

Association of Sympathetic Denervation, Myocardial Hypoperfusion, and Fibrosis with Ventricular Arrhythmias in Chronic Chagas Cardiomyopathy

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Abstract

Background: Chronic Chagas cardiomyopathy (CCC) manifests as heart failure, thromboembolic events, and sudden cardiac death (SCD). Although SCD may be the presenting event, there is still no recommendation for early cardioverter/defibrillator implantation in current guidelines.

Objective: To evaluate the correlation between autonomic denervation, myocardial hypoperfusion, fibrosis, and ventricular arrhythmias in patients in the early stages of CCC.

Methods: Cross-sectional study of 29 patients with CCC and preserved left ventricular function who underwent SPECT with iodine-123-meta-iodobenzylguanidine (¹²³I-mIBG), myocardial perfusion SPECT with technetium-99m sestamibi (^{99m}Tc-MIBI), and cardiac magnetic resonance (CMR) with gadolinium, divided into two groups according to on 24h Holter findings: arrhythmia (> 6 ventricular premature complexes/hour and/or nonsustained ventricular tachycardia; n = 15) or no-arrhythmia (< 6 ventricular premature complexes/hour and no ventricular tachycardia; n = 14).

Results: Significant correlations were observed between parameters of the three cardiovascular imaging modalities and the presence of ventricular arrhythmia. Denervation on mIBG correlated moderately with diffuse fibrosis, represented by ECV on CMR (r = 0.55, P = 0.002). Hypoperfusion by MIBI-SPECT correlated with fibrosis by both LGE (r = 0.66, P = 0.005) and extracellular volume (ECV) (r = 0.56, P = 0.002). We also observed a moderate correlation between the extent of myocardial areas with denervation and hypoperfusion (r = 0.48, P = 0.007).

Conclusion: The presence of autonomic denervation, myocardial hypoperfusion, and fibrosis was associated with ventricular arrhythmia in the early stages of CCC. A combination of these parameters can improve stratification of SCD risk in these patients.

Keywords: Chagas Disease; Sympathetic Denervation; Cardiac Arrhythmias.

Introduction

Chagas disease (CD) is among the neglected tropical diseases recognized by the World Health Organization. There are 300,000 new cases and 50,000 deaths from CD every year.¹⁻³ Sudden cardiac death (SCD) is the leading cause of mortality in chronic Chagas cardiomyopathy (CCC), representing the most dramatic course of CD,^{4,5} and is closely associated with the presence of ventricular arrhythmia and myocardial dysfunction.^{6,7} However, there is also a high incidence of SCD and malignant ventricular arrhythmia in young patients still in the early stages of the disease, when

the left ventricular ejection fraction (LVEF) is normal or only slightly depressed.^{8,9}

In 1916, Carlos Chagas reported: “Also quite frequent are sudden deaths in the cardiac forms of the disease. Sometimes they die still young, fully active, and in an apparently satisfactory state of health.”¹⁰

Indeed, the clinical course of CCC is variable, and identification of patients at risk of death remains a challenge. Rassi et al. proposed a simple risk score with six independent prognostic variables used to predict death.¹¹ Although this tool has good applicability in clinical, many patients who experienced SCD were not classified as high risk by the score, nor did they qualify for primary prevention with an implantable cardioverter/defibrillator (ICD) according to current guidelines. Furthermore, this model disregards the role of dysautonomia, as has already been demonstrated in other studies.¹²⁻¹³

It is well known that the presence of myocardial fibrosis, associated with areas of denervation and microvascular changes, creates an arrhythmogenic substrate. However, the stage of the disease at which these changes occur is still unknown.

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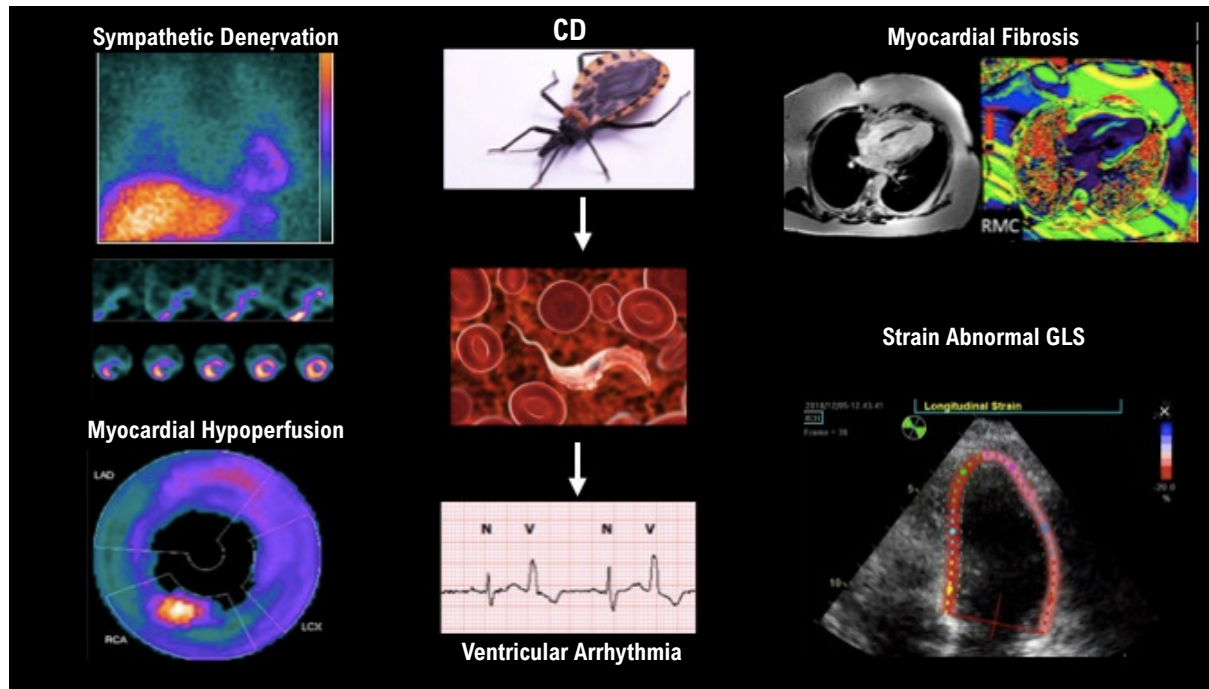
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Central Illustration: Association of Sympathetic Denervation, Myocardial Hypoperfusion, and Fibrosis with Ventricular Arrhythmias in Chronic Chagas Cardiomyopathy



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The objective of the present study was to correlate sympathetic denervation as assessed by ^{123}I -mIBG (mIBG) single photon emission computed tomography (SPECT), myocardial hypoperfusion by technetium ($^{99\text{m}}\text{Tc}$) sestamibi SPECT (MIBI), and fibrosis by cardiac magnetic resonance (CMR) with the incidence of ventricular arrhythmias in patients with stage A and B1 CD (Central Illustration).

Methods

Population

This prospective cross-sectional study was carried out with outpatients recruited from the CD Clinical Research Laboratory at Fundação Oswaldo Cruz (Rio de Janeiro, Brazil) who were aged ≥ 18 years, had tested positive for *T. cruzi* on two types of serology, preserved LVEF ($\geq 45\%$), and New York Heart Association (NYHA) functional class I.

The exclusion criteria were presence of other heart disease, renal impairment, pregnancy, or breastfeeding. CD was classified according to the Brazilian consensus.²

Participants were divided into two groups according to the results of 24-hour Holter monitoring, based on the CAST study: those with six or more ventricular premature complexes per hour and/or nonsustained ventricular tachycardia, and those with fewer than six VPCs per hour and no ventricular tachycardia.¹⁴

The study was approved by the Ethics Committee of Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz (CAAE: 63064516.1.0000.5262).

Routine measurements

Patients underwent a 12-lead ECG, 24-hour Holter monitoring with a digital recorder (H3™; Mortara, Milwaukee, WI, USA), and two-dimensional transthoracic echocardiography (Vivid 7®; General Electric Medical Systems, Milwaukee, WI, USA).

Subsequently, they underwent CMG, mIBG scintigraphy, and a resting myocardial perfusion MIBI scan.

CMR protocol

All patients underwent CMR on a 3.0-T scanner (Magnetom Prisma; Siemens AG, Erlangen, Germany). Cine images were acquired in long- and short-axis views. Modified look-locker inversion recovery (MOLLI) T1 mapping images were obtained from short-axis views of the ventricle before and 15 minutes after contrast infusion. The MOLLI 5(3)3 sequence design was used for pre-contrast (native) T1 mapping, while the 4(1)3(1)2 design was used for post-contrast acquisition. Breath-hold late gadolinium enhancement (LGE) images were acquired 10 minutes after contrast infusion, in an inversion-recovery segmented gradient echo sequence. Myocardial fibrosis mass on LGE was characterized by semiquantitative visual scoring.

The extent of LGE was scored on a 5-point scale in each of the 17 myocardial segments on the short-axis images.¹⁵

MIBG and MIBI protocols

Patients received 185 MBq of mIBG by slow intravenous injection one hour after oral administration of 20 mL of a 10% potassium iodide solution. Planar images (anterior projection) and CT images were acquired with the patient supine, 15 minutes (early) and 3 hours (late) after radiotracer injection, on a SPECT/CT dual-head hybrid gamma camera (Symbia 16T; Siemens Healthineers, Germany) with a low-energy, high-resolution parallel-hole collimator. Planar images were obtained for 5 minutes. CT images were acquired with a semicircumferential orbit, in 32 projections at a rate of 60 s/projection, a 20% energy window centered at 159 keV, and a 64×64 -pixel acquisition matrix with a pixel size of 0.6 cm. For quantitative analysis of mIBG, the early and late heart-to-mediastinum (H/M) ratios and the myocardial washout rate (%) were calculated as recommended in the current literature (Figure 1).^{16,17}

Resting SPECT images were acquired 30 minutes after peripheral intravenous injection of 555 MBq of ^{99m}Tc -MIBI with the gated SPECT technique, using the same equipment and parameters described above, with a 20% energy window centered at 140 keV. All SPECT images were followed by CT images to obtain attenuation correction maps.

Processing and analysis of scintigraphic images

Perfusion and innervation images were analyzed in Syngo P software (Siemens Healthineers), aligned so as to permit simultaneous visualization of the three orthogonal planes (short, horizontal long, and vertical long axes). Two blinded, experienced observers analyzed the images visually using a 17-segment LV model. MIBI and mIBG uptake were scored semiquantitatively

(0, normal; 1, mild uptake reduction; 2, moderate uptake reduction; 3, severe uptake reduction; 4, no uptake). Summed perfusion and sympathetic innervation scores were calculated to represent the extent and severity of the respective defects. MIBI total perfusion deficit (TPD) and ventricular function were automatically calculated by QPS/QGS software (Cedars Sinai Medical Center, Los Angeles, CA, USA). The innervation/perfusion mismatch, corresponding to viable but denervated myocardium, was also calculated. Segments exhibiting normal MIBI uptake and reduced mIBG uptake were considered to have innervation/perfusion mismatch.

Statistical analysis

Continuous variables were expressed as means, medians, and standard deviations. Categorical variables were expressed as proportions. Between-group differences were analyzed by the nonparametric Mann-Whitney test.

Spearman coefficients were calculated to test for correlation between areas with sympathetic denervation, myocardial hypoperfusion, and fibrosis.

Significance was accepted at $P \leq 0.05$. All analyses were performed in the SPSS Version 24.0 software environment (IBM Corp, Armonk, NY, USA).

Results

The sample consisted of 29 patients with chronic CD, all categorized as NYHA functional class I. The mean age was 58.5 ± 9.9 years, and 18 patients (62%) were female; the sex distribution did not differ between the arrhythmia and no-arrhythmia groups.

Twenty-two patients (76%) were asymptomatic, and the only medications recorded were antihypertensives and statins. To assess functional capacity and detect myocardial ischemia, all patients underwent cardiopulmonary exercise testing (CPET), which confirmed functional class I and did not reveal any changes suggestive of exercise-induced ischemia. Clinical characteristics are described in Table 1.

Patients in the arrhythmia group had significantly greater areas of compromised cardiac sympathetic innervation, myocardial hypoperfusion, innervation/perfusion mismatch (Figure 2), and fibrosis than patients in the no-arrhythmia group. The findings obtained on cardiovascular imaging in the arrhythmia and no-arrhythmia groups are summarized in Table 2 and Figure 3.

Sympathetic denervation detected on mIBG scintigraphy correlated moderately with diffuse fibrosis, as represented by ECV on CMR images ($r = 0.55$, $P = 0.002$). Hypoperfusion on MIBI-SPECT imaging correlated with fibrosis using the LGE ($r = 0.66$, $P = 0.005$) and ECV ($r = 0.56$, $P = 0.002$) techniques. We also found a moderate correlation between the extent of denervation and the extent of hypoperfusion ($r = 0.48$, $P = 0.007$), as exemplified in Figure 4.

Global longitudinal strain (GLS) on echocardiography correlated inversely with mIBG and MIBI-SPECT scores, as well as with measures of fibrosis on CMR. Patients with GLS had more myocardial hypoperfusion ($r = -0.59$, $P = 0.001$), sympathetic denervation ($r = -0.48$, $P = 0.008$), and fibrosis as represented by LGE ($r = -0.68$; $P = 0.003$) and ECV ($r = -0.45$, $P = 0.01$).

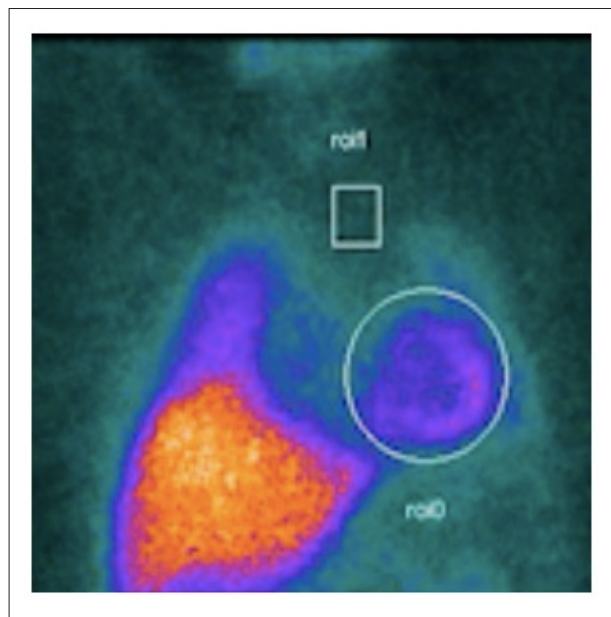


Figure 1 – Scintigraphy with mIBG-I123 - Anterior planar image with areas of interest over the superior mediastinum (rectangular) and left ventricle (circular) to calculate the heart/mediastinum ratio.

Table 1 – Baseline profile of the study population

Clinical condition	No Arrhythmia Group (n = 14)	Group Arrhythmia (n = 15)	Total (n = 29)
Age, years – mean (± SD)	55.5 (± 10.6)	61.2 (± 8.0)	58.5 (± 9.9)
Sex, female – n (%)	9 (50)	9 (50)	18 (62)
Clinical form – n (%)			
Indeterminate	7 (64)	4 (36)	11 (38)
Stage A	3 (50)	3 (50)	6 (21)
Stage B1	4 (33)	8 (67)	12 (41)
Symptoms – n (%)			
Asymptomatic	9 (41)	13 (59)	22 (76)
Palpitations	4 (67)	2 (33)	6 (21)
Syncope	1 (50)	1 (50)	2 (7)
Medications – n (%)			
Beta-blocker	1 (33)	2 (67)	3 (10)
ACEI or ARB	5 (31)	11 (69)	16 (55)
Diuretics	2 (33)	4 (67)	6 (21)
Statins	5 (50)	5 (50)	10 (34)

SD: standard deviation; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker.

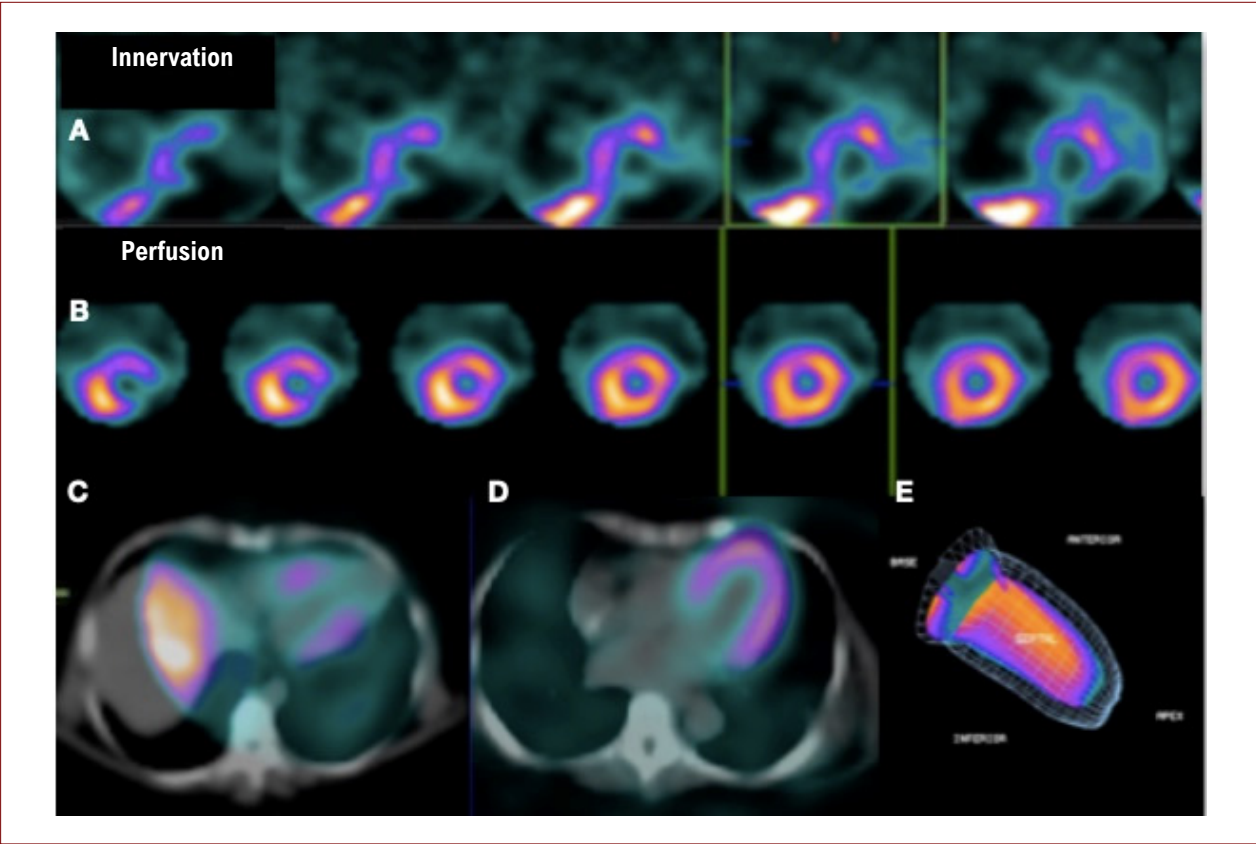


Figure 2 – Short axes of mIBG scintigraphy and MIBI scintigraphy showing extensive myocardial sympathetic denervation in the apical, inferior and inferolateral segments (A), with preserved myocardial perfusion (B); corresponding SPECT/CT fusion images with mIBG (C) and MIBI (D), indicating significant denervation/perfusion mismatch in a patient with chronic chagasic heart disease and ventricular arrhythmia. Three-dimensional reconstruction of the left ventricle using the gated-SPECT technique to evaluate ventricular systolic function (E).

Table 2 – Cardiac imaging features

	No Arrhythmia Group (n = 14)		Arrhythmia Group (n = 15)		p-value ^a
	Mean	SD	Mean	SD	
Echocardiogram					
E/e' ratio	7.9	0.6	10.9	1.5	0.11
Indexed LA volume (mL/m2)	20.3	1.2	30.6	3.5	0.02
LV GLS (%)	- 20.2	0.7	- 16.3	1.0	0.04
LVEF (%)	63.9	5.2	61.3	8.3	0.31
123I-mIBG scintigraphy					
H/M ratio, early	1.81	0.18	1.72	0.21	0.20
H/M ratio, late	1.83	0.14	1.73	0.26	0.20
Washout rate (%)	25.2	7.4	27.5	1.3	0.52
Summed score	5.6	4.9	23.2	18.7	< 0.01
99mTc-MIBI scan					
Summed rest score	0.29	0.6	4.7	6.8	0.02
TPD (%)	0.43	0.6	5.9	7.6	0.01
Gated-SPECT LVEF (%)	67.5	11.0	56.8	21.7	0.10
Mismatch					
MIBG-MIBI	5.4	4.8	18.5	17.5	0.01
Cardiac Resonance (%)					
LVEF (%)	70.7	3.2	57.9	12.1	< 0.01
LGE (%)	4.0	2.9	14.3	13.5	0.04

SD: standard deviation; LA: left atrium; GLS: global longitudinal strain; LVEF: left ventricular ejection fraction; mIBG: iodine-123-metaiodobenzylguanidine; H/M: heart/mediastinum; SPECT: single photon emission computed tomography; MIBG-MIBI: innervation/perfusion mismatch; LGE: late gadolinium enhancement; CMR: cardiac magnetic resonance imaging; MIBI: technetium-99m sestamibi; TPD: total perfusion deficit; LV: left ventricle. ^a Mann-Whitney test.

Discussion

The present study found that, in patients with early-stage CCC and preserved ventricular function, the extent of cardiac denervation, myocardial perfusion abnormalities, and percentage of fibrosis correlated with a higher incidence of ventricular arrhythmias.

Most studies to date have analyzed patients in the more advanced stages of CCC, with impaired cardiac function and high risk of death – patients in whom ICD implantation would already be indicated for secondary prevention of SCD.^{7,11} However, SCD may be the first presenting symptom of CD, affecting young individuals with normal LV function; these sudden deaths have major social and economic impact in endemic countries. Given this research gap, the present study was aimed at a subgroup considered to be at low risk within the natural history of CD, most patients being asymptomatic (76%) and having preserved LV function, but with an uncertain prognosis.

CCC is considered an arrhythmogenic cardiomyopathy. Previous studies with mIBG imaging have demonstrated that denervation can occur early in patients with normal LV function^{18,19} and may also be associated with ventricular tachycardia in CCC with mild ventricular dysfunction and

few or minor regional abnormalities.²⁰⁻²² In addition to confirming this finding of early denervation, the present study showed that patients with CD and ventricular arrhythmias had significantly larger areas of sympathetic denervation than those without arrhythmias, and that these areas also correlated with myocardial hypoperfusion. Several pathological processes can contribute to this phenomenon: sympathetic and parasympathetic neuronal depopulation induced by the parasite itself or by an adverse immune reaction during the acute phase of CD; circulating antibodies capable of binding to cholinergic and adrenergic receptors; and microvascular derangements.^{23,24}

We also demonstrated larger areas of hypoperfusion on resting MIBI scintigraphy in the arrhythmia group, although these patients had no anginal complaints, no known CAD, and no evidence of exercise-induced ischemia on CPET. In CD, hypoperfusion has been attributed to changes in the coronary microcirculation associated with the perivascular inflammation typical of the diffuse Chagas myocarditis. Studies of patients with CCC have demonstrated that chest pain and perfusion defects on perfusion scintigraphy did not correlate with obstructive epicardial atherosclerotic disease on coronary angiography,²⁵⁻²⁶ which strongly suggests a correlation between disturbances in the coronary

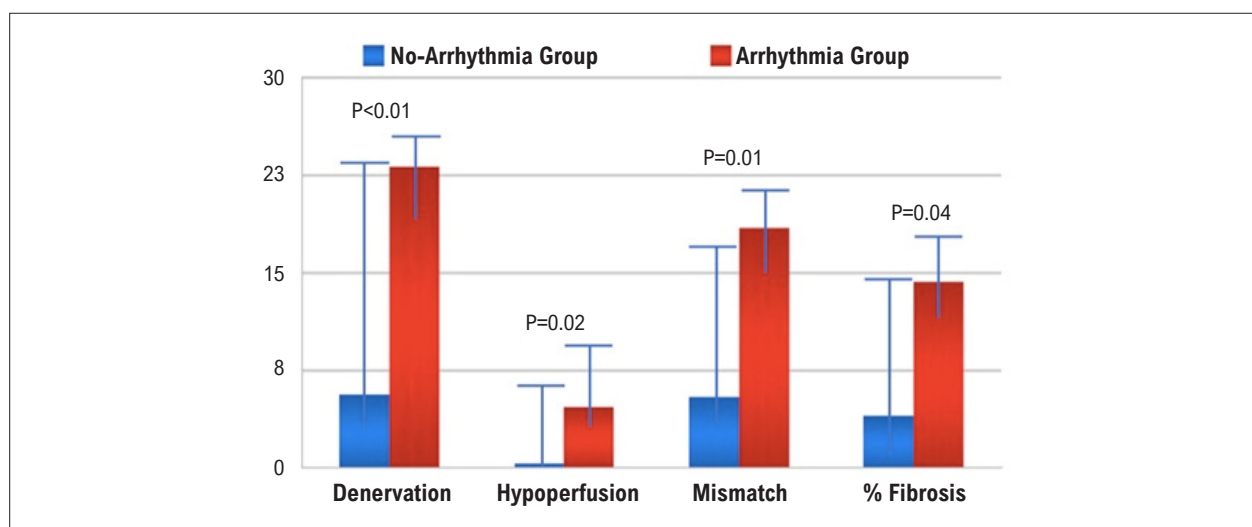


Figure 3 – Bar graph illustrating the average hypoperfusion sympathetic denervation scores, innervation/perfusion mismatch and percentage of fibrosis between the groups of chagasic patients with and without ventricular arrhythmias.

	mIBG-SPECT	MIBI-SPECT	GLS (ECHO)
ECV (CMR)	0.55''	0.56''	–0.45'
LGE (CMR)	0.48'	0.66''	–0.68''
GLS (ECHO)	–0.48'	–0.59''	** P < 0.01 * P < 0.05

Figure 4 – Correlations between cardiac sympathetic denervation (mIBG) scores, myocardial hypoperfusion (MIBI) by nuclear SPECT techniques, fibrosis by ECV and LGE techniques of CMR and GLS by transthoracic ECHO in patients with chronic chagasic heart disease and ventricular arrhythmias. ECHO: echocardiography; ECV: extracellular volume; CMR: cardiac magnetic resonance imaging; GLS: global longitudinal strain; LGE: delayed enhancement.

microcirculation, hypoperfusion, and progression to regional fibrosis, as previously observed from experimental and human pathology evidence.²⁷⁻²⁹ These findings support a role of regional perfusion abnormalities in the pathogenesis of myocardial damage in CCC. In the present study, these findings were replicated in patients still in the early stages of the disease.

Furthermore, we found that areas of innervation/perfusion mismatch were associated with a higher incidence of ventricular arrhythmias. It has been postulated that innervation/perfusion mismatch may predispose to fatal ventricular arrhythmias in CCC with ventricular dysfunction.^{21-23,30} Although the pathophysiology is still unclear, areas so affected may be hypersensitive to catecholamines, with upregulation of β -adrenergic receptors, increased automaticity, and exaggerated responses to sympathetic activation.³¹

In our sample, fibrosis mass as estimated by CMR was also associated with ventricular arrhythmias and correlated with hypoperfusion and denervation. Regarding this finding, Gadioli et al.²¹ reported a correlation of ventricular arrhythmias with the extent of cardiac sympathetic denervation, but not with fibrosis, in patients with CCC and

mild ventricular dysfunction. However, it is worth noting that their study did not use CMR and considered perfusion changes on MIBI as indicative of fibrosis, which may be a limitation, as this finding may simply represent abnormalities in the microcirculation without fibrosis or scarring.

Fibrosis is a known arrhythmogenic substrate in ischemic and nonischemic LV dysfunction,³² including CCC.^{33,34} Fibrotic lesions disrupt intercellular junctions, alter the cardiac electrical potential, and form reentrant circuits for arrhythmias.³⁵ The extent of fibrosis as assessed by late enhancement on CMR can be used to identify high-risk patients. Recently developed techniques, such as T1 mapping and ECV assessment, can further refine this stratification, as demonstrated in a previous study by our group³⁶ which showed the presence of diffuse interstitial fibrosis on T1 mapping even in the undetermined form of CD, as well as an independent association between ventricular arrhythmias and ECV in CCC – which was confirmed by the current study.

Corroborating the findings of early changes in cardiac function before global and regional abnormalities develop, we observed in this study a reduction in LV GLS in the arrhythmia group as compared to the no-arrhythmia group.

This reduction in GLS in the arrhythmia group was inversely correlated with sympathetic denervation, myocardial hypoperfusion, and fibrosis, which opens fascinating avenues for further refinement of risk stratification. GLS reflects the longitudinal deformation of the myocardium in a more sensitive and reproducible way than LVEF.^{37,38} Azevedo et al.³⁹ demonstrated a significant association between GLS and myocardial mechanical dispersion with nonsustained ventricular tachycardia in 77 patients with CCC. Recently, reductions in GLS were also observed in the undetermined form of the disease, before the onset of fibrosis.⁴⁰

The novelty of the present study lies in our finding that, even in “low-risk” patients at the earliest stages of CCC, a significant association between ventricular arrhythmias and the various pathophysiological mechanisms involved in the genesis of SCD is already present, as demonstrated by different cardiovascular imaging methods.

Limitations

The sample size of this study was relatively small. Nevertheless, we were able to observe significant associations of fibrosis, hypoperfusion, and myocardial denervation with ventricular arrhythmias and increased risk of SCD in CCHD.

Conclusions

Sympathetic denervation (detected by mIBG), myocardial hypoperfusion (detected by MIBI), and fibrosis (represented by ECV and LGE on CMR) correlate significantly with the incidence of ventricular arrhythmias in patients with CCHD and preserved left ventricular function. These findings may aid in the development of tools to improve SCD risk stratification and identify patients who may benefit from specific therapy, such as ICD implantation.

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Author Contributions

Conception and design of the research: Brito ASX, Moll-Bernardes RJ, Almeida AS, Rosado-de-Castro PH, Sousa AS; acquisition of data and analysis and interpretation of the data: Brito ASX, Moll-Bernardes RJ, Pinheiro MVT, Camargo C, Siqueira FPR, Glavam AP, Almeida AS, Mendes FSNS, Rosado-de-Castro PH, Sousa AS; statistical analysis and writing of the manuscript: Brito ASX, Moll-Bernardes RJ, Sousa AS; obtaining financing: Brito ASX, Moll-Bernardes RJ, Rosado-de-Castro PH, Sousa AS; critical revision of the manuscript for intellectual content: Brito ASX, Moll-Bernardes RJ, Pinheiro MVT, Mendes FSNS, Rosado-de-Castro PH, Sousa AS.

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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Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz under the protocol number 63064516.1.0000.5262. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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