Current vision of a disease with high mortality that is progressively dispersing throughout the world: Chagasic heart disease

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The sympathetic denervation studies and the studies of microvascular involvement are the most important tools for early detection of Chagas heart disease. Especially the 123I-123I-MIBG-SPECT or 11C-meta-hydroxyephedrine-PET studies since everything starts from sympathetic denervation. Also it is advisable to insist on the assessment of other parameters of early involvement of left ventricular systolic function to understand the importance of the additional information provided by the analysis of the parameters of ventricular remodeling, synchrony, and GLS in patients with normal left ventricular ejection fraction and in the absence of ventricular dilatation for early detection of myocardial dysfunction.

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INTRODUCTION

Chagas disease was described in 1909 by Carlos Chagas.[1] This disease is caused by the protozoan *Trypanosoma cruzi* (hematophagous insects) by means of the transcutaneous inoculation of the infected excreta.

In the last 30 years, the prevalence of the disease has been reduced from 18 million in 1990 to 8 million in 2005. Today, approximately *6* million people[2] have an incidence of 1.85 per 100 people per year. Despite this, the prevalence is very high and worrying due to the complications of the disease. In 2016, the United States had the seventh highest prevalence of Chagas infections in the Western Hemisphere, with > 300,000 infected individuals estimated to be living in the United States.[3] Of those, an estimated 30,000 to 45,000 will go on to develop Chagas heart disease.[3]

Recently published data by the Spanish National Statistics Institute (Spanish Agency of Medicines and Medical Devices) from 2010 to 2018 by Navarro et al observed that in Spain 55,367 out of 2,602,285 migrants originally from endemic countries were living with Chagas disease in Spain in 2018, accounting for a prevalence of 2.1%.[4] Only 1% of these cases (613/455,566) were children aged 14 years or less resulting in

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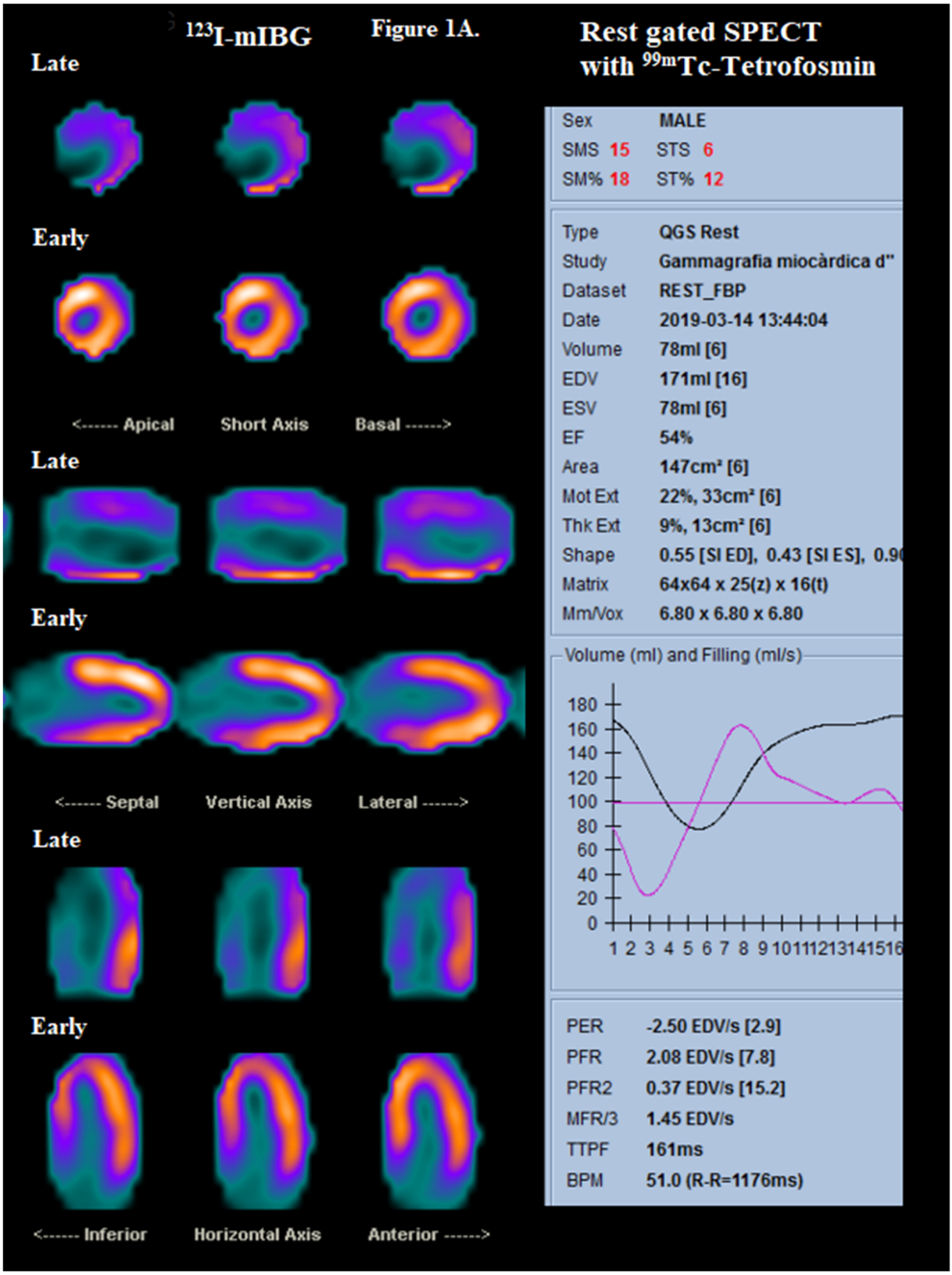
(a)


123I-mIBG
Figure 1A.
Rest gated SPECT
with 99mTc-Tetrofosmin
Late
Early
<------ Apical
Short Axis
Basal ------>
Late
Early
<------ Septal
Vertical Axis
Lateral ------>
Late
Early
<------ Inferior
Horizontal Axis
Anterior ------>
Sex MALE
SMS 15 STS 6
SM% 18 ST% 12
Type QGS Rest
Study Gammagrafia miocàrdica d"
Dataset REST_FBP
Date 2019-03-14 13:44:04
Volume 78ml [6]
EDV 171ml [16]
ESV 78ml [6]
EF 54%
Area 147cm² [6]
Mot Ext 22%, 33cm² [6]
Thk Ext 9%, 13cm² [6]
Shape 0.55 [SI ED], 0.43 [SI ES], 0.9
Matrix 64x64 x 25(z) x 16(t)
Mm/Vox 6.80 x 6.80 x 6.80
Volume (ml) and Filling (ml/s)
180
160
140
120
100
80
60
40
20
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
PER -2.50 EDV/s [2.9]
PFR 2.08 EDV/s [7.8]
PFR2 0.37 EDV/s [15.2]
MFR/3 1.45 EDV/s
TTPF 161ms
BPM 51.0 (R-R=1176ms)

◀**Figure 1.** All images corresponded to the same patients. (A) On the left: Sympathetic denervation (^{123}I-mIBG) in anterior, septal and apical regions. On the right: Gated SPECT with ^{99m}Tc-Tetrofosmin, changes in motility and left ventricular thickening with normal left ventricular ejection fraction and dilated left ventricle in diastole. (B) Differences in the interpretation of the sympathetic denervation image with and without attenuation correction in early and late images. In late images with or without attenuation correction, the intensity and extent of denervation is higher, although less significant in images without attenuation correction. (C) ^{123}I-mIBG heart/mediastinum (H/M) ratio in early and late images. *SE%*, percentage of myocardium with early ^{123}I-mIBG uptake defect; *SES*, summed early score; *SDS*, summed difference score; *SLS*, summed late score; *SL%*, percentage of myocardium with late ^{123}I-mIBG uptake defect.

a prevalence of 0.1%.[4] The indexes of underdiagnosis and undertreatment were heterogeneous across different Spanish autonomous regions, but the overall index of underdiagnosis was around 71%, and the overall index of undertreatment was 82.5% in patients aged 15 years or older, and 60% in children.[4]

Chagas disease has an acute phase and a chronic phase. The acute phase may be asymptomatic, or as a nonspecific febrile illness, symptomatic in 1% of infected patients. Also, the chagasic myocarditis is infrequent (1 to 5 of every 10,000 infected patients), although with high mortality.[5] An estimated 10% to 30% of people harboring the parasite will develop symptomatic chronic Chagas disease years or decades later.[6,7] In the chronic phase, the Chagas disease is subdivided in 4 clinical presentations[2]: indeterminate, digestive, cardiac, or mixed (both digestive and cardiac). These forms correspond to the progression of Chagas disease. Furthermore, the progress of heart damage can be classified into 5 different evolutionary forms (A, B1, B2, C, D)[2,5,8]:

Chagas Intermediate (A): Normal ECG. Normal echocardiogram. Asymptomatic.
Chagas cardiomyopathy (B1): Abnormal ECG. Abnormal echocardiogram with normal left ventricular ejection fraction. Without clinical heart failure.
Chagas dilated cardiomyopathy (B2): Abnormal ECG. Abnormal echocardiogram with left ventricular dysfunction. Without clinical heart failure.
Chagas dilated cardiomyopathy with heart failure (C): Patients with ventricular dysfunction and clinical heart failure (NYHA functional class I, II, III, or IV).
Chagas dilated cardiomyopathy with heart failure (D): Patients with refractory clinical heart failure at rest.

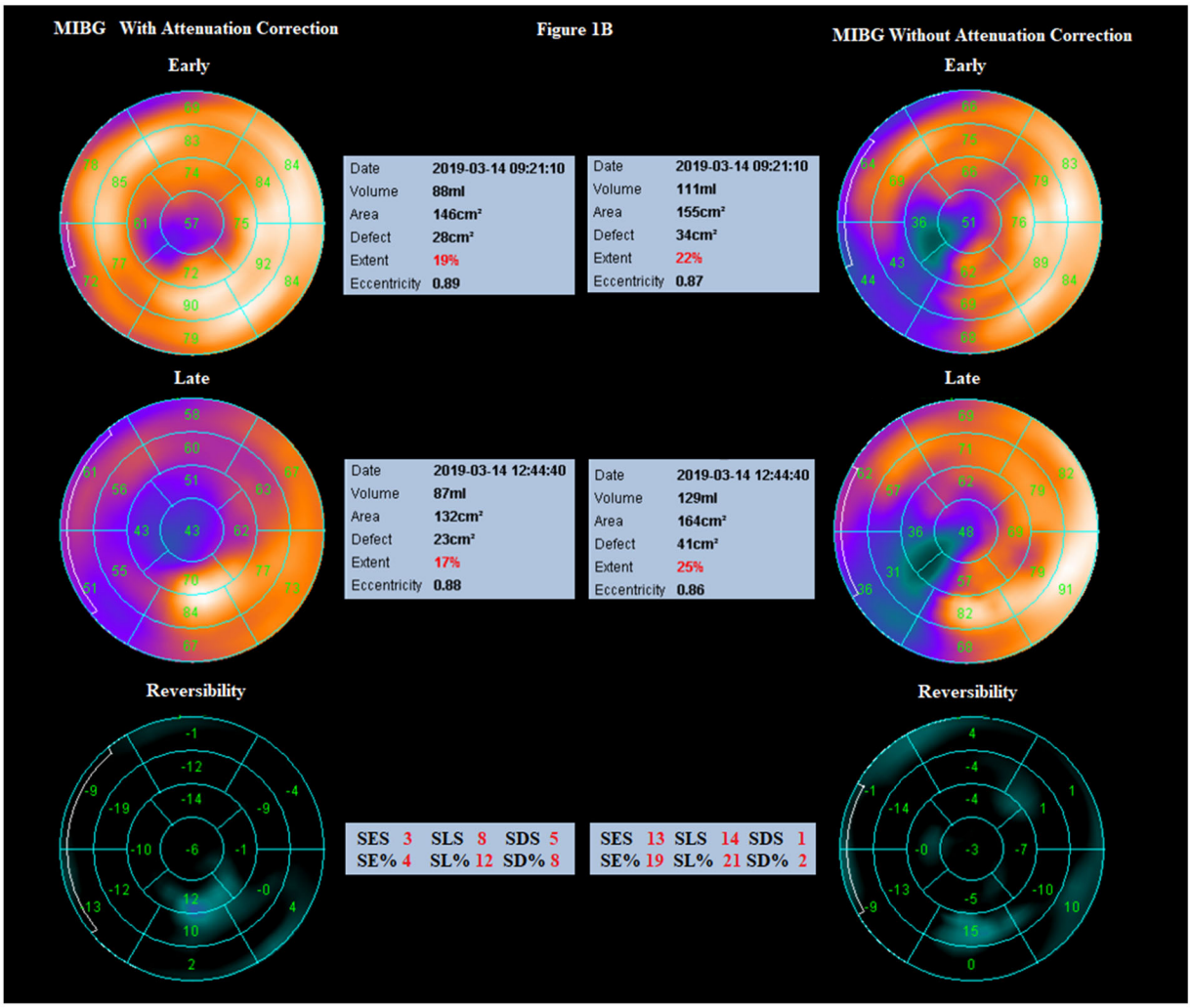
The mega esophagus and megacolon appear in 5% to 10% of patients, although Chagas cardiomyopathy is by far the most serious form of the disease.[9,10] Moreover, these patients can remain throughout life with the so-called indeterminate form, or develop a full-blown chronic Chagas cardiomyopathy (30%-40%), which leads to sudden death, complex arrhythmias, ventricular aneurysms, heart failure, and thromboembolism.[10,11] Therefore, the importance of this topic lies in the early diagnosis of Chagas disease to detect early or prevent cardiac involvement, as well as, diagnosing Chagas disease in patients with already established cardiomyopathies, because the Chagasic cardiomyopathy has a fourfold higher morbidity and mortality than do typical patients with cardiomyopathies.[12] Hence, the use of tools that allow diagnosis as early as possible is a priority.

DISCUSSION OF CURRENT STUDY PUBLISHED IN THE JOURNAL NUCLEAR CARDIOLOGY

In the current issue of the Journal Nuclear Cardiology, Xavier de Brito et al presents a study titled ''Autonomic denervation, myocardial hypoperfusion and fibrosis may predict ventricular arrhythmia in the early stages of Chagas cardiomyopathy''. This was a cross-sectional study conducted on 29 outpatients from the Clinical Research Laboratory for Chagas Disease. In all of the patients the myocardial sympathetic innervation was evaluated with I-123-labeled metaiodobenzylguanidine (^{123}I-MIBG) with SPECT (^{123}I-MIBG-SPECT), the myocardial fibrosis with LGE-MRI, and the perfusion imaging with MIBI-SPECT. Regardless of the fact that the number of patients is a very small series and that the coronary anatomy was not studied in any patient, this study shows how early detection of myocardial involvement can be done in patients with Chagas disease. The authors discussed that the extent of cardiac sympathetic denervation, myocardial hypoperfusion and fibrosis was associated with the presence of ventricular arrhythmia in the early phases of Chagas heart disease. They, also, reported that sympathetic denervation by ^{123}I-MIBG-SPECT before any remodeling or change in left ventricular function had occurred, with a correlation to ventricular electrical instability. This data is very important from the clinical point of view, and is consistent with previous studies.[13–16]

For example, Barizon et al[13] found that combined myocardial analysis of the extent and location of autonomic denervation, hypoperfusion, and scarring may allow for a better understanding of the pathophysiology of Chagas cardiomyopathy. Velasco and Morillo suggest that there exists a strong association between areas of myocardial denervation and perfusion defects during stress, while areas of fibrosis were smaller and without association.[14] Therefore, these studies add to the idea that autonomic denervation and microvascular dysfunction are closely interrelated in Chagas disease,

(b)



(c)

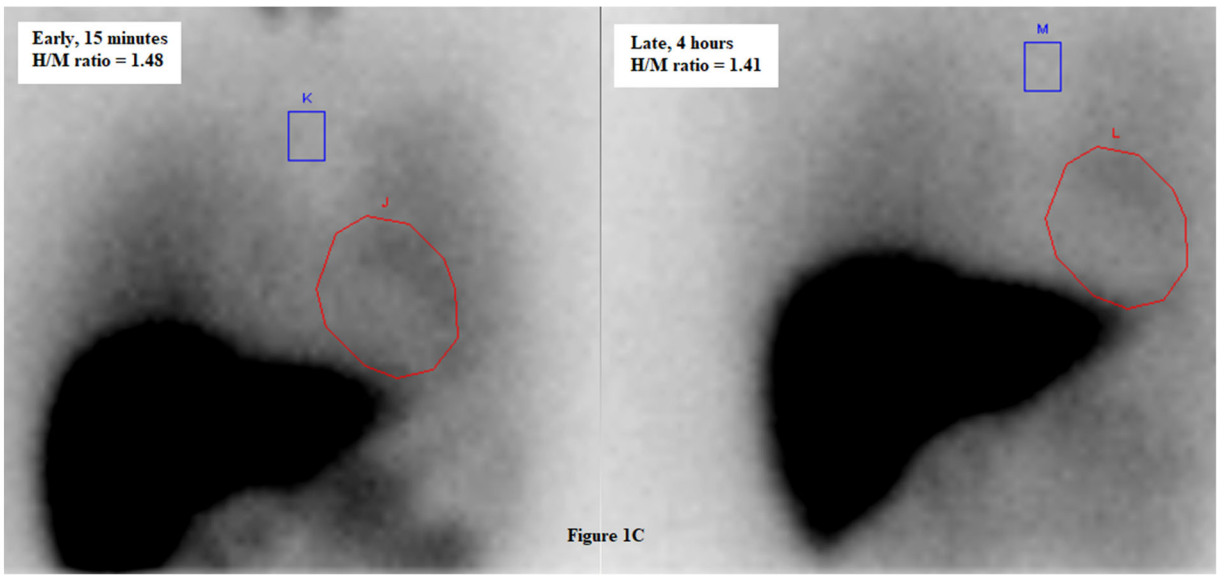


Figure 1. continued.

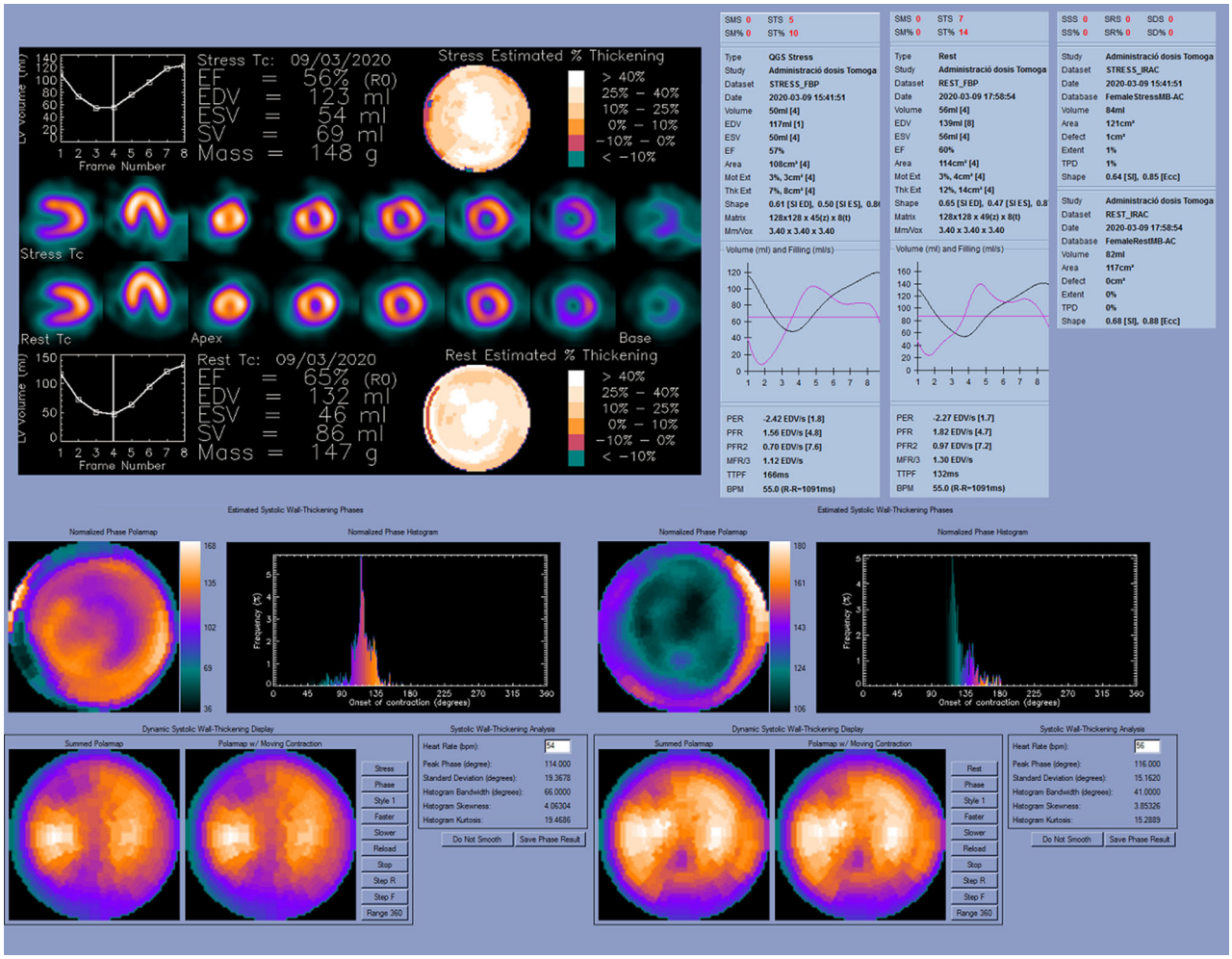


Figure 2. Patient with normal left ventricular ejection fraction, motility, thickening and myocardial perfusion (^{99m}Technetium-Tetrofosmin) studied with SyncToolTM (Emory Cardiac ToolboxTM) and QGS® software package in the same day. Ventricular dyssynchrony (Bandwidth 66°) is observed on exercise stress imaging.

and fibrosis seems to appear late in the process.[14,15] Previously, Rabelo et al[16] observed a reduction in coronary flow reserve measured with transthoracic dipyridamole (0.84 mg·kg^{-1} in 6 minutes) stress echocardiography in patients with Chagas disease compared to control subjects. Coronary flow reserve was assessed on left anterior descending artery using pulsed Doppler as the ratio of maximal peak vasodilation (dipyridamole) to rest diastolic flow velocity. Moreover, Torres et al[17], evaluated the coronary endothelial function infusing acetylcholine into the left anterior descending coronary artery of patients with Chagas' heart disease. Coronary blood flow was measured with a Doppler flow velocity catheter and by quantitative coronary cineangiography. They observed that patients with Chagas' heart disease have an abnormality of the coronary endothelium-dependent vasodilation. In addition, the patients with Chagas disease may have myocardial perfusion abnormalities with normal coronary arteries, in the same way as patients with coronary artery disease.[18–20] For this reason, it is important to assess the coronary anatomy in patients with chronic Chagas heart disease.

In the study of Gladioli et al[21] no correlation was detected between myocardial fibrosis and ventricular arrhythmias. In this series of 43 patients with chronic Chagas cardiomyopathy and left ventricular ejection fraction $\geq$ 35%, patients were divided into three groups: patients with sustained ventricular tachycardia, patients with non-sustained ventricular tachycardia on 24-hours Holter monitoring, and patients without ventricular arrhythmias. All patients were evaluated by ^{123}I-

Table 1. Cardiac prognostic variables in Chagas disease

Author	Year	Research	n	Predictor	Event
Mady et al[28]	1994	Echocardiogram	104	Maximal oxygen consumption Functional class Left ventricular ejection fraction	Mortality
Salles et al[29]	2003	Electrocardiogram and Echocardiogram	738	QT-interval dispersion > 65 ms (HR: 1.45) Maximum QTc interval ≥ 465 ms (HR: ?) LV end-systolic dimension (HR: 1.36)	Sudden cardiac death
Salles et al[30]	2004	Electrocardiogram		T-wave axis deviation	Sudden cardiac death
Viotti et al[31]	2004	Echocardiogram	849	ECG abnormalities LV diastolic dimension LV systolic dimension Ejection fraction	Death
Rassi et al[32]	2006	Clinical score	424	Risk Score: New York Heart Association class III or IV (5 points), (HR: 13.9). Evidence of cardiomegaly on radiography (5 points), (HR: 9.2) LV systolic dysfunction on echocardiography (3 points), (HR: 8.5) NSVT on 24-h Holter monitoring (3 points), (HR: 5.7) Low QRS voltage on electrocardiography (2 points), (HR: 2.6) and male sex (2 points), (HR: 2.3) Also QRS fragmentation	Death
Rassi et al[33]	2007	Clinical study (meta-analysis was not feasible)	3928	Impaired left ventricular function, New York Heart Association class III/IV, cardiomegaly, and NSVT Left ventricular dysfunction and NSVT, (HR: 15.1)	All-cause mortality Sudden cardiac death
Acquatella et al[5]	2007	Echocardiogram (meta-analysis)	3242	Left ventricular apical aneurysm	Mortality
Nunes et al[34]	2008	Echocardiogram	158	Systolic and diastolic function of the right ventricular Right ventricular Tei index (HR: 5.29)	Death of progressive heart failure and sudden death

Table 1 continued

Author	Year	Research	n	Predictor	Event
Gonçalves et al [35]	2010	Electrocardiogram	120	Polymorphic ventricular extrasystoles or high-degree left-branch block	All-cause mortality Sudden cardiac death
Lima-costa et al[36]	2010	Clinical study		B-type natriuretic peptide (HR: 2.7) alone or in association with atrial fibrillation (HR: 3.19)	Stroke mortality
Miranda et al[24]	2011	^{123}Iodine-MIBG-SPECT	26	Sympathetically denervated viable myocardium	SVT
da Matta et al[37]	2012	Clinical study	329	Pacemaker rhythm (HR: 2.7) and coronary artery disease (HR: 2.6)	Stroke
Sabino et al[38]	2013	Clinical study		Asymptomatic *T cruzi*-seropositive blood donors	Chagas cardiomyopathy
de Souza et al[39]	2015	Clinical score	373	QT-interval dispersion (3 points), Syncope (2 points), Ventricular extrasystoles (1 point), and Severe dysfunction of the left ventricle (1 point)	Sudden death
Gadioli et al[21]	2018	^{123}Iodine-MIBG-SPECT	43	Extent of cardiac sympathetic denervation MIBG-MPI mismatch score	Non-SVT, SVT
Senra et al[40]	2018	Cardiac magnetic resonance	130	Myocardial fibrosis > 12.3 g (HR: 2.1)	All-cause mortality, heart transplantation, antitachycardia pacing or appropriate shock from an implantable cardioverter-defibrillator, and aborted sudden cardiac death
Moraes et al[41]	2018	Electrocardiogram	557	Abnormal P-wave axis (HR: 1.48) Abnormal QRS axis (HR: 1.34) Abnormal T-wave axis (HR: 1.35)	All-cause mortality
Saraiva et al[42]	2020	Echocardiogram	392	Left atrial function assessed on three-dimensional echocardiographic Imaging	New-onset atrial fibrillation
Nunes et al[12]	2021	Laboratory	1088	T. cruzi antibody level at baseline (HR: 2.25)	Chagas Cardiomyopathy and death
Gadioli et al[22]	2022	^{123}Iodine-MIBG-SPECT	18	Regional and global myocardial sympathetic denervation Mild-moderate defect (HR: 3) Severe defect-absent uptake (HR: 8.7) MIBI defect (HR: 2.6)	Development of regional systolic dysfunction

Table 1 continued

Author	Year	Research	n	Predictor	Event
Echeverría et al[43]	2022	Echocardiogram	177	Left ventricular election fraction < 40% (HR: 3.15) Longitudinal strain by speckle tracking > -9 (HR: 2.82) E/e' ratio > 8.1 (HR: 2.5)	Composite endpoint of death, left ventricular assist device implantation or cardiac transplantation

Not all studies analyze HR
HR, hazard ratio; *LV*, left ventricular; *NSVT*, non-sustained ventricular tachycardia; *SVT*, sustained ventricular tachycardia

MIBG-SPECT and MIBI-SPECT. The authors concluded that the extent of regional myocardial sympathetic denervation assessed by ^{123}I-MIBG-SPECT imaging correlated quantitatively with the presence of ventricular arrhythmia, suggesting a relevant role played by the regional myocardial sympathetic denervation in triggering severe ventricular arrhythmia in patients with chronic Chagas cardiomyopathy. Also in another small series (n = 18) it was observed that myocardial denervation is a progressive derangement, which parallels the progression of left ventricular dysfunction in patients with chronic Chagas cardiomyopathy. In other words, the regional myocardial sympathetic denervation is topographically correlated with the ulterior development of wall motions abnormalities in this myocardial disease.[22,23] Thus, in clinical practice it is important to assess the perfusion and innervation mismatch patterns, since they integrate information on fibrosis and denervation.

In this study Xavier de Brito et al used attenuation correction (AC) for the SPECT images, although the myocardial sympathetic denervation defects localization by ventricular regions is not discussed. Not all studies of Chagas heart disease with ^{123}I-MIBG-SPECT use AC. This technical aspect is relevant because in Chagas heart disease the topographic distribution of ^{123}I-MIBG uptake defects are predominant in the inferior, posterior-lateral, and apical walls.[21,24] The localization of the denervation defect is part of the pathophysiology of sustained ventricular tachycardia. So, the sustained ventricular tachycardia arises from the basal portion of the inferior and posterior left ventricular walls, which are the regions most frequently involved in the ^{123}I-MIBG defects.[21,24] Possibly in the future, all ^{123}I-MIBG-SPECT studies should be done with AC. Figure 1A-C show the differences in the interpretation of ^{123}I-MIBG-SPECT early and late images with and without an attenuation correction from our laboratory. In this figure, we can see the difference in the intensity and extent of cardiac sympathetic denervation between an early study and a late study with ^{123}I-MBIG. Currently, there are no prognostic data available regarding this parameter in patients with Chagas heart disease.

The left ventricular global longitudinal strain (GLS), the peak-emptying-rate, remodeling (end-diastolic left ventricular shape index, end-systolic left ventricular shape index and eccentricity index) and the synchronization parameters (standard deviation, bandwith) allows us to observe early systolic dysfunction. These parameters are relevant and all can be assessed with SPECT or PET images in patients with Chagas disease. The importance of the concept of being able to detect ventricular systolic dysfunction in its initial phases lies in the worse prognosis and progressiveness

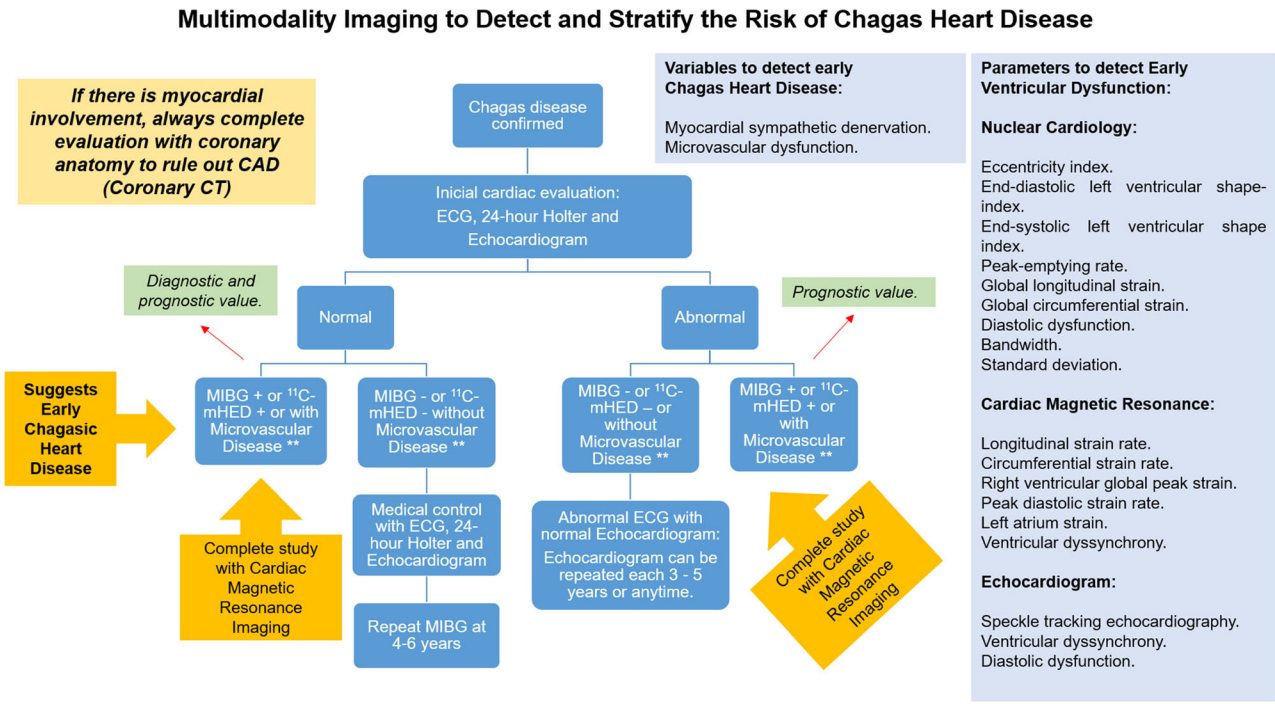


Figure 3. Perspective and future direction for the cardiac study in patients with Chagas disease. Differentiating between the diagnosis of early myocardial involvement and the early systolic dysfunction is a must. The diagnosis of Early Heart Disease is prior to the diagnosis of Early Systolic Dysfunction. **The assessment of microvascular disease by means of myocardial flow analysis with CZT-SPECT imaging provides additional information of myocardial perfusion, remodeling, synchrony, global longitudinal strain and peak-emptying-rate, in the same study.

of heart muscle disease. Chagas systolic dysfunction is possibly one of the worst prognosis. In BETTER-HF study (patients without Chagas), it was observed that myocardial contractility as assessed by GLS has a good discrimination for the identification of severe cardiac denervation. Also, GLS may allow for a more readily accessible estimation of the degree of autonomic denervation in advanced heart failure patients.[25] Kawakubo et al compared adenosine-stressed global circumferential strain and GLS values obtained from ^{13}N-ammonia PET images with global myocardial flow reserve values.[26] They observed that feature-tracking-derived strain values from a single PET scan could provide a clinically reasonable assessment of regional myocardial motility.

The left ventricular dyssynchrony is another important aspect of Chagas heart disease because it is an additional tool to evaluate the early myocardial dysfunction**.** Recently Athayde et al[27] evaluated 40 patients with chronic Chagas cardiomyopathy. They found that in severe left ventricular dyssynchrony with non-left bundle branch block, the evaluation of GLS and ventricular dyssynchrony between rest and exercise is able to reclassify myocardial function and to identify subgroups with contractile reserve and significant dyssynchrony. Figure 2 shows dyssynchrony at rest that increases with exercise in a patient with Chagas heart disease and normal left ventricular ejection fraction, information provided from our laboratory.

PROGNOSIS AND FUTURE DIRECTIONS

There are multiple clinical studies of electrocardiography, echocardiography, magnetic resonance, and nuclear cardiology in relation to the prognosis of Chagas heart disease (Table 1). All studies assess the cardiac event in patients with established Chagas heart disease. Despite its importance, the concept that must be taken into account is that the diagnosis of *Chagas heart disease per se is the most important poor prognostic variable to the life of the patient*. That is because the development of *Chagas heart disease should be considered a major cardiac event* due to its high mortality. Recently, Cutshaw et al[44] in a systematic meta-analysis found older and male patients with Chagas disease are more likely to have cardiomyopathy, although it cannot be identified causal relationships due to the high heterogeneity of the predominantly retrospective study designs in current literature.

During the follow-up of patients with Chagas disease, we *do not have to wait for left ventricular systolic dysfunction* to predict the cardiac prognosis, since sympathetic denervation itself is a predictor of ventricular arrhythmias and sudden death. *Autonomic myocardial denervation may be a more sensitive marker of cardiac involvement in Chagas disease* than finding it by other imaging modalities.[13]

In addition, *myocardial flow analysis* is very important in patients with Chagas disease, since it has a diagnostical value for early myocardial involvement, prognostic value, rather than a pathophysiological value.

Finally, and as we can see, since most cardiac imaging studies do not have a significant number of patients, *multicenter studies* should be performed in the future. On the other hand, the *multimodality of imaging* in patients with Chagas disease provides additional diagnostic and prognostic information (Figure 3).

In conclusion, in the future and from the point of view of cardiac imaging, the *sympathetic denervation studies and the studies of microvascular involvement are the most important tools for early detection of Chagas heart disease*. Especially the ^{123}I-^{123}I-MIBG-SPECT or ^{11}C-meta-hydroxyephedrine-PET studies since everything starts from sympathetic denervation. Also it is advisable to insist on the assessment of other parameters of *early involvement of left ventricular systolic function* to understand the importance of the additional information provided by the analysis of the parameters of ventricular *remodeling, synchrony, and GLS* in patients with normal left ventricular ejection fraction and in the absence of ventricular dilatation for early detection of myocardial dysfunction.

Disclosures

The authors declare no conflicts of interest.

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