

Myocardial Involvement in Chagas Disease: From the Perspective of Cardiovascular Magnetic Resonance Assessment

Acometimento Miocárdico na Doença de Chagas: Uma Perspectiva a partir da Avaliação pela Ressonância Magnética Cardiovascular

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Abstract

Chagas disease represents an important public health problem, especially in endemic countries in Latin America. Chronic cardiomyopathy is its most frequent clinical presentation. Myocardial involvement has a multifactorial pathogenesis and can lead to heart failure, thromboembolic events, arrhythmias, and sudden death. In this context, cardiovascular magnetic resonance imaging (CMR) is an excellent noninvasive method for investigating myocardial damage and understanding the mechanisms and consequences of these injuries. CMR has high spatial resolution and tissue characterization capacity, enabling a highly reliable morphofunctional analysis and the identification of risk markers for adverse events in patients with Chagas disease. This exam is very useful for the diagnosis and follow-up of these patients in the routine clinical setting.

Introduction

Despite efforts to reduce new cases of Chagas disease, especially by interrupting its transmission by domiciled triatomines and serological screening in blood banks, its prevalence remains high worldwide. A recent estimate by the World Health Organization points to 6–7 million people infected by the protozoa *Trypanosoma cruzi* worldwide, most of them residing in one of the 21 Latin American countries where Chagas disease is considered endemic, in addition to approximately 70 million people at risk of contracting it in this region.¹ An estimated 30–40% of infected individuals will develop clinical presentations in the chronic phase of the disease, with cardiomyopathy being the most frequent and severe presentation.² Cardiac impairment have a multifactorial pathogenesis and include silent myocarditis related to parasite persistence and autoimmune reactions after the infection, in addition to microvascular disorders and autonomic denervation, which lead to heterogeneous cases of dilated heart disease and changes in the cardiac electrical-

conduction system.³ After almost 30 years since the first clinical studies on chronic Chagas disease cardiomyopathy (CCDC) by cardiovascular magnetic resonance imaging (CMR), this method has helped increase our understanding of the pathology and improved staging and risk stratification in routine clinical practice.^{4–6}

This study aimed to revisit myocardial involvement in patients with Chagas disease from the perspective of CMR findings. It focused on morphofunctional changes in the left and right ventricles, including the characterization of myocardial fibrosis and its relationship with functional changes and cardiac arrhythmias, also addressing the prognostic value of CMR findings in cardiovascular risk stratification in CCDC patients.

Regional changes, aneurysms, and thrombi in the left ventricle

CMR is a reference method for cardiac morphofunctional assessment. Its high spatial resolution provides high-quality heart images, enabling very reliable and reproducible measurements. Furthermore, the assessment of ventricular systolic performance by CMR, particularly the calculation of ejection fraction, is based on the measurement of cavity volumes without the need for geometric assumptions.⁷ These properties improve the assessment of patients with Chagas disease, especially considering the peculiarities of this clinical condition.⁸

Regional left ventricular (LV) systolic function changes are relatively common in patients with Chagas disease, thus limiting volumetric estimates either from linear measurements or by endocardial measurements based on only two two-dimensional cardiac image projections. Clinical studies using CMR to assess LV wall motion show that the inferolateral and apical regions are the most frequently affected in patients with Chagas disease, corroborating the knowledge obtained over time using other diagnostic methods.^{9,10} Although the reason for this segmentally distributed myocardial damage is not fully understood, evidences suggest that mechanisms related to microvascular ischemia caused by Chagas disease are involved in its pathogenesis.^{11,12}

Another particularity of CCDC is the onset of ventricular aneurysms, more frequently in the apical region.¹³ These changes can range from small aneurysms with a narrow neck, to large aneurysmal dilatations with a wide neck and dyskinetic walls. The noninvasive assessment of these abnormalities can be challenging using other imaging methods such as echocardiography. On the one hand, small lesions may not be easily perceived, especially in

Keywords

Chagas disease; Ventricular dysfunction; Magnetic resonance imaging.

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Manuscript received 1/24/2022; revised 1/25/2022; accepted 1/27/2022

DOI: 10.47593/2675-312X/20223501eabc285



conventional echocardiographic imaging planes, which often shorten the visualized apical region (Figure 1).

On the other hand, in cases of large lesions, it may not be possible to analyze the entire aneurysmal region in the same image plane due to the smaller extension of the echocardiographic near field. Such obstacles can be overcome by CMR, which routinely includes the acquisition of planes transverse to the long LV axis encompassing the entire apical region and the complete visualization of apical aneurysms (Figure 2).

In CCDC patients, the prevalence of LV apical aneurysms on CMR is 20–28%, with no sex-based difference.^{14–16} Ventricular aneurysms are risk factors for intracavitary thrombosis, especially when located in the apical region in patients with a reduced LV ejection fraction.¹⁷ Myocardial lesions associated with blood stasis resulting from reduced ventricular systolic function predispose an individual to thrombus formation, which can provoke thromboembolic phenomena in CCDC.¹⁸ The presence of prominent apical myocardial trabeculae commonly causes differential diagnostic difficulties. The avascularity of the thrombi is easily noticeable on CMR images

obtained by myocardial perfusion sequences with infusion of a paramagnetic gadolinium-based contrast agent. The images acquired by this technique show thrombi as low-intensity signal structures surrounded by areas of increased signal generated by intracavitary blood content and adjacent viable myocardium. Non-viable myocardium and sessile thrombi can be differentiated by delayed enhancement present in scar regions but absent in thrombotic structures. Despite these attributes, the use of CMR to investigate ventricular aneurysms and thrombi has not been the focus of clinical studies of patients with Chagas disease. In this context, the use of CMR is noteworthy for risk stratification of thromboembolic events, but its use in CCDC patients has not been well established.¹⁹

Right ventricle in Chagas disease

The cardiac form of Chagas disease can affect both ventricles. Experimental *T. cruzi* infection models demonstrated prominent right ventricular (RV) lesions with inflammatory infiltrate, edema, parasitism, and myocardial fiber degeneration

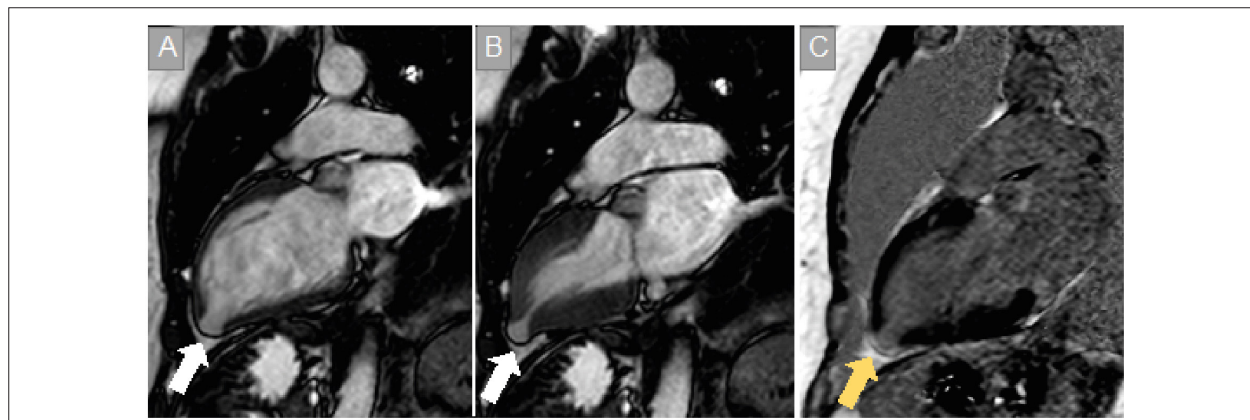


Figure 1 – Narrow neck aneurysm at the apex of the left ventricle. Two-chamber tomographic sections obtained by cine-magnetic resonance imaging in ventricular diastole (A) and systole (B) showing a small apical aneurysm region. Myocardial scar evidenced by hypersignal intensity in the region of the aneurysm in a delayed gadolinium enhancement sequence (C).

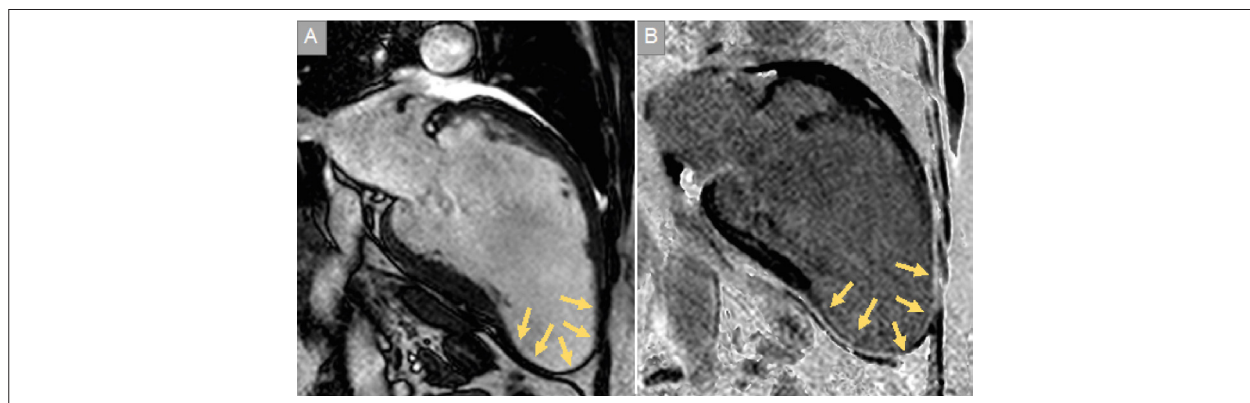


Figure 2 – Wide neck aneurysm at the apex of the left ventricle. Two-chamber tomographic sections obtained in cine-magnetic resonance imaging in diastole showing parietal thinning and cavity enlargement in the apical region (A). Delayed gadolinium enhancement sequence showing an extensive hypersignal region compatible with transmural fibrosis in the aneurysmal area (C).

in the acute phase in addition to RV dilatation progressively developing over the chronic phase.²⁰⁻²² RV dilatation and parietal thinning are common findings in necropsy studies of CCDC patients. On the other hand, histological analysis shows the replacement of RV muscle fibers by fibro-adipose tissue, more frequently in the apical region, that may show aneurysmal conformation.²³

The first detailed descriptions of clinical presentations of CCDC were highlighted by a remarkable and predominant right heart failure with signs and symptoms of intense systemic congestion.²⁴ Seminal studies using radionuclide ventriculography supported the hypothesis of early and predominant RV involvement in CCDC.^{25, 26} More recent studies associated RV systolic dysfunction with a worse prognosis in patients with heart failure due to Chagas disease, who are at a higher risk of death and require urgent heart transplantation.²⁷

Thus, it is essential to examine the RV of patients with Chagas disease during clinical follow-up. However, the peculiar characteristics of this chamber, particularly its thin walls and complex geometry, may be obstacles to its analysis. Nevertheless, CMR presents a spatial resolution of the RV endocardial borders that is relatively superior to other imaging methods used in clinical routine, providing reliable and reproducible volumetric estimates.²⁸ In addition, RV ejection fraction calculation requires no geometric assumptions similarly to the analysis of this parameter in the LV.²⁹

A clinical study using CMR to calculate RV ejection fraction in the chronic phase of Chagas disease reported RV systolic dysfunction in 37% of the 158 evaluated patients.³⁰ Most patients with right ventricular dysfunction in the investigation had a concomitantly reduced LV ejection fraction. However, RV systolic dysfunction was observed alone in approximately 4% of the studied population, including patients with the indeterminate form of the disease (Figure 3). Although the RV presents histopathological changes early after *T. cruzi* infection, the signs of its systolic dysfunction usually appear late in the disease course, when the LV ejection fraction is reduced with a subsequent pulmonary arterial pressure

increase. In this condition, RV structural lesions prevent it from adapting to the increased afterload, ultimately leading to right heart failure.³¹

Myocardial fibrosis and LV systolic dysfunction

Chagas disease myocardial fibrosis results from a multifactorial pathogenic mechanism that includes myocarditis related to parasite persistence, an autoimmune reaction triggered by the parasitic infection, and microvascular ischemia.³ Delayed gadolinium enhancement shows areas of myocardial necrosis and fibrosis usually at 10 min after the intravenous infusion. This technique has high sensitivity and specificity for myocardial scar investigation and is the current method of choice for this purpose.⁷

In the chronic phase of Chagas disease, delayed enhancement can identify scar areas early in the indeterminate form of the disease.³² However, the prevalence of fibrosis identified by CMR at this disease stage is not well established since most populations studied to date are relatively small. The combined analysis of studies reporting delayed enhancement in patients with the indeterminate form shows the occurrence of myocardial scar in 19% of the pooled population (Table 1).^{9,10, 32-39} Myocardial fibrosis progressively increases with disease progression, being considered a marker of CCDC severity.⁹ The higher the proportion of delayed enhancement in relation to the LV mass, the lower the ejection fraction of this chamber and the worse the estimated functional class.^{9, 10} However, the correlation between fibrosis extent and LV systolic function appears nonlinear. Small scar areas are seen in ventricles with normal systolic function, even when ventricular function is examined by more sensitive methods (Figure 4).³⁹ Patients with Chagas disease and a fibrotic mass on CMR greater than 10% present significantly lower LV systolic function than those with less extensive fibrosis.³⁶

The most frequent areas of delayed myocardial enhancement in Chagas disease are the inferolateral and apical regions of the LV. Although there is an association between fibrosis and myocardial wall motion abnormalities,

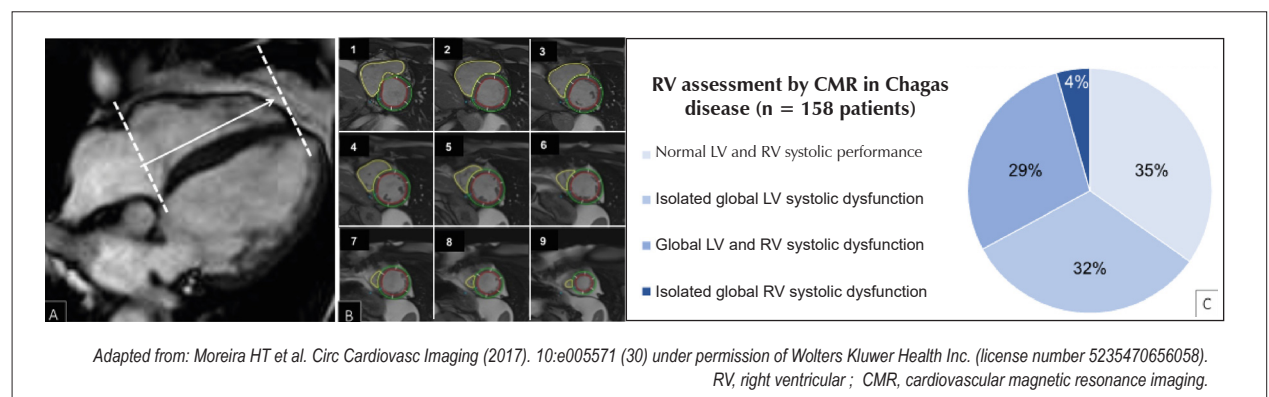


Figure 3 – Right ventricular assessment in patients with Chagas disease. RV scan limits shown in a four-chamber cine-magnetic resonance section (A). Short-axis sections from the basal to the apical region for RV endocardial border delineation (yellow lines), thus allowing the calculation of end-diastolic and systolic volumes and ejection fraction (B). A cohort of 158 patients with Chagas disease evaluated by magnetic resonance imaging showed global RV systolic dysfunction commonly associated with concomitant depressed LV systolic function, although isolated RV dysfunction has also been identified, even in cases of the indeterminate form of the disease.

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small areas of delayed enhancement may be seen in myocardial segments with normal mobility. However, more extensive scars, particularly those affecting at least 50% of the myocardial wall, are usually related to areas of LV hypokinesia and akinesia. The distribution of LV fibrosis in Chagas disease varies. Subendocardial and transmural patterns are the most common, being indistinguishable from sequelae of infarction caused by coronary artery disease. Mesocardial and subepicardial patterns are also common.^{9,10} While myocardial scars present a homogeneously and localized pattern in some individuals, diffuse fibrosis of varied patterns are seen in others. In both cases, the presence of speckled pattern scars can be an obstacle to their quantification (Figure 5).

Recently, a serial cardiac assessment of CCDC patients

by CMR associated myocardial fibrosis with a decreased LV ejection fraction.⁴⁰ The percentage of LV mass with signs of delayed enhancement significantly increased from $13 \pm 8\%$ to $18 \pm 14\%$ in subjects evaluated over a mean 5-year follow-up. However, the prognostic value of this finding remains uncertain. Issues related to the reproducibility of delayed myocardial enhancement measurements represent a limitation in the interpretation of serial assessment results. In this context, investigating factors related to the onset of myocardial scars in patients not previously presenting this finding can improve our understanding of the progression of myocardial damage in Chagas disease.

Myocardial fibrosis and ventricular arrhythmias

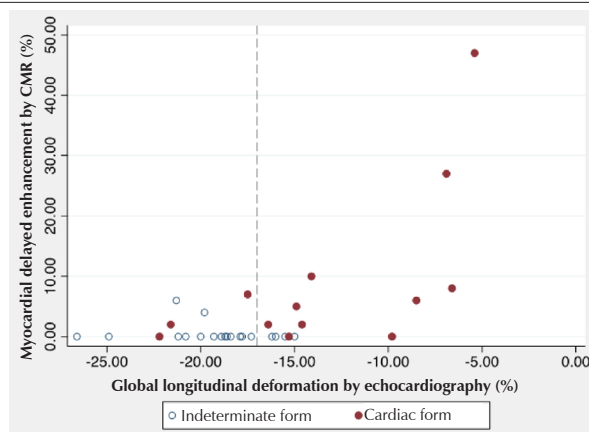
CCDC is considered an arrhythmogenic cardiomyopathy due to frequent cardiac electrical conduction system abnormalities and arrhythmias.⁴¹ Sudden cardiac death can occur at any stage of the disease, especially as a result of malignant ventricular arrhythmias such as sustained ventricular tachycardia.⁴² Myocardial fibrosis foci are the main arrhythmogenic substrates in the chronic form of Chagas disease, although other mechanisms such as microvascular disorders and sympathetic denervation also play a role in the pathogenesis of ventricular arrhythmias in this clinical condition.^{43,44}

The high spatial resolution of CMR to detect, characterize, and quantify myocardial fibrosis is a major advantage for the noninvasive risk stratification of adverse events in patients with Chagas disease, including malignant ventricular arrhythmias. Cross-sectional and case-control studies showed that areas of delayed myocardial enhancement on CMR are highly prevalent findings in patients with Chagas disease and a clinical history of concomitant sustained ventricular tachycardia.^{9,45} Notably,

Table 1 - Prevalence of delayed myocardial enhancement by CMR in patients with the indeterminate form of Chagas disease.

Authors	Patients with the indeterminate form evaluated by CMR	Presence of delayed myocardial enhancement
Rochitte et al. ⁹	15	3 (20)
Regueiro et al. ¹⁰	27	2 (7)
Noya-Rabelo et al. ³²	17	6 (35)
Tassi et al. ³³	26	5 (19)
Torreão et al. ³⁴	16	2 (13)
Lee-Felker et al. ³⁵	50	4 (8)
Uellendahl et al. ³⁶	11	3 (27)
Melendez-Ramirez et al. ³⁷	8	4 (50)
Pinheiro et al. ³⁸	16	7 (44)
Romano et al. ³⁹	19	2 (11)
Total	205	38 (19)

CMR, cardiac magnetic resonance.



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CMR, cardiac magnetic resonance; LV, left ventricular

Figure 4 – Correlation between extent of myocardial fibrosis assessed by delayed enhancement on magnetic resonance imaging and LV systolic function assessed by speckle tracking echocardiography is nonlinear in Chagas disease. Patients with small fibrotic areas (generally smaller than 10% of the myocardial mass) may have normal global LV systolic function (to the left of the dashed line, which represents the normal limit of global longitudinal myocardial deformation). A systolic global longitudinal strain lower than 15% (specific value for the software used for analysis) is usually associated with the presence of myocardial fibrosis. Additionally, the presence of myocardial scars is shown in two patients with the indeterminate form of the disease.

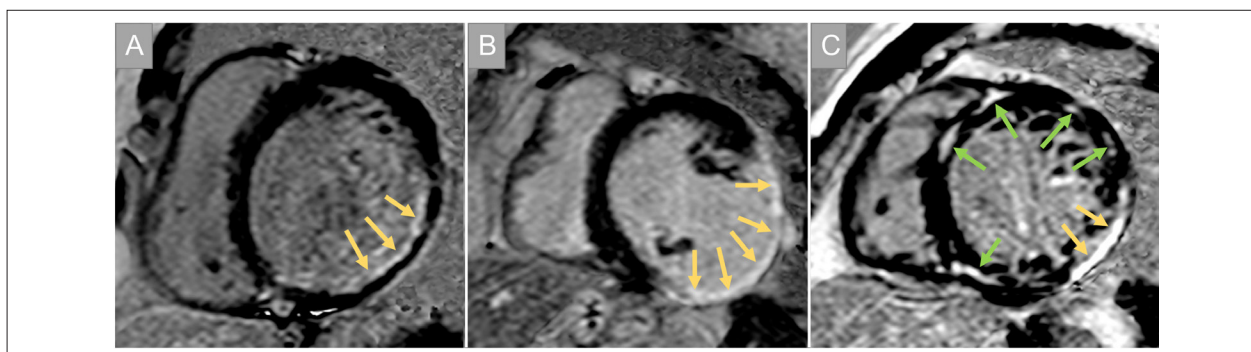


Figure 5 – Myocardial LV scars evidenced in short-axis tomographic sections using the delayed gadolinium enhancement technique. Subendocardial fibrosis in the inferolateral region of the LV (A) and transmurular fibrosis involving the anterolateral, inferolateral, and inferior LV regions (B). Diffuse and mixed myocardial fibrosis pattern with an area of transmurular scar (yellow arrows) in the inferolateral region and the foci of diffuse mesocardial scars (green arrows) involving other LV regions (C).

fibrosis identified by CMR may be the only myocardial abnormality found in Chagas patients presenting electrical instability, defined by frequent ventricular premature beats or episodes of sustained or non-sustained ventricular tachycardia.³³ In addition, myocardial scars identified by CMR are anatomically correlated with regions showing signs of autonomic denervation and ischemia assessed by myocardial perfusion scintigraphy, suggesting an inextricable participation of these factors in the pathogenesis of ventricular arrhythmias in CCDC.⁴⁶

A transmurular myocardial fibrosis pattern is more frequently noted on CMR in Chagas patients with sustained ventricular tachycardia than in those without this clinical sign. The presence of two or more continuous myocardial segments with transmurular delayed enhancement is associated with a history of sustained ventricular tachycardia regardless of age, sex, LV ejection fraction, and the percentage of delayed enhancement.⁴⁵

In addition, myocardial scar characterization by CMR can be an auxiliary tool in ventricular tachycardia ablation in patients with CCDC.⁴⁷ Scar patterns that are transmurular or have subepicardial involvement, usually present in the inferolateral segments of the LV, often lead to predominantly epicardial reentrant circuits.⁴⁸ Under these conditions, combined endocardial and epicardial ablation is more effective at stopping malignant ventricular arrhythmias in CCDC patients in the short and long term.⁴⁹

New CMR techniques seem promising for assessing interstitial fibrosis in patients with Chagas disease. A cross-sectional study of 47 Chagas patients demonstrated that higher interstitial fibrosis by its CMR-derived extracellular volume is associated with non-sustained ventricular tachycardia regardless of ejection fraction and delayed LV myocardial enhancement quantification.³⁸

Prognostic value of myocardial fibrosis in chronic Chagas heart disease

In Chagas disease patients, prognostic assessments can identify individuals at greater risk of cardiovascular events throughout the disease course, thus helping decision-

making regarding the need for specialized follow-up and therapeutic planning. LV systolic dysfunction is the most consistent predictor of death in patients with Chagas disease.⁵⁰ However, other factors, such as male sex, New York Heart Association functional class III/IV, low-voltage QRS complexes on an electrocardiogram, cardiomegaly on chest radiography, and non-sustained ventricular tachycardia identified on 24-hour electrocardiographic monitoring also indicate higher risk of adverse events and high mortality in this clinical setting. These predictors are gathered in the score proposed by Rassi et al. that was originally developed and validated for the risk stratification of death in patients with CCDC.⁵¹ In a cross-sectional study, the greater extent of myocardial fibrosis assessed by CMR was positively correlated with Rassi score.³⁶

Two recent longitudinal studies demonstrated the role of myocardial fibrosis identification and quantification by CMR in the risk stratification of this clinical condition.^{14, 15} In a prospective cohort of 140 CCDC patients, myocardial scar was related with the occurrence of combined sustained ventricular tachycardia and cardiovascular death at a median 3-year follow-up period. A significant association was also reported between myocardial fibrosis and the combined outcome including hospital admission for heart failure. Also, the greater the extent of myocardial scar, the greater the risk of these combined events regardless of age and LV ejection fraction (Figure 6).¹⁴ In another retrospective cohort of 130 CCDC patients, the presence and greater extent of delayed myocardial enhancement were related to a high incidence of the combined outcome of overall mortality, heart transplantation, appropriate implantable cardioverter-defibrillator therapy, and aborted sudden death in a median 5-year follow-up period. In that study, the presence of a fibrotic mass equal to or greater than 12.3 g was significantly and independently associated with the combined outcome studied. Additionally, a bivariate analysis including fibrotic mass and the Rassi risk score as predictive variables showed the association of both with the composite outcome.¹⁵ Remarkably, the absence of fibrosis in these studies was an excellent marker of the non-occurrence of adverse events in patients with CCDC. However, the question remains about the

role of myocardial fibrosis in prognostic reclassification after use of the Rassi score, especially in individuals initially stratified by this classification system as being at low or intermediate risk.⁵² Nevertheless, these recent studies demonstrated the potential benefits of myocardial scar assessment by CMR in the stratification of cardiovascular risk in Chagas patients, while the role of this evaluation in clinical decision-making may be demonstrated in future clinical trials.

Myocarditis assessment of Chagas patients

Myocarditis due to parasitic persistence is considered one of the main pathogenic mechanisms of myocardial injury by Chagas disease.⁵³ In the acute phase, severe myocarditis can lead to death, although this has been noted in only a small number of symptomatic patients. However, the prevalence of myocardial inflammation in the acute phase of the disease is probably underestimated due to diagnostic difficulty. In the chronic phase, low-intensity myocarditis is recognized as a key pathological mechanism in the genesis of myocardial lesions in Chagas disease. Exacerbations can occur in immunosuppressed patients, reactivating parasite replication and causing severe myocarditis, acute heart failure, and death.

Despite the outstanding role of CMR in the noninvasive assessment of myocarditis, its use in patients with Chagas disease has been scarcely reported in the scientific literature. A cross-sectional study of 54 patients with Chagas disease using conventional CMR techniques showed that myocardial hyperemia and edema, considered criteria for the noninvasive diagnosis of myocarditis, can occur in all phases of CCDC, even early in patients with preserved LV systolic function or with the indeterminate form.³⁴ As highlighted by the authors, these subclinical abnormalities show the risk of more severe conditions and can increase our understanding of the natural history of the disease.

In addition to traditional strategies for investigating suspected myocarditis, the CMR myocardial mapping

technique provides a quantitative and more objective analysis of areas of myocardial edema. A case of Chagas myocarditis in an adult patient reported that this technique helped diagnose myocarditis in the acute phase and over the follow-up period, showing progressive regression of the edematous myocardial areas in serial CMR tests.⁵⁴ The use of myocardial mapping in the chronic phase of Chagas disease is promising, as it may reveal subclinical changes and identify individuals at high risk of progressing to more advanced CCDC stages.

Conclusions

CMR assesses myocardial involvement in Chagas disease with highly reliable and reproducible cardiac morphofunctional characterization, especially in the presence of regional LV systolic function changes and RV dysfunction. CMR has high sensitivity for detecting myocardial scars, proving a valuable tool for cardiovascular risk stratification in CCDC patients. The presence and greater extent of myocardial fibrosis areas on CMR are associated with LV systolic dysfunction and the occurrence of ventricular arrhythmias in these patients. In addition, clinical cohorts have recently demonstrated the prognostic value of delayed myocardial gadolinium enhancement areas with adverse cardiovascular events such as hospital admissions for heart failure, sustained ventricular tachycardia, and sudden cardiac death. More advanced CMR techniques, such as myocardial mapping for the assessment of myocardial edema and diffuse fibrosis, were recently used in the clinical evaluation of patients with Chagas disease with very promising preliminary results.

Authors' contribution

Manuscript concept and writing: Moreira HT; Critical review for important intellectual content: Volpe GJ, Schmidt A

Conflict of interest

The authors have declared that they have no conflict of interest.

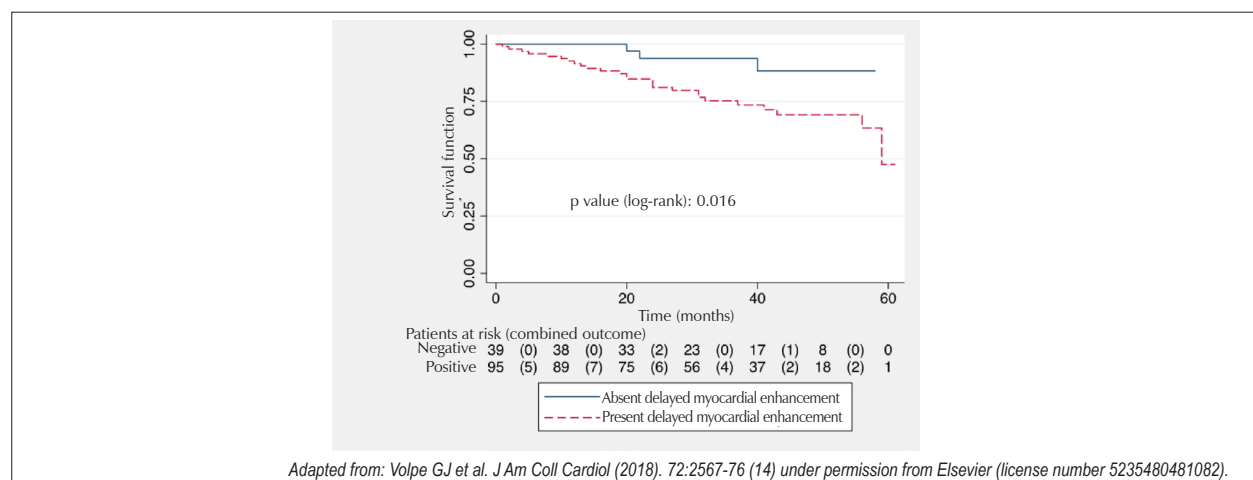


Figure 6 – Association between myocardial fibrosis and the occurrence of the combined outcome of cardiovascular death, sustained ventricular tachycardia, or hospitalization for heart failure in patients with chronic Chagas heart disease. The presence of delayed myocardial enhancement by CMR is a risk predictor of the combined outcome compared with the absence of myocardial scar.

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