Myocardial Perfusion Imaging and Cardiac Involvement in the Indeterminate Phase of Chagas Disease

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Abstract

Background: **Myocardial perfusion imaging (MPI) has been used in the assessment of chagasic heart disease.**

Objective: **To investigate the value of gated-single photon emission computed tomography (gated-SPECT) MPI to detect early cardiac involvement in chagasic patients in the indeterminate phase, who present segmental motion abnormalities detected by tissue Doppler imaging (TDI)-derived strain.**

Methods: **Forty individuals (mean age: 25±2 years, 50% males) from an endemic area of Chagas disease and with positive serologic diagnosis, were included. All underwent gated-SPECT two-day (stress-rest) MPI and echocardiography.**

Results: **Thirty individuals (75%) showed a normal scan. In three cases (8%) the MPI was slightly abnormal, and in seven it was equivocal. In all cases with reversible defects, the affected segments were coincident with those with motion abnormalities. A post-stress left ventricular ejection fraction (LVEF) reduction ≥ 5% (ΔLVEF ≤ -5%) was found in 11 out of 40 individuals (28%). Both the phase-derived standard deviation and the histogram bandwidth showed a significant difference between post-stress and rest. In both cases there was a slight dyssynchrony at rest which normalized at post-stress.**

Conclusions: **A stress-rest gated-SPECT is a valid approach to detect early myocardial alterations, as well as intraventricular dyssynchrony in the indeterminate phase of Chagas disease in patients with segmental motion abnormalities previously detected by TDI-derived strain. (Arq Bras Cardiol. 2013;100(2):114-119)**

Keywords: **Myocardial Reperfusion; Radionuclide Imaging; Chagas Disease; Stroke Volume.**

Introduction

Chagas disease continues to be a serious health and economic problem in most Latin American countries. Moreover, as a consequence of growing global migration, an increasing number of imported cases have now been detected in non-endemic areas, such as North America and several countries of Europe, Asia and Oceania[1,2].

Chagas disease is characterized by three phases: acute, indeterminate and chronic. The heart is the most severely and frequently affected organ, and Chagas heart disease is an inflammatory cardiomyopathy characterized by chronic fibrosing myocarditis and progressive impairment of myocardial contractile function[3].

In the indeterminate phase, usually of long duration (from 10-30 years), there is an absence of clinicopathological evidence of heart involvement and this is usually accompanied by either a normal electrocardiogram (ECG) or one with minor disturbances of cardiac rhythm[2]. Nevertheless, it has been shown that 25-30% of chagasic patients in the indeterminate phase have some degree of cardiac impairment[4-7], and 33% of patients will develop chronic cardiomyopathy between 10 and 30 years after the initial infection[8]. Thus, it is of utmost importance to adequately identify those patients who will develop this heart impairment in order to implement early therapeutic interventions.

Myocardial perfusion imaging (MPI) with nuclear medicine techniques has been used in chronic chagasic cardiomyopathy[9-11], but to our knowledge, there is little data about the indeterminate phase of the disease[12].

Therefore, the objective of the present study was to investigate the value of using gated-single photon emission computed tomography (gated-SPECT) MPI to detect early cardiac involvement in a group of chagasic patients in the indeterminate phase of the disease, who presented segmental motion abnormalities detected by tissue Doppler imaging (TDI)-derived strain.

Methods

Ethics Statement

This study complies with the Declaration of Helsinki. The ethics committee of the Institute of Cardiology approved the study

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and written informed consent was obtained from all patients prior to their inclusion in the study.

Study population

We studied 40 individuals (mean age: 25±2 years, 50% males) from an endemic area of Chagas disease, temporary residents in Cuba, with positive serologic diagnosis for Chagas disease, and who had been diagnosed five years before inclusion in the present study. They were referred to the Nuclear Medicine Department of our center after segmental motion abnormalities were demonstrated by TDI-derived strain, and were recruited between August 2010 and July 2011. The following inclusion criteria were adopted: male or female subjects with two positive serologic tests for Chagas disease, without clinical evidence of organic lesions, capable of undergoing exercise stress test on treadmill or bicycle. Exclusion criteria were: evidence of any cardiac impairment; alcoholism or drug abuse; pregnancy and lactation.

Each patient underwent a technetium-99m methoxy-isobutyl-isonitrile (^{99m}Tc-MIBI) gated-SPECT following a two-day protocol (exercise stress / rest).

Echocardiography

The echocardiographic study was performed using a Philips iE33 (Philips Ultrasounds, Bothell, Washington, USA) equipped with a 2.5 MHz-4 MHz transducer. Images were obtained in the transverse plane at the level of the papillary muscles and apical four-chamber view with second harmonic, high temporal resolution imaging (60-100 images/s) and a high-quality ECG signal. The images were stored in digital format for subsequent offline analysis (by using Q Lab. SQ software for automated analysis of myocardial deformation). Ventricular volumes and left ventricular ejection fraction (LVEF) were calculated by modified biplane Simpson and Teicholz methods, as well as by tridimensional echocardiography.

Three cine loops from the three standard apical planes (four-chamber, two-chamber, and long-axis) were recorded in harmonic B-mode and color tissue Doppler mode simultaneously and separately. The loop with the best quality was chosen for analysis. The frame rates were between 200 and 400 Hz, with an angle of less than 20 degrees between the longitudinal strain of the segments and the ultrasound beam.

The cut-off value of the maximal systolic longitudinal strain was -20% ± 5 [13].

Gated-SPECT MPI

On the first day of the study, all patients underwent a symptom-limited treadmill exercise stress test (MTM-1 500 med, Schiller, Switzerland) using the Bruce protocol. At peak exercise, a dose of 740 MBq of ^{99m}Tc-MIBI was administered intravenously, and the patient continued to exercise for an additional period of 60-90 seconds when possible. Post-stress images were acquired at 45 minutes to one hour after tracer injection using a rotating dual-head gamma camera (Nucline Spirit DHV, Mediso, Hungary) equipped with low-energy, high-resolution, parallel-hole collimators, with a 20% energy window centered on the 140 keV photopeak. Sixty-four projections (20 seconds per projection), eight frames/cycle, with a 64x64 matrix obtained over an 180^0 orbit. On the following day, resting images were acquired one hour after the intravenous injection of 740 MBq of ^{99m}Tc-MIBI. Imaging tests were always performed in the supine position.

SPECT images were reconstructed using filtered back-projection with a Butterworth filter, order 7 and a cut-off frequency of 0.25 cycles/pixel. No attenuation or scatter correction was applied.

Scintigraphic image interpretation

Semiquantitative visual interpretation of images employed short-axis and vertical long-axis tomograms divided into 17 segments[14]. Each segment was scored by the consensus of two expert independent observers who were unaware of the clinical and angiographic data, using a five-point scoring system (from 0=normal to 4=absence of myocardial uptake). Disagreements, including any score in each SPECT segment were resolved by consensus. Segments with reduced tracer uptake were considered to be reversible defects, if the score decreased ≥1 point from stress to rest.

The assessment of regional wall motion (WM) was performed by visual inspection of gated tomograms in cine mode for semiquantitative scoring. The LV myocardium was divided into 17 segments. A four-point scoring system was used for segmental wall motion evaluation: 0=normal; 1=mildly hypokinetic; 2=moderately hypokinetic; 3=severely hypokinetic, and 4 = akinetic or dyskinetic. An operator-independent analysis of regional WM, LVEF, left ventricular end-diastolic volume, end-systolic volume and stroke volume was made using dedicated software (Emory Cardiac Toolbox).

The phase-derived indices were measured from the rest and post-stress gated-SPECT. The method has been extensively described[15]. In brief, three-dimensional count distributions were extracted from each of the eight LV short-axis data sets, submitted to Fourier data analysis, which generated a three-dimensional phase distribution (0-360^0) spanning the entire R-R interval and represented on a histogram. The peak phase represented the peak of the phase histogram; the standard deviation (SD) phase, the standard deviation of the phase distribution; whereas the histogram bandwidth (BW) represented the duration of the cardiac cycle during which 95% of the myocardium initiated contraction.

Statistical Analysis

Categorical variables are expressed as numbers and percentages, and compared between the two groups using the chi-square test and the Fisher's exact test. Continuous variables are expressed as mean ± standard deviation and compared by the Mann-Whitney U test or the Wilcoxon matched-paired test when necessary. A p value < 0.05 was considered significant.

Results

Patient Characteristics

Six patients were smokers. None had high blood pressure, diabetes mellitus or dyslipidemia.

According to antitrypanosomal therapy with benznidazole, patients were divided into two groups: Group I (n=22), who had received this therapy and Group II (n=18), who had not received it.

Stress characteristics are shown in Table 1. No differences were found between both groups. Patients did not experience angina during the stress test and none had ST depression. Chronotropic incompetence was detected in only one case.

Gated-SPECT MPI

Myocardial Perfusion and Left Ventricular Function

Thirty individuals (75%) showed a normal scan. In three cases (8%) the MPI was slightly abnormal, showing reversible perfusion defects in the inferior and lateral segments in the first case, anterior and inferior in the second, and inferior and inferoseptal in the third one. Of these, in two cases there was also a post-stress LVEF reduction. In seven cases the MPI was equivocal (SDS ≤ 3). Of these, three (43%) showed a post-stress LVEF reduction. In all cases with reversible defects on MPI, the affected segments were coincident with the segments with wall motion abnormalities detected by TDI-derived strain. No patient with abnormal gated-SPECT was a current smoker.

Although not significant, there was a tendency to a higher post-stress LVEF reduction in non-treated cases *vs*. those treated: mean ΔLVEF (LVEF at stress – LVEF at rest) was -1% for the whole group, 1% for Group I, and -3% for Group II. The case with the chronotropic incompetence (non-treated) showed a normal perfusion on MPI, but a ΔLVEF of -5%. Ventricular volumes were all within normal values.

A post-stress LVEF reduction ≥ 5% (ΔLVEF ≤ -5%) was found in 11 out of 40 individuals (28%). Of these, seven (39%) corresponded to non-treated cases, while only four (18%) were treated.

Mean transient ischemic dilation value was 1.00±0.09. No difference was found between treated and non-treated cases.

Intraventricular Synchronism

Intraventricular synchronism parameters are shown in Figure 1. Both the phase-derived standard deviation and the histogram bandwidth showed a significant difference between post-stress and rest acquisitions (p=0.002 and p=0.04, respectively). In both cases, there was a slight intraventricular dyssynchrony at rest which normalized at post-stress. Nineteen individuals (47%) exhibited an abnormal phase-derived SD at rest, while 17 (43%) showed an abnormal histogram BW at rest. In 13 cases (33%) both indices were abnormal at rest. No significant differences were found according to the antitrypanosomal therapy.

Discussion

Our results show some interesting findings: first, in individuals with the indeterminate phase of Chagas disease who have abnormal segmental motion determined by TDI-derived strain, MPI can demonstrate cases with the presence of perfusion defects (8%), as well as post-stress LVEF reduction (28%); second, MPI can also detect the presence of some degree of intraventricular dyssynchrony at rest, which normalized at post-stress.

Myocardial Perfusion and Left Ventricular Function

Regional wall motion and myocardial perfusion abnormalities have been found in Chagas cardiomyopathy by using MPI, both with thallium-201[10,16] and with technetium-labeled compounds[11,19]. Moreover, a marked topographic association between myocardial perfusion, cardiac innervation and wall motion abnormalities has been shown[18]. Nonetheless, to our knowledge, until the present day, there has been only one publication in which the authors describe how they performed gated-SPECT MPI in the indeterminate phase of the disease[12].

Moura et al[12] found, contrary to our results, that rest-stress MPI by using 99mTc-MIBI was not an effective method to detect early myocardial alterations in the indeterminate phase of Chagas disease. All patients had normal perfusion and only one case presented signs of ventricular dysfunction[12]. In our case, however, we did find perfusion and wall motion abnormalities, although not very frequently. This is logical considering the fact that these patients do not have clinical manifestations during the indeterminate phase of the disease. One explanation for this discrepancy could be the two-step protocol we used: only patients with segmental motion abnormalities detected by TDI-derived strain were submitted to the gated-SPECT MPI, which increased the possibilities of abnormal MPI findings.

In chagasic patients, in addition to the myocardial impairment resulting from parasitism of myocardial fibers and autoimmune reaction[17,19], investigations in human autopsies[20,21],

Table 1 - Stress Results

	Total (n=40)	Group I (n=22)	Group II (n=18)	p
Exercise duration (min)	13 ± 2	13 ± 2	13 ± 2	NS
METS	12.6 ± 3.1	12.5 ± 3.4	12.6 ± 2.7	NS
%MHR achieved	89 ± 7	90 ± 6	88 ± 8	NS
Peak systolic BP (mm Hg)	136 ± 17	139 ± 13	132 ± 20	NS
Peak diastolic BP (mm Hg)	83 ± 10	85 ± 9	79 ± 11	NS

MHR: maximal heart rate; BP: blood pressure; Values are expressed as mean ± standard deviation; p value (Group I vs. Group II).

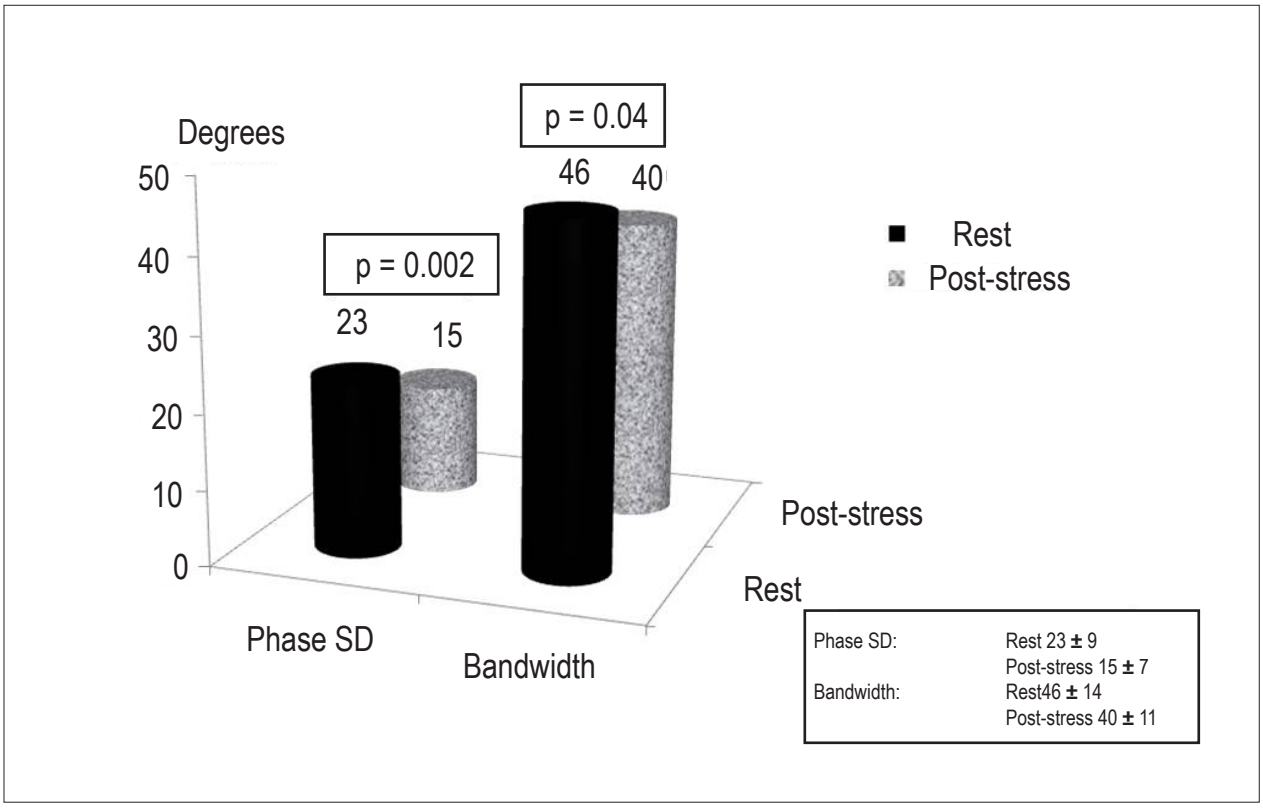

Figure 1 - *Intraventricular synchronism parameters. Both the phase-derived standard deviation and the histogram bandwidth showed a significant difference between post-stress and rest acquisitions (p=0.002 and p=0.04, respectively). In both cases there was a slight intraventricular dyssynchrony at rest which normalized at post-stress. Phase SD: phase-derived standard deviation.*

as well as experimental studies[22,23] have suggested that derangements of the coronary microcirculation affect regional myocardial perfusion through myocytolysis and reparative fibrosis[2,19]. In accordance with this, reversible perfusion defects have been found in patients with Chagas cardiomyopathy and angiographically normal epicardial coronary arteries[10], suggesting the possibility of abnormal myocardial blood flow regulation at the microvascular level.

Hiss et al[11] have demonstrated a positive correlation between the extent of perfusion defects and the severity of left ventricular systolic dysfunction, both in the early stages of Chagas disease[16], as well as during the five-year follow-up[11]. Thus, one explanation for our MPI results could be that our cases were at a very early phase of the disease, and therefore, we only found a small percentage of reversible perfusion defects (8%). But it should also be considered that 17% of cases had equivocal MPI results and, although these only reflect very minor abnormalities, it might be interesting to undertake a long-term follow-up taking into account the role of microvascular alterations in the pathogenesis of myocardial impairment in Chagas cardiomyopathy.

Intraventricular Synchronism

To our knowledge there has been only one study published on the subject of prevalence and prognostic value of ventricular dyssynchrony in Chagas disease[24]. The authors included 56 patients with cardiomyopathy and all were studied by echocardiography. The prevalence of interventricular dyssynchrony was 34% and the intraventricular dyssynchrony was 85%, but they did not find that dyssynchrony was a strong predictor of clinical events[24].

Echocardiographic methods, although very useful and extended, are not very reproducible. On the contrary, nuclear medicine techniques do not have this limitation, and it has been shown that both phase-derived standard deviation and histogram bandwidth are the indices obtained by Fourier phase analysis in a gated-SPECT MPI, which allow the assessment of intraventricular synchronism[15,25,26].

The fibrosis characterized by a diffuse and dense interstitial accumulation of collagen that encloses myocardial fibers in Chagas heart disease[3] may involve all areas of the heart, including the conduction system. This explains the frequent occurrence of atrioventricular and intraventricular blocks, as well as sinus node dysfunction in these patients. It is possible that these intraventricular blocks cause some degree of intraventricular dyssynchrony, depending on the stage and progression of the disease.

Consistent with this, our cases showed a slight intraventricular dyssynchrony at rest, expressed both in phase-derived standard deviation and histogram bandwidth values. Cut-off values for a significant dyssynchrony have been set at 43^0 for the phase-derived standard deviation and at 135^0 for the histogram bandwidth[27], higher than our mean values: 23^0 and

46⁰, respectively. However, it is convenient to point out that these values were set for patients with dilated cardiomyopathy who were studied prior to cardiac resynchronization therapy, where it was of utmost importance to predict who would or would not respond to this therapy. On the contrary, our cases were chagasic patients at the early stage of the disease, where this difference, although small, should be taken into account.

Recently it has been published that there is no difference between rest and stress phase-derived indices[28], probably due to a long interval between injection at stress and the image acquisition, making these values similar to those acquired at rest. However, in the case of our investigation, there is a difference, albeit small, and the rest dyssynchrony normalized with stress. We have no clear explanation for this finding and to our knowledge there is no previous work published on this subject. One possible explanation might be that, due to the early stage of the disease in this group of patients, to perform a high level of exercise could improve the conduction due to the stimulation by catecholamines.

Limitations

Some of the limitations of the study are that: firstly, a small sample of patients was included; secondly, it lacks follow-up data which will be the subject of further investigation and, thirdly, we were not able to have a control group of patients because it is not ethical to irradiate persons without justifiable clinical reasons, as in this case. For this reason, we only included patients with abnormal segmental motion determined by TDI-derived strain. Thus, the study should be considered one of hypothesis-generating.

It has been demonstrated that the main cardiac alterations with dilated cardiac chambers and heart failure appear later in the evolution of the Chagas disease and, at this point, these manifestations are generally irreversible, so that detecting incipient alterations could help these patients through a more personalized and early treatment.

Conclusions

A stress-rest gated-SPECT is a valid approach to detect early myocardial alterations as well as intraventricular dyssynchrony in the indeterminate phase of Chagas disease inpatients with segmental motion abnormalities previously detected by TDI-derived strain. Thus, a two-step protocol: echocardiography at first, and gated-SPECT MPI in the second place, could be applied in these patients.

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