobasal and midseptal segments. When two systolic velocities, Sm1 and Sm2 were observed, the one with greater amplitude was recorded. (10)

Dobutamine echo stress protocol

The dobutamine echo stress test was performed in accordance with the standard protocol, (11) with a continuous dobutamine IV infusion in increased doses of 5, 10, 20, 30 and 40 gammas/kg/min, at stages of 3 minutes each. At each stage HR, BP, and ECG were assessed.
A continuous echocardiographic recording was performed with the described method to assess the left ventricular wall motion and detect new contractile abnormalities in each stage.

During the maximum dobutamine dose, LV mitral filling flow and DTI derived Vm were determined in the previously described segments.

Early and A peak wave velocities of the mitral flow were measured at the maximum heart rate that both could be differentiated during the dobutamine infusion (Figure 1).

**Reason for the test suspension:** frequent and/or multifocal premature ventricular complexes, ventricular or atrial tachycardia, low blood pressure (< 90 mmHg), elevated blood pressure (> 200 mmHg), angina pectoris, presence of new abnormalities in the segmental wall motion, having reached 85% of the maximum heart rate or the 40 gammas/kg/min dobutamine dose.

The images were recorded on continuous videotape and digitalized via a stress echo module (Echopac, Vingmed 800) for comparison between them and to allow ulterior analysis of the LV segmental wall motion.

The acquisition of images in all the patients was performed by the same operator. Patients with positive serum for Chagas disease were compared with a group of 15 normal subjects of similar ages in whom the same controls and tests were performed.

HR, SBP, DBP, LVDD, LVSD, FS, FSA, E and A waves of the mitral flow and DTI Vm recorded at baseline were compared with those obtained with the maximum dobutamine dose in both groups (Tables 1 and 2).

**Statistical Analysis**
The continuous variables are expressed as mean ± SD; changes in HR, SBP and DBP, FS, Em, Am and Sm at baseline and after the peak dobutamine dose were compared with Wilcoxon rank test (Kiwistat 2001), p < 0.05 was considered significant.

**RESULTS**
There were no significant differences between groups A and B in regards to sex and age. Both groups population was in functional class I and presented a normal ECG.

By the inclusion criteria, all the patients showed normal LV wall motion in the baseline echocardiogram.

**Dobutamine infusion and DTI assessment**
The maximum dobutamine dose reached was 40 gammas/kg/min in all the assessed patients.

The DTI assessment recording added an average duration of 3 minutes to the echo study with conventional dobutamine. Baseline HR was similar in both groups. With the peak dobutamine dose significant difference in the maximum HR were observed. Although the HR in group A increased, the values reached were lowest in regards to the control group: group A: 120 ± 22 bpm and group B 151 ± 10 bpm (p < 0.01). Only 6 patients (15%) in group A reached 85% of the forecasted HR. SBP and DBP increase was not significant in both group A (Table 1) as well as in group B (Table 2).

During the stress echo, 7 patients with Chagas disease showed infrequent, non complex premature ventricular beats.

**Quantitative and qualitative LV wall motion analysis**
Post dobutamine, LV FS and FSA increased in both groups without significant differences between them. In group A uniform increase in the parietal motility was noted (hyperkinesias) in 38 patients and one patient showed a new apical segment abnormality.

**Mitral Doppler Flow and DTI**
The E and A mitral flow baseline waves did not show significant differences between both groups: E wave group B 0.70 ± 0.14 m/sec versus group A 0.83 ± 0.15

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**Fig. 1. Mitral flowchart, E and A waves in a patient with Chagas disease during dobutamine infusion with 141 bpm HR.**
m/sec (NS); A wave B 0.74 ± 0.05 m/sec versus group A 0.77 ± 0.15 m/sec (NS). There were no significant differences post dobutamine either in these velocities: E wave, group B 0.66 ± 0.09 m/sec versus group A 0.86 ± 0.18 m/sec; A wave group B 0.86 ± 0.07 m/sec versus group A 0.85 ± 0.21 m/sec.

Baseline values of DTI velocities did not show significant differences between both groups: Em wave group B 0.13 ± 0.02 m/sec versus group A 0.14 ± 0.03 m/sec; Am wave group B 0.11 ± 0.04 m/sec versus group A 0.14 ± 0.04 m/sec; Sm wave group B 0.12 ± 0.09 m/sec versus group A 0.14 ± 0.06 m/sec.

Post dobutamine, peak DTI velocities showed significant differences between both groups: Em wave group B 0.19 ± 0.04 m/sec versus group A 0.15 ± 0.04 m/sec (p < 0.05); Am wave group B 0.19 ± 0.05 m/sec versus group A 0.15 ± 0.05 m/sec (p < 0.05) and Sm wave group B 0.25 ± 0.08 m/sec versus group A 0.17 ± 0.05 m/sec (p < 0.05) (Figures 2 and 3).

Post dobutamine, in group A myocardial diastolic and systolic velocities increased without significance: Em 9% (0.14 m/sec versus 0.15 m/sec), Am 6% (0.14 m/sec versus 0.15 m/sec) and Sm > 100% (0.12 m/sec versus 0.25 m/sec) (Figure 4).

Only in 7 patients of group A there was a mean increase in DTI velocities greater than 80% (5 patients Sm wave and 2 patients Am wave), although these did not reach the sub maximum HR (chronotropic deficit).

In normal subjects, myocardial diastolic and systolic velocities increased significantly: Em 46% (0.13 m/sec versus 0.19 m/sec), Am 72% (0.11 m/sec versus 0.19 m/sec) and Sm > 100% (0.12 m/sec versus 0.25 m/sec) (Figure 3).

**DISCUSSION**

Dobutamine stress echo is a safe and trust method for the detection of ischemia and myocardial viability and in risk stratification of the coronary artery disease. Also, this method allows quantifying regional wall motion disorders not only in patients with coronary artery disease, but also in those with heart diseases cardiomyopathies. (12, 13) DTI allows analyzing segment behaviour through Vm with a high spatial and temporal resolution. (8) Vm abnormalities induced by dobutamine stress echo at different points of the segments would allow serial determination of the regional myocardial function quantification. (14) The utility of dobutamine stress echo with DTI to detect myocardial viability has been described (15). Payne et al showed that the method can be applied to quantify functional myocardial reserve. (16)
The quantitative analysis of myocardial contractility with a pharmacological stress test added with DTI analysis in patients with Chagas heart disease has not yet been thoroughly assessed. Therefore, the objective of the study was to analyze Vm modifications during dobutamine stress echo besides segmental LV wall motion analysis, aimed at determining the status of contractile myocardial reserve in this patient population.

In a recent study in patients with Chagas disease of undetermined phase, Cianciulli et al (17) observed that the pattern of mitral filling showed abnormalities in the diastolic function of the LV with reversal of the E/A relation. Our work, coincident with the studies by Barros et al (18) and Migliore et al (19) showed at baseline an E/A relation >1, similar to the control group. This difference could be attributed to not similar populations. Acquatella et al, when assessing with dobutamine stress echo patients with Chagas heart disease with and without baseline wall motion abnormalities observed chronotropic incompetence and a lower contractile increase even in patients without heart disease. Likewise, the group that showed apical parietal abnormality at rest also showed a biphasic response to dobutamine, attributable to viable myocardium but eventually ischemic despite of having a normal coronary arteriogram (6). These authors attribute this biphasic response to multiple mechanisms, such as myocardial ischemia, beta-adrenoreceptors dysfunction and structural myocardial damage of variable extension.

Yamada et al observed with DTI that a myocardial systolic velocity lower than 12 cm/sec at stress peak allowed defining abnormal segments with 86% sensitivity and a 96% specificity in the baseline regions and 81% - 89% respectively in the mean segments (8).

Post-dobutamine, in our group of patients with Chagas disease (group A), although an increase in FS and FSA was observed, systolic Vm increase (15%) was very low compared to the control group (higher than 100%). In regards to diastolic Vm, a fails to rise during stress test was observed. This lack of increment in diastolic Vm could suggest associated diastolic dysfunction. (17)

In the present study, the observed discordances between ventricular function parameters (FS and FSA) and tissue Vm in this group of patients are coincident with those shown by Bach et al in patients with mitral regurgitation without regional wall motion abnormalities, where a lack of increment in post-dobutamine Vm in regions with normal contractility was detected (20, 21). Dobutamine DTI shows higher sensitivity than the ejection fraction to evaluate contractility through Vm modifications, having shown that the increase of the latter is higher than 100% in healthy hearts. (16) Inadequate increase of tissue systolic Vm with dobutamine in our population would show a higher sensitivity of this method in regards to the qualitative
In studies with DTI it has been observed that HR increase due to the effect of dobutamine is correlated to an increase in myocardial velocities. (15) Chronotropic incompetence present in our patients could be associated to an inotropic incompetence expressed by the lesser increase of systolic myocardial velocities. (21) Due to the reduced number of patients that after reaching post-dobutamine sub-maximum HR did not significantly increased Vm, it can not be inferred that both alterations are simultaneous, but it reveals the importance that both assessments have, that of the HR and Vm increase, in the evaluation of patients with Chagas disease. Therefore Vm assessment in this pathology would allow a more precise quantitative evaluation of the contractile phase.

**Study limitations**

Myocardial velocities were recorded in only two ventricular segments to allow obtaining images faster and more efficiently, thus improving the study feasibility. DTI assessment at the apical 4-chambers view allows analyzing only the contractility in the longitudinal axis of the mentioned segments.

In regards to the behaviour of myocardial velocities at different HR, for methodology reasons we did not assess the increase in DTI velocities with each HR increase. However, in patients that reached a sub-maximum HR (7 patients) an inotropic deficit was found (scarce increase in DTI velocity). Although this group represents 17% of the population, we cannot infer a close relation between the increase in heart rate and increase in myocardial velocities. An increased number of patients with these characteristics would allow determining the correlation between them.

Our protocol did not include atropine administration because the objective of our study was not the assessment of contractility at a sub-maximum HR to cause ischemia, but to assess the inotropic response with maximum doses of dobutamine.

**CONCLUSIONS**

The scarce increase of myocardial velocities in DTI during dobutamine stress echo associated with chronotropic deficit would evidence the presence of incipient systolic and autonomic dysfunction in a population of patients with positive serology for Chagas disease without clinical heart disease (undetermined phase).

This finding would imply the presence of intermediate stages in the sub clinical phase of the disease and its use during this phase could be beneficial for the clinical management and follow up of these patients. It would be necessary to carry out follow up studies in a larger population to determine the meaning of these observations more precisely throughout the course of the disease.
RESUMEN

Aprecio farmacológico en la enfermedad de Chagas. Estudio con eco-Doppler

Las velocidades miocárdicas evaluadas por Doppler pulsado tisular (DPT) presentan un incremento promedio del 140% bajo efecto del eco estrés con dobutamina en sujetos normales.

Objetivos

El propósito del estudio fue investigar si el eco estrés con dobutamina asociado con el DPT del ventrículo izquierdo (VI) podría evidenciar miocardiopatía incipiente en pacientes con enfermedad de Chagas sin cardiopatía demostrada por exámenes convencionales. Se estudiaron 39 pacientes (14 hombres y 25 mujeres), cuya edad media era de 44 años (rango 29 a 67), seropositivos para enfermedad de Chagas sin cardiopatía evidente (grupo A). Se determinaron la frecuencia cardíaca (FC) y la tensión arterial sistólica y diastólica (TAS y TAD). Se realizaron radiografía de tórax y ECG. Por eco-Doppler se midieron los siguientes parámetros: diámetros del ventrículo izquierdo diastólico (DDVI) y sistólico (DSVI), fracción de acortamiento (FA), motilidad segmentaria y fracción de acortamiento de área del VI (FAA), velocidades (V) E, A (m/seg) y relación E/A del flujo mitral. Con DPT se evaluaron en los segmentos basal de la pared anterolateral y medio del septum inferior las velocidades miocárdicas (Vm) diastólicas Em (velocidad miocárdica durante el llenado rápido), Am (velocidad miocárdica durante la contracción auricular), sistólica Sm y relación Em/Am. Se administró dobutamina en dosis de hasta 40 gammas/kg/min y se repitieron las determinaciones con la dosis máxima. Estos resultados se compararon con los obtenidos en 15 sujetos normales (grupo B).

Resultados

Posdobutamina, la FC se incrementó de 65 a 120 latidos por minuto (bpm) en el grupo A (p < 0,001) y de 74 a 151 bpm en el grupo B (p < 0,001). La FC máxima alcanzada fue menor en el grupo A que en el grupo B: 120 versus 151 bpm (p < 0,01). La motilidad parietal fue normal en 38 pacientes (grupo A). Posdobutamina, los incrementos de las Vm respecto de las Vm basales fueron en el grupo A: Em 9% (ns), Am 6,6% (ns) y Sm 15% (ns) y en el grupo B: Em 46% (p < 0,05), Am 72% (p < 0,01) y Sm 108% (p < 0,01). Posdo-butamina, la FA y la FAA se incrementaron en forma significativa en ambos grupos.

Conclusiones

Los pacientes con enfermedad de Chagas evidenciaron incompetencia cronotrópica y un incremento menor de las Vm luego del estrés respecto de los sujetos normales. El escaso incremento de las Vm con dobutamina podría sugerir la presencia de una miocardiopatía incipiente.

Palabras clave>Enfermedad de Chagas - Ecografía Doppler - Dobutamina - Ecodiagnosticas de Estrés - Miocardiopatía chagásica

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