Abstract

The well-known occurrence of Chagas disease in endemic areas has become a worldwide problem, and cardiac magnetic resonance allows the early detection of cardiac involvement and complications of this disease. Cardiac magnetic resonance is a useful tool in all phases of Chagas disease, and new promising techniques using T1 mapping and extracellular volume measurements are able to detect cardiac involvement even earlier than conventional techniques.

Introduction

The protozoan Trypanosoma cruzi is the causal agent of Chagas disease (CD), considered a significant global health problem. It affects the young productive population and is responsible for losses of around 752,000 working days in endemic countries. The migratory flux between endemic and non-endemic countries has spread CD worldwide and turned it into a global health problem, especially in countries with little knowledge on CD and its transmission.

The natural progression of CD is divided in acute and chronic phases. The chronic phase is subdivided into indeterminate and determinate forms. The pathogenesis of CD involves an inflammatory response, as well as cellular damage and fibrosis that can be identified by cardiac magnetic resonance (CMR) imaging sequences.

Keywords

Chagas Disease/complications; Chagas Cardiomyopathy/complications; Fibrosis; Heart Failure; Magnetic Resonance Imaging/methods; Gadolinium/radiation effects; Extracellular Volume; T1 Mapping; Endemic Diseases.

CMR has been applied to evaluate several cardiomyopathy etiologies; it is considered efficient in the diagnosis of the different stages of CD and for determining prognosis, in addition to being a non-invasive method that does not expose the patient to ionizing radiation.

Different CMR sequences are available to confirm early or late cardiac involvement in patients with CD and to investigate heart failure of unknown causes where typical findings of CD could provide additional diagnostic information.

The diagnostic role of CMR in acute CD

Most patients with acute CD are oligosymptomatic and hardly ever seen in non-endemic areas; it is estimated that only 1–2% of the cases are diagnosed. In this phase, mortality is high and some patients develop severe myocarditis, meningoencephalitis, or both. Accurate diagnosis in the acute phase is particularly important because of the high probability of cure reached through the use of antiparasitic drugs.

The consequences of heart muscle inflammation resulting from cardiac cell injury caused by T. cruzi and its related immune reactions can be identified by CMR using T2-weighted and late gadolinium enhancement (LGE) sequences for detecting myocarditis.

The T2-weighted sequence is able to identify areas of signal hyperintensity corresponding to myocardial edema using inversion pulses to suppress blood contrast and fat signals. On the other hand, the LGE sequence reveals regions of myocardial necrosis/fibrosis due to myocardial injury. This sequence is performed 10–20 min after the injection of a gadolinium-based contrast agent that reaches the myocardium and is distributed within the extracellular space; areas containing dead heart muscle cells retain the gadolinium and generate white images (Figure 1).
Fortunately, antiparasitic drugs cure 50-80% of patients with acute CD and are able to prevent progression to the chronic phase. However, since most patients are unaware of the disease and the diagnosis is hardly performed during the acute phase, it usually resolves spontaneously.

The diagnostic role of CMR in chronic CD

Approximately 30% of non-treated patients develop chronic CD after the acute phase. Most of them remain in the indeterminate form, with neither clinically apparent disease nor radiologic or electrocardiographically evident abnormalities for a long period or even a lifetime. In the chronic phase, CD can only be diagnosed by positive serology and/or xenodiagnosis tests.

CMR allowed the observation of myocardial fibrosis (MF) and edema in some patients in the chronic phase of CD; this contradicted the classical definition of this phase and revealed a less benign scenario than previously believed. Rochitte et al., used LGE in patients at various stages of CD and have demonstrated MF in 20% of patients in the indeterminate form. Moreover, Torreão et al., revealed evidences of myocardial inflammation even long after the acute phase using T2-weighted and early gadolinium enhancement sequences, which corroborated histopathological findings in vivo.

Approximately 30% to 40% of patients with CD will develop a determinate form of the disease 10–30 years after infection, with cardiac and/or digestive involvement; 5% to 10% will develop it directly after the acute phase.

Chronic Chagas cardiomyopathy is the most important complication of CD and its pathogenesis is related to parasite-induced and immune-mediated myocardial injury, cardiac dysautonomia, and ischemia. It can present itself as heart failure, cardiac arrhythmia, and pulmonary or systemic thromboembolism.

The small and progressive damage secondary to chronic myocarditis and myocardial perfusion abnormalities results in regional cardiac dysfunction. Extensive regional damage leads to cardiac enlargement, myocardial dysfunction, and heart failure, which is responsible for mortality rates of around 50% in 4 years. Cardiac involvement is usually biventricular, with a more pronounced failure of the right ventricle (RV). Some patients may develop isolated RV dysfunction that can be detected early by CMR (Figure 2).

The assessment of cardiac volumes and function can be performed using cine CMR. This technique presents advantages over echocardiography mainly in RV measurement, which can be performed directly by the Simpson method instead of being calculated by geometric approximation. Cine CMR provides an excellent myocardium-to-cavity contrast ratio, allowing the accurate delineation of endocardial borders; this is especially important in patients with significant changes in ventricular geometry such as ventricular apical aneurysm, a typical finding of chronic CD (Figure 3). Owing to these advantages, it is considered a gold standard technique for assessing volume and cardiac function.
Adding myocardial tagging in cine CMR improves the detection of regional dysfunction through the visualization of myocardial deformation, which is an early abnormality of CD. The assessment of myocardial deformation has recently advanced through speckle-tracking echocardiography and feature tracking by CMR. These techniques provide the assessment of ventricular dynamics, including the performance of quantitative segmental analyses of ventricular function, while global systolic function is still preserved. Although the role of feature tracking by CMR in CD still needs to be assessed and standardized, speckle-tracking echocardiography has been extensively studied in patients with this disease.

Due to the very low sensitivity of echocardiography in detecting RV systolic dysfunction in patients with CD, speckle-tracking echocardiography has been used in the detection of RV impairment and the early involvement of the left ventricle (LV) even in patients with preserved LV ejection fractions.

An analysis performed in patients in early stages of CD observed, through CMR, a decrease in global longitudinal and circumferential LV strain only in patients with MF.

The progressive myocardial destruction with consequent replacement fibrosis has been described by pathological studies and can also be observed by CMR. MF was first quantified on LGE–CMR by Rochitte et al., who demonstrated its presence in

Figure 2 – A 50-year-old man present isolated RV involvement secondary to chronic Chagas disease easily detected by cine-CMR sequence.

Figure 3 – Examples of complications of chronic Chagas disease in two representative patients. First patient: (a-b) cine-CMR reveals typical ventricular apical aneurysm (vorticilar) (arrows). Second patient: (c) LGE-CMR reveals apical thrombus (arrow) and LV myocardial fibrosis.
68.6% of patients in all cardiac phases of CD. The amount of MF progressively increased from the indeterminate to determinate forms of the disease. The more MF, the worse the ventricular dysfunction and clinical condition of the patient. Researchers also found that the most affected regions were the apex and inferolateral regions of the LV, with a predominance of midwall and subepicardial layers (Figure 4). An atypical pattern was found in 46.9% of the analyzed LV segments, including subendocardial and transmural patterns that were indistinguishable from the fibrosis secondary to coronary disease (Figure 5).\textsuperscript{10}

Another study evaluated sex differences by CMR. Investigators found significantly more fibrosis and ventricular dysfunction in male patients with CD than in female patients. The distribution of MF was also different between both sexes, where men displayed more transmural fibrosis than women.\textsuperscript{25}

Finally, considering that an apical ventricular aneurysm increases the risk of intracardiac thrombosis and thromboembolic phenomena, ventricular thrombus can be easily recognized by using LGE–CMR.\textsuperscript{26}

**CMR as a risk stratification tool**

Sudden cardiac death is responsible for 55% to 65% of all deaths in CD.\textsuperscript{27} The close relationship of MF, ventricular arrhythmias, and sudden cardiac death has been described by several studies on ischemic and nonischemic cardiomyopathies.\textsuperscript{28–32}

Distinguishing different patterns of MF and determining its extent by LGE–CMR provides important information that allows physicians to distinguish the etiology of cardiomyopathies and improve prognosis scores. White et al.,\textsuperscript{33} demonstrated that the etiology of aborted sudden cardiac death or sustained monomorphic ventricular tachycardia was changed in 50% of the cases where patients were evaluated by CMR in comparison to conventional diagnostic investigation with transthoracic echocardiography and coronary angiography.\textsuperscript{33}

The use of MF in the prediction of adverse events in patients with CD was assessed by Uellendahl et al.,\textsuperscript{34} the authors correlated MF with prognostic data using the validated Rassi score, which identifies patients at risk (low, intermediate, or high) of dying prematurely. This correlation

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**Figure 4 – LGE-CMR showing classic cardiac involvement in chronic Chagas disease (arrows). In a-e, midwall and subepicardial myocardial fibrosis in the LV inferolateral regions (short axis view). In f, myocardial fibrosis in the LV apex (three-chamber view).**

Figure 5 – An 83-year-old woman with positive serological tests for Chagas disease and atypical LGE that simulates transmural infarction. In a and b, myocardial fibrosis in the circumflex artery territory (lateral wall - arrows). In c, coronary angiography showing absence of coronary artery disease.

evidenced a progressive increase in MF from low- to high-risk Rassi score groups and also confirmed a strong association among MF, cardiac dysfunction, and arrhythmia.\textsuperscript{34}

Recently, Senra et al.,\textsuperscript{35} identified MF in 76.1% of patients with chronic Chagas cardiomyopathy and defined a cutoff value for the myocardial fibrosis mass of 12.3 g for predicting the combined endpoint (all-cause mortality, heart transplantation, antitachycardia pacing or appropriate shock from an implantable cardioverter-defibrillator [ICD], and aborted sudden cardiac death). The study had an average follow-up of 5 years with an area under the curve of 0.79 (95% confidence interval [CI] 0.72–0.87). The MF observed on CMR was an independent predictor of the combined endpoint.\textsuperscript{35}

LGE imaging represents a powerful tool to identify patients at higher risk of cardiovascular events and who would benefit from an ICD.\textsuperscript{36,37} Furthermore, the presence of MF in patients with heart failure who underwent device implantation revealed a high likelihood of appropriate ICD therapy, while its absence predicted a low risk of appropriate therapy.\textsuperscript{38}

**Future perspectives**

T1 mapping and extracellular volume measurements represent potentially powerful emerging techniques that have allowed the assessment of myocardial affection at early stages of CD, where LGE images still cannot be obtained. By employing these techniques, it is possible to assess the replacement and permeation of myocardial tissue in several cardiomyopathy etiologies.\textsuperscript{39–46} Extracellular volume estimation uses hematocrit and T1 values (pre- and post-contrast)\textsuperscript{47} and has a strong correlation with extracellular matrix.\textsuperscript{48–50} Similarly to LV ejection fraction, the extracellular volume is an important prognostic tool in the evaluation of cardiomyopathies.\textsuperscript{51,52} In CD, native T1 and extracellular volume increase along with disease severity; abnormal values may be seen even in the indeterminate form of the disease and in regions without MF. This prompts these parameters as tools for identifying and monitoring early myocardial damage, in addition to performing risk stratification (Figure 6).\textsuperscript{53}

**Conclusions**

Despite the difficulties of using CMR in clinical settings, especially in endemic areas of CD with budget limitations, the early detection of cardiac involvement by CMR has an important impact on the clinical approach and disease prognostics.

Although CD was discovered more than 100 years ago, recent technological advances have allowed a better understanding of this disease and the early detection of cardiac involvement. CMR has the potential to detect not only biventricular systolic dysfunction in the chronic cardiac phase, but also myocardial inflammation (by T2-weighted and early gadolinium enhancement imaging) and MF (by LGE imaging) in the acute and indeterminate phases, even when no other tests show abnormalities.

CMR is also valuable for predicting adverse events. T1 mapping and extracellular volume sequences are promising techniques for assessing Chagas cardiomyopathy before MF becomes apparent.
Figure 6 – Examples of LGE, extracellular volume, native and post-contrast T1 mid-cavity short axis images in patients with indeterminate form (a, b, c, and d, respectively) and with reduced LV ejection fraction (e, f, g, and h, respectively). In the indeterminate form, we note homogeneous myocardial signal in all sequences, showing no interstitial enlargement. In the Chronic Chagas cardiomyopathy, we see LGE in inferolateral wall, interventricular septum and myocardial junctions; in T1 mapping and extracellular volume sequences, those alterations are more pronounced, showing interstitial fibrosis in LGE-negative areas, as anterolateral and inferior walls.

Author contributions
Conception and design of the research: Pacheco AB. Rochitte CE. Acquisition of data: Pacheco AB, Melo, RJL. Analysis and interpretation of the data: Pacheco AB, Rochitte, CE. Writing of the manuscript: Pacheco AB, Melo, RJL. Critical revision of the manuscript for intellectual content: Rochitte CE.

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This article does not contain any studies with human participants or animals performed by any of the authors.


