

ORIGINAL RESEARCH

Myocardial Injury in Patients With Acute and Subacute Chagas Disease in the Brazilian Amazon Using Cardiovascular Magnetic Resonance

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BACKGROUND: Chagas disease is a neglected tropical disease that is still considered a global health emergency. In the Amazon region, most of the reports are of acute cases that are associated with oral transmission. This study aimed to evaluate myocardial injury in patients with acute Chagas disease before and after treatment.

METHODS AND RESULTS: We evaluated 23 patients with acute Chagas disease in 3 different stages of progression. Group 1 had 12 patients evaluated during the acute phase, at the time of diagnosis, and 1 year after treatment, and Group 2 had 11 patients in the late postacute phase who were evaluated 5.2 years on average after diagnosis and treatment. ECGs with the Selvester score, 24-hour Holter exam, and cardiovascular magnetic resonance imaging were performed. The mean age of the 23 patients was 44.3 ± 18.9 years, and they were mostly men (15/65.24%) from Amazonas state (22/95.6%). In 69.6% ($n=16$) of the patients, some ECG alterations were found, the most frequent being left anterior fascicular block and ventricular repolarization. In Group 1, the 24-hour Holter exam showed atrial tachycardia in 3 (25%) patients and ventricular extrasystoles in 2 (16.7%) patients. In Group 2, 1 patient had ventricular extrasystoles. Myocardial injury was observed in 7 patients (58.3%) at the acute phase and in 5 (50%) patients at the 1-year follow-up in Group 1 and in 2 (18.2%) patients in Group 2.

CONCLUSIONS: This article describes, for the first time, myocardial injury shown by cardiovascular magnetic resonance imaging in a group of patients with acute Chagas disease and reveals the importance of early detection and follow-up of the cardiac impairment in these patients.

Key Words: acute Chagas disease ■ Brazilian Amazon ■ myocardial injury

Chagas disease (CD) is a neglected tropical disease that is still considered a global health emergency. It is estimated that >7 million people are infected with *Trypanosoma cruzi* worldwide, and >70 million people live in areas with a constant risk of transmission.^{1,2} In Latin America, the disease is endemic in 21 countries, including Brazil, where it is estimated that

more than a million people are living with CD, and this results in ≈ 4000 deaths every year.³

In the Amazon region, most reports are of acute cases associated with oral transmission that has occurred as the result of the ingestion of juices made from palm fruits (eg, açai berry, palm tree wine, sugar cane, and guava juices).⁴ Clinically, these acute cases

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CLINICAL PERSPECTIVE

What Is New?

- The prevalence of Chagas disease in western Amazonia has been growing significantly through the oral route transmission and attributed to the consumption of contaminated food.
- Acute Chagas disease can cause myocardial injury that can be detected by cardiovascular magnetic resonance with potential prognostic and diagnostic value.

What Are the Clinical Implications?

- A low-cost and easily accessible tool such as the Selvester score could be an alternative in the detection of early myocardial injury in acute Chagas disease.

Nonstandard Abbreviations and Acronyms

ACD	acute Chagas disease
CD	Chagas disease
G1	group 1
G1-FU	group 1 with 1-year follow-up
G2	group 2
LGE	late gadolinium enhancement
MF	myocardial fibrosis
SS	Selvester score

may present nonspecific symptoms and for which treatment with benznidazole (Rochagan) is able to achieve 90% efficacy.⁵

Chagas cardiomyopathy is the main cause of morbidity and mortality, and myocardial injury can be precisely detected by cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE) technique.⁶ However, this condition is mostly described in the chronic phase of CD.⁷ CMR is an imaging technique that is a significant technological development widely used in the diagnosis, monitoring, and treatment of cardiovascular diseases, especially in cardiomyopathies, with regard to diagnostic and prognostic differentiation.⁸

Postinflammatory myocardial injury can be safely identified by CMR with delayed enhancement, which is as an important predictor of arrhythmia and sudden death in several nonischemic cardiomyopathies, such as hypertrophic cardiomyopathy and chronic chagasic cardiomyopathy, and may be useful in risk stratification in patients with CD.⁹

To our knowledge, there are no studies that assessed the presence of myocardial injury by CMR

involving a series of cases of acute CD (ACD) or with follow-up evaluation after treatment. In addition, in the Amazon region, the aspects of the cardiac involvement of the disease, such as the evaluation of myocardial injury and cardiac arrhythmias, are not well known. Thus, the aim of this study was to investigate the presence and magnitude of myocardial injury in autochthonous patients with CD in the acute and posttreatment phases in the Brazilian Amazon using CMR.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Patient Population

This longitudinal study was carried out at the CD outpatient clinic of the Tropical Medicine Foundation Dr Heitor Vieira Dourado and followed up autochthonous patients from the western Amazon who were diagnosed with ACD.

Three groups at different stages of disease progression were included: group 1 (G1) with 12 patients with ACD evaluated before the start of treatment (G1) and with 1 year follow-up (G1-FU) after the end of treatment with benznidazole and group 2 (G2) with 11 late postacute patients evaluated 5.2 years on average after diagnosis and treatment. All patients were diagnosed by direct parasitological examination and a thick smear test and treated with benznidazole (Rochagan), 5 to 7 mg/kg for 60 days according to the II Brazilian Consensus on Chagas Disease, 2005 and 2015.^{5,10}

ECG Analysis and Dynamic Electrocardiography (24-Hour Holter Exam)

All patients underwent a standard 12-lead ECG (10 mm/mV and 25 mm/s). The ECG analysis was performed blindly by 2 experienced cardiologists, following the criteria established in the Brazilian Electrocardiogram Guidelines.¹¹ The evaluation of the Selvester score (SS) followed the recommendations established by Loring et al,¹² in which each point was designed to correspond to $\approx 3\%$ of left ventricular injury. The patients underwent prolonged ECG monitoring (24-hour Holter exam) to allow the detection and reproduction of arrhythmia tracings for a longer period.

Selvester QRS Score

The SS is a 12-lead ECG analysis in which the QRS complex is adjusted for sex and age in the parameters of duration and amplitude (millivolt). Each column of the score table¹² represents an ECG alteration (right

bundle branch block, left anterior fascicular block, left ventricular hypertrophy, left bundle branch block) or no alteration, and the score is recorded for each of these possibilities. The percentage of left ventricular scars estimated by ECG was calculated by multiplying the overall QRS score by 3 because each point in the score corresponds to 3% of total mass of the left ventricle (LV). Afterward, the differences in points and percentages obtained by the 2 observers were compared during a meeting, during which no disagreements were detected.

CMR Imaging and Analysis

CMR imaging with LGE was performed on all selected patients using a Philips Ingenia 1.5 T Scanner. The functional evaluation used conventional cine resonance using steady-state free precession gradient echo. Tissue characterization assessed the presence of myocardial edema using T2-weighted sequence with fat suppression and the presence of myocardial fibrosis (MF) by LGE with 2-dimensional and 3-dimensional acquisitions. The intravenous contrast material used was gadobutrol (0.1 mmol/kg), a gadolinium-based contrast agent.

Data analysis was performed by a specialist in cardiac imaging with >5 years of experience in CMR analysis. A quantitative functional assessment was carried out to obtain the structural measurements of diastolic and systolic diameters of the LV, diastolic wall thickness, anterior systolic diameter of the left atrium, left atrial volume by biplane measurements, mean lateral diameter of the right ventricle, and the presence of pericardial effusion and the functional measurements of LV and right ventricle diastolic and systolic volumes and ejection fraction.

In LGE, image locations by the American Heart Association segmentation, degree of transmural, pattern, and amount of LGE in grams and as a percentage of LV mass were measured. Quantitative measures of LGE used as specialized and dedicated software using a threshold method with a 5-SD cutoff (pixel intensities 5 SDs above the normal myocardium were considered as LGE).

Statistical Analysis

Clinical and epidemiological data were organized using the Excel 2016 program and analyzed using the SPSS 28 IBM software. For categorical variables, the Fisher exact test was used, and the results are presented in tables with absolute and relative frequencies. The distribution of continuous variables was tested for normality using the Kolmogorov–Smirnov test. For those with normal distribution, the paired Student *t* test was used with the results presented as mean±SD.

To compare the percentage of LGE, the Fisher exact test was used. The correlation between the

score of the SS and LGE (percentage in mass LV) was done using the Spearman correlation. A 95% CI was assumed for all statistical tests, and the results were considered statistically significant when $P<0.05$.

Ethical Considerations

This study is also part of a research funding call (No. 30/2013) issued by Fundação de Amparo à Pesquisa do Estado do Amazonas (FAPEAM/AM) and was approved by the Research Ethics Committee of Amazonas State University (Manaus, AM, Brazil) under the approval number 31812914.9.0000.5016/923.701, December 2014.

It was also supported by a previous call and approved by the Human Research Ethics Committee of the Fundação de Medicina Tropical Dr Heitor Vieira Dourado (FMTHVD) on March 7, 2007, under number 1836, Certification number 027.0.114.000-06, and carried out in accordance with Resolution 466/12 of the Brazilian National Health Council and the ethical guidelines of the 1975 Declaration of Helsinki. All participants signed an informed consent form approved by the Research Ethics Committee of the Tropical Medicine Foundation Dr Heitor Vieira Dourado, Manaus, AM, Brazil, under the approval number 66077017.8.0000.0005/2.043.174 in May 2017.

RESULTS

Baseline Characteristics

We included 23 patients whose average age was 44.3±18.9 years. The majority were men (15/65.24%) from the state of Amazonas (22/95.6%) and had an epidemiological history of acute oral disease (18/78.3%). In 16 (69.5%) patients, 2 *T. cruzi* strains (TcI and TcIV) were identified, with a predominance of 13 (81.2%) for the TcIV strain (Table 1). All patients were asymptomatic from the cardiovascular point of view.

ECG Analysis

The ECG was abnormal in 7/12 (58.3%) patients in G1, in 5/10 (50%) patients in G1-FU, and in 4/11 (36.4%) patients in G2. The alterations found most frequently were left anterior fascicular block and ventricular repolarization alteration in 21.7% of patients. No alterations in ventricular repolarization were found in these patients after 1 year of follow-up (Table 2).

Dynamic Electrocardiography (24-Hour Holter Exam)

Dynamic electrocardiography (24-hour Holter exam) in the G1 patients demonstrated the presence of isolated and monomorphic ventricular ectopic in 2 (16.7%) patients, supraventricular arrhythmias of the type

Table 1. Baseline Characteristics of Patients With Acute and Subacute Chagas Disease

Variables	Total (N=23)	G1 (n=12)	G2 (n=11)	P value
Age, y	44.3±18.9	47.6±23.2	40.6±12.9	0.392*
Sex				0.027†
Female	8 (34.8)	7 (58.3)	1 (9.1)	
Male	15 (65.2)	5 (41.7)	10 (90.9)	
Origin, state				1.000†
Amazonas	22 (95.7)	11 (91.7)	11 (100)	
Roraima	1 (4.3)	1 (8.3)	0	
Transmission				0.155
Oral	18 (78.3)	11 (91.7)	7 (63.7)	
Vectorial	5 (21.7)	1 (8.3)	4 (36.3)	
<i>T. cruzi</i> DTU	16	10	6	1.000†
TcI	3 (18.8)	2 (20)	1 (16.7)	
TcIV	13 (81.2)	8 (80)	5 (83.3)	

Data are provided as mean±SD, number, or number (percentage). DTU indicates discrete type unit; G1, group 1; G2, group 2; and *T. cruzi*, *Trypanosoma cruzi*.

*Unpaired Student *t* test.

†Fisher exact test.

unsupported supraventricular tachycardia (atrial tachycardia) in 3 (25%) patients, pre-ventricular excitation in 1 (8.3%) patient, and atrial fibrillation as the base rhythm in 1 (8.3%) patient. In G2, 349 isolated and monomorphic ventricular ectopics were identified in 1 (9.1%) patient (Table 2).

Selvester QRS Score

In all patients, before the start of treatment (G1), an average score of 17% left ventricular mass injury was observed in the evaluation performed using the SS, with a variation between 3% and 39%. In the G1-FU patients, after 1 year of treatment, an average score of 11% left

Table 2. Alterations in the ECG and 24-Hour Holter Exam in Patients With Acute and Subacute Chagas Disease

Variables	G1 (n=12)	G1-FU (n=10)	P value
ECG			
Ventricular repolarization alteration	3 (25)	...	
Left anterior fascicular block	2 (16.7)	3 (25)	0.070*
Atrial fibrillation	1 (8.3)	1 (8.3)	
Pre-excitation	1 (8.3)	1 (8.3)	
24-h Holter exam			
Ventricular extrasystoles	3 (25)	...	
Paroxysmal supraventricular tachycardia	3 (25)	...	
QRS Selvester score	17.7±11.8	11.1±6.9	0.057†

Data are provided as mean±SD or number (percentage). G1 indicates group 1; and G1-FU, group 1 with 1-year follow-up.

*Fisher exact test.

†Paired Student *t* test.

ventricular mass injury was observed, with a variation between 0% and 21%. Regarding the percentage of injury in G2 patients, an average of 4% LV mass was observed and varied from 0% to 12% (Table 2).

Cardiovascular Magnetic Resonance

In CMR, the presence of LGE was observed in 7 patients (58.3%) in G1. In G1-FU, there was loss of follow-up in 2 patients and, of the 10 remaining patients evaluated, 7 (70%) showed delayed enhancement (Table 2). In G2, fibrosis was detected in 2 (18.2%) patients (Figure 1).

The assessment of left and right ventricular function were analyzed in all patients, and no alterations were observed in right ventricle function (Table 3). A total of 6 patients who presented fibrosis in the pretreatment phase underwent posttreatment evaluation, and 4 (66.75%) presented persistent MF.

In the G1-FU patients, 1 developed MF that was previously undetected. The mean±SD percentage of LGE before treatment was 2.1±3.2. In the follow-up, the mean±SD was 1.5±1.4. There was no statistical difference ($P=0.607$; Table 4). A very weak positive correlation was observed between the percentage of injured LV mass and the SS points ($\rho=0.004$; Figure 2).

Table 4 describes the follow-up of each patient in the G1/G1-FU with regard to the presence or absence of delayed enhancement, edema, percentage of delayed enhancement, and location of alterations according to their pattern and myocardial segment.

DISCUSSION

This study demonstrated for the first time that myocardial injury by CMR is present in patients with ACD. All patients were native to the western Brazilian Amazon, and most of the cases were the result of oral transmission attributed to a history of regional fruit juice consumption, such as açai (*Euterpe oleraceae*), which is part of the local population's diet.¹³ This new epidemiological profile has been progressively registered in this region, and it is believed that food contamination by triatomines probably occurs when the juices are processed. As a result, this is now considered one of the most important routes of CD infection in Brazil.^{14–17}

As recommended by the Brazilian Ministry of Health, all ACD cases should be treated with benznidazole, and there should be a follow-up of the patient during and after treatment. However, in the Amazon, this is not always the case because cases are rarely monitored, especially because most of them come from remote areas, which prevents patients from returning to the reference clinics. As a result, this compromises the recommendation for follow-up and contributes to the evolution of the disease.⁵

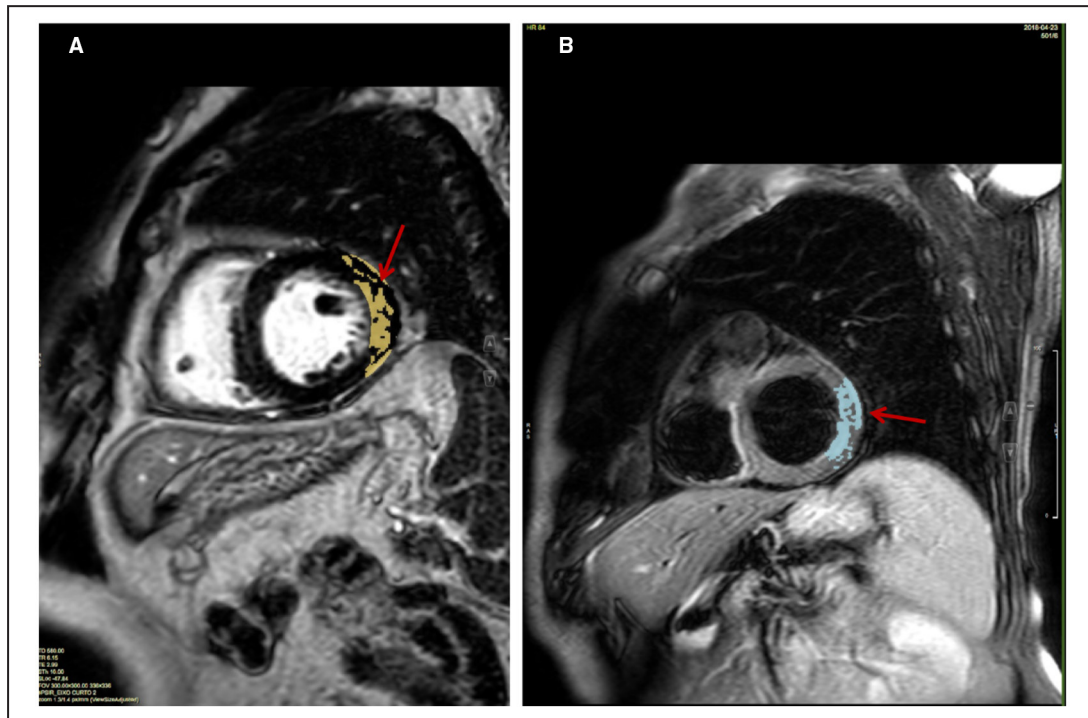


Figure 1. Delayed enhancement in cardiovascular magnetic resonance in (A) the medial inferolateral segment and (B) edema in the medial inferolateral. Both arrows indicate delayed enhancement.

ECG Analysis

In our study, 56.63% of patients had an abnormal ECG in the acute period of the disease (G1), 25% being ventricular repolarization alteration, followed by left anterior fascicular block, atrial fibrillation, and pre-excitation. The predominance of the ventricular repolarization alteration variable in G1 demonstrates a possible myocardial impairment in the pretreatment acute phase, which was not found in G1-FU. This suggests that this alteration, which is related to the acute phase of the disease, may have disappeared as a result of early treatment. The ECG exam is considered the most appropriate, especially when it comes to mild impairment of the heart,¹⁸ and the ventricular repolarization alterations found during the ECG exam are frequent and used in diagnostic screening and are thus considered the primary indicator of the disease.¹⁹

Table 3. Description of the Presence of Myocardial Fibrosis and Ejection Fraction in the Acute and Subacute Phases of Patients in 2 Groups Evaluated Using CMR

Delayed enhancement	G1 (n=12)	G1-FU (n=10)	P value
LGE present	7 (58.3%)	7 (70.0%)	0.042*
LGE absent	5 (41.7%)	3 (30.0%)	
LV ejection fraction, %	62.8±7.7	65.2±8.5	0.336†

Data are described as mean±SD or number (percentage). CMR indicates cardiovascular magnetic resonance; G1, group 1; G1-FU, group 1 with 1-year follow-up; LGE, late gadolinium enhancement; and LV, left ventricle.

*Fisher exact test.

†One-way ANOVA post hoc Bonferroni.

Dynamic Electrocardiography (24-Hour Holter Exam)

In a report presented by Marques et al.²⁰ after an outbreak attributed to the consumption of guava juice at a school in Venezuela, the most common arrhythmias were supraventricular arrhythmias, which occurred in most cases. Ventricular arrhythmias were observed to be less common. During our study, the 24-hour Holter exam showed that both ventricular extrasystoles and paroxysmal supraventricular tachycardia were found in G1, but subsequently not recorded in G1-FU.

Selvester QRS Score

The SS has already been evaluated for testing chronic DC and presents good correlation with CMR; in addition, it may be important for risk stratification in this group of patients.²¹ The SS in our study was positive for myocardial injury in G1 and G1-FU (4.5 points [range, 3–7 points] and 4 points [range, 2–5 points], respectively); however, G2 did not present a score to confirm this alteration (1 point [range, 0–3 points]) because a positive result is given when the score is >3 points.

Cardiovascular Magnetic Resonance

Through CMR, the presence of late enhancement was detected in the patients in G1 and G1-FU (58.3% and 50%, respectively); however, there was no significant

Table 4. Evolution of the Presence and Location of Injury on CMR Before and After CMR Treatment

Identification No.	Age, y	Sex	DTU	Acute phase (n=12)				Follow-up (n=10)			
				Standard CMR	LGE segment	LGE (%)	Edema	Standard CMR	LGE segment	LGE (%)	Edema
01	28	Male sex	TcIV	Subepicardium	Anteroseptal basal, anterolateral medial	1.8	Anterior lateral medial (3.9%, T2 ratio=1.8)	Lost to follow-up			
02	43	Male sex	TcIV	Absence of fibrosis			No	Lost to follow-up			
03	60	Female sex	Tcl	Junctional	Inferoseptal medial	2.3	No
04	74	Female sex	Tcl	Focal	Inferolateral medial	2.8	No	Focal	Inferolateral medial	1.3	No
05	51	Female sex	TcIV	Absence of fibrosis			No	Absence of fibrosis			No
06	19	Female sex	TcIV	Junctional	Inferoseptal medial	0.7	No	Junctional	Inferoseptal medial	0.7	No
07	22	Male sex	TcIV	Junctional, linear mesocardial	Inferoseptal medial and apical	0.8	No	Junctional, linear mesocardial	Inferoseptal medial and apical	2.3	No
08	35	Female sex	TcIV	Focal	Inferolateral basal	1.1	No
09	65	Female sex	TcIV	Absence of fibrosis			No	Absence of fibrosis			No
10	21	Female sex	TcIV	Junctional, focal	Anteroseptal basal, inferior medial	2.5	No	Junctional, focal	Anteroseptal basal, inferior medial	1.4	No
11	63	Male sex	...	Multifocal	Inferolateral basal, inferior medial	10.8	Inferolateral medial (6.7%, T2 ratio=1.9)	Multifocal	Lateral, basal, medial, and apical	4.7	Lateral medial
12	90	Male sex	...	Focal	Inferolateral basal	1.8	No	Focal	Inferolateral basal	1.6	No

CMR indicates cardiovascular magnetic resonance; DTU, discrete typing unit; and LGE, late gadolinium enhancement.

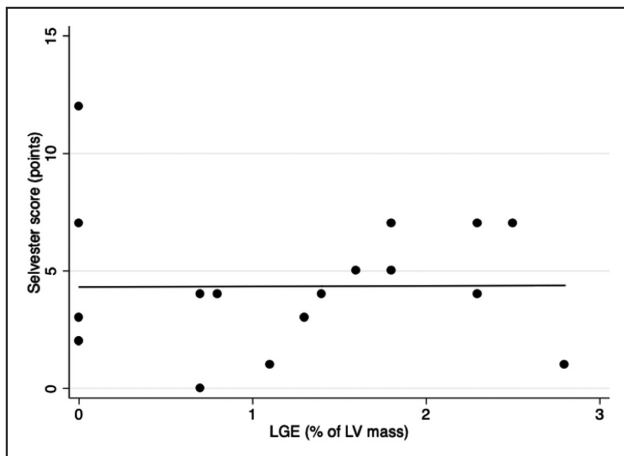


Figure 2. Spearman correlation between percentage of LV mass and the Selvester scoring points ($P=0.991$; $\rho=0.004$). LGE indicates late gadolinium enhancement; and LV, left ventricle.

difference in impairment when these patients were evaluated after 1 year of follow-up. Nonetheless, fibrosis was detected in G2 in only 18.2% of the analyzed group. Fibrosis and myocardial inflammation have been demonstrated in all chronic phases of the disease, with or without heart disease, without ventricular dysfunction, and the amount of fibrosis correlates with the severity of the clinical form, functional class, LV ejection fraction, and LV dilation.²²

CMR has great accuracy in detecting regions of MF in patients with chronic CD. Because we know that these areas of fibrosis can be predictors of the development of malignant arrhythmias, this test becomes a fundamental tool and increases the possibility of detecting this risk early, even with preserved ventricular function.⁹ Schmidt et al²² also reported the potential of CMR in detecting the regions of MF in patients with chronic CD cardiomyopathy and confirmed that this is a potentially valuable tool in the noninvasive risk prediction of these patients suffering sudden death, even in those with LV ejection fraction still preserved.

The presence of MF in patients with CD with clinical cardiomyopathy is well established by the use of CMR. Its quantification is related to the Rassi score,²³ a prognostic score validated for CD. According to Uellendahl et al,²⁴ MF deserves to be investigated using CMR, as it is considered as an independent prognostic factor, which emphasizes its value as a prognostic tool for risk stratification of the disease. In the literature, there is only 1 case report study of ACD using CMR (de Sousa et al²⁵), in which fibrosis was not detected in three different periods after treatment initiation (Day 5, Day 26 and Day 56), only edema, which regressed after treatment. This is the first case series study that used this tool in the evolution, stratification, and follow-up of cases.

Studies reinforce the hypothesis that MF in CD is related to arrhythmias and sudden death, which has already been suggested in electrophysiological evaluation.²² However, the amount of myocardial injury detected in the evaluation of our patients was considered insufficient to generate arrhythmias of malignant character.

One of the limitations of the study is the fact that the patients in G2 were not the same as those evaluated in G1 and G1-FU because they were recruited after diagnosis, although they were in fact all diagnosed and treated with benznidazole in the same way. The study presents a small number of patients because it is a rare disease and it occurs in sporadic outbreaks in remote regions that are difficult to access.

CONCLUSIONS

In this cohort of Amazon autochthonous patients with ACD, myocardial injury by CMR was detected in the pretreatment acute phase and also in the follow-up 1 year after treatment. In another group of patients with 5.2 years of follow-up after ACD, only a mildly persistent myocardial injury (18.2%) was detected. The occurrence of myocardial injury in autochthonous patients with ACD in the Amazon reveals the importance of follow-up in the cardiology clinic.

The correlation between fibrosis detected by CMR and SS—a simple and easily accessible test—represents a good tool for the early detection and stratification of patients with myocardial involvement in the acute and subacute phases of CD. This is even more pertinent when one remembers that the Amazon is a region of vast territorial extension with many remote areas and access to CMR may prove difficult for many patients.

ARTICLE INFORMATION

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Disclosures

None.

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