Diagnostic Challenges of Chagas Cardiomyopathy and CMR Imaging

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ABSTRACT

Chagas disease comprises a poorly understood and studied clinical scenario, and the Chagas cardiomyopathy is the more representative field of these difficulties. Different from other cardiomyopathies, there is a discrepancy between its severity and poor prognosis and the low efficiency specific diagnostic and therapeutic available tools. Recently, cardiac magnetic resonance has evolved as an important cardiologic method of detailed and accurate myocardial evaluation. It has already been proved as a valuable test for cardiac functional and structural analysis. Considering the vast area that must be studied and researched regarding this cardiomyopathy, cardiac magnetic resonance is being considered an important recent tool for this purpose. The current use of this imaging method for Chagas cardiomyopathy is reviewed. For the proper image interpretation, the relevant pathophysiological aspects are remembered and the natural history of the Chagas disease is briefly reviewed.

The Brazilian physician Carlos Chagas described Chagas disease—or American trypanosomiasis—106 years ago. Today, the disease remains with many aspects still poorly understood or unresolved, such as factors related to clinical pleomorphism, prognosis, specific treatment, and prevention methods [1].

There are 2 consecutive phases in Chagas disease presentation: acute and chronic [1,2]. The acute phase is usually asymptomatic or may present as a self-limiting febrile illness. When present, the symptoms begin 1 to 2 weeks after contact with the insect or even a few months after transfusion with infected blood. There is an intense inflammatory reaction in the *Trypanosoma cruzi* portal of entry ("chagoma"). In the conjunctiva, this can result in unilateral periorbital edema, eyelid edema, and pre-auricular adenopathy (Romaña sign). Other manifestations include fever, myalgia, malaise, sweating, hepatosplenomegaly. Cardiac involvement occurs in >90% of cases and is characterized by myocarditis, with or without pericardial effusion [2]. The electrocardiogram (ECG) may show low voltage, diffuse changes in repolarization and conduction abnormalities. Treatment with antiparasitic drugs in this phase, such as benznidazole, usually cures the acute manifestations and prevents the development of the chronic phase. The acute symptoms resolve spontaneously in >90% of cases within 6 to 8 weeks.

The chronic phase remains throughout the patient's life. After the acute phase symptoms' completion, 60% to 70% of patients remain carriers of the parasite, but they do not have clinical manifestations. This is the indeterminate form of disease [3]. These patients have positive serologic tests against *T. cruzi*, but they are asymptomatic and have normal ECG, chest X-rays, and esophagus and colon tests. Over their lives, the remaining 30% to 40% of patients will develop the cardiac and/or digestive clinical manifestations of the disease. This typically occurs 10 to 30 years after the infection, at an approximate rate of 2% to 3% per year [4]. Other rare forms of evolution are direct progression from the acute to the clinical manifestations of chronic phase (5% to 10% of patients) and the reactivation of the disease in chronically infected patients who become immunosuppressed.

Cardiac involvement in the chronic phase is characterized as Chagas cardiomyopathy (ChC) and is the most important clinical aspect of the disease because of its poor prognosis. ChC is classified into 4 stages (A, B, C, and D) according to the level of cardiac involvement. Stage A is characterized by the indeterminate form of the disease. When the ECG manifestations are established in the absence of symptoms, ChC is classified as stage B. The onset of symptoms determines the C and D stages. In stage D, the symptoms of heart failure are present at rest or are refractory to treatment. Sudden death can occur at any stage, even before the onset of symptoms [5]. In the early stages of ChC, conduction disturbances are noted, as well segmental changes in contractility and diastolic dysfunction. Systolic dysfunction is installed later and is often accompanied by arrhythmias, advanced conduction blocks, sudden death (SD), and thromboembolic events [2].

In relation to other cardiomyopathies, ChC has peculiar aspects. Patients are mostly men who initiate clinical presentation between 30 and 50 years of age and have positive epidemiological factors (endemic areas). Regarding the clinical aspects, right heart failure usually predominates and is accompanied by palpitations, syncope, and thromboembolic events. The usual cardiologic diagnostic tests also demonstrate specific aspects in this cardiomyopathy.

The authors report no relationships that could be construed as a conflict of interest.
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GLOBAL HEART

VOL. 10, NO. 3, 2015
ISSN 2211-8160/$36.00.
http://dx.doi.org/10.1016/j.gheart.2015.07.005

ECG often shows right bundle branch block associated with left anterior hemiblock and ventricular premature beats, whereas Holter monitoring shows frequent ventricular arrhythmias and bradyarrhythmias. Morphologically, other peculiar aspects are also found: left ventricle with apical aneurysm; inferolateral hypokinesia/akinesia; and intracavitary thrombus. Myocardial perfusion can be altered in the absence of coronary stenoses [2].

Several theories have been used in an attempt to explain the pathogenesis of cardiac involvement that occurs in Chagas disease: direct aggression of the parasite; parasympathetic denervation with consequent continuous increase in sympathetic tone (parasympathetic theory); immunological mechanisms triggered by the parasite and/or autoimmune, microvascular, and coronary flow abnormalities resulting from perivascular inflammation, endothelial dysfunction, and platelet activation [6,7]. The result of the continued action of 1 or more of these mechanisms is a significant myocardial structural modification associated with inflammation, necrosis, hypertrophy, and ventricular dilation. Bands of fibrous tissue replace cardiac myocytes and an important feature of ChC is the accumulation of extracellular collagen that encloses fibers or groups of fibers (Figure 1) [8,9]. Interestingly, these pathological changes can also be found in patients with indeterminate form. Mady et al. [10] performed endomyocardial right ventricle biopsy in 20 patients with indeterminate form. The majority (60%) presented histopathological changes under optical microscopy (edema, mononuclear infiltrate, degenerative lesions, and increased volume of myocyte cells). Fibrosis was found in 25% of cases [10].

CARDIAC MAGNETIC RESONANCE—MAIN TECHNIQUES

Cardiac magnetic resonance (CMR) is an imaging test in cardiology that produces high spatial resolution images, without the use of ionizing radiation and with no spatial limitation. It consists of pulse sequences with different characteristics, each aiming at the analysis of different aspects of the heart. The sequences to be used in a protocol will depend on the test objectives and the information requested. The protocols generally begin with sequences of cine resonance that analyze the morphological and functional characteristics of the cardiac chambers. Nowadays, this is done with high temporal and spatial resolution because of the development of a special gradient-echo sequence with a steady-state free precession acquisition. This sequence generates images with high contrast between the myocardium and the cavity, based on the tissue T_2/T_1 ratio being less prone to artifacts generated by blood flow. Thus, images with clear definition of the endocardial and epicardial borders are produced, which is an essential step in an accurate measurement of cavity volumes and ventricular mass. From these data, the ejection fraction of both ventricles is calculated, always using the Simpson method. The myocardial contractility can be analyzed (subjectively or quantitatively), as well as the presence of ventricular aneurysms and parietal thinning. Considering that the steady-state free precession is a sequence with low values of repetition time (TR) and echo time (TE), it can image the heart in motion with short periods of apnea (6 to 8 s). Because of such developments achieved by CMR, this diagnostic method is considered the gold standard in the

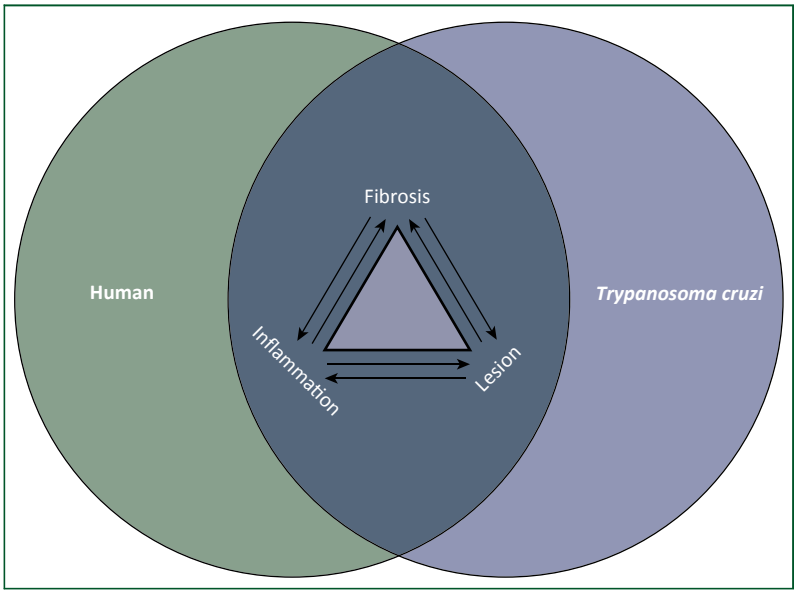

FIGURE 1. Unifying hypotheses for the pathogeny of Chagas disease [9].

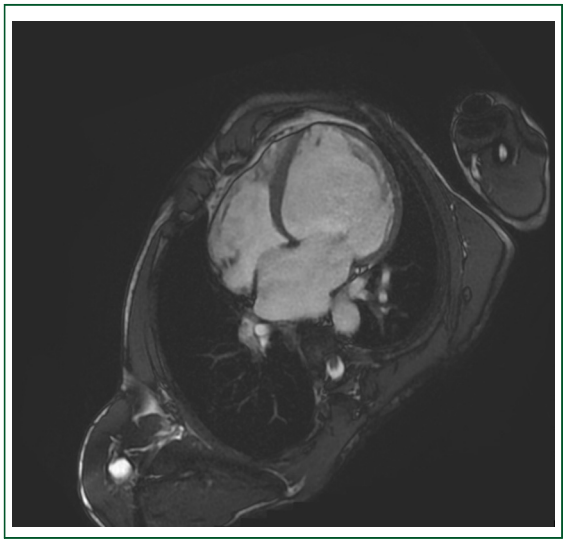

FIGURE 2. SSFP sequence. Considering its properties, the steady-state free precession (SSFP) sequence enables a highly accurate analysis of the cardiac chambers (volume, mass, and function).

evaluation of volume, mass, and cardiac systolic function (Figure 2) [9].

Despite these significant advances in the cardiac functional assessment, it is through the myocardial structural assessment that CMR revealed important diagnostic and prognostic information in cardiology. This is the tissue characterization and is performed by the use of pulse sequences that can generate static and high spatial resolution images that allow a high-quality tissue analysis. With this, it is possible to analyze the formation of the cardiac structures for the presence of water, iron, thrombus, or collagen. The sequences used are spin-echo and gradient-echo. The spin-echo sequences are always ECG-gated and acquired at mid-diastole. Its parameters (TR and TE) can be changed in order to obtain images that are T_1-or T_2-weighted and thereby to differentiate tissues. Using spin-echo sequences it is possible to analyze, for example, the parietal thinning, pericardial thickening, and effusion. The gradient-echo sequence consists of a radiofrequency pulse with a flip angle alpha, followed by the application of opposing polarity magnetic field gradients to bring the spins into coherence for the formation of the imaging echo. The result is proton density, T_1-, T_2-, or T_2*-weighted images [9]. Because it can be loaded into T_2*, this sequence allows the analysis of myocardial iron content. However, the main use of this sequence is combined with a paramagnetic contrast agent (gadolinium-based contrast). Gadolinium is composed of small molecules, which readily diffuse into the extracellular space, and decreases tissue T_1 and T_2, mainly T_1. At low doses, there is a linear relationship between the concentration of gadolinium tissue and the signal strength acquired from the T_1-weighted gradient-echo sequence. Moreover, the gradient-echo sequence has a short acquisition time when using large flip angles and short TR. Thus, using this sequence and displaying the first pass of gadolinium in the tissues, it is possible to assess the myocardial perfusion. Slices are selected in the short axis of the left ventricle, and the first pass of gadolinium in the myocardium is then analyzed after intravenous injection (0.05 to 0.10 mmol/kg contrast). This can be done at rest, in use of coronary vasodilators (adenosine/dipyridamole) or dobutamine, allowing perfusion examination at rest and under pharmacological stress [11].

Regarding the CMR tissue characterization properties, a gradient-echo sequence with an inversion-recover preparation pre-pulse was developed to detect necrosis and/or fibrosis in the myocardium. This is the myocardium-delayed enhancement (MDE) or late gadolinium enhancement (LGE) sequence and is performed 10 to 20 min after intravenous gadolinium injection (0.2 mmol/kg). As previous noted, gadolinium fills out only the extracellular normal myocardial space. During the time after the injection, the gadolinium is readily washed-out from the structurally normal myocardium. Differently, the myocardium that owns structural changes enables increased gadolinium distribution volume and, consequently, longer wash-out time. At the time of image acquisition, this myocardium appears with a high signal and is white, with excellent contrast to the normal myocardium that appears with a low signal and is dark. This technique enabled the diagnosis of myocardial injury areas with high accuracy and differentiation. It also made it possible to quantify the necrosis and/or fibrosis area(s). In the context of myocardial ischemic disease, this means the establishment of the myocardial infarction extension and viability. In other cardiomyopathies, this enables the evaluation of the necrosis and/or myocardial fibrosis pattern formation and, through this, the etiology of the cardiomyopathy can be inferred [12].

CARDIAC MAGNETIC RESONANCE IN CHAGASIC CARDIOMYOPATHY—CORRELATION BETWEEN THE PATHOPHYSIOLOGICAL ASPECTS AND THE IMAGES' CHARACTERISTICS

During the natural evolution of Chagas disease, 30% to 40% of patients will progress to chronic forms, at the rate of 2% to 3% per year. Of these, only 10% to 20% of them will exhibit cardiovascular symptoms. Thus, in some patients the cardiac changes will only be recognized with the aid of auxiliary diagnostic tests such as ECG, echocardiography, and CMR.

As previously noted, in the indeterminate form, the patients are asymptomatic, have serological and/or parasitological positivity, with normal ECG, radiological studies of the heart, esophagus, and colon. This definition was created in the 1980s. Since then, newer cardiologic noninvasive studies have demonstrated some abnormalities in this patient population: depression of blood pressure and chronotropic responses during exercise; stress-induced ventricular arrhythmias; decreased fractional shortening and mean velocity of circumferential fiber shortening in the left ventricle; and abnormalities of diastolic function and changes in segmental contractility, among other findings [13]. Similarly, CMR has also showed that 20% of patients in the indeterminate form have evidence of myocardial fibrosis, with no change in the associated segmental contractility [9].

As has already been described, ChC has unique characteristics compared with those of other myocardiopathies. Regarding the pathophysiological aspects, it is proper for this cardiomyopathy to have a high formation of collagen bands, creating an intense structural modification. Considering the characteristics described, CMR can noninvasively demonstrate this structural disarray associated with a high formation of collagen.

Before considering all contributions that CMR can bring to the study of ChC, one should better detail the peculiar aspects of the ChC pathophysiology that have relevant implications for the interpretation of the images.

The pathophysiological mechanisms present in the development of ChC are not fully elucidated [7]. Histopathological findings are diffuse myocarditis, with

myocytolysis and reparative fibrosis. It is believed that this cardiomyopathy is a result of joint action of dysautonomia, vascular changes, and immunological phenomena, as has already been described. In patients with Chagas disease, there is an intense neuronal reduction in heart intramural ganglia resulting in a decrease in the parasympathetic inhibitor tonus. In other cardiomyopathies, neurohumoral activation and post-synaptic desensitization of beta receptors are found and are reversible with medical treatment. Dysautonomia found in ChC is responsible for a continuous increase in sympathetic tone, which would lead to a catecholaminergic cardiomyopathy, SD, and vasospasm.

Other possible pathophysiological mechanisms present in ChC are the vascular changes. The presence of perivascular inflammation would lead to structural changes in the microcirculation, with luminal reduction by intimal hyperplasia, both are findings of histological studies in ChC. These vascular structural changes would eventually result in disturbances in vasodilation and vasoconstriction of the coronary microcirculation, causing small ischemic and necrotic areas. The cell necrosis would be replaced by reparative scar tissue. ChC necropsy studies showed extensive fibrosis, which correlates with the severity of the disease [14]. In addition, the perivascular inflammation was also responsible for the endothelial dysfunction present in these patients, with a consequent reduction in the production of protective vasoactive substances and increased tissue concentration of vasoconstrictor and platelet activating agents. Thromboembolic phenomena would be the result. In fact, you can find clinical ECG changes suggestive of ischemia, segmental changes in ventricular contractility, and perfusion deficits in scintigraphic studies. The left ventricular lateral wall is the most often affected site (terminal circulatory zone). Surprisingly, the coronary angiographic studies of these patients usually do not indicate the presence of obstructive epicardial coronary disease.

The supposed involvement of immunologic mechanisms in the ChC is based on the histological findings of myocarditis, on the time discrepancy between the late inflammatory reaction and acute infection, and on the small amount of parasites found in the tissues. The ChC inflammatory infiltrate consists of macrophages, $CD8^+$ and $CD4^+$ lymphocytes, adhesion molecules, in addition to humoral presence of inflammatory cytokines, particularly interferon gamma, tumor necrosis factor alpha, and interleukins 6 and 4130 [7].

Cardiac pathological studies of chagasic patients showed a diffuse increase in the thickness of the collagen fibers of the perimysial matrix, that is, fibers that surround the cardiac muscle bundles (diffuse interstitial fibrosis), with no increase in the fibers of the endomysial matrix (surrounding individual myocytes). Additionally, scar regions were characterized by the absence of myocytes; presence of lymphocytic inflammatory infiltrate; myocytes with degenerative signs; and dense, starry, and rich collagen areas (reparative fibrosis) [15].

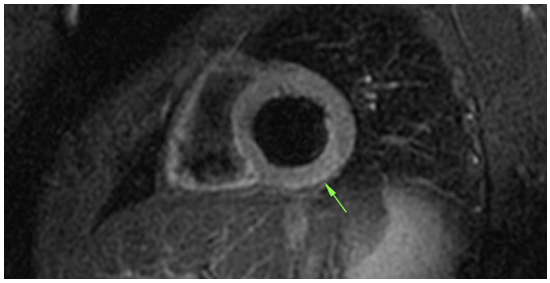

FIGURE 3. Tissue characterization: myocardial edema shown in a fast spin-echo sequence. This short-axis image of the left ventricle shows a hypersignal area in the lateral segment (green arrow) that comprises an area of myocardial edema.

In summary, the described pathophysiological processes are responsible for the main findings of ChC in CMR: myocardial edema; altered myocardial perfusion; changes in global and segmental contractility; aneurysm formation; intracardiac thrombi; and large areas of myocardial fibrosis detected by late gadolinium enhancement technique (Figures 3 to 6).

Rochitte et al. [16] were the first investigators who studied patients with ChC using the LGE sequence: 15 of them in the indeterminate form; 26 patients known to be carriers of the cardiac form; and 10 patients in the cardiac form with confirmed previous episode of ventricular tachycardia (VT) and normal coronary angiography. Analyzing the LGE as an indicator of myocardial fibrosis and/or necrosis, the investigators demonstrated its presence in 68.6% of patients, with a heterogeneous pattern, without the subendocardial involvement, mostly in the left ventricular inferolateral basal and apical segments, not simulating the pattern found in coronary patients (Figure 7). The extent of myocardial fibrosis demonstrated by LGE correlated with the severity of the disease and was inversely correlated with the left ventricular function.

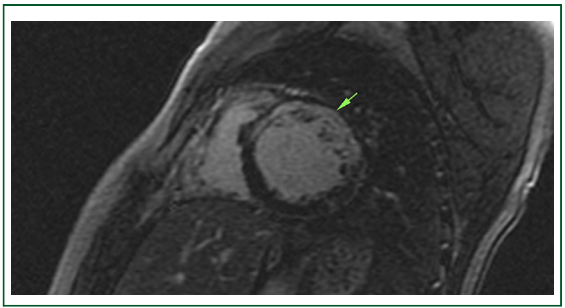

FIGURE 4. Myocardial fibrosis and/or necrosis. This short-axis gradient-echo myocardium delayed-enhancement image of the left ventricle shows a heterogeneous area in the subendocardial region of the anterior segment (green arrow).

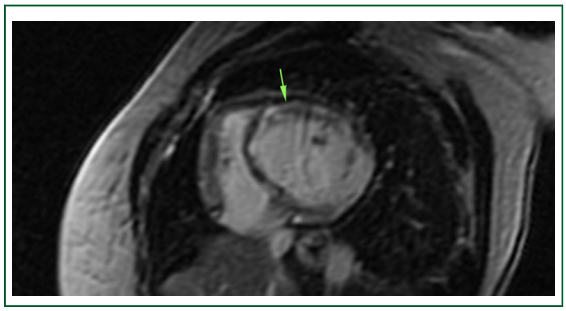

FIGURE 5. Myocardial fibrosis and/or necrosis. This is a short-axis gradient-echo myocardium delayed-enhancement image. The arrow indicates a hypersignal area in the mesocardial region of the left ventricular anterior segment.

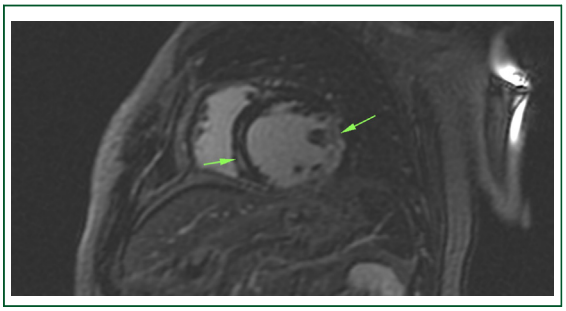

FIGURE 7. Myocardial fibrosis and/or necrosis. This is a short-axis gradient-echo myocardium delayed-enhancement image that shows subendocardial and mesocardial patterns (green arrows) of myocardium delayed enhancement in the same patient.

Myocardial fibrosis was present in all individuals with previously documented episodes of VT.

Regueiro et al. [17] also studied the CMR findings in patients with Chagas disease, but who were living in nonendemic regions. Patients were divided into 3 groups: indeterminate form; ChC with only ECG changes; and those with ChC with echocardiographic abnormalities. The most severe cases (last group) had greater left ventricular involvement (larger diameters and lower ejection fraction). Some changes have been demonstrated only by CMR: 16% of the second group patients presented with LGE, and 3% showed dyskinesia not verified by echocardiography. The prevalence of delayed enhancement in the study population was 24% and was higher (52%) in the third group of patients. The appearance of LGE was very heterogeneous, being subendocardial in 26.8%, midwall in 14.0%, subepicardial in 22.6%, and transmural in 36.0%. The presence of LGE was significantly associated with lower left ventricular ejection fraction and was more common at the apex and in the inferolateral segment. In this study, the correlation between LGE and arrhythmic events was not checked.

In the early stages of cardiac involvement, the changes can be discrete and detected only through more accurate methods. This occurs with the segmental alterations in contractility. Regarding these early features, the cine resonance sequence presents high spatial and temporal resolution, producing high accurate images for the assessment of segmental contractility. If required, this analysis can be completed by the myocardial tissue tagging, which allows the tracking of discrete points of tissue within the myocardium and more accurate evaluation of the regional myocardial deformation. As the changes become more pronounced, there is deterioration in global and segmental contractility, parietal thinning, and formation of aneurysms and thrombi. Of these, the apical aneurysm is characteristic (the vortex lesion or vortical lesion) and clearly demonstrated by CMR (Figures 8 and 9). In advanced stages, cine resonance shows greatly diminished global contractility, a decrease in ejection fraction, and diffuse parietal thinning [9].

THE USE OF CMR IN THE PREDICTION OF CARDIAC ARRHYTHMIAS

VT is the main mechanism of SD in developed countries. The most common causes in these countries are coronary artery disease in patients >30 years of age and myocarditis, hypertrophic cardiomyopathy, and congenital heart disease

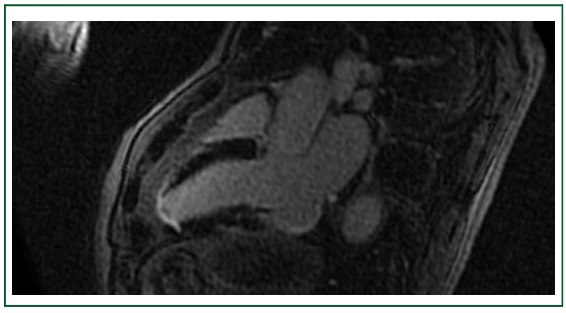

FIGURE 6. Myocardial fibrosis and/or necrosis. This is a long-axis gradient-echo myocardium delayed-enhancement image. In the left ventricular apical segment there is a hypersignal area that indicates fibrosis.

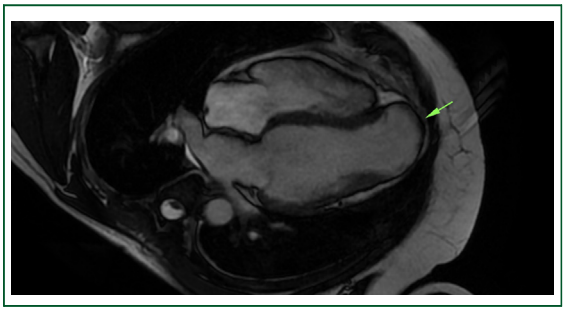

FIGURE 8. Vortex lesion. This is a long-axis steady-state free precession image of the left ventricle. It is possible to note an apical aneurism (arrow). This is characteristic of the Chagas cardiomyopathy.

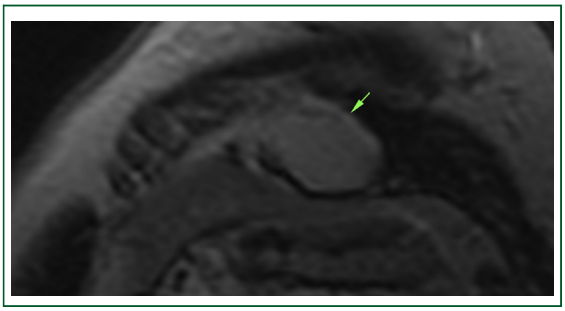

FIGURE 9. Vortex lesion. This is a short-axis gradient-echo myocardium delayed-enhancement image of the vortex lesion shown in Figure 8. The arrow indicates a hypersignal area that corresponds to myocardial fibrosis and/or necrosis.

in subjects <30 years of age. Currently, the measures implemented to reduce the risk of SD are drug therapy in order to stabilize the underlying disease and the use of implantable cardioverter-defibrillator. Therefore, it is essential to identify individuals at increased risk of SD who deserve these therapies. Although coronary artery disease, New York Heart Association class III, and left ventricular ejection fraction are independent predictors of SD, it still lacks a more robust screening tool to identify patients at risk. In this context, CMR is able to suggest the pathophysiological mechanism underlying heart disease in SD survivors by analyzing the presence and pattern of LGE in these patients. Furthermore, when using the sequence of myocardial edema associated with LGE, CMR can differentiate between acute and chronic conditions. In fact, the extent of permanently established myocardial injury was related to future arrhythmic events in both ischemic and nonischemic contexts [15,18].

VT is a common consequence of ChC, accounting for an annual mortality rate from 0.2% to 19% among these patients. Mello et al. [19] studied 41 subjects with ChC associated with ventricular dysfunction and/or ECG changes using CMR. Of these, 26 patients (63%) had clinically manifested VT. CMR showed the presence of LGE indicating myocardial fibrosis in all patients. The presence of ≥2 segments of the left ventricular wall containing transmural scars was more frequent in the group with a previous VT (73% vs. 40%, $p = 0.036$), and its presence constituted a predictor of the occurrence of arrhythmia, even after adjusting for the ejection fraction, age, sex, and percentage of LGE (relative risk: 4.1, 95% confidence interval: 1.06 to 15.68; $p = 0.04$). These patients were followed for 1.5 years. Patients with no previous VT, those without transmural scars, and those with <6% fibrosis in the myocardium did not present with new events. On the other hand, 3 patients presented with SD. They all had ≥1 transmural scar seen in CMR and none had a previous history of VT [19].

SUMMARY

CMR has evolved as an important cardiological tool, and its clinical use has been increasing recently. Regarding ChC, CMR can be used as an accurate and detailed assessment of the cardiac chambers. Therefore, the segmental contractility, the left ventricular aneurysms, parietal thinning, and left and right ventricular ejection fraction and volumes are well defined. Myocardial perfusion can be determined at rest and under stress and the presence of intracavitary thrombus can also be determined. More importantly, the myocardial areas of necrosis and/or fibrosis can be analyzed noninvasively. As mentioned earlier, the reparative fibrosis is characteristic of this cardiomyopathy and is believed to be responsible for many aspects of its poor prognosis. Using CMR, these areas can be quantified, analyzed, followed, and related to clinical aspects, such as severe ventricular arrhythmias, symptoms of heart failure, SD, and major events. Nowadays, the interstitial fibrosis is studied by CMR using the T_1 mapping, and such protocol can reveal new information regarding ChC. Combined with the LGE sequence, this broad fibrosis analysis can be translated into advancements in the pathophysiological understanding, prognostic/therapeutic definitions, and, potentially, survival improvements.

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