Advanced Imaging in Chagas Heart Disease: From Diagnosis to Sudden Death Risk Stratification.

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Abstract

Chagas disease constitutes a relatively prevalent condition in Latin America and is increasing worldwide, with a wide spectrum of clinical subsets. Imaging modalities are critical for adequate diagnosis, staging and prognosis of this entity. Currently Echocardiography and Cardiac Magnetic Resonance are the most valuable techniques for this purpose. Evidence for both modalities has increased in the last years, as the role of advanced techniques such as Speckle Tracking Echocardiography has been explored. We aim to review the evidence of advanced imaging in the spectrum of patients with Chagas Heart Disease.

Key words: Chagas Disease; Advanced Imaging; Late Gadollinium Enhancement; Strain Imaging.

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Introduction

Chagas disease constitutes a parasite-infection derived condition with a global estimated prevalence of 8 to 12 million infected patients, primarily in Latin America[1] where it represents the most common cause of non-ischaemic cardiomyopathy. Due to increasing migration to North America and Europe there is a prevalence of 67,000 in Spain[2] and more than 300,000 patients in the United States.[3] Chagas disease is characterized by a long asymptomatic period after which, only 20 to 30% of patients will ultimately develop heart disease[4], and only 10 to 20% of these patients will develop symptoms. Mortality associated with this entity is explained by the development of heart failure[5] and sudden cardiac death (SCD) caused by ventricular arrhythmias.[6]

Chagas Disease is classified into four stages, similar to heart failure. Patients who do not have structural heart disease, Stage A. Patients with structural Heart Disease, either with ECG changes (B1), or global left ventricular dysfunction, low left ventricular ejection fraction (LVEF) (B2). Symptomatic patients with low LVEF (C) and symptomatic patients refractory to medical treatment requiring specialized interventions (D).[7]

Since a positive serology for *Trypanozoma cruzi*, is common among all stages, imaging constitutes the cornestone for diagnosis of Chagas Heart Disease (CHD) and is fundamental for risk stratification, as the main cause of death of these patients is sudden death accounting for two thirds, followed by heart failure (20-30%), and thromboembolism (10-15%).[8] As imaging techniques have evolved chest X ray and cine ventriculography have been rapidly replaced by echocardiography and cardiac magnetic resonance. This review will focus in the different modalities currently used to evaluate patients with Chagas Heart disease for diagnosis and risk stratification.

2. Echocardiography.

Echocardiography is an essential imaging modality and constitutes the first step for assessment of patients with positive serology for *T. Cruzi* because of the amount of information provided by this method, low cost and availability. Echocardiography has been an integral part of the diagnosis, follow-up and prognosis in patients with Chagas disease.

2.1 Early phase.

There are few studies describing the imaging findings of CHD. Echocardiography shows abnormalities in one half of patients. The most frequent finding is pericardial effusion of varying

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degrees, with mild and moderate in the majority, whilst only 5% present with massive pericardial effusion. The majority of patients have normal left and right ventricular dimensions and systolic function, however some degree of myocardial damage is detected in 20% of patients, usually manifesting as anterior or apical dyskinesia. Some patients present with severe heart failure, global left ventricular hypokinesia and ventricular dilatation.

2.2 Indeterminate phase.

By definition, symptoms and imaging abnormalities are absent. Echocardiography is often normal, however advanced techniques such as stress testing can identify abnormal relaxation using tissue Doppler.[13] With dobutamine stress echocardiography, abnormal left ventricular contractile reserve has been found.[14]

2.3 Chronic phase.

Echocardiographic abnormalities in patients with CHD mimic chronic ischaemic or idiopathic dilated cardiomyopathy. Typical findings are segmental wall motion abnormalities in the presence of normal epicardial coronary arteries. Nearly one half of patients have apical left ventricular aneurysms with extension to the apical and mid-portions of the inferolateral wall. In 25% of patients a dilated and globally hypokinetic left ventricle is seen. Microvascular dysfunction has been proposed to cause segmental wall motion abnormalities although there is no firm explanation for the involvement of specific myocardial segments.[9,10]

Left ventricular ejection fraction is the most robust parameter for evaluating systolic function. In CHD 2D echocardiography has proved to be very valuable for prognosis, and is the strongest independent predictor of mortality.[11] A risk score for predicting mortality has been developed and validated, it includes clinical, electrocardiographic and echocardiographic variables, the presence of segmental or global wall motion abnormalities had a HR of 2.46.[6] Apical thrombus is a frequent finding and the use of contrast agents can increase its detection.

Left ventricular diastolic dysfunction is common in CHD[12] even in patients with the indeterminate form.[13] With tissue and pulsed Doppler echocardiography the entire spectrum of diastolic dysfunction can be characterized. Left atrium volume reflects left ventricular end-diastolic pressure; consequently left atrial indexed volume is a prognostic marker in CHD. Increasing volume by 1 ml/m2SC raises 4.7 times the risk of cardiac events.[15]

Right ventricular dysfunction is also a component in CHD,[16] and is related to prognosis in patients with low LVEF.[17] However because of the complex anatomy of the right ventricle its echocardiographic assessment by conventional echocardiographic parameters is suboptimal as these measures ignore the contribution of the right ventricular outflow tract. RT3D echocardiography of the RV is an attractive technique as it directly measures volume and does not rely on geometric assumptions. Its role in CHD has not been explored and is definitely worth doing.

Myocardial mechanics can be quantified with a relatively novel technique, 2D speckle tracking echocardiography (STE).[18] The myocardial fibre changes in length during the cardiac cycle in different directions, longitudinal, circumferential, and radial. Strain (e) describes change in length, and is expressed with a percentage. STE is currently under extensive study in cardiomyopathies,[19] valvular heart disease,[20] stable coronary artery disease[21] and acute coronary syndromes,[22] where it has proven useful for identifying subclinical myocardial dysfunction, fibrosis, dyssynchrony, and to improve the prognostic value of echocardiography.

García-Álvarez[23] demonstrated impaired global radial strain (GRS) and global circumferential strain (GCS) in patients with CHD, which worsened gradually from asymptomatic stage to chronic form with systolic dysfunction. Interestingly the inferior and inferolateral wall were predominantly affected. On the other hand global longitudinal strain (GLS) was only impaired in patients with systolic dysfunction. In other studies lower values of GLS have been identified in patients with late gadolinium enhancement (LGE) assessed by CMR, however they correlate poorly, and the addition of GLS to EF, showed no incremental benefit to identify patients with LGE.[24] An example of STE in a patient with CHD is shown in Figures 1 and 2.

Left atrial function is closely related to left ventricular diastolic function. An interesting finding in the study of Nunes[15] is that left atrial contractile function assessed with 3DRTE and 2DSTE is reduced only in symptomatic patients with CHD, reflecting the importance of the atrial contribution to the presence of symptoms. In contrast left atrial conduit function was reduced in patients with ECG abnormalities and a normal LVEF, suggesting conduit atrial function is impaired earlier in the natural history of CHD.

2.4 Risk stratification.

Risk stratification of SCD in patients with CHD is far from optimal. The role of myocardial mechanics for SCD prediction has not been evaluated in patients with CHD. However it has been shown to be useful in other subsets of patients. In patients with hypertrophic cardiomyopathy, the addition of left atrial volume index >34 ml/m2SC and GLS worse than -14%, has been proved to be useful to predict appropriate ICD discharge.[25]

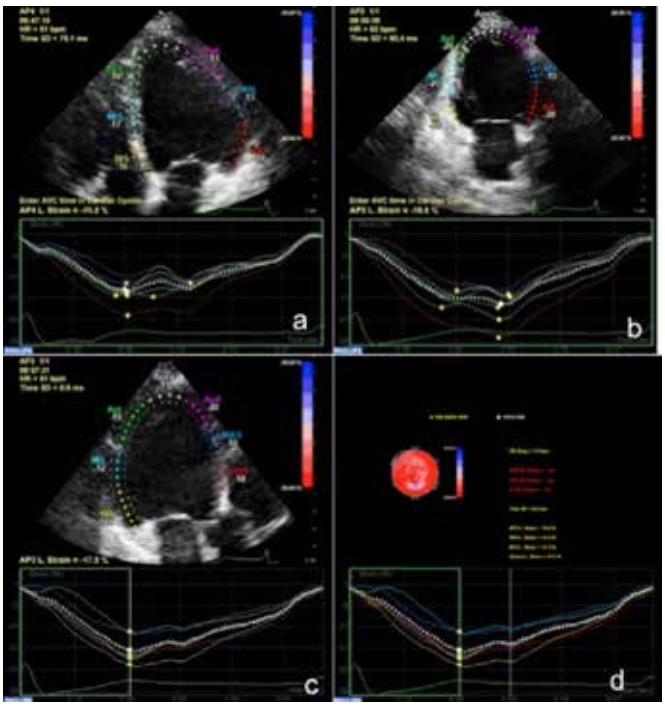

Figure 1. STE for Global longitudinal strain in a patient with CHD, with a mid inferolateral aneurysm and 3D LVEF of 34%. a) Four chamber view, b) Two chamber view c) Apical long axis view. d) Bull's eye, note the low GLS -17%, segmental strain is lower in the aneurysm region mid inferolateral segment.

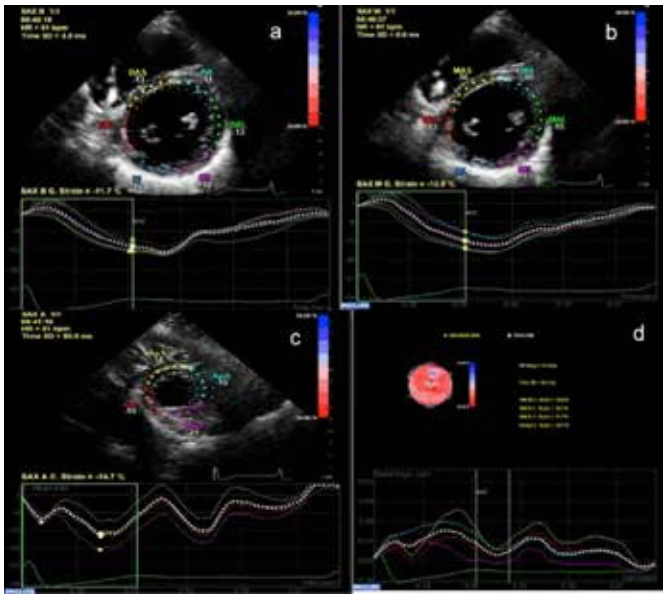

Figure 2. Circunferential Strain curves, a) Basal short axis view, b) midpapillary muscle short axis view, c) apical short axis view. Global circunferential strain is reduced – 12.7, supporting the presence of myocardial dysfunction.

In post-myocardial infarction patients the role of mechanical dispersion measured with 2DSE, reflecting heterogeneity in myocardial tissue which may the substrate for arrhythmia may be useful.

A cut off > 70 ms has been found as optimal to predict arrhythmic events.[26] Given the importance of SCD in patients with CHD, the role of myocardial mechanics should be explored, specially in patients with LVEF > 35% in whom, ICD is not currently supported by current guidelines,[27] but arrhythmic events clearly occur.[28]

3 Cardiac Magnetic Resonance (CMR)

Cardiac magnetic resonance (CMR), due to its high spatial resolution, currently is considered the gold standard in the evaluation of volume, mass, and cardiac systolic function with the advantage of not using ionizing radiation.[29] The sequences used depend on the test objectives. Morphological images of the heart are acquired with dark blood imaging sequences, in which protons in slowly moving structures such as the myocardium provide high signal and rapidly moving ones, as blood flow result in signal void ("Dark blood").[29]

Myocardial volumes and LVEF are measured in an accurate and highly reproducible manner applying the Simpson´s summation of discs method with steady-state free precession (SSFP) techniques.[30] CMR through the use of proton relaxation times T1, T2, and T2* can characterize myocardial tissue, differentiating intra-myocardial accumulation of water, iron, thrombus or collagen. T1 images are often used for contrast-enhanced studies, whereas T2 and T2* are used without contrast. Paramagnetic contrast agents such as gadolinium facilitate water visualization in the intravascular or extravascular space since they shorten the T1 relaxation time and increase the signal intensity of regions with high contrast concentration, therefore it can be used to assess myocardial perfusion (imaging of first pass) and necrotic or fibrotic myocardium (delayed enhancement). T2 imaging is sensitive to regional or global increases of myocardial water content, and can be used to identify edema, as the one that occurs in acute myocarditis. T2* is an excellent marker for iron overload and is used in hemochromatosis.

3.1 Acute disease.

No studies with CMR have evaluated acute CHD. Histopathology in the acute phase demonstrates intense parasitism with prominent inflammatory changes. Myocarditis is intense and diffuse causing myocyte necrosis, interstitial edema, vascular dilation, and mononuclear and polymorphonuclear infiltration.[31]

In experimental studies CMR proved to be sensitive to detect interstitial edema and myocardial infiltration with lymphocytes in acute heart disease such as transplant rejection, acute myocarditis, and acute myocardial infarction.[32] Bocchi studied the correlation between endomyocardial biopsy, CMR and Gallium-67 myocardial uptake for the noninvasive diagnosis of myocarditis in CHD; the results suggest that CMR is an alternative method for the diagnosis of the acute inflammatory process associated with CHD.[33]

3.2 Intermediate and chronic phases

CMR identifies fibrosis and in the setting of CHD it correlates with disease severity and prognostic factors.[34,35] Rochitte was the first to evaluate the presence of myocardial fibrosis in patients with CHD, patients with structural heart disease had a prevalence of CMR LGE of 84% and 100% in those with a history of ventricular tachycardia. The pattern of LGE was subendocardial or transmural in more than 50% of segments in the absence of coronary artery disease (CAD), supporting the role of dysautonomia and microvascular dysfunction in structural changes in CHD. The presence of LGE has been proved to be useful for prediction of clinical events in patients with CHD, with death, heart failure or pacemaker implantation being rare in patients without LGE.[36]

As previously stated SCD and VT are prevalent in patients with CHD, the correlation of LGE with VT has motivated research of its role for risk stratification in patients with CHD.[37] Fibrosis has proven useful for SCD risk stratification in other patient subsets such as dilated cardiomyopathy where it has been correlated to appropriate ICD discharge.[38,39] However current evidence is lacking for supporting CMR LGE for risk stratification in CHD. The sole trial evaluating the value of CMR LGE, for this disease included a low number of patients and a low event rate was seen, LGE was qualitatively assessed. LGE was observed in all patients, transmural LGE in more than 2 segments was a predictor of clinical VT (RR 4.1; 95% CI: 1.06 - 15.68; p = 0.04), because of a wide CI, and low event rates this results are insufficient for routine use of CMR predict SCD. Further studies are needed to adequately define the role of CMR for risk stratification in patients with CHD. Clinical Applications of CMR in patients with CHD are shown in Figures 3 and 4.

4 Myocardial Perfusion Scintigraphy.

Clinical studies using this imaging modality have shown a high prevalence of reversible perfusion defects in the absence of obstructive coronary artery disease[40] and its presence precedes left ventricular systolic dysfunction. Nuclear medicine has proved sympathetic denervation correlates positively with perfusion defects and is found before regional wall motion abnormalities.[41] Patients with CHD and without low LVEF can present reversible perfusion defects, related to microvascular changes, which eventually progress to fixed defects and systolic left ventricular dysfunction. This is supported by a trial involving 36 seropositive

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Table 1. Summary of evidence on all imaging modalities.

Study	Method	Year	Population	Main findings
Rochitte	CMR	2005	51 Seropositive patients. Indeterminate 15 CHD 26 VT 10	Fibrosis in: Indeterminate 20% CHD 84% VT100% Predominantly in the inferolateral region and apex. Fibrosis correlated inversely with LVEF
Mello	CMR	2012	41 patients CHD, ventricular dysfunction or segmental WMA 26 VT 15 no VT	Transmural LGE 70% VT And 19 % no VT. Two or more transmural segments were predictors of clinical VT (RR 4.1; 95% CI: 1.06 - 15.68; p = 0.04
Volpe	CMR	2014	121 Patients positive serology	Events: Death, pacemaker or heart failure No events in patients without LGE. LGE more than 5% of core scar (HR 0.2 per %, p = 0.017) LGE more than 5% of grey-zones (HR 2.19 per %; p < 0.001) were independent predictors of events.
Viotti	2D Echocardiography	2004	849 patients 505 Indeterminate 257 ECG abnormalities 87 ventricular dysfunction	Stage A 13 % WMA Stage B1 33% WMA Stage B2 70% WMA
Macedo	2D STE and CMR	2015	58 seropositive patients 29% Indeterminate 27% ECG abnormalities 43% Ventricular dysfunction	Lower GLS in patients with LGE. (–20.3 ± 3.2% and –14.7 ± 5.6%) moderate correlation for Preseverved EF and poor correlation with reduced EF. No incremental benefit of GLS when adjusted for EF por identifying LGE.
García-Álvarez	2D STE	2011	44 Controls 32 Indeterminate 22 CCC (Chronic Chagas Cardiomyopathy) 15 ECG abnormalities 7 LVEF <50%	GRS, GCS. Impaired CCC>indeterminate>controls (predominant inferior an inferolateral at papillary muscle level) GLS impaired in CCC vs. Control Torsion and Twist impaired in indeterminate form
Nunes	2D Echocardiography	2009	194 Patients with CHD and ventricular dysfunction.	Found predictors of cardiac events in multivariate analysis. LAV HR, 1.047; 95% CI, (1.035-1.059; P .001) RV Tei Index HR. 3.539, 95% CI (1.115-11.229 .032) E/E' > 8 HR 2.537 95% CI, (1.064-6.053)
Nascimento	2D, TDI, 2DSTE, 3DRTE	2013	152 CHD Patients 69 indeterminate 32 ECG abnormalities 25 Low LVEF no HF symptoms 26 symptomatic HF	LA εneg peak reduced in patients with symptomatic HF. LA εpos peak peak reduced in pts. With low LVEF with o without symptoms Survival analysis for MACE LA εneg peak (hazard ratio, 1.21; 95% CI, 1.02–1.44; P = .03)
Hiss	SPECT	2009	36 CHD patients 20 showed reversible perfusion defects, which ruled out obstructive CAD.	Between the first and final evaluation, a significant positive correlation was observed between the increase in the index of perfusion defect at rest and the reduction of LVEF between the 2 evaluations (R = 0.4211; p = 0.0105) Significant topographic correlation was found between reversible defects and the appearance of new rest perfusion defects (p<0.0001).
Simoes	SPECT	2000	Group I. 12 CHD patients with no cardiac involvement Group II. 13 patients without ECG abnormalities or ECO abnormalities but with LVEF >0.5 Group III. 12 patients with LVEF < 0.5 18 Controls	Myocardial perfusion defects (reversible, fixed, and paradox) were observed in group I (83%), group II (69%), and group III (83%). A marked topographic association between perfusion, innervation, and wall motion abnormalities assessed by gated- SPECT perfusion studies was observed in all the groups.

patients in whom myocardial perfusion imaging with SPECT demonstrated progression of reversible to fixed perfusion defects in a time interval of 5.6 +/- 1.5 years.[42] Interestingly perfusion defects were more common in segments in which wall motion abnormalities have been proved to predominate. However the role MPI in CHD in the clinical scenario is limited.

5. Optimal Imaging selection for patients with CHD.

As it has been pointed out, multiple imaging modalities are available and their role in diagnosis and risk stratification is complementary and depends on the availability in each center. A summary of the existing evidence for each imaging modality is shown in table 1. Echocardiography constitutes

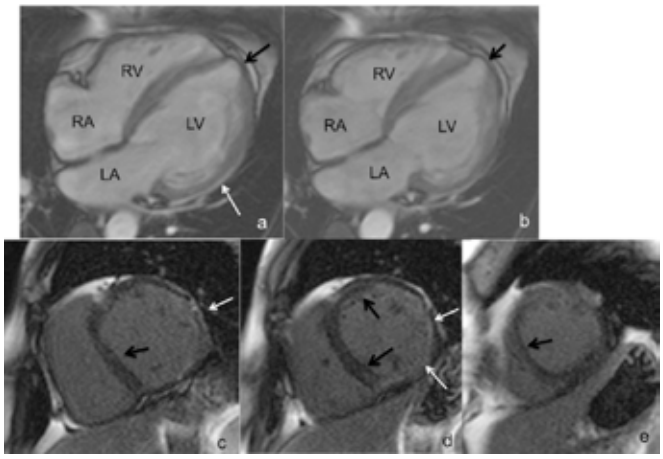

Figure 3. CMR, Four chamber view in diastole (a) and systole (b). Low LVEF 24%, lateral wall thining (white arrow) and apical aneurysm (black arrow). Inversion recovery sequence in the basal, mid and apical short axis, shows transmural LGE in the inferolateral wall (white arrows) and intramyocardial LGE in the septal and anterior wall (black arrows).

the initial imaging modality and a comprehensive evaluation provides robust diagnostic and prognostic data. Novel echocardiographic techniques such as strain are currently under study, and as yet there are insufficient data to apply them to clinical practice. CMR is complementary and can be useful in the differential diagnosis and prognosis, by identifying LGE. In our center patients are first referred to the echocardiography laboratory for a comprehensive examination, and CMR is routinely performed latter.

Declarations of Interest

The authors declare no conflicts of interest.

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The authors agree to abide by the requirements of the "Statement of publishing ethics of publishing in biomedical journals.[43]

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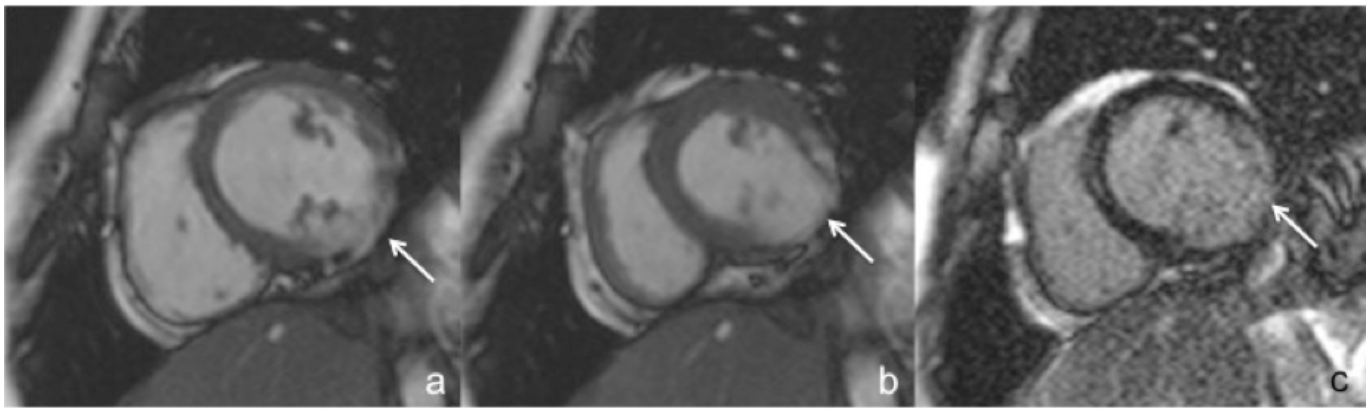

Figure 4. CMR short axis mid papillary level in diastole a, and systole b. Note myocardial thinning, inferior and inferolateral dyskinesia (white arrow). Late Gadollinium sequence shows enhancement in this segments. This patient had a moderately reduced systolic function (LVEF 44%)

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