Myocardial involvement in Chagas disease: Insights from cardiac magnetic resonance

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ABSTRACT

Background: Chagas’ disease is becoming a public health problem in Europe because of migratory movements. Cardiomyopathies are the most serious and frequent manifestation of Chagas’ disease but normal 2D-echocardiography; N = 21)—were studied. The presence of wall motion abnormalities and delayed enhancement (DE) by CMR was more frequent in the inferolateral and apical segments. DE distribution in the myocardial wall was heterogeneous (subendocardial 26.8%, midwall 14.0%, subepicardial 22.6%, and transmural 36.0% of total myocardium). Pattern of DE in Chagas’ disease may mimic that of both ischemic and nonischemic cardiomyopathies, with especial predilection for the apical and inferolateral segments of the left ventricle. These findings support that myocardial involvement in chronic Chagas’ cardiomyopathy (CCC) may be due to both microvascular disturbances and chronic myocarditis and may favor CCC in the differential diagnosis of patients with compatible epidemiological history and heart failure of uncertain etiology.

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1. Background

Chagas’ disease represents a major cause of morbidity and mortality in Latin America [1] and an emerging health problem in countries where the disease is not endemic as a result of growing population’s movements [2–4]. Chronic Chagas’ cardiomyopathy (CCC) is the most serious and frequent manifestation of Chagas’ disease and the main cause of mortality among these patients [5] and is associated to a poorer survival compared with other forms of cardiomyopathies [6]. Currently, the diagnosis of CCC is based on clinical, X-ray, electrocardiographic (ECG) and, when available, echocardiographic findings. In patients with a positive serology for Trypanosoma cruzi (T. cruzi), criteria for CCC include an increased cardiothoracic ratio (>0.5) on chest X-ray, complete right bundle-branch block, left anterior hemiblock, as well as other conduction and rhythm disturbances or regional wall motion abnormalities, reduced left ventricular ejection fraction (LVEF), increased left ventricular (LV) end-diastolic diameter or apical aneurysms [7,8]. However these abnormalities are usually seen in advanced stages of the disease when the prognosis is already poor. Early detection of heart involvement in seropositive individuals remains challenging.

Cardiac magnetic resonance (CMR) has emerged as a non-invasive modality to assess tissue characteristics, particularly myocardial necrosis or fibrosis using contrast delayed enhancement (DE). The usefulness of CMR for the evaluation of patients with ischemic and non-ischemic cardiomyopathies has been repetitively demonstrated and is currently recommended by clinical practice guidelines [9]. CMR imaging has been used in murine models of Chagas’ disease as a tool to

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understand the pathophysiology of the disease [10,11]. However this method has been scarcely used in the study of patients with CCC [12,13]. Moreover, there is no information available about the CMR pattern in Chagas' disease patients living in non-endemic areas and the correlation between CMR findings and clinical status, ECG and echocardiography in those patients. Recognition of the CMR pattern of CCC would be useful to early detect myocardial involvement in seropositive patients and also to help in the differential diagnosis of patients with heart failure of unknown etiology. Additionally, it could shed some light on the pathophysiology of myocardial involvement by T. cruzi. Therefore, our aim was to describe CMR characteristics in patients with different forms of Chagas' disease living in a non-endemic area, focusing on its correlation with the clinical status as well as the differentiation of the DE pattern from other etiologies.

2. Methods

2.1. Study population

Consecutive Chagas' disease patients evaluated at our Institution who underwent CMR from July 2007 to March 2010 were included. All patients received T. cruzi serological tests. Diagnosis of Chagas' disease was established on microbiologic confirmation by any combinations of at least two positive commercial serological tests using different antigens [14]: ELISA using T. cruzi lysate (Ortho-Clinical Diagnostics®, Johnson & Johnson®), ELISA with recombinant antigens (BioELISA Chagas®, Biokit) and indirect immunofluorescence (Immunofluor Chagas®, Biocientifica). Patients with history of cardiac diseases such as heart failure disease as diagnosed by echocardiography or suspected or diagnosed coronary artery disease (patients referring typical symptoms, evidence of a positive stress test or stenosis in a coronary angiography) were excluded. Patients with two or more cardiovascular traditional risk factors for coronary artery disease or referring alcohol consumption more than 8 g per day in women and 16 g per day in men were excluded. Patients with clinical evidence of active infection by other causal agent were also excluded. The study was approved by the Ethics Committee of our institution.

2.2. Patient classification

Patients meeting the inclusion criteria were categorized into 3 groups: Group 1, patients in the indeterminate form of Chagas' disease defined as those with positive serology of Chagas' disease and normal ECG, normal LV dimensions and LV global and regional systolic function by 2D echocardiography; Group 2, patients with CCC confirmed by ECG abnormalities (complete right bundle-branch block and/or left anterior hemiblock, complete left bundle-branch block, ventricular premature beats, ST abnormalities Q waves, low voltage QRS, sinus bradycardia ≤ 50 beats/min or advanced atrioventricular block) b normal 2D-echocardiography (LV dimensions and LV regional systolic function); and Group 3, patients with CCC with regional wall motion abnormalities and/or LV end-diastolic diameter ≥ 55 mm and/or LVEF <50% on echocardiography.

Clinical examination, blood analysis including ions, creatinin and blood count, chest X-ray, ECG, 2D echocardiogram and CMR studies were performed in all patients. Patients with subendocardial or transmural DE pattern on CMR underwent a stress test to minimize the possibility of ischemic heart disease.

2.3. Cardiac magnetic resonance

CMR studies were performed in a 1.5-T scanner (General Electrics Signa HD-x, Milwaukee, Wisconsin) under electrocardiographic gating and using an eight-element cardiac phased-array receiver surface coil. Regional and global LV function was assessed with a standard steady state free precession cine pulse sequence (FIESTA) in sequential 10 mm thick short axis slices, with no gap between them, to accomplish full ventricular coverage. In addition, standardized 2-, 3- and 4-chamber long-axis views were acquired systematically. A 256 × 256-pixel matrix prescribed over a mean field of view of 380 mm yield a mean spatial resolution of 1.5 × 1.5 × 10 mm. A standard T1-weighted segmented inversion-recovery fast gradient-echo pulse sequence was carried out in identical slice positions as in cines 10 min after intravenous administration of gadodiamide-DTPA (Omniscan, Amersham Health, Madrid) at a dose of 0.2 mmol/kg, resulting in a typical voxel size of 1.5 × 1.5 × 10 mm. A single slice was acquired at end-expiration in each breath-hold to minimize respiratory motion artifacts. Inversion time was adjusted to null normal myocardium. An experienced observer masked to clinical data performed manual planimetry of the endocardial borders (including papillary muscles and trabeculae) and epicardial borders (excluding epicardial fat) at end-systolic and end-diastolic frames to compute LV mass, LV and right ventricular (RV) end-diastolic and end-systolic volumes, LVEF and RV ejection fraction (RFV) using commercially available software (Report card, GE, Milwaukee, Wisconsin). Three-dimensional volumes were calculated as the sum of area × slice thickness for all short axis slices. Ventricle volumes were indexed for body surface area by using Dubois formula. Those areas of myocardial DE on contrast-enhanced images (signal intensity 2 SD above that of normal nulled myocardium) were manually planimetered and summed to compute scar/fibrosis size, expressed as the percentage of total LV mass. The pattern of DE was labeled according to the 17-segment model by an experienced radiologist and a cardiologist and classified as subendocardial scar when extending no more than 50% of the wall thickness affecting the endocardium, transmural scar when extending at least 50% of the wall from the endocardium, epicardial as a scar affecting the epicardial layer but extending no more than 50% of the LV wall, and mid-myocardial scar when viable myocardium was noted in both the endocardial and epicardial sides.

2.4. Statistical analysis

Continuous baseline variables were expressed as mean ± standard deviation (SD) or median (interquartile range) values depending on normality assessed by the Shapiro–Wilk test. Categorical variables were expressed as total number (percentages) and compared between groups using Chi-square test or Fisher's test as appropriate. Differences in continuous variables were analyzed using either ANOVA test or Kruskall–Wallis test depending on variable distribution. Post-hoc analysis between groups was adjusted by Bonferroni method. Correlations between LV volumes and LVEF were assessed using Spearman coefficient. Statistical analysis was performed with SPSS 18.0.

3. Results

3.1. Patient characteristics

A total of 67 consecutive patients were included, 27 patients in Group 1, 19 patients in Group 2 and 21 patients in Group 3. All patients were originally from Latin America, the highest proportion was from Bolivia (N = 57, 85.1%) and the remaining subjects were from Brazil (N = 2, 3.0%), Venezuela (N = 1, 1.5%), Colombia (N = 2, 3.0%), Paraguay (N = 2, 3.0%) and Ecuador (N = 1, 1.5%). All of them were residents in Spain at the time of inclusion in the study. Patient characteristics are shown in Table 1. Median age was 42 years (ranging from 28 to 83) and 41.8% were men. With the exception of two patients in Group 3 who showed mild anemia (hemoglobin values higher than 105 g/L), renal function and hemoglobin values were within normal ranges. The majority of patients (79.1%) were in NYHA functional class I, NYHA functional class II was present in 31.6% of patients in Group 2 and 33.3% of Group 3. A total of 52 (82.5%) patients had received treatment with benznidazole prior to CMR with similar distribution in the three groups.

3.2. Cardiac magnetic resonance findings

CMR characteristics are shown in Table 2. Patients in group 3 showed significantly higher LV end-diastolic volumes, higher end-systolic volumes, and lower LVEF as compared to the other groups. CMR-derived LV volumes and LVEF showed high correlation with echocardiographic measurements (r = 0.77 for LV end-diastolic volume by CMR and LV end-diastolic diameter by echocardiography and r = 0.80 for LVEF by both imaging modalities). There were no differences in LV myocardial mass between groups. The presence of wall motion abnormalities determined by CMR was more frequently found in the inferolateral and apical segments (Fig. 1). CMR showed apical dyskinesia with transmural DE in two patients (2.9%) from Groups 1 and 2, which was not previously observed on the 2D-echocardiography. DE was observed in 16 (23.9%) patients with a higher proportion in Group 3 (11 patients, 52.4%). The presence of DE was more frequently found in the inferolateral and apical segments (Fig. 2), which correlated with the incidence of wall motion abnormalities. On the other hand, DE distribution was highly heterogeneous (Figs. 2 and 3), being subendocardial in 26.8%, midwall in 14.0%, subepicardial in 22.6%, and transmural in 36.0% of total segments with DE. The presence of DE was significantly associated with lower LVEF, RVEF and higher indexed LV end-diastolic volume and left atrial area (Table 3). DE was detected in a lower proportion in patients previously treated with benznidazole although this difference was not statistically significant (21.2% vs. 33.3%, p = 0.33). Additionally, patients with DE had a trend toward worse
NYHA functional class compared to patients without DE, although DE was found in 10 patients with normal NYHA functional class.

4. Discussion

The aim of our study was to characterize the CMR pattern in a wide spectrum of Chagas’ disease patients living in non-endemic areas. The most significant findings are the following: first, DE indicating myocardial scar or fibrosis was present in an important percentage of patients (more than 50% of patients with echocardiographic abnormalities) and was associated with other markers of LV involvement; second, DE was predominantly found in the apex and infero-lateral wall of the LV and had a very heterogeneous distribution inside the myocardium, which is in concordance with prior pathologic studies [15–17]; third, we describe that CMR can be abnormal in patients with mild or no alterations in ECG or 2D-echocardiography and normal NYHA functional class (therefore previously classified as indeterminate form). In this sense, CMR appears as a useful tool to early detect myocardial involvement in seropositive patients.

4.1. Prevalence of delayed enhancement in CCC

A previous study assessed CMR myocardial DE in 51 patients with CCC [12], showing an overall prevalence of DE of 68.6% and up to 88.9% in CCC patients with ventricular tachycardia. Patients included in that study significantly differ from our population, as the former had more advanced cardiac involvement and were recruited from Chagas endemic areas. Accordingly, the incidence of DE found in our study was lower. Moreover, our patients were free of possible reinfections as they lived in non-endemic areas. Re-infection in mouse models of T. cruzi infection has been previously proposed as a possible explanation of early progression to a more severe form of CCC motivated by a greater cardiac fibber fragmentation, fibrosis and necrosis [16–19]. Additionally, patients were globally younger and previously treated with benznidazole, which might have decreased parasitism and myocarditis as previously suggested in experimental and clinical models [19,20]. Indeed, the incidence of DE in patients previously treated with benznidazole was slightly lower as compared to patients without previous pharmacologic treatment. The fact of including patients in less advanced stages of the disease underscores the potential usefulness of CMR to early diagnose myocardial involvement and improve risk stratification.

4.2. Delayed enhancement pattern in CCC

The characterization of CMR pattern in Chagas’ disease is not clearly known, despite CCC is currently included in the differential diagnostic list of cardiomyopathy. We describe a specific CMR pattern that is characteristic of Chagas' disease and is associated with mortality and increased risk of arrhythmias. The presence of DE in the apex and infero-lateral wall of the LV is of particular relevance, as it could be used to identify patients at higher risk for cardiovascular complications.
diagnoses of heart failure in non-endemic areas where the prevalence of Chagas' disease is increasing due to migratory flows. We observed an extremely heterogeneous DE pattern, with common features with ischemic cardiomyopathy (more than half of patients had sub-endocardic or transmural pattern) but also with other non-ischemic cardiomyopathies as myocarditis or Fabry' disease where typically epicardial or intramyocardial DE can be found. Of interest, 22.3% of patients of our CCC patients had epicardial DE. Furthermore, although present in all segments, the most frequent localization of DE within the LV was at the apical or inferobasal segments, which differs from ischemic cardiomyopathies in which DE matches a coronary territory distribution.

Pathological basis of CCC seems to be multifactorial [21–25], with a combination of persistent myocardial and pericardial inflammation and microvasculature disturbances. Several experimental and clinical studies have described the presence of severe microvascular dilatation, microthrombi and endothelial cell dysfunction [26,27]. It has been suggested [28] that these microvascular disturbances may cause...
impaired myocardial irrigation in distal areas of the coronary arteries, especially at the watershed zones between them. That could explain predominant fibrotic lesions at the LV apex, a watershed zone between the anterior descending and the posterior descending arteries, and the LV infero-lateral wall, a watershed zone between the right and circumflex coronary arteries.

4.3. Clinical implications of DE findings in CCC

CMR could be used as a clinical tool in order to early detect myocardial involvement in Chagas’ disease. Given the low availability of CMR in some endemic areas, this might be difficult to implement, but may be a reasonable imaging technique to apply in non-endemic, developed areas. Also in this sense, we and others have previously reported the potential utility of brain natriuretic peptide and comprehensive echocardiographic studies assessing diastolic function in order to early detect myocardial involvement and improve risk stratification among Chagas’ disease patients [29–32]. Additionally, the heterogeneous pattern of DE CMR in CCC should be taken into account in the differential diagnosis of cardiomyopathy and heart failure in non-endemic areas, where this pathology has been up to now common. As any DE pattern could theoretically be consequence of CCC, focused epidemiological history of the disease appears critical in suspecting diagnosis. Finally, CMR could help to better localize arrhythmogenic substrate as it is currently done in patients with ischemic cardiomyopathy [33,34].

4.4. Study limitations

Some study limitations should be recognized. Although patients were generally young and free of cardiovascular risk factors, concern about the possibility of ischemic heart disease in patients with subendocardial or transmural DE pattern was raised in our study. In order to minimize this possibility, stress test was obtained in all those cases and resulted normal. Coronary artery disease was dismissed without performing a coronary angiography to avoid radiation and minimal but possible complications derived from the procedure. Although we recognized that to definitely rule out coronary angiography could have been needed, the negative predictive value of the exercise test in these circumstances is very high. Endomyocardial biopsy was not performed in our study population, which could have been interesting to evaluate the correlation between the anatomicopathological findings and CMR imaging; however, sensitivity of biopsy in Chagas’ disease has been

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**Table 3**

Clinical, ECG and CMR characteristics according to presence of delayed-enhancement on CMR.

<table>
<thead>
<tr>
<th></th>
<th>Total (N = 67)</th>
<th>With DE (N = 16)</th>
<th>Without DE (N = 51)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal ECG</td>
<td>34 (50.7%)</td>
<td>14 (41.2%)</td>
<td>20 (58.8%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>NYHA FC I</td>
<td>14 (20.9%)</td>
<td>6 (37.5%)</td>
<td>8 (15.7%)</td>
<td>0.06</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>57 (10.0%)</td>
<td>44 (34.8)</td>
<td>58 (11.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVEDV index (ml/m²)</td>
<td>89.4 (35.0)</td>
<td>124.7 (52.9)</td>
<td>80.9 (22.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RVET (%)</td>
<td>53.3 (9.8)</td>
<td>48.9 (12.5)</td>
<td>55 (9.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>RVEDV index (ml/m²)</td>
<td>58.2 (16.6)</td>
<td>68.1 (18.2)</td>
<td>56 (14.6)</td>
<td>0.34</td>
</tr>
<tr>
<td>Left atrial area (mm²)</td>
<td>23.6 (7.1)</td>
<td>27.1 (7.5)</td>
<td>21.7 (5.7)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as median (interquartile range) values; categorical variables are expressed as number of patients (%). ECG: Electrocardiogram; NYHA FC: New York Heart Association functional class; LVEF: Left ventricle ejection fraction; LVEDV: Left ventricle end-diastolic volume indexed to body surface area; RVET: Right ventricle ejection fraction; RVEDV: Right ventricle end-diastolic volume indexed to body surface area. P = P value between groups.
shown to be low when the fibrosis or inflammation is patchy or focal [35], as it occurred in most patients included in our study. Finally, contrast echocardiography was not used in this study, justifying why echocardiography could have missed small areas of apical dyskinesia, as it was the case in two patients who later underwent CMR.

In conclusion, the pattern of DE in Chagas’ disease resembles that of both ischemic and nonischemic cardiomyopathies, with a special predilection for the apical and infero-basal segments of the left ventricle. Such findings in CMR of patients with compatible epidemiological history and heart failure of uncertain etiology should favor CCC in the differential diagnosis, even in non-endemic areas where the prevalence of the disease is increasing.

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