Scintigraphy for the Detection of Myocardial Damage in the Indeterminate Form of Chagas Disease

Ivana Moura Abuhid[2], Enio Roberto Pietra Pedroso[1], Nilton Alves de Rezende[1]

Faculdade de Medicina da Universidade Federal de Minas Gerais[1]; Instituto de Medicina Nuclear e Diagnóstico Molecular[2], Belo Horizonte, MG - Brazil

Abstract

Background: Non-invasive cardiological methods have been used for the identification of myocardial damage in Chagas disease.

Objective: To verify whether the rest/stress myocardial perfusion scintigraphy is able to identify early myocardial damage in the indeterminate form of Chagas disease.

Methods: Eighteen patients with the indeterminate form of Chagas Disease and the same number of normal controls, paired by sex and age, underwent rest/stress myocardial scintigraphy using sestamibi-99mTc, aiming at detecting early cardiac damage.

Results: The results did not show perfusion or ventricular function defects in patients at the indeterminate phase of Chagas disease and in the normal controls, except for a patient who presented signs of ventricular dysfunction in the myocardial perfusion scintigraphy with electrocardiographic gating.

Conclusion: The results of this study, considering the small sample size, showed that the rest/stress myocardial scintigraphy using sestamibi-99mTc is not an effective method to detect early myocardial alterations in the indeterminate form of Chagas disease. (Arq Bras Cardiol. 2010; [online]. ahead print, PP.0-0)

Key words: Scintilography; myocardium/injuries; ventricular function; Chagas disease.

Introduction

Chagas disease is known for its high morbidity and mortality. It presents a broad range of clinical signs that vary according to the geographical area, possibly reflecting genetic factors related to both man and the parasite[1]. It is estimated that Chagas disease affects around 16 to 18 million individuals in South America, with cardiac involvement being the most severe complication, present in a third of the infected patients throughout their lifetime[2,3].

Clinical and experimental studies divide the cardiac involvement in Chagas disease in three distinct phases: an initial myocarditis, followed, most of the times, for a period of 10 to 30 years of complete absence of cardiac manifestations or symptoms in other systems, which is called the indeterminate phase and, finally, the cardiomyopathy or the involvement of other organs (established Chagas disease)[4,5].

The cardiac involvement in Chagas disease constitutes, most of the time, a cardiomyopathy that can manifest as cardiac arrhythmia, left ventricular apical aneurism, congestive heart failure, systemic thromboembolism and sudden death[6]. All these aspects have a great impact on the work capacity, on the premature disability for certain activities and early death, becoming a social and public health problem for those asymptomatic patients who present positive serological markers for the disease, that is, those patients classified as having the "indeterminate" form of Chagas disease[7].

This aspect is important because the possibility of identifying the patients with a higher risk for the development of cardiopathy could, in theory, allow a better distribution of these individuals in the labor market.

According to the currently accepted criteria, the diagnosis of the indeterminate form of Chagas disease requires the patient to present at least one positive serological test, but no cardiovascular or digestive system signs and/or symptoms, normal conventional electrocardiogram and no alterations at the heart, esophagus and large intestine X-rays (criteria of Araxa). Therefore, the indeterminate form ends only at the onset of cardiovascular or digestive symptoms or when radiological or electrocardiographic abnormalities appear[3].

In turn, necropsy studies, as well as more sensitive methods such as ergometry, autonomic activity studies, high-resolution echocardiography, echocardiography associated with the TEI index and dynamic electrocardiography, at varied degrees, have shown that approximately 25% to 30% of the chagasic patients classified as having the indeterminate form of the

Mailing address: Nilton Alves de Rezende •
Rua Aimorés 462/116 - Funcionários - 30140-070 - Belo Horizonte, MG - Brazil
E-mail: narezende@terra.com.br
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disease presented some degree of cardiac involvement[8-17]. As pointed out before, approximately one-third of the patients with the indeterminate form of the disease develop myocardiopathy 10 to 30 years after the initial infection[18]. Therefore, it is important to establish the risk stratification for the early identification of the cardiac involvement at this phase of the disease, which would allow early therapeutic interventions to be carried out, as well as a possible reallocation of workers in the production chain, preventing social conflicts[6,12].

The Nuclear Medicine methods routinely used in the assessment of cardiac function have been used in established Chagasic cardiomyopathy[19-23]. However, the usefulness of the myocardial perfusion scintigraphy with sestamibi-99mTc synchronized to the ECG, simultaneously assessing the myocardial perfusion and the ventricular function, in opposition to other noninvasive cardiological assessment methods, had not been systemically used in an attempt to identify early myocardial damage in the indeterminate form of Chagas disease.

Patients and methods

The research project was approved by the Department of Internal Medicine of the School of Medicine of UFMG and all patients gave their free and informed consent before study enrolment. Eighteen patients with the indeterminate form of Chagas disease and 18 normal controls were studied. In addition to demographic data (age and sex), the risk factors for coronary artery disease - CAD - (arterial hypertension, diabetes mellitus, smoking status, dyslipidemia and family history of CAD, as well as previous coronary event - typical angina or myocardial infarction). The diagnosis of the indeterminate form of the disease followed the criteria of Araxa meeting: positive serological marker for the disease, absence of cardiovascular or digestive signs and/or symptoms, normal conventional electrocardiogram, chest X-ray, contrast X-ray of the esophagus and opaque enema. The control individuals were recruited from the Laboratory of Nuclear Medicine and paired by sex and age with the Chagasic patients. The control group was not submitted to chest, esophagus and large intestine X-ray. Individuals who presented at least one proven risk factor for CAD were excluded from both groups. The myocardial scintigraphy with sestamibi-99mTc was carried out before and after physical exertion. The technetium-labeled sestamibi was prepared according to the manufacturer's instructions (Cardiolite; Bristol Myers Squibb GmbH) and each patient and respective control received 1110 MBq of Sestamibi-99mTc administered by IV route. All scintigraphy images were obtained in dual-head gamma cameras (GE Health Care, Milwaukee, WI) before and after physical exertion, with 48-hour intervals, using the Single-Photon Emission Computed Tomography (SPECT), synchronized with the electrocardiogram (Gated-SPECT). Image interpretation was based on the direct visual analysis and also on the quantitative verification of the perfusion images obtained automatically with the software programs CEQUAL, ECtoll-box and QGS/QPS for simultaneous assessment of the ejection fraction. A semi-quantitative analysis of the perfusion was carried out using the Summed Stress Score (SSS). The left ventricular contractility was assessed through the analysis of the LV wall motility, by visualizing the sub-endocardial outline. All examinations were interpreted by two specialists in Nuclear Medicine blinded to the clinical status of the patients.

The Student's *t* test was used to compare the means of the quantitative variables obtained at the scintigraphy in the two groups, both at rest and after exertion and statistical significance was set at 5%. The statistical analysis was carried out using the SPSS software package.

Results

All patients met the criteria for the diagnosis of the indeterminate form of Chagas disease and did not present risk factors for CAD. Ten patients were males and age varied from 32 to 53 years (mean of 43.2 years). Sex and age were similar in the control group. The results of the myocardial scintigraphy with sestamibi-99mTc before and after physical exertion are shown in Table 1. In chagasic patients, the mean left ventricular ejection fraction (LVEF) was 54.1±8.6 at rest and 57.3±10.5 after physical exertion. Although small, this difference was statistically significant,s (p=0.004; 95%CI= -5.25_ - -1.16). In the control group, the LVEF was 55.9±9.1 and 58.1±10.3 at rest and after physical exertion (p=0.003; 95%CI= -4.38 - -1.67). There was no difference between the groups at rest (p=0.064; 95%CI= -4.98 - -1.89) and after physical exertion (p=0.066; 95%CI= -4.78 - -1.80). The percentage of increase in LVEF after exertion was similar between the groups o(5.6%). Both Chagasic patients and normal controls presented a normal pattern of radioisotope distribution in the myocardial walls at the qualitative and quantitative analyses before and after physical exertion.

Only one patient (#9) presented myocardial dysfunction characterized by diffuse hypercontractility of myocardial walls and reduced LVEF obtained by the automated processing of the QGS (Quantitative Gated SPECT) program, of which lower limit of normality is 44%[24]. This patient was re-evaluated two months later to verify a possible methodological error, when it was verified that he had started to present cardiovascular symptoms and was receiving pharmacological treatment for heart failure.

Discussion

The rest/stress myocardial perfusion scintigraphy is a noninvasive prognostic and diagnostic investigation method for several cardiovascular diseases, including coronary artery disease (CAD)[25]. In our study, only one patient, initially diagnosed with the indeterminate form of Chagas disease, presented scintigraphy alterations. This patient presented ventricular extrasystoles at the exercise test, signs of LV dysfunction at the functional analysis with diffuse hypocontractility of the myocardial walls and decreased LVEF both at rest and after physical exertion, but normal perfusion aspect. It is possible that this patient was wrongly classified as having the indeterminate form of Chagas disease according to the criteria of Araxa, as two months later the patient was already receiving pharmacological treatment for heart failure. This is a relevant aspect, as the use of more sensitive diagnostic

Table 1 – Rest/Stress Myocardial Perfusion Scintigraphy with sestamibi-99mTc in the indeterminate form of Chagas Disease

Patient, sex* and age**	Rest					Stress				
	Perfusion Image	Funcional analysis				Perfusion Image	SSS	Funcional analysis			
		LVEF (%)	ESV (ml)	EDV (ml)	LVC			LVEF (%)	ESV (ml)	EDV (ml)	LVC
1, M, 52	Normal	55	51	113	Normal	Normal	0	54	55	116	Normal
2, M, 35	Normal	47	62	117	Normal	Normal	0	52	53	111	Normal
3, F, 45	Normal	57	33	78	Normal	Normal	1	63	24	66	Normal
4, F, 54	Normal	61	36	91	Normal	Normal	3	67	28	83	Normal
5, F, 41	Normal	69	22	73	Normal	Normal	1	73	19	68	Normal
6, M, 32	Normal	51	57	117	Normal	Normal	0	50	58	117	Normal
7, F, 53	Normal	68	19	58	Normal	Normal	2	82	11	59	Normal
8, M, 35	Normal	45	70	125	Normal	Normal	1	45	67	122	Normal
9a,M, 47(***)	Normal	39	96	15l	Decreased	Normal	1	41	85	119	Decreased
9b, M, 47	Normal	40	72	140	Decreased	Normal	0	42	77	132	Decreased
10,M, 42	Normal	45	62	113	Normal	Normal	0	47	70	120	Normal
11,M, 38	Normal	56	37	85	Normal	Normal	1	66	26	78	Normal
12,M, 45	Normal	54	45	98	Normal	Normal	2	62	29	77	Normal
13,M, 48	Normal	50	45	90	Normal	Normal	0	53	42	91	Normal
14,F, 43	Normal	67	30	90	Normal	Normal	0	63	27	73	Normal
15,F, 43	Normal	59	37	89	Normal	Normal	2	61	33	86	Normal
16,F, 42	Normal	55	27	61	Normal	Normal	0	56	25	57	Normal
17,F, 42	Normal	56	40	91	Normal	Normal	1	57	38	87	Normal
18,M,41	Normal	52	47	97	Normal	Normal	0	53	41	86	Normal

**(years); **M - male, F - female; (***) = this patient repeated the scintigraphy two months later; LVEF - left ventricular ejection fraction; ESV - end systolic volume (upper limit =67 ml); EDV - end diastolic volume (upper limit - 137 mL); LVC - left ventricular contractility; SSS - Summed Stress Score - summation of values attributed to each myocardial segment, representative of the stress phase.*

methods for myocardial dysfunction raise doubts about the use of the criteria of Araxa for the definition of the indeterminate form of Chagas disease, which should be reviewed.

The absence of symptoms, the plain chest X-ray and the normal electrocardiogram are not enough to exclude the functional myocardial involvement.

This fact is demonstrated by the normal results of the examinations of this patient #9 in this case series, who presented ventricular dysfunction at the perfusion scintigraphy. Therefore, the normal two-dimensional echocardiographic results[12] or other noninvasive cardiologic diagnostic methods[15,17] should be considered as diagnostic criteria of the classic indeterminate form of Chagas disease. Relevant also in this context are the results of the radionuclide angiography that showed right ventricular involvement in patients with the indeterminate and exclusive digestive form of Chagas disease[26], as well as studies using metaiodinebenzylguanidine (mIBG) labeled with ssIm-sesaram, como ^{123}I and Thallium-201 that showed alterations in the inferoapical innervation of the left ventricle, with or without apical perfusion defect in 12 patients that presented the indeterminate form of Chagas disease[27]. These facts co-substantiate the idea that patients with normal ECG and radiological results can, in fact, present function alterations in one or the other ventricle, as demonstrated by patient #9 in this case series. As the LV global systolic dysfunction is the most important prognostic factor of morbidity and mortality in Chagas disease, the early identification with more sensitive methods and the specific treatment of these patients, could, in theory, improve survival and reduce the morbidity[12]. All the other patients, as well as the controls, presented normal qualitative and quantitative perfusion and functional tests at rest and after exertion.

The pathogenesis of the Chagasic cardiomyopathy remains unclear. Several studies have suggested that after the acute inflammatory phase of the disease, a "silent" myocarditis is established or persists at the indeterminate phase of the disease, with progressive destruction of the myocardial fibers and reparative fibrosis. The mechanisms involved in this process include a microangiopathy, characterized by edema of endothelial cells, demonstrated by *in vitro* studies, in animal models and also in humans. Neurogenic mechanisms are also mentioned, inflammation in response to the presence of the parasite in cardiac fibrocells and autoimmune mechanisms that would favor the myocardial damage[12,28]. Patients with Chagas disease and chest pain suggestive of myocardial ischemia submitted to coronary angiography presented normal coronary arteries in most cases, but also, mild perfusion alterations detected by Thallium-201 suggestive of myocardial

ischemia, possibly due to microvascular disease, which could be responsible for the patients' angina symptoms[22].

However, it must be emphasized that these studies were carried out at the chronic phase of the disease and using the radiotracer Thallium-201, a marker of both cell membrane flow and integrity. In our study, the examinations were carried out during the indeterminate phase of the disease and the use of sestamibi-99mTc, a marker that is nearly exclusive of regional myocardial flow could explain, at least in part, the normal results observed in the study.

Considering the small sample size, possibly due to the inclusion criteria that included the opaque enema being carried out in Chagasic patients, the patients with the so-called indeterminate form of the disease presented a homogenous distribution of the radionuclide in the myocardial walls, similar to what was observed in normal individuals. Therefore, the myocardial scintigraphy does not have enough sensitivity and specificity for the detection of early myocardial damage in the indeterminate form of Chagas disease.

As the request for myocardial perfusion scintigraphy becomes more frequent, however, more patients with the indeterminate form of Chagas disease can occasionally be referred for assessment of the clinical suspicion of coronary artery disease. Although myocardial scintigraphy studies have demonstrated perfusion defects, that were either fixed, reversible or with a reverse distribution pattern in the chronic phase of the disease using Thallium-201, our study showed a normal myocardial perfusion with sestamibi-99mTcin in patients with the indeterminate form of the disease.

Therefore, in patients with the indeterminate form of Chagas disease, the presence of normal post-stress scintigraphy images can suggest a low probability of coronary artery disease and the presence of transient perfusion defects induced by physical exertion or pharmacological stress must be considered indicative of myocardial ischemia, possibly related to CAD.

In turn, a homogenous distribution pattern of the radionuclide associated with indicators of ventricular dysfunction, as observed in patient #9, suggests a higher probability of primary cardiomyopathy than coronary artery disease.

The myocardial perfusion scintigraphy with electrocardiographic gating (G-SPECT) is acknowledged as being useful in the differentiation between ischemic and non-ischemic etiologies of cardiomyopathy. Patients with ischemic myocardial disease present more severe and extensive defects, associated with areas of segmental hypokinesis or akinesis, whereas patients with non-ischemic etiology present a more homogenous perfusion pattern, with diffuse hypokinesis.

Thus, it is unlikely that the ischemic etiology is the cause of the cardiomyopathy in patients with normal perfusion scintigraphy. In such cases, the most probable cause is a primary cardiomyopathy. Considering these facts, the assessment of myocardial dysfunction in the indeterminate form of Chagas disease using more sensitive methods, such as the autonomic dysfunction tests, must precede the myocardial perfusion scintigraphy. In patients with established cardiomyopathy, the rest/stress myocardial perfusion scintigraphy would only be useful to differentiate the ischemic from the non-ischemic etiology.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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