

Multimodality imaging evaluation of Chagas disease: an expert consensus of Brazilian Cardiovascular Imaging Department (DIC) and the European Association of Cardiovascular Imaging (EACVI)

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Aims

To develop a document by Brazilian Cardiovascular Imaging Department (DIC) and the European Association of Cardiovascular Imaging (EACVI) to review and summarize the most recent evidences about the non-invasive assessment of patients with Chagas disease, with the intent to set up a framework for standardized cardiovascular imaging to assess cardiovascular morphologic and functional disturbances, as well as to guide the subsequent process of clinical decision-making.

Methods and results

Chagas disease remains one of the most prevalent infectious diseases in Latin America, and has become a health problem in non-endemic countries. Dilated cardiomyopathy is the most severe manifestation of Chagas disease, which causes substantial disability and early mortality in the socially most productive population leading to a significant economical burden. Prompt and correct diagnosis of Chagas disease requires specialized clinical expertise to recognize the unique features of this disease. The appropriate and efficient use of cardiac imaging is pivotal for diagnosing the cardiac involvement in Chagas disease, to stage the disease, assess patients' prognosis and address management. Echocardiography is the most common imaging modality used to assess, and follow-up patients with

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Chagas disease. The presence of echocardiographic abnormalities is of utmost importance, since it allows to stage patients according to disease progression. In early stages of cardiac involvement, echocardiography may demonstrate segmental left ventricular wall motion abnormalities, mainly in the basal segments of inferior, inferolateral walls, and the apex, which cannot be attributed to obstructive coronary artery arteries. The prevalence of segmental wall motion abnormalities varies according to the stage of the disease, reaching about 50% in patients with left ventricular dilatation and dysfunction. Speckle tracking echocardiography allows a more precise and quantitative measurement of the regional myocardial function. Since segmental wall motion abnormalities are frequent in Chagas disease, speckle tracking echocardiography may have an important clinical application in these patients, particularly in the indeterminate forms when abnormalities are more subtle. Speckle tracking echocardiography can also quantify the heterogeneity of systolic contraction, which is associated with the risk of arrhythmic events.

Three-dimensional (3D) echocardiography is superior to conventional two-dimensional (2D) echocardiography for assessing more accurately the left ventricular apex and thus to detect apical aneurysms and thrombus in patients in whom ventricular foreshortening is suspected by 2D echocardiography. In addition, 3D echocardiography is more accurate than 2D Simpson's biplane rule for assessing left ventricular volumes and function in patients with significant wall motion abnormalities, including aneurysms with distorted ventricular geometry. Contrast echocardiography has the advantage to enhancement of left ventricular endocardial border, allowing for more accurate detection of ventricular aneurysms and thrombus in Chagas disease.

Diastolic dysfunction is an important hallmark of Chagas disease even in its early phases. In general, left ventricular diastolic and systolic dysfunction coexist and isolated diastolic dysfunction is uncommon but may be present in patients with the indeterminate form. Right ventricular dysfunction may be detected early in the disease course, but in general, the clinical manifestations occur late at advanced stages of Chagas cardiomyopathy. Several echocardiographic parameters have been used to assess right ventricular function in Chagas disease, including qualitative evaluation, myocardial performance index, tissue Doppler imaging, tricuspid annular plane systolic excursion, and speckle tracking strain.

Cardiac magnetic resonance (CMR) is useful to assess global and regional left ventricular function in patients with Chagas diseases. Myocardial fibrosis is a striking feature of Chagas cardiomyopathy and late gadolinium enhancement (LGE) is used to detect and quantify the extension of myocardial fibrosis. Myocardial fibrosis might have a role in risk stratification of patients with Chagas disease. Limited data are available regarding right ventricular function assessed by CMR in Chagas disease.

Radionuclide ventriculography is used for global biventricular function assessment in patients with suspected or definite cardiac involvement in Chagas disease with suboptimal acoustic window and contraindication to CMR. Myocardial perfusion scintigraphy may improve risk stratification to define cardiac involvement in Chagas disease, especially in the patients with devices who cannot be submitted to CMR and in the clinical setting of Chagas patients whose main complaint is atypical chest pain. Detection of reversible ischemic defects predicts further deterioration of left ventricular systolic function and helps to avoid unnecessary cardiac catheterization and coronary angiography.

Conclusion

Cardiac imaging is crucial to detect the cardiac involvement in patients with Chagas disease, stage the disease and stratify patient risk and address management. Unfortunately, most patients live in regions with limited access to imaging methods and point-of-care, simplified protocols, could improve the access of these remote populations to important information that could impact in the clinical management of the disease. Therefore, there are many fields for further research in cardiac imaging in Chagas disease. How to better provide an earlier diagnosis of cardiac involvement and improve patients' risk stratification remains to be addressed using different images modalities.

Keywords

Chagas disease • Chagas cardiomyopathy • echocardiography • three-dimensional echocardiography • speckle tracking echocardiography • cardiac magnetic resonance • nuclear cardiology • radionuclide ventriculography • myocardial sympathetic innervation

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Introduction

Chagas disease, caused by the protozoan *Trypanosoma cruzi*, remains one of the most prevalent infectious diseases in Latin America and has become a health problem in non-endemic countries.^{1,2} Although public health programs have significantly reduced the prevalence of Chagas disease in Latin America in recent decades, awareness of the number of infections in the USA and non-endemic countries in Europe continues to rise.³

Dilated cardiomyopathy is the most severe manifestation of Chagas disease and is characterized by heart failure, ventricular aneurysms, conduction disturbances, ventricular arrhythmias, thromboembolism, and sudden death.^{4,5} The early mortality and substantial disability caused by this disease, which often manifests in the socially most productive population (i.e. young adults), result in a significant economical burden. Chagas cardiomyopathy (CCM) usually requires long-term treatment, and can include specialized care, with pacemaker and cardioverter defibrillator implantation, and heart transplantation, with further increase of the costs related to the disease.⁶

The pathogenesis of chronic CCM has not been completely elucidated. Most investigators believe that the main pathogenetic mechanisms of CCM are dependent on the parasite driven inflammatory reaction and the adverse host immune response.⁷ Autoimmunity mechanisms, probably related to the parasite persistence, involving polyclonal activation, molecular self-mimicry by parasite antigens or cryptic epitopes may also be implicated in the development of CCM.⁷ Two other mechanisms are thought to contribute to the pathogenesis of CCM: neurogenic disturbances and microvascular derangements.^{7,8}

Prompt and correct diagnosis of Chagas disease requires specialized clinical expertise to recognize the unique features of this disease. The appropriate and efficient use of cardiac imaging is pivotal for diagnosing the cardiac involvement in Chagas disease, to stage the disease, assess patients' prognosis and address management.

Accordingly, Brazilian Cardiovascular Imaging Department (DIC) and the European Association of Cardiovascular Imaging (EACVI) developed this document to review and summarize the most recent evidences about the non-invasive assessment of patients with Chagas disease, with the intent to set up a framework for standardized and efficient use of cardiovascular imaging to assess cardiovascular morphologic and functional disturbances, as well as to guide the subsequent process of clinical decision-making.⁹

Epidemiology, diagnosis, clinical manifestations, and prognosis

Chagas disease is endemic in Latin American countries, where nearly 6 million people are currently estimated to be infected with *T. cruzi*.¹⁰ Argentina, Brazil, Mexico, and Bolivia were the countries with higher estimated number of infected people (1.5, 1.2, 0.9, and 0.6 million,

respectively).¹¹ These numbers, much lower than previous estimates, seem to reflect the good result of coordinated multi-country initiatives, supported by Pan American Health Organization and World Health Organization, for vectorial and blood-borne transmission control.

Due to migration flows from Latin American endemic countries to the USA, Europe, and other developed countries, Chagas disease patients can now be found in alarming numbers outside the endemic countries. In Europe, the prevalence of Chagas disease in Latin American immigrants is high (4.2%), particularly in migrants from Bolivia and Paraguay,¹² although a reliable estimate on how many infected persons are living in Europe is still lacking.¹³

Chagas disease is transmitted to humans by infected triatomine bugs, through blood transfusion, organ transplantation, congenital transmission, oral ingestion of contaminated materials, or accidental contamination during laboratory work.¹⁴ The natural history of Chagas disease is characterized by two well-established phases (Figure 1). The acute phase, with high-grade parasitaemia and proliferation of amastigote forms in various organs, lasts from 4 to 8 weeks, is usually oligosymptomatic and is diagnosed in only 1–2% of the cases. The mortality rate is around 1% in the acute period, usually due to severe myocarditis or meningoencephalitis tissues.^{15,16} Given the high rates of pericardial effusion, echocardiography is indicated in patients present with acute Chagas disease.

The chronic phase is characterized by two distinct clinical forms. The indeterminate form, which is usually installed 4–10 weeks after infection, is defined by seropositivity, and lack of radiologic, electrocardiographic and clinical manifestations of cardiac and digestive disease.¹⁷ However, cardiovascular abnormalities can be detected using specific non-invasive tests, such as echocardiogram,^{18,19} cardiac magnetic resonance (CMR) and autonomic tests.^{20–22} Although most patients remain with the indeterminate form throughout life, others evolve to a determined form of the disease 10–30 years after the acute infection, affecting specific organs, such as the heart, oesophagus and colon, which characterize distinct chronic cardiac, digestive, or mixed forms.²³ The progression from indeterminate to cardiac form occurs at an average rate of around 2% per year.^{24,25}

The cardiac form is usually initially defined by the presence of typical electrocardiographic abnormalities that encompass a wide spectrum of presentations, from minor electrocardiographic alterations with normal left ventricular (LV) systolic function, to various forms of arrhythmia, and to dilated cardiomyopathy with heart failure.^{17,26,27} The CCM, which constitutes the most serious complication of the disease, occurs in 20–40% of those individuals tested serologically positive.²⁸ Up to 15–20% of patients with indeterminate form develop digestive alterations in some endemic areas, but the prevalence seems to vary among countries possibly due to different inoculated strain.¹⁴

The chronic cardiac form manifests itself by one of the three main syndromes, which can occur in association: heart failure, cardiac arrhythmias, and pulmonary or systemic thromboembolism. The initial manifestations of CCM are generally mild and most patients have asymptomatic electrocardiogram (ECG) alterations, such as right bundle branch block and bradycardia,²⁶ and minor echocardiographic abnormalities, e.g. regional wall motion abnormalities²⁹ (Table 1). Ventricular arrhythmias are important manifestations of CCM and non-sustained ventricular tachycardia is an established marker of higher risk of death.^{30,31}

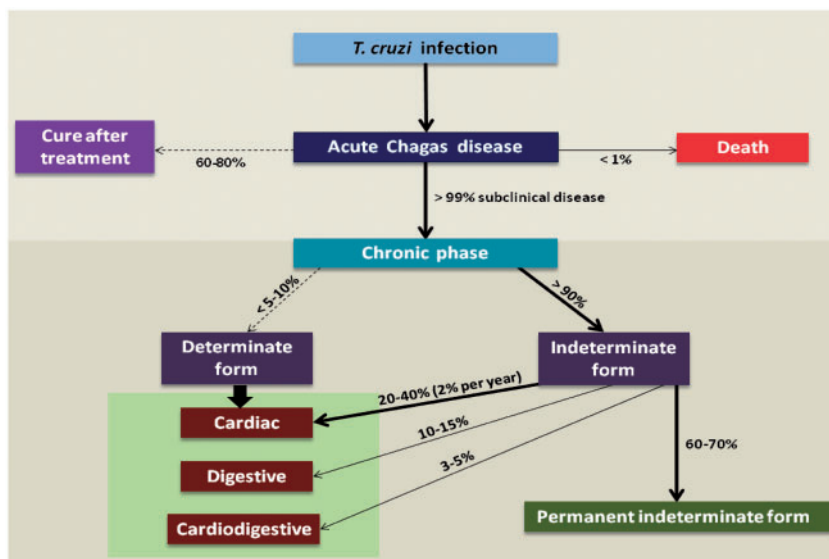


Figure 1 Natural history of Chagas disease. Adapted from *Lancet* 2010;375:1388–1402. A direct progression from the acute phase to a clinical form of Chagas disease has been recorded in less than 5–10% of cases.

Table 1 Stages in the development of heart failure due to Chagas disease

Stages	Findings
A	Patients present no symptoms of heart failure, and no structural heart disease (normal ECG and chest X-ray)
B1	Asymptomatic patients with ECG changes (arrhythmias or conduction disorders); mild echocardiographic contractile abnormalities with normal global ventricular function can also be present
B2	Patients with impaired left ventricular ejection fraction who have never had any signs or symptoms of heart failure
C	Patients with left ventricular dysfunction and prior or current symptoms of heart failure
D	Patients with symptoms of heart failure at rest, refractory to maximized medical therapy (NYHA IV) that require specialized and intensive interventions

ECG, electrocardiogram; NYHA, New York Heart Association.

Patients with more advanced disease frequently have heart failure, which is associated with an ominous prognosis and seems to be carrying higher mortality risk than ischaemic or idiopathic dilated cardiomyopathies.^{32,33}

Stroke is also a cause of death in association with advanced heart disease,³⁴ but could also be the first sign of CCM in asymptomatic patients and those with mild LV systolic dysfunction.³⁵ LV aneurysm, mural thrombus, and atrial fibrillation are risk factors for stroke related to CCM.³⁶

The aetiologic diagnosis of chronic Chagas disease is based on serological assays because the direct detection of parasites is difficult due to very low levels or even absence of parasitaemia.³⁷ There are several techniques used for detection of antibodies against the *T. cruzi* including indirect immunofluorescence, enzyme immunoassays (ELISAs), haemagglutination and rapid test provided by different manufacturers.³⁸ Their sensitivity may vary significantly and Chagas disease should be screened by 2 different parallel assays.³⁹ However, as the ELISA tests were more broadly used in the blood bank setting, the sensitivity of the assays improved and the current predominant consensus is that a single highly sensitive assay can be used for the initial *T. cruzi* screening, so that, if negative, it would rule out this aetiology.³⁸

Regarding the prognosis of the disease, several risk markers have been recognized, and a systematic review identified that impaired LV function, New York Heart Association class III/IV, cardiomegaly, and non-sustained ventricular tachycardia are the most important predictors of poor prognosis in patients with chronic CCM.⁴⁰ Using a validated prognostic scoring system, based on clinical, radiological, echocardiographic and Holter monitoring/stress testing, Chagas disease patients can be stratified into three risk groups: low, intermediate, and high.³⁰ For those at low risk, 90% will still be alive after 10 years, in comparison with only 16% of those at high risk. Prognostic factors have been used to build a risk score for death that is helpful for clinical decision making³⁰ (Table 2).

Key points

- 20–40% of patients with Chagas disease will evolve to chronic Chagas cardiomyopathy, which can be asymptomatic or manifest by heart failure, cardiac arrhythmias, and/or thromboembolism
- Brady or tachyarrhythmias or stroke may be the first manifestation of Chagas cardiomyopathy

- Chronic form of Chagas cardiomyopathy evolving to heart failure carries higher mortality
- Impaired LV systolic function, New York Heart Association class III/IV, cardiomegaly, and non-sustained ventricular tachycardia are important predictors of poor prognosis in patients with chronic Chagas disease

LV systolic function

Echocardiography

Echocardiography is the most commonly used imaging modality for assessment and follow-up of patients with Chagas disease.⁴¹ Echocardiography allows to stage patients (A, B, C, and D) according to international recommendations adapted to the Chagas disease (Table 1).^{17,41} In early stages of cardiac involvement, echocardiography may demonstrate segmental LV wall motion abnormalities and diastolic dysfunction.^{4,42,43} The most commonly involved LV regions are the basal inferior and inferolateral walls (Figure 2; Supplementary

Videos 1 and 2), and the apex, which cannot be attributed to obstructive coronary artery.⁴⁴ Wall motion abnormalities can be detected in more than one wall in the same patient. The extent of regional wall motion abnormality varies from hypokinesis to akinesis and aneurysm. The presence of segmental abnormalities identifies individuals at risk of further LV function global deterioration.⁴⁵

Wall motion abnormalities can be found in around 10% of patients in the early stages of cardiac involvement and they can be associated with ventricular arrhythmias.⁴⁶ As the disease progresses to LV dilatation and dysfunction, the prevalence of segmental wall motion abnormalities increases to about 50% of patients.^{47,48}

Detection of regional wall motion abnormalities by visual assessment is subjective and highly dependent on the skills of the interpreter. Moreover, subtle changes in segmental contractility may be missed by visual assessment. Strain measurement using speckle tracking echocardiography is a new method that allows a more precise and quantitative measurement of the regional myocardial function, overcoming the subjective evaluation by conventional echocardiography (Figures 3 and 4).^{49,50} Since segmental wall motion abnormalities are frequent in Chagas disease, speckle tracking echocardiography may have an important clinical application in these patients, particularly in the indeterminate forms when abnormalities are more subtle. A study including 125 patients with Chagas disease found that global longitudinal, circumferential, and radial LV strain were reduced in the patients who had cardiac fibrosis on CMR despite normal global and segmental LV systolic function by echocardiography.⁵¹ Specifically, the patients with fibrosis had lower radial LV strain in the basal inferoseptal wall than patients without cardiac fibrosis ($27 \pm 17\%$ vs. $60 \pm 15\%$).

Speckle tracking echocardiography can also quantify the heterogeneity of systolic contraction, which is associated with the risk of arrhythmic events. A recent study showed that mechanical dispersion was associated with malignant ventricular arrhythmias in patients with CCM independent of LV ejection fraction (Figure 5).⁵²

LV apical aneurysms are a typical finding in patients with CCM and can be helpful in making the aetiologic diagnosis in dilated cardiomyopathy (Figure 6; Supplementary Videos 3 and 4).^{4,44,47} This abnormality may be missed if only conventional apical views are acquired.

Table 2 Score for predicting all-cause mortality in Chagas disease (Rassi's score)³⁰

Predictors	Points		
New York Heart Association class III or IV	5		
Cardiomegaly (chest X-ray)	5		
Segmental or global wall motion abnormality (echo)	3		
Non-sustained ventricular tachycardia (24 h Holter)	3		
Low QRS voltage (ECG)	2		
Male sex	2		
Risk category	5-years mortality	10-years mortality	Total points
Low	2%	10%	0–6
Intermediate	18%	44%	7–11
High	63%	84%	12–20

ECG, electrocardiogram.

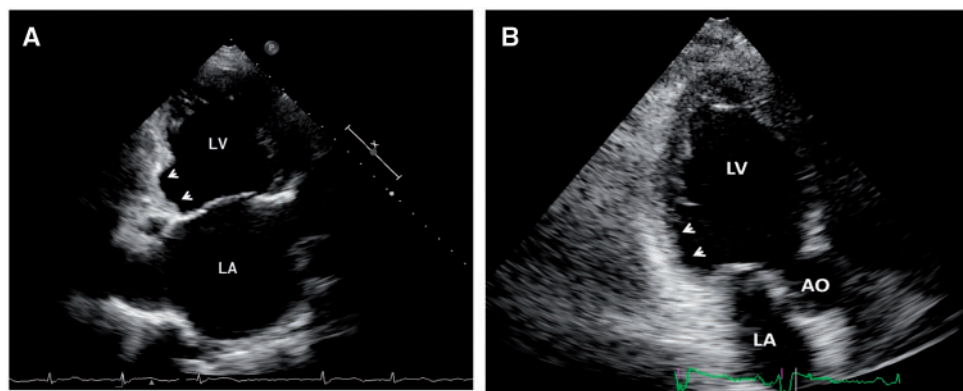


Figure 2 (A) Apical two-chamber view 2D echocardiographic image showing akinesis of the basal segment of the inferior wall. (B) Apical long-axis view showing akinesis of the basal segment of the inferolateral wall.

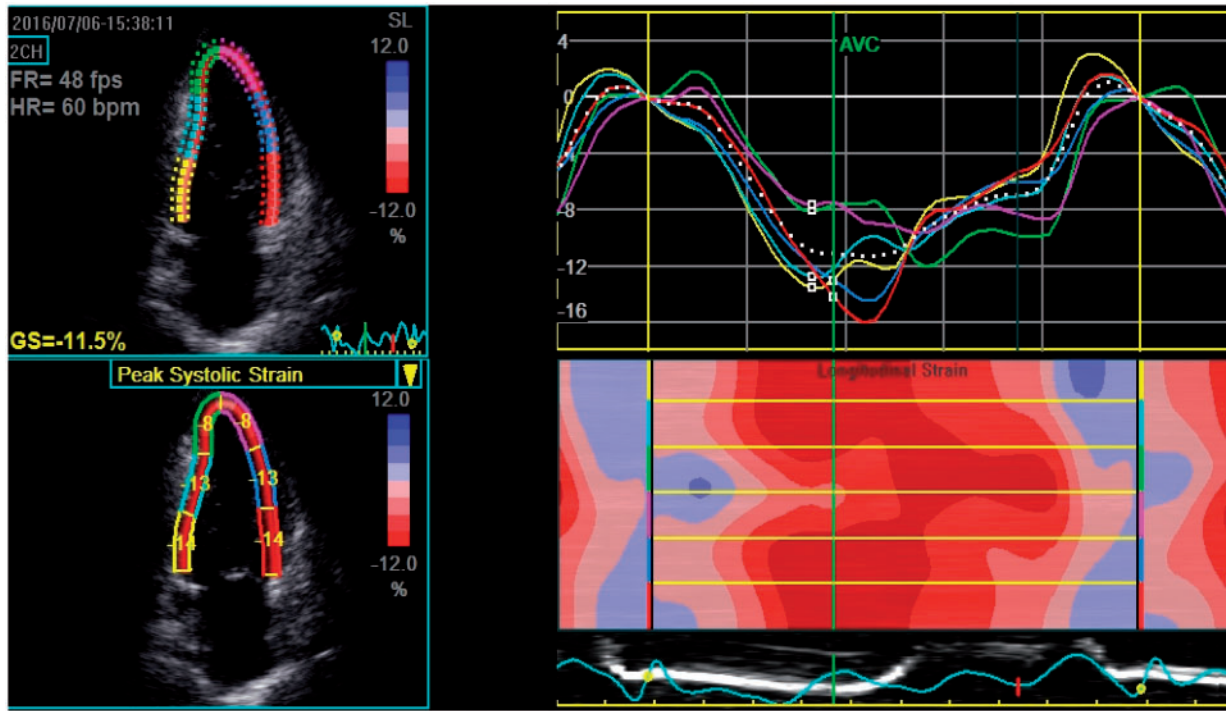


Figure 3 Left ventricular longitudinal strain at apical two-chamber view (left, upper panel) in an asymptomatic patient with Chagas disease and normal global left ventricular ejection fraction. The regional strain values are displayed both as regional strain (left, lower panel) and time curves (right, upper panel) as well as in an M-mode parametric colourization (right, lower panel). AVC, aortic valve closure.

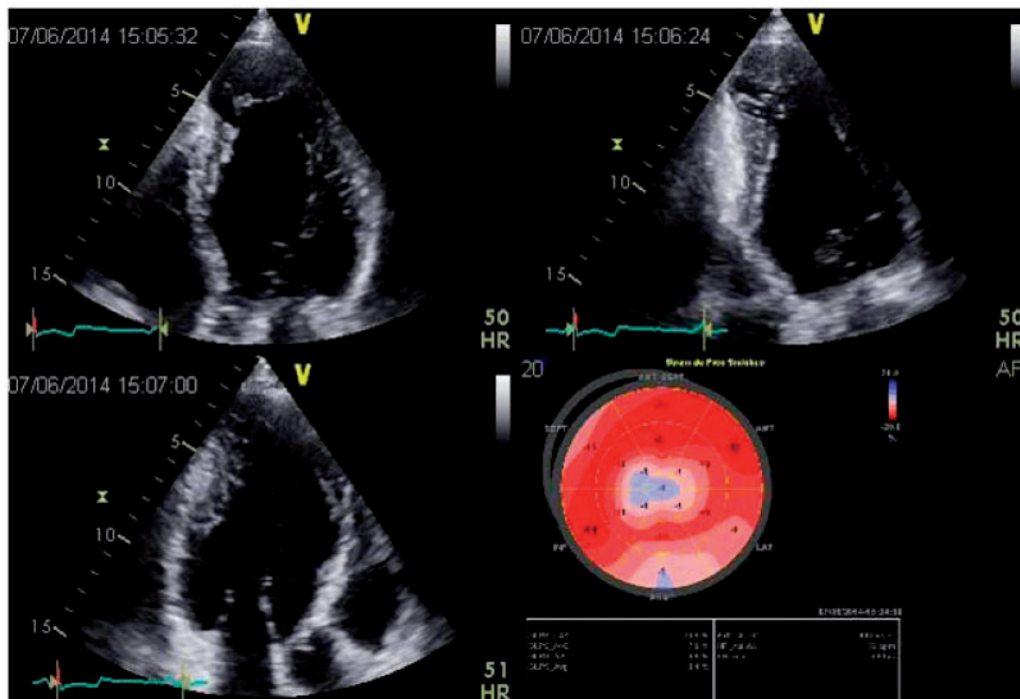


Figure 4 Computation of peak LV global longitudinal strain by using the speckle tracking technique on three conventional apical views: four-chamber (left, upper panel), two-chamber (right, upper panel), and apical long axis (left, lower panel). LV segmental values of longitudinal strain are displayed both as numbers and as parametric colorization on a bull's eye display (right, lower panel). There is an apical aneurism that is seen in each view.

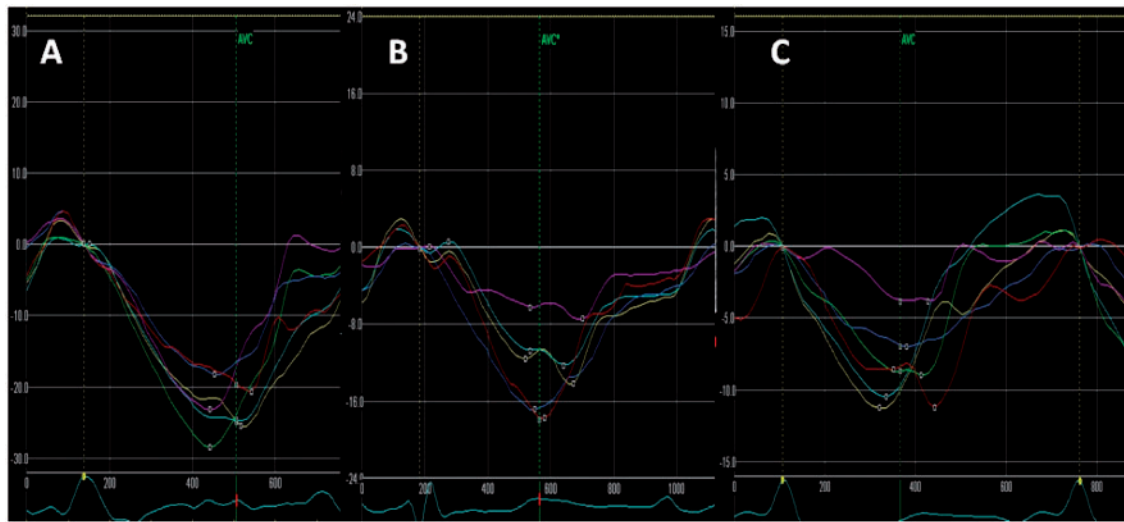


Figure 5 2D LV longitudinal strain in Chagas disease. Note the progressive decrease in LV longitudinal strain from patient in indeterminate form (A) to the patients with cardiac form of Chagas disease (B and C). Each figure depicts the LV longitudinal strain curves for each of 6 segments analysed at the four-chamber view.

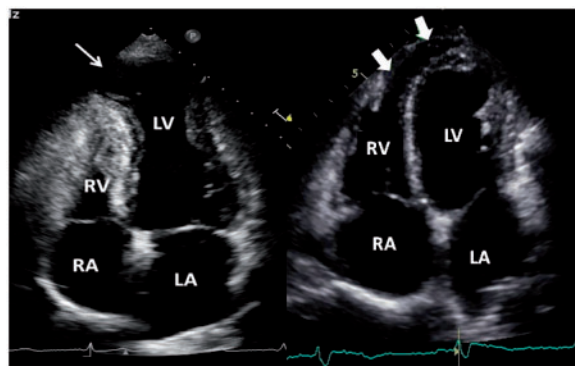


Figure 6 Apical four-chamber views showing left ventricular apical aneurysm (thin arrow, on the left), and right ventricular aneurysm (broad arrows, on the right) with a relatively normal left ventricle.

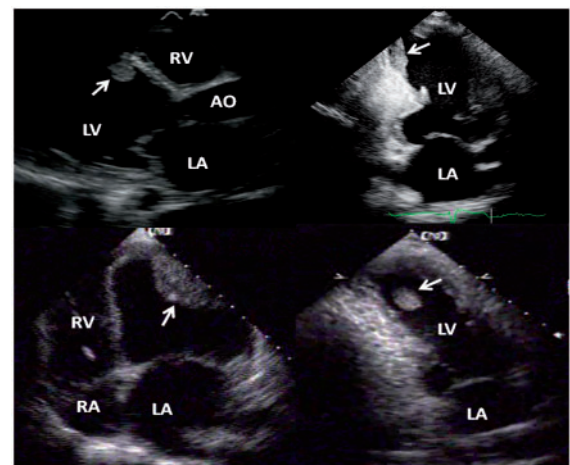


Figure 7 Echocardiographic images showing different locations of thrombus inside of the left ventricle.

In order to identify aneurysms, a careful examination requires not only standard views but also angulated apical views. Frequently, a modified four- and two-chambers views aiming posteriorly may be necessary to detect apical aneurysms and thrombus. The size of the aneurysm may range from small (like a ‘hollow punch’) to large with extensive wall thinning, similar to ischaemic aneurysms.^{44,47} Aneurysms are not limited to the apex or to the inferolateral wall,⁴⁴ they can also be found in interventricular septum and anterolateral walls, being more prevalent in patients with global LV systolic dysfunction.^{44,47} Previous studies using 2D echocardiography reported that the LV aneurysm prevalence was 8.5% (ranging from 1.6 to 8.6%) in asymptomatic patients but increased to 55% (ranging from 47 to 64%) in patients with moderate or severe LV global systolic

dysfunction.^{44,47,48} Right ventricular (RV) aneurysms are uncommon, but some patients have apical aneurysms affecting both ventricles (Figure 6; Supplementary Video 4). Intraventricular mural thrombi can be associated with aneurysms and are important risk factors for the occurrence of systemic embolisms including stroke^{35,36,53,54} (Figure 7; Supplementary movies 5 and 6).

Contrast echocardiography has the advantage to enhancement of LV endocardial border, allowing for more accurate detection of ventricular aneurysms and thrombus in Chagas disease.⁴⁴ With the apical four-chamber view, using contrast echo, it should be usually possible to clearly visualize the RV and LV cavities.

In Chagas disease, 3D echocardiography is superior to 2D echo for assessing more accurately the LV apex and thus to detect apical aneurysms/thrombus in patients in whom LV foreshortening is suspected by 2D echo (Figure 8). In addition, 3D echo is more accurate than 2D Simpson's biplane rule for assessing LV volumes and EF in patients with significant wall motion abnormalities, including aneurysms with distorted LV geometry.

Although segmental wall motion abnormalities are among the most characteristic findings of cardiac involvement in Chagas disease, their pathogenesis has not been defined. Since the epicardial coronary arteries are angiographically normal it has been hypothesized that microvascular involvement leads to ischaemia and necrosis in distal watershed areas of the coronary territories.^{55,56} This could explain the prevalence of fibrotic lesions⁵⁵ and perfusion defects in inferior, inferolateral and apical segments.⁵⁶ Accordingly, the regions of late gadolinium enhancement (LGE) (signifying myocardial fibrosis/scarring) in the post-contrast CMR images are predominantly localized in the apex, inferior and inferolateral walls.⁵⁷

More advanced disease is characterized by global LV dilatation and diffuse hypokinesia. LV systolic dysfunction is the strongest predictor of death in CCM.^{40,58}

Key points

- Echocardiography is the most common imaging modality used to assess, stage, and follow-up of patients with Chagas disease
- In early stages of cardiac involvement, echocardiography may demonstrate segmental LV wall motion abnormalities
- Segmental wall motion abnormalities are more frequent in inferior and inferior-lateral walls and at the apex and may range from hypokinesia to aneurysms
- Apical aneurysms are the landmark lesions in Chagas disease, but they can be missed in conventional 2D apical views due to apical foreshortening, dropout or near-field artefacts

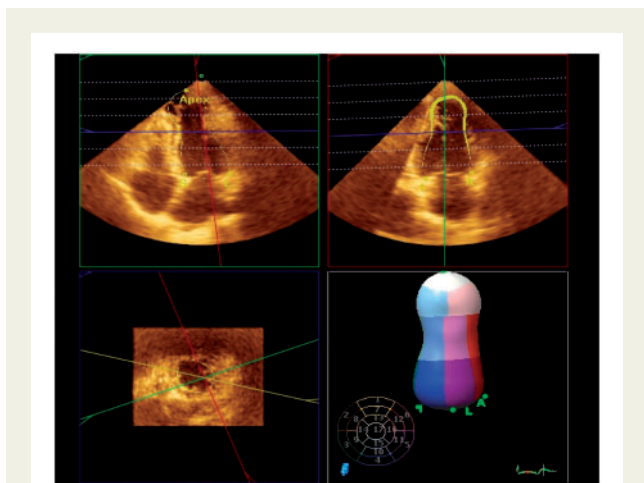


Figure 8 3D echocardiography of a patient with chronic Chagas disease showing apical aneurysm with preserved contractility at basal segments of the left ventricle. Semiautomatic endocardial border detection is shown by yellow line and the lower right panel shows regional-ventricular analysis.

- The use of contrast is highly recommended whenever the image quality is suboptimal (>2 LV segments not visible, as recommended by guidelines) and when apical involvement is either suspected or unclear
- Speckle tracking longitudinal strain and 3D echocardiography appear to be accurate and reproducible methods to assess LV systolic function in Chagas disease and should be used when available and feasible

Cardiac magnetic resonance

Due to its unique ability to differentiate tissue characteristics, CMR allows non-invasive tissue characterization in CCM. CMR can demonstrate all the typical features of the cardiac involvement in Chagas disease such as the presence of myocardial oedema, and altered myocardial perfusion in the early stages, as well as global and segmental wall motion abnormalities, aneurysm formation, intracardiac thrombi and myocardial fibrosis areas detected by the LGE sequence in the most advanced stages (Figure 9).

A study⁵⁹ showed that 20% of patients in the indeterminate form of Chagas disease have evidence of myocardial fibrosis, without any associated wall motion abnormality. In CCM, CMR highlights the structural derangement associated with intense collagen formation. Moreover, the apical aneurysms can be easily demonstrated by CMR (Figure 10). In advanced stages, the cine sequences show decreased global contractility and ejection fraction with diffuse parietal thinning.⁵⁹

Regions of LGE with a heterogeneous pattern at delayed enhancement CMR images have been reported in 68.6% of patients at different stages of Chagas disease.⁵⁷ The extension of myocardial fibrosis correlated with the severity of the LV systolic dysfunction, which was also present in all patients with previously documented episodes of ventricular tachycardia.⁵⁷

Another study⁶⁰ reported that, in patients with Chagas disease the prevalence of LGE was 24% in the overall study population. Particularly, in patients with only electrocardiographic abnormalities, LGE was found in 16% of patients and 3% had segmental dyskinesia (aneurysm) not detected with echocardiography. Conversely 52% of the patients with CCM had LGE indicating myocardial fibrosis and/or necrosis. The LGE appearance was heterogeneous: subendocardial in 26.8%, midwall in 14.0%, subepicardial in 22.6%, and transmural in 36.0% of the patients. The presence of LGE was significantly associated with lower LV ejection fraction and was more commonly located at the apex and inferolateral walls. In this study, a correlation between LGE and arrhythmic events was identified. Thus, early detection of oedema and/or myocardial fibrosis by CMR may potentially identify patients at risk of disease progression.⁵⁷

In 41 patients with Chagas disease and cardiac involvement, myocardial fibrosis was detected in all the 26 patients (63%) who had ventricular tachycardia.⁶¹ The presence of two or more LV segments containing transmural LGE constituted a predictor of the occurrence of arrhythmia after adjustment for LV ejection fraction, age, gender and the area of LGE. Patients without previous ventricular tachycardia, or transmural LGE, and those with less than 6% of fibrosis in the myocardium showed no new arrhythmic events. Furthermore, three patients died of sudden death, and all of them had at least one segment with transmural LGE at CMR and no previous history of ventricular tachycardia.⁶¹

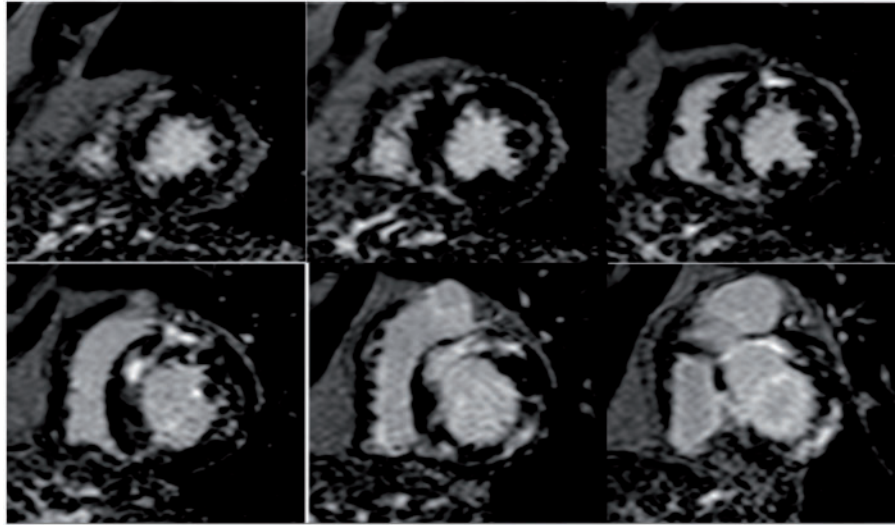


Figure 9 Cardiac magnetic resonance short axis images showing lateral and septal myocardial fibrosis with a delayed enhancement sequence.

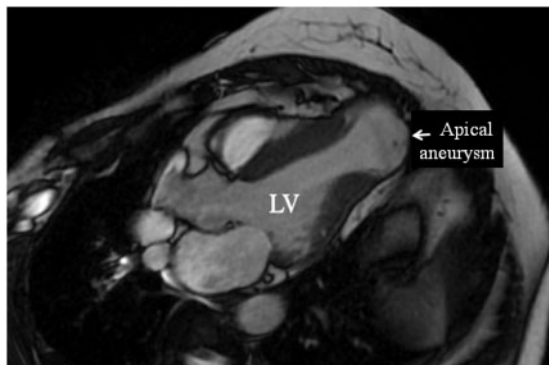


Figure 10 Cardiac magnetic resonance showing the typical apical aneurysm in a patient with Chagas disease.

Key points

- CMR should be indicated in selected patients with severe ventricular arrhythmias to quantify the extension of myocardial fibrosis and risk of sudden death with potential impact on indication of implantable cardioverter-defibrillator.
- CMR should be indicated for LV ejection fraction evaluation when contrast echocardiography/3D echo is not available or unsatisfactory
- It remains to be clarified whether in the patients with the indeterminate form of the disease, evidence of oedema or fibrosis at CMR can predict future progression to the cardiomyopathy

Radionuclide ventriculography

Planar ECG-gated radionuclide ventriculography (RNV) is an alternative method for LV systolic function assessment in patients with suspected or definite cardiac involvement in Chagas disease when CMR is

not feasible or available.⁶² RNV was used to assess global LV function, and also allows the adequate evaluation of regional ventricular wall motion, particularly the characterization of the apical aneurysm.⁶² Moreover, data about LV function are robust and reproducible.

Key points

- RNV is used for LV systolic function assessment in those patients in whom CMR is not feasible or available.
- RNV should be indicated for LV ejection fraction measurement and regional wall motion evaluation when contrast echocardiography/3D echo is not available or unsatisfactory

LV diastolic function

Chagas disease may also lead to impairment of diastolic function, which can occur early in the disease.^{18,43,63} Usually, the first abnormality is impaired LV relaxation with prolonged E-wave deceleration time. Further progression of the disease leads to decreased LV compliance and results in increased filling pressures.^{4,28,51,63}

In some studies, prevalence of diastolic abnormality ranges from 10% of patients with indeterminate form to almost 100% in patients with CCM and heart failure.^{43,48,63} Other studies enrolling patients with the indeterminate form did not show any impairment of diastolic function.^{64,65} Differences regarding patient population sampling, controls selection and echocardiographic diastolic parameters used to define diastolic dysfunction, may explain discrepant results.

More recently, key variables to assess LV diastolic function including tissue Doppler imaging have been used that allow comparison among the studies. In particular, e' velocity at tissue Doppler echocardiography appeared to be the best parameter to identify the progressive worsening of the LV diastolic dysfunction.^{43,63}

Echocardiographic parameters of diastolic function in CCM are also correlated with brain natriuretic peptide levels.^{66–68} A previous study including 59 patients with dilated CCM showed a strong

correlation between LA volume and BNP levels.⁶⁶ In another study, BNP levels correlated with diastolic function patterns regardless of systolic function. The E/e' ratio was the only parameter of diastolic function that was independently associated with BNP levels.⁶⁷

Key points

- Isolated LV diastolic dysfunction is uncommon but may appear early in the natural history of chronic Chagas cardiomyopathy, and has been described in patients with the indeterminate form of the disease
- Diastolic and systolic dysfunction coexist in most patients with more advanced stages of the disease
- Left atrial volume and E/e' ratio correlate with brain natriuretic peptide levels in Chagas cardiomyopathy

RV function

RV systolic dysfunction may be an early finding in the natural history of Chagas disease and has been detected in patients with the indeterminate and digestive forms.^{19,69,70} Several indexes and methods have been used to describe RV dysfunction in patients with Chagas disease showing somewhat discrepant results. These mixed data may be attributed to the different methods used to assess RV function as well as to the composition of the various groups of patients included in each study.

Isolated right-sided heart failure is not frequent and usually RV dysfunction is associated with LV dysfunction at advanced stages of CCM.^{4,28,71} However, direct damage to the RV myocardium due to Chagas disease itself can also contribute to RV dysfunction.^{72–74} It is important to emphasize that RV dysfunction may occur without symptoms or signs of heart failure, but may be aggravated by the burden generated by chronic pulmonary hypertension secondary to LV systolic dysfunction. In such circumstances RV dysfunction carries an adverse prognostic meaning.⁷⁰ Also, the concomitance of RV dysfunction explains why systemic congestion can predominate over pulmonary congestion in some patients with heart failure due to CCM.⁷¹

Echocardiography for RV function assessment

RV dysfunction has been reported in all stages of Chagas disease,^{19,69,70,72,73} most commonly associated with LV dysfunction. Several echocardiographic parameters have been used to assess RV function in Chagas disease, including qualitative evaluation, myocardial performance index, tissue Doppler imaging, tricuspid annular plane systolic excursion, and speckle tracking strain.^{63,64,73}

Cardiac magnetic resonance

Previous studies in Chagas disease using CMR have focused on the LV and there are limited data on RV function. A study including 158 patients with Chagas disease showed that RV systolic dysfunction assessed by CMR was more commonly associated with reduced LV ejection fraction. Isolated RV dysfunction was not frequent, which was identified in only 4.4% of the patients.⁷⁵

Radionuclide ventriculography

Previous studies using RNV to assess quantitatively RV function have documented early and predominant RV dysfunction in patients with the indeterminate and gastrointestinal forms of Chagas disease.^{69,70} This particular feature explains why heart failure syndrome in some CCM patients may present more prominent systemic than pulmonary congestion.⁷⁴

Key points

- Early and predominant RV dysfunction may be present in some patients with Chagas disease, and in some those with the isolated gastrointestinal or the indeterminate forms of Chagas disease
- It remains to be clarified whether RV dysfunction is predominantly secondary to chronic pulmonary hypertension induced by LV systolic dysfunction or reflects primarily a direct myocardial damage
- Although RNV is a well validated and reproducible technique to evaluate the RV, limited data are available in Chagas disease.

Disturbances of the coronary circulation

Although the epicardial coronary arteries are angiographically normal in the vast majority of patients with Chagas disease studied because of atypical angina, there is limited evidence of abnormal regulation at the macrovascular level.⁷ Moreover, much more evidence has been gathered from several studies pointing to functional and structural microvascular derangements likely to contribute to ventricular dysfunction in Chagas disease.⁵⁶

On the basis of sporadic cases of myocardial infarction occurring in Chagas patients with non-obstructed epicardial coronary arteries, coronary vasospasm has been postulated to cause such events.⁷⁶ However, controlled studies aiming at detection of abnormal macrovascular coronary regulation in Chagas patients produced mixed results, using various endothelium dependent and endothelium independent stimuli such as hyperventilation, nitrates, acetylcholine and adenosine.^{56,77,78}

Wall motion abnormalities have been detected during standard dobutamine stress echocardiography in patients with Chagas disease, despite absence of haemodynamically significant obstructions of epicardial coronary arteries.⁷⁹ Abnormal flow regulation at the microvascular level has been demonstrated by several investigators.^{80,81–83} using myocardial perfusion scintigraphy (*Figure 11*). Myocardial perfusion defects occur at early stages of Chagas disease at a microvascular level and precede the appearance of regional systolic wall motion abnormalities.^{56,83–86} These data further support the hypothesis that coronary microvascular disturbances may cause ischaemic myocardial damage in CCM.

Key points

- Wall motion abnormalities may be induced during stress echocardiography in Chagas disease patients despite angiographically normal coronary arteries
- Myocardial perfusion defects occur at early stages of cardiac involvement in Chagas disease, before the appearance of regional wall motion abnormalities
- Perfusion defect locations are correlated with subsequent development of regional myocardial fibrosis

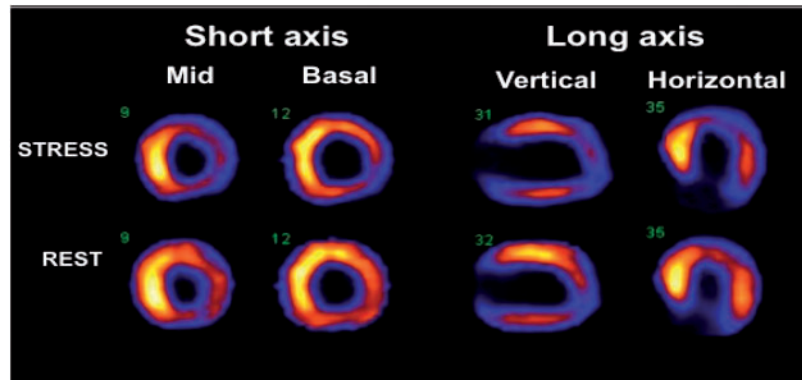


Figure 11 Myocardial perfusion scintigraphy. Images of myocardial perfusion scintigraphy at rest and during exercise showing mostly reversible regional myocardial perfusion defects in the apical and inferolateral left ventricular segments.

- Detection of reversible ischaemic defects predicts further deterioration of LV systolic function

Myocardial sympathetic innervation

Necropsy studies documented severe cardiac autonomic denervation in CCM, more severe than in other cardiomyopathies.^{87,88} Moreover, functional abnormalities of the reflex autonomic control of the heart rate have been demonstrated using several methods of investigation.⁷ More recently, studies using myocardial scintigraphy with iodine-123-metaiodobenzylguanidine (¹²³I-MIBG) have shown that defects of ¹²³I-MIBG uptake can be documented in the majority (68%) of the patients with Chagas disease.^{56,85,89} Of note, ¹²³I-MIBG defects were detected in 33% of the patients without any other evidence of cardiac involvement. Patients with more severe LV dysfunction presented a higher prevalence of ¹²³I-MIBG defects (92%). The areas of myocardial sympathetic denervation were topographically correlated with the regions also exhibiting fixed and reversible myocardial perfusion defects and abnormal segmental LV wall motion. These areas were predominantly the inferior, postero-lateral and apical LV walls (Figure 12). These findings suggested that myocardial sympathetic denervation is an early phenomenon in the pathophysiology of Chagas disease, preceding the development of regional LV wall motion abnormalities. This concept was corroborated by an independent study showing abnormal ¹²³I-MIBG uptake even in patients with Chagas disease and no apparent cardiac involvement.⁹⁰

One investigation in 26 patients with Chagas disease and normal or mildly reduced LV ejection fraction showed that patients with sustained ventricular tachycardia had higher ¹²³I-MIBG summed score and a higher number of mismatch defects (sympathetic denervation with preserved perfusion) per patient than patients with no arrhythmias.⁸⁹ Both groups had similar 99mTc-Sestamibi-SPECT summed score. The presence of ≥ 3 mismatch defects was strongly associated with the occurrence of sustained ventricular tachycardia (93% sensitivity, 82% specificity). These findings suggest a possibly relevant role of myocardial sympathetic denervation as a triggering

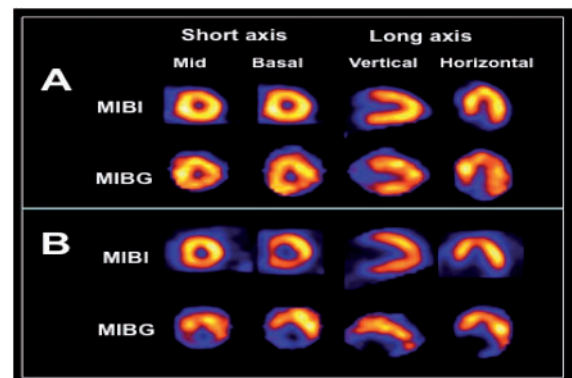


Figure 12 Myocardial sympathetic innervation. Images of resting myocardial perfusion scintigraphy (^{99m}TcMIBI) and of sympathetic innervation (¹²³I-MIBG) with tomographic sections of two orthogonal planes (short and long axis). Severely impaired ¹²³I-MIBG uptake with normal myocardial perfusion involves predominantly the inferior, posterior-lateral, and apical left ventricular walls (A) Control; (B) Patient with Chagas disease.

mechanism of malignant ventricular arrhythmias, and that ¹²³I-MIBG imaging may be useful to stratify the risk of sudden cardiac death in Chagas disease.⁸⁹

Key points

- Myocardial sympathetic denervation is an early occurrence in patients with Chagas disease and can be detected using myocardial scintigraphy with iodine-123-metaiodobenzylguanidine
- The extension of myocardial sympathetic denervation correlates with the severity of LV dysfunction
- Extent of cardiac sympathetic denervation may be a marker of ventricular arrhythmias with potential for risk stratification of sudden death in Chagas disease

Table 3 Echocardiographic predictors of outcomes in Chagas disease

Author/year	Number of patients	Characteristics of Chagas disease patients	Follow-up duration	Outcomes	Echocardiography predictive variables ^a	Other prognostic factors
Viotti et al. (2005) ⁹⁴	856	Indeterminate form and heart disease, without heart failure	8 y	Progression of the disease or cardiovascular death	LV end-systolic diameter	Age, ICD, SVT, and benzimidazole treatment
Rassi Jr et al. (2006) ³⁰	424	Heart disease	7.9 ± 3.2 y	All cause-mortality	LV systolic dysfunction subjectively estimated	NYHA class, cardiomegaly, NSVT, QRS voltage and male
Benchimol Barbosa (2007) ⁹⁵	50	Indeterminate form and heart disease	84.2 ± 39 m	Cardiac death or documented ventricular tachycardia	Apical aneurysm and LVEF	Isolated PVC count
Theodoropoulos et al. (2008) ⁹⁶	127	Heart failure with LV systolic dysfunction	25 ± 19 m	All cause-mortality	LVEF	NYHA class IV, no BB therapy, digoxine use, low serum sodium levels
Issa et al. (2010) ^{97,b}	68	Irreversible chronic heart failure	1326 ± 39 d	Death or heart transplant	LV end-diastolic diameter	BB therapy
Sarabanda and Marin-Neto (2011) ⁹⁸	56	Heart disease with either sustained VT or NSVT	38 ± 16 m	All cause-mortality and sudden death	LVEF < 40%	None
Ribeiro et al. (2011) ⁹⁹	113	Indeterminate form and heart disease	106 ± 28 m	Cardiovascular death	LVEF	T-wave variability, NSVT and QRS > 130 ms
Bestetti et al. (2011) ¹⁰⁰	231	Chronic heart failure	19 m	Death or heart transplant	LV end-systolic diameter	No BB therapy and inotropic support
Duarte et al. (2011) ¹⁰¹	56	Dilated cardiomyopathy	21 ± 14 m	Death or hospitalization	Rassi's score	LV dyssynchrony was not associated with events
Nunes et al. (2012) ⁷¹	232	Dilated cardiomyopathy	3.4 y	Death or heart transplant	LVEF, RVMPI, LA volume, and E/e' ratio	NYHA class
Nascimento et al. (2013) ⁶³	251	Indeterminate form and heart disease	842 ± 245 d	All-cause mortality, stroke, heart transplant, worsening HF or arrhythmias	E' velocity and peak negative global LA strain	None
Rassi et al. (2014) ¹⁰²	60	Heart failure with severe LV systolic dysfunction	24 m	Cardiovascular death	Indexed LA volume	None

AF, atrial fibrillation; BB, beta-blocker; CI, confidence interval; ICD, intraventricular conduction disorders; d, days; LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVSD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; m, months; NYHA, New York Heart Association; QTd, QT dispersion; RVMPI, Right ventricular myocardial performance index; SVT, sustained ventricular tachycardia; NSVT, non-sustained ventricular tachycardia; VT, ventricular tachycardia; Y, years.

^aMultivariate analysis.

^bClinical trial; 456 patients with heart failure were enrolled, and Chagas cardiomyopathy was present in 68 patients.

Imaging modalities for risk stratification

Echocardiography can provide key data to guide therapy and prognosis. Several echocardiographic variables have been described as predictors of mortality in Chagas disease.⁹¹ Early studies have identified

- LV dysfunction and specially low-ejection fraction obtained by echocardiography as the strongest predictor of death.^{30,40,44,58,92}
- Subsequently, echocardiographic parameters to assess LV filling pressure have been reported to have additive value for risk stratification of patients with impaired LV systolic function.⁹²

Table 4 Characteristics suggestive of Chagas disease in patients living in non-endemic countries

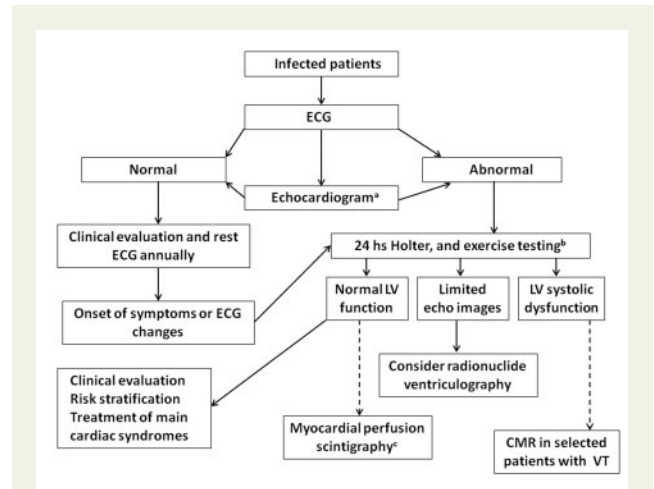
Epidemiological profile	Individuals who were born in, or have lived in endemic areas or a child of a mother from endemic country
Clinical features	Cardiac rhythm disorders, heart failure, thromboembolic events, chest pain without evidence of epicardial coronary artery disease. Association with megaesophagus or megacolon
ECG abnormalities	Sinus bradycardia, right bundle branch block with or without left anterior fascicular block, atrioventricular blocks, frequent premature ventricular beats, and primary ST and T wave abnormalities
Echocardiographic findings	Segmental wall motion abnormalities, mainly inferior and inferolateral walls, left ventricular apical aneurysms, thrombus, and dilated cardiomyopathy with right ventricular dysfunction
CMR and nuclear imaging methods	Myocardial fibrosis, regional myocardial perfusion defects, and sympathetic denervation

The ratio of early transmitral velocity to tissue Doppler mitral annular early diastolic velocity (E/e' ratio), an accepted non-invasive method to estimate LV filling pressures, is also an independent predictor of mortality in patients with CCM.^{43,63,71}

A previous study showed that the inclusion of the E/e' ratio has improved the risk prediction model beyond established risk parameters in patients with CCM including functional class, LV ejection fraction, and RV function.⁹² However, E/e' ratio appears to have different effects on mortality in the setting of CCM.⁷¹ In patients with mild or moderate LV systolic dysfunction, an E/e' ratio > 15 was a powerful predictor of mortality. In contrast, in patients with severe systolic dysfunction, an increased E/e' ratio was inversely associated with mortality.⁷¹ Although the underlying mechanism to explain these findings remains to be clarified, it suggests that Chagas disease has some specific features compared with heart failure from other aetiologies.

Increased left atrial (LA) volume has been shown to be an independent predictor of survival in CCM, adding incremental prognostic value to clinical factors, LV ejection fraction, and Doppler-derived parameters of diastolic function.⁴⁸ More recently, a study showed that LA contractile function assessed by peak negative global LA strain was an independent predictor of clinical events, defined as the occurrence of a combined endpoint of all-cause mortality, stroke, heart transplantation, atrial fibrillation, or admission for worsening HF or cardiac arrhythmias.⁶³ Although LA contractile function was depressed in all groups of patients with the cardiac form, LA contractile function was depressed only in those with heart failure.⁶³

RV systolic involvement is a marker of Chagas disease severity associated with functional capacity⁹³ and survival.⁷³ A study in 158 patients with dilated CCM found that RV function, assessed by RV myocardial performance index was a predictor of death, independent of

**Panel A** Diagnostic flow chart and suggested periodicity of assessment.¹⁰⁵

ECG, electrocardiogram; CMR, cardiac magnetic resonance.

^aIt is reasonable to perform an echocardiogram on every patient at the diagnosis of Chagas disease, and it should be repeated during follow-up if the ECG becomes abnormal. Echocardiogram should be repeated every 3–5 years in the patients with preserved left ventricular ejection fraction and more often in those who have reduced ejection fraction at the diagnosis or when clinical status change with worsening heart failure or embolic events.

^b24h Holter monitor is specially recommended in patients with major ECG changes, including sinus node dysfunction, atrioventricular block, or frequent premature ventricular contractions, and should be repeated when clinical status change, or when with pre-syncope or syncope supervenes. Exercise testing at the diagnosis may be indicated: as a substitute for Holter when this method is not available, to detect arrhythmia; as a pre-employment evaluation to guide physical activities; in those candidates for cardiac transplantation; it should be repeated in those patients who develop new symptoms at the same periodicity as the Holter test.

^cIt can be done to assess myocardial perfusion or myocardial sympathetic innervation, mainly for patients who complain of atypical chest pain, so as to avoid unnecessary cardiac catheterization. It may also be useful to further stratify the risk of LV systolic deterioration and the appearance of malignant arrhythmia. No recommendation can be currently be set for its periodicity.

functional class and LV ejection fraction.⁷³ Other subsequent studies assessing risk stratification in Chagas disease have confirmed the fundamental role of RV function in predicting prognosis.^{58,71,92}

In summary, several echocardiographic variables have been associated with increased mortality (Table 3).^{30,63,71,91,94–102} The prognostic role of new echocardiographic techniques like speckle tracking echocardiography and three-dimensional echocardiography is promising but its ultimate usefulness for clinical purposes remains to be defined.

Cardiac magnetic resonance may have a role to stratify patients at risk of ventricular arrhythmias and progression to heart failure by detecting and quantifying the extension of myocardial fibrosis.^{57,61,103,104}

Radionuclide methods may improve risk stratification to define cardiac involvement in Chagas disease in patients with devices precluding CMR

studies, and to identify perfusion defects and myocardial sympathetic denervation derangements that are associated with progression of LV dysfunction and appearance of malignant ventricular arrhythmia.^{62,87}

The main features suggestive of Chagas disease in patients living in non-endemic zones are shown in *Table 4*. These characteristics help physicians from outside Latin America to be aware of Chagas disease.

As echocardiography is widely available with relatively low cost, it became the imaging method of choice to evaluate patients with Chagas disease. Advantages and disadvantages of each imaging modality in the setting of Chagas disease are shown in *Table 5* (supplementary data). An algorithm of diagnostic steps in Chagas disease and assessment periodicity is also shown in *Panel A*.

Key points

- Presence and extension of LGE are predictive of severe ventricular arrhythmias, heart failure, and sudden death
- It remains to be clarified whether in the patients with the indeterminate form of the disease, evidence of oedema or fibrosis at CMR can predict future progression to the cardiomyopathy

Conclusions and future research

The early mortality and substantial disability caused by CCM result in a significant economic impact. Cardiac imaging is crucial to detect the cardiac involvement in patients with Chagas disease, stage the disease, and stratify patient risk and address management. Since unfortunately, most patients live in regions with limited access to imaging methods and point-of-care, establishment of simplified protocols, could improve the access of these remote populations to important information provided by diagnostic methods that could impact in the clinical management of the disease.

There are many fields open for further research in cardiac imaging in Chagas disease. The role of speckle tracking echocardiography to allow for an earlier diagnosis of cardiac involvement and improve patients' risk stratification remains to be addressed in properly powered outcome studies. Although three-dimensional echocardiography should be theoretically more accurate than conventional 2D echocardiography in measuring LV volumes and ejection fraction in ventricles with distorted geometries like those with regional aneurysms, whether this improved accuracy would translate into increased prognostic power remains to be proved. The role of three-dimensional echocardiography could be particularly useful to assess RV involvement and its prognostic impact. The prognostic role of the presence and extension of areas of myocardial oedema and/or fibrosis by CMR to predict future progression to cardiomyopathy, heart failure, severe ventricular arrhythmias, and sudden death should be addressed in well-designed multicentre outcome studies. Finally, the role of myocardial perfusion scintigraphy and assessment of myocardial sympathetic innervation for an early diagnosis of cardiac involvement and prognosis in patients with Chagas disease remains to be established.

Supplementary data

Supplementary data are available at *European Heart Journal—Cardiovascular Imaging* online.

Review

This document was reviewed by members of the EACVI Scientific Documents Committee for 2014–2016 and 2016–2018. EACVI reviewers included: Dr Victoria Delgado, Prof. Bernard Cosyns, Prof. Erwan Donal, Dr Alessia Gimelli, Prof. Frank Flachskampf, Assoc. Prof. Kristina Haugaa, Prof. Nuno Cardim, Dr Massimo Lombardi, Dr Denisa Muraru, and Dr Raluca Dulgheru.

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