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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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Abbreviations:

^{123}I-MIBG, iodine-123-metaiodobenzylguanidine

CCM, Chagas cardiomyopathy

CMR, cardiac magnetic resonance

LA, left atrium/atrial

LGE, late gadolinium enhancement

LV, left ventricle/ventricular

RNV, radionuclide ventriculography

RV, right ventricle/ventricular

DEFINITIONS: Two terms will be used throughout the paper: "Chagas disease" is a broad term to describe the disease in general, as caused by the infection with the *T. cruzi*, and "Chagas cardiomyopathy" refers to a form of presentation of Chagas disease, characterized by left ventricular enlargement with systolic function impairment, prominent disturbances of electric generation and conduction causing sudden death and multiple thromboembolic manifestations.

1: Introduction

Chagas disease, caused by the protozoan *Trypanosoma cruzi (T. 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 United States 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]

2: Natural history, diagnosis, clinical manifestations and prognosis

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. [10] 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 to 2% of the cases. The mortality rate is around 1% in the acute period, usually due to severe myocarditis or meningoencephalitis tissues.[11, 12] Given the high rates of pericardial effusion, echocardiography is indicated in patients with acute *T. cruzi* infection, irrespective of symptoms.

The chronic phase is characterized by two distinct clinical forms. The indeterminate form, which is usually installed 4 to 10 weeks after infection, is defined by seropositivity, and lack of radiologic, electrocardiographic and clinical manifestations of cardiac and digestive disease. [13] However, cardiovascular abnormalities can be detected using specific non-invasive tests, such as echocardiogram,[14, 15] cardiac magnetic resonance (CMR) and autonomic tests.[16-18]. 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, esophagus and colon, which characterize distinct chronic cardiac, digestive or mixed forms.[19] The progression from indeterminate to cardiac form ocurrs at an average rate of around 2% per year. [20, 21]

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.[13, 22, 23] The CCM, which constitutes the most serious complication of the disease, occurs in 20-40% of those individuals tested serologically positive .[24] 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.[25]

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 ECG alterations, such as right bundle branch block and

bradycardia,[26] and minor echocardiographic abnormalities, e.g. regional wall motion abnormalities.[27] **(Table 1).** The greater the extent of the myocardial damage, particularly LV dilatation, the more frequent and complex are the ECG abnormalities, in particular more complex ventricular arrhythmias and atrial fibrillation.[28]

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 ischemic or idiopathic dilated cardiomyopathies.[29, 30]

Stroke is also a cause of death in association with advanced heart disease,[31] but could also be the first sign of CCM in asymptomatic patients and those with mild LV systolic dysfunction.[32] LV aneurysm, mural thrombus, and atrial fibrilation are risk factors for stroke related to CCM.

CCM is a frequent cause of pacemaker implantation in patients living or coming from endemic countries, since advanced heart blocks and sinus sick syndrome are common manifestations of the disease.[33] Ventricular arrhythmias are important manifestations of CCM and non-sustained ventricular tachycardia is an established marker of higher risk of death.[34, 35] Patients with sustained ventricular tachycardia may require specific therapies, especially invasive procedures such as the implantation of cardioverter defibrillators and catheter or surgical ablation.[36]

The etiologic 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), hemaglutination 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 etiology.[38]

Regarding the prognosis of the disease, Chagas disease is a powerful predictor of death,[40] even in the elderly.[31] Several risk markers have been recognized, and a systematic review identified that impaired LV function, New York Heart Association class III/IV, cardiomegaly, and nonsustained ventricular tachycardia are the most important predictors of poor prognosis in patients with chronic Chagas cardiomyopathy. [41] 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.[34] For those at low risk, 90% will still be alive after ten 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 making. [34] **(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 tachy-arrhythmias or stroke may be the first manifestation of Chagas cardiomyopathy
- Chronic form of Chagas cardiomyopathy evolving to heart failure carries higher mortality compared to other etiologies of heart failure.

- The etiologic diagnosis of chronic Chagas disease is based on serological assays
- Impaired LV systolic function, New York Heart Association class III/IV, cardiomegaly, and nonsustained ventricular tachycardia are important predictors of poor prognosis in patients with chronic Chagas disease

3. Left ventricular systolic function

3.1 *Echocardiography*

Echocardiography is the most commonly used imaging modality for assessment and follow-up of patients with Chagas disease. [42] The presence of echocardiographic abnormalities is of utmost importance, since it allows to stage patients (A, B, C and D) according to international recommendations adapted to the Chagas disease **(Table 1).** [13, 42] In early stages of cardiac involvement, echocardiography may demonstrate segmental LV wall motion abnormalities and diastolic dysfunction.[4, 43, 44] The most commonly involved LV regions are the basal inferior and inferolateral walls **(Figure 2),** and the apex, which cannot be attributed to obstructive coronary artery. [45] 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.[46]

The prevalence of segmental wall motion abnormalities varies according to the stage of the disease. 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.[47] As the disease progresses to LV dilatation and dysfunction, the prevalence of segmental wall motion abnormalities increases to about 50% of patients. [48, 49]

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).**[50, 51] 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.[52] Specifically the patients with fibrosis had lower radial LV strain in the basal inferoseptal wall than patients without cardiac fibrosis (27 ± 17% vs 60 ± 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).** [53]

LV apical aneurysms are a typical finding in patients with CCM and can be helpful in making the etiologic diagnosis in dilated cardiomyopathy **(Figure 6).**[4, 45, 48] This abnormality may be missed if only conventional apical views are acquired. In order to identify aneurysms, a careful examination requires not only standard views but also angulated apical views. Frequently, a modified 4 and 2-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 ischemic aneurysms. [45, 48] Aneurysms are not limited to the apex or to the inferolateral wall [45], they can also be found in interventricular septum and anterolateral walls, being more prevalent in patients with global LV systolic dysfunction.[45, 48] 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.[45, 48, 49] Right ventricular (RV) aneurysms are uncommon, but some patients have apical aneurysms affecting both ventricles **(Figure 7).** Intraventricular mural thrombi can be associated with aneurysms and are important risk factors for the occurrence of systemic embolisms including stroke [54-57]**(Figures 8 and 9).**

Contrast echocardiography has the advantage to enhancement of LV endocardial border, allowing for more accurate detection of ventricular aneurysms and thrombus in Chagas disease.[45] With the apical 4-chamber view, using contrast echo, it should be usually possible to clearly

visualize the RV and LV cavities.

In Chagas disease, three-dimensional 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 10)** 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 angiographycally normal it has been hypothesized that microvascular involvement leads to ischemia and necrosis in distal watershed areas of the coronary territories **(Figure 11).** [58, 59] This could explain the prevalence of fibrotic lesions [58] and perfusion defects in inferior, inferolateral and apical segments.[59] Accordingly, the regions of late gadolinium enhancement (LGE) (signifying myocardial fibrosis/scarring) in the post-contrast cardiac magnetic resonance (CMR) images are predominantly localized in the apex, inferior and inferolateral walls. [60]

More advanced disease is characterized by global LV dilatation and diffuse hypokinesia. LV systolic dysfunction is the strongest predictor of death in CCM. [61, 62]

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 hypokinesis 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 artifacts
- The use of contrast is highly recommmended 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
- More advanced stages of Chagas disease are characterized by global left ventricular remodeling and dysfunction

- **3.2 *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 edema, 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 late gadolinium enhancement (LGE) sequence in the most advanced stages **(Figures 12).**

A study [63] 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 13).** In advanced stages, the cine sequences show decreased global contractility and ejection fraction with diffuse parietal thinning.[63]

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.[60] 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.[60]

Another study [64] 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 edema and/or myocardial fibrosis by CMR may potentially identify patients at risk of disease progression[60].

In 41 patients with Chagas disease and cardiac involvement, myocardial fibrosis was detected in all the 26 patients (63%) who had ventricular tachycardia[65]. 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 [65].

Key points

- Cardiac magnetic resonance 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 indicaton of implantable cardioverter-defibrillator.
- Cardiac magnetic resonance 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 edema or fibrosis at CMR can predict future progression to the cardiomyopathy

3.3 *Radionuclide ventriculography*

Planar ECG-gated radionuclide ventriculography (RNV) is an alternative method for biventricular function assessment in patients with suspected or definite cardiac involvement in Chagas disease with suboptimal acoustic window and contraindication to CMR.[66] RNV was used initially to assess global LV function, and also allows the adequate evaluation of regional ventricular wall motion, particularly the characterization of the apical aneurysm, the most typical wall motion abnormality in Chagas heart disease.[66]

Key points

- Radionuclide ventriculography is used for biventricular function assessment in those patients in whom echocardiography presents limitation for adequate quantitative evaluation

- Radionuclide ventriculography should be indicated for LV ejection fraction measurement and regional wall motion evaluation when contrast

echocardiography/3D echo is not available or unsatisfactory

4. Left ventricular diastolic function

Chagas disease may also lead to impairment of diastolic function, which can occur early in the disease.[14, 44, 67] 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, 24, 52, 67]

LV diastolic dysfunction has been reported in all forms of chronic Chagas disease, including those without LV systolic dysfunction, but its prevalence and severity gradually increases from the indeterminate form to the more advanced stages of the cardiac form. 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. [44, 49, 67]. Other studies enrolling patients with the indeterminate form did not show any impairment of diastolic function.[68, 69] 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, which allows 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.[44, 67]

Echocardiographic parameters of diastolic function in CCM are also correlated with brain natriuretic peptide levels. [70-72] A previous study including 59 patients with dilated CCM showed a strong correlation between LA volume and BNP levels. [70] 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. [71]

Key points:

- Isolated left ventricular 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

5. Right ventricular 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 .[15, 73, 74] 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 Chagas cardiomyopathy.[4, 24, 75] However, direct damage to the RV myocardium due to Chagas disease itself can also contribute to RV dysfunction.[76-78]. 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.(74) Also, the concomitance of RV dysfunction explains why systemic congestion can predominate over pulmonary congestion in some patients with heart failure due to CCM.(75).

5.1 ***Echocardiography for RV function assessment***

A study assessing RV function in Chagas disease showed prolongation of RV free wall isovolumic contraction time in patients in the indeterminate form of Chagas disease compared to controls.[15] RV free wall isovolumic contraction time was obtained by measuring the interval between the Q wave of the ECG and the beginning of the systolic wave at the tricuspid annulus using tissue Doppler imaging.

In contrast, in a study assessing RV function by longitudinal speckle tracking strain in 78 asymptomatic Chagas disease patients with normal LV function, showed no difference of strain values in patients compared to controls.[68]

Another study in patients with CCM, [76] evaluating qualitatively RV morphology and function by 2D echocardiography found that RV dysfunction was associated with impairment of the LV function. Similarly, a further study reported that RV systolic dysfunction was present only in CCM patients with left-sided HF, as assessed by RV tissue Doppler imaging, longitudinal speckle tracking strain, and tricuspid annular plane systolic excursion. [67]

RV systolic involvement is a marker of Chagas disease severity and represents a strong predictor of mortality. 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 functional class and LV ejection fraction.[77] Other subsequent studies assessing risk stratification in Chagas disease have confirmed the fundamental role of RV function in predicting prognosis.[62, 75, 79] RV function has also been reported to be an important determinant of exercise capacity in CCM.[80] In a study including 65 patients with Chagas heart disease, RV systolic annular velocity by tissue Doppler imaging was associated with peak VO_2, regardless of the influence of age, gender, and LV systolic function[80].

The analysis of RV function by echocardiographic methods has several limitations. Novel echocardiographic techniques, including three-dimensional and 2D speckle-tracking echocardiography seem promising. However, the clinical values of these parameters need to be better established in patients with Chagas disease.

5.2 *Cardiac magnetic resonance*

Cardiac magnetic resonance (CMR) is considered a "gold standard" for RV morphological and functional assessment, especially to calculate RV volumes and ejection fraction. However, previous studies in Chagas disease using CMR have focused on the LV and there are limited data on RV function. In CCM patients with heart failure, CMR showed lower RV ejection fraction with higher end-systolic and end-diastolic volumes in those patients with LV dysfunction compared to those with preserved LV systolic function.[81]

5.3 *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.[73, 74] This particular feature explains why heart failure syndrome in some CCM patients may present more prominent systemic than pulmonary congestion.[78] **(Figure 14)**

Key points

- Early and predominant right ventricular 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
- Limited data are available regarding RV function assessed by CMR in Chagas disease

6. 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 gatthered from several studies pointing to functional and structural microvascular derangements likely to contribute to ventricular dysfunction in Chagas disease. [59]

On the basis of sporadic cases of myocardial infarction occurring in Chagas patients with non-obstructed epicedial coronary arteries, coronary vasospasm has been

postulated to cause such events [82]. 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 [59, 83, 84].

6.1 Stress echocardiography and coronary flow reserve

A study with dipyridamole stress echocardiography showed that coronary flow reserve (CFR) was impaired in Chagas disease patients in indeterminate form compared to controls. [85] **(Figure 15)** The impaired CFR in Chagas disease patients supports the concept that perfusion abnormalities caused by disturbances of coronary blood flow regulation at the microvascular levels may play a role in Chagas disease progression. Wall motion abnormalities have been detected in the posteroinferior wall segments during standard dobutamine stress echocardiography in patients with Chagas disease [86], a finding that supports that myocardial damage in Chagas heart disease may be related to microvascular disturbances. In fact, segmental LV wall motion abnormalities are commonly detected at rest in Chagas heart disease, despite absence of hemodynamically significant obstructions of epicardial coronary arteries.

Key points

- most patients have angiographycally normal coronary arteries but it is uncertain if coronary regulation at the macrovascular level is impaired
- coronary flow reserve may be impaired in the early stages of cardiac involvement
- wall motion abnormalities may be induced during stress in Chagas disease patients despite angiographically normal coronary arteries
- functional and structural abnormalities of coronary microcirculation may contribute to development and progression of ventricular dysfunction in Chagas disease

6.2 *Myocardial Perfusion Scintigraphy*

In patients with CCM, reduced myocardial perfusion, both at rest and during exercise, was first reported by measuring global myocardial flow with the old ^{86}Rubidium method [87, 88]. Regional myocardial perfusion abnormalities in Chagas disease patients with normal coronary arteries have subsequently been confirmed by other independent investigators [89, 90]. These findings were consistent with abnormal flow regulation at the microvascular level **(Figure 16).** Myocardial perfusion defects occur at early stages of Chagas disease at a microvascular level and precede the appearance of regional systolic wall motion abnormalities. [59, 90-93] These data further support the hypothesis that coronary microvascular disturbances may cause ischemic myocardial damage in CCM.

Key points

- 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
- Detection of reversible ischemic defects predicts further deterioration of left ventricular systolic function

7. Myocardial sympathetic innervation

Necropsy studies documented severe cardiac autonomic denervation in CCM, more severe than in other cardiomyopathies [94, 95]. 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 (^{123}I-MIBG) have shown that defects of ^{123}I-MIBG uptake can be documented in the majority (68%) of the patients with Chagas

disease. [59, 92, 96] Of note, ^{123}I-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 ^{123}I-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 17)** 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 ^{123}I-MIBG uptake even in patients with Chagas disease and no apparent cardiac involvement. [97]

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 ^{123}I-MIBG summed score and a higher number of mismatch defects (sympathetic denervation with preserved perfusion) per patient than patients with no arrhythmias.[96] 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 mechanism of malignant ventricular arrhythmias, and that ^{123}I-MIBG imaging may be useful to stratify the risk of sudden cardiac death in Chagas disease.[96]

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 left ventricular dysfunction
- Extent of cardiac sympathetic denervation may be a marker of ventricular arrhythmias with potential for risk stratification of sudden death in Chagas disease

8. 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[98]. Early studies have identified LV dysfunction and specially low ejection fraction obtained by echocardiography as the strongest predictor of death. [34, 45, 61, 62, 79] 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 [79].

The ratio of early transmitral velocity to tissue Doppler mitral annular early diastolic velocity (E/e' ratio), an accepted noninvasive method to estimate LV filling pressures, is also an independent predictor of mortality in patients with CCM.[44, 67, 75]

A previous study showed that the inclusion of the of 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 [79]. However, E/e' ratio appears to have different effects on mortality in the setting of CCM [75]. 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 [75]. Although the underlying mechanism to explain these findings remains to be clarified, it suggests that Chagas disease has some specific features compared to heart failure from other etiologies.

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.[49] 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 **(Figure 18).**[67] Although LA conductive function was depressed in all groups of patients with the cardiac form, LA contractile function was depressed only in those with heart failure.[67]

RV systolic dysfunction is an independent predictor of survival in patients with CCM, adding incremental prognostic value to clinical data and to the severity of LV dysfunction.[77]

In summary, several echocardiographic variables have been associated with increased mortality **(Table 3).** [34, 67, 75, 98-107] 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.[60, 65, 108, 109]

Radionuclide methods may improve risk stratification to define cardiac involvement in Chagas disease in patients with devices precluding cardiac magnetic resonance studies, and to identity perfusion defects and myocardial sympathetic denervation derangements

that are associated with progression of LV dysfunction and appearance of malignant ventricular arrhythmia.[66, 93]

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.

Advantages and disadvantages of each imaging modality in the setting of Chagas disease are shown in **Table 5**. As echocardiography is widely available with relatively low cost, it became the imaging method of choice to evaluate patients with Chagas disease. An algorythm of diagnostic steps in Chagas disease and assessment periodicity is also shown in Panel A (on page 45).

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 edema or fibrosis at CMR can predict future progression to the cardiomyopathy

9. Conclusions and future research

More than a hundred years after its discovery by the Brazilian scientist Carlos Chagas, Chagas disease continues to pose significant burden to affected people, mostly Latin American residents and immigrants to non-endemic areas including Europe, Japan, and the United States. The early mortality and substantial disability caused by this disease 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 two-dimensional 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 edema 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 multicenter 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.

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References

1. Coura JR, Vinas PA. Chagas disease: A new worldwide challenge. *Nature*. 2010;465:S6-7
2. Requena-Mendez A, Aldasoro E, de Lazzari E, Sicuri E, Brown M, Moore DA, et al. Prevalence of chagas disease in latin-american migrants living in europe: A systematic review and meta-analysis. *PLoS neglected tropical diseases*. 2015;9:e0003540
3. Angheben A, Boix L, Buonfrate D, Gobbi F, Bisoffi Z, Pupella S, et al. Chagas disease and transfusion medicine: A perspective from non-endemic countries. *Blood transfusion = Trasfusione del sangue*. 2015;13:540-550
4. Nunes MC, Dones W, Morillo CA, Encina JJ, Ribeiro AL, Council on Chagas Disease of the Interamerican Society of C. Chagas disease: An overview of clinical and epidemiological aspects. *Journal of the American College of Cardiology*. 2013;62:767-776
5. Rassi A, Jr., Rassi A, Little WC. Chagas' heart disease. *Clinical cardiology*. 2000;23:883-889
6. Rassi Jr A, Rassi A, Marin-Neto JA. Chagas heart disease: Pathophysiologic mechanisms, prognostic factors and risk stratification. *Memorias do Instituto Oswaldo Cruz*. 2009;104 Suppl 1:152-158
7. Marin-Neto JA, Cunha-Neto E, Maciel BC, Simoes MV. Pathogenesis of chronic chagas heart disease. *Circulation*. 2007;115:1109-1123
8. Tarleton RL. Parasite persistence in the aetiology of chagas disease. *International journal for parasitology*. 2001;31:550-554
9. Badano LP, Miglioranza MH, Edvardsen T, Colafranceschi AS, Muraru D, Bacal F, et al. European association of cardiovascular imaging/cardiovascular imaging department of the brazilian society of cardiology recommendations for the use of cardiac imaging to assess and follow patients after heart transplantation. *European heart journal cardiovascular Imaging*. 2015;16:919-948
10. Prata A. Clinical and epidemiological aspects of chagas disease. *Lancet Infect Dis*. 2001;1:92-100
11. Botoni FA, Ribeiro AL, Marinho CC, Lima MM, Nunes MD, Rocha MO. Treatment of chagas cardiomyopathy. *Biomed.Res.Int.* 2013;2013:849504
12. Rocha MO, Ribeiro AL, Teixeira MM. Clinical management of chronic chagas cardiomyopathy. *Front Biosci.* 2003;8:e44-e54
13. Ministerio da Saude. Secretaria de Vigilancia em S. [brazilian consensus on chagas disease]. *Revista da Sociedade Brasileira de Medicina Tropical*. 2005;38 Suppl 3:7-29
14. Barros MV, Rocha MO, Ribeiro AL, Machado FS. Doppler tissue imaging to evaluate early myocardium damage in patients with undetermined form of chagas' disease and normal echocardiogram. *Echocardiography*. 2001;18:131-136
15. Barros MV, Machado FS, Ribeiro AL, Da Costa Rocha MO. Detection of early right ventricular dysfunction in chagas' disease using doppler tissue imaging. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*. 2002;15:1197-1201

16. Molina RB, Matsubara BB, Hueb JC, Zanati SG, Meira DA, Cassolato JL, et al. Dysautonomia and ventricular dysfunction in the indeterminate form of chagas disease. *Int.J.Cardiol.* 2006;113:188-193
17. Oliveira E, Ribeiro AL, Assis SF, Torres RM, Rocha MO. The valsalva maneuver in chagas disease patients without cardiopathy. *Int.J.Cardiol.* 2002;82:49-54
18. Rocha AL, Lombardi F, Costa Rocha MO, Barros MV, Val B, V, Reis AM, et al. Chronotropic incompetence and abnormal autonomic modulation in ambulatory chagas disease patients. *Ann.Noninvasive.Electrocardiol.* 2006;11:3-11
19. Coura JR. Chagas disease: What is known and what is needed--a background article. *Mem.Inst.Oswaldo Cruz*. 2007;102 Suppl 1:113-122
20. Ribeiro AL, Rocha MO. [indeterminate form of chagas disease: Considerations about diagnosis and prognosis]. *Rev.Soc.Bras.Med.Trop.* 1998;31:301-314
21. Sabino EC, Ribeiro AL, Salemi VM, Di Lorenzo OC, Antunes AP, Menezes MM, et al. Ten-year incidence of chagas cardiomyopathy among asymptomatic trypanosoma cruzi-seropositive former blood donors. *Circulation*. 2013;127:1105-1115
22. Ribeiro AL, Sabino EC, Marcolino MS, Salemi VM, Ianni BM, Fernandes F, et al. Electrocardiographic abnormalities in trypanosoma cruzi seropositive and seronegative former blood donors. *PLoS neglected tropical diseases*. 2013;7:e2078
23. Ribeiro AL, Marcolino MS, Prineas RJ, Lima-Costa MF. Electrocardiographic abnormalities in elderly chagas disease patients: 10-year follow-up of the bambui cohort study of aging. *Journal of the American Heart Association*. 2014;3:e000632
24. Ribeiro AL, Nunes MP, Teixeira MM, Rocha MO. Diagnosis and management of chagas disease and cardiomyopathy. *Nat Rev Cardiol*. 2012;9:576-589
25. Prata A. Clinical and epidemiological aspects of chagas disease. *Lancet Infect.Dis.* 2001;1:92-100
26. Ribeiro AL, Sabino EC, Marcolino MS, Salemi VM, Ianni BM, Fernandes F, et al. Electrocardiographic abnormalities in trypanosoma cruzi seropositive and seronegative former blood donors. *PLoS.Negl.Trop.Dis.* 2013;7:e2078
27. Barros MV, Rocha MO, Ribeiro AL, Machado FS. Tissue doppler imaging in the evaluation of the regional diastolic function in chagas' disease. *Eur.J.Echocardiogr.* 2001;2:94-99
28. Carrasco HA, Guerrero L, Parada H, Molina C, Vegas E, Chuecos R. Ventricular arrhythmias and left ventricular myocardial function in chronic chagasic patients. *Int.J.Cardiol.* 1990;28:35-41
29. Pereira Nunes Mdo C, Barbosa MM, Ribeiro AL, Amorim Fenelon LM, Rocha MO. Predictors of mortality in patients with dilated cardiomyopathy: Relevance of chagas disease as an etiological factor. *Rev Esp Cardiol*. 2010;63:788-797
30. Freitas HF, Chizzola PR, Paes AT, Lima AC, Mansur AJ. Risk stratification in a brazilian hospital-based cohort of 1220 outpatients with heart failure: Role of chagas' heart disease. *International journal of cardiology*. 2005;102:239-247
31. Lima-Costa MF, Matos DL, Ribeiro AL. Chagas disease predicts 10-year stroke mortality in community-dwelling elderly: The bambui cohort study of aging. *Stroke*. 2010;41:2477-2482
32. Carod-Artal FJ, Gascon J. Chagas disease and stroke. *Lancet Neurol.* 2010;9:533-542
33. Bimbi BJ, Unger P, Vandenbossche JL, Silance PG, Van LY. Chagas disease: Don't forget it in latin american patients with heart block! *Acta Cardiol*. 2014;69:206-208
34. Rassi A, Jr., Rassi A, Little WC, Xavier SS, Rassi SG, Rassi AG, et al. Development and validation of a risk score for predicting death in chagas' heart disease. *The New England journal of medicine*. 2006;355:799-808

35. Ribeiro AL, Cavalvanti PS, Lombardi F, Nunes Mdo C, Barros MV, Rocha MO. Prognostic value of signal-averaged electrocardiogram in chagas disease. *J Cardiovasc Electrophysiol*. 2008;19:502-509
36. Barbosa MP, Carmo AA, Rocha MO, Ribeiro AL. Ventricular arrhythmias in chagas disease. *Rev Soc.Bras.Med.Trop.* 2015;48:4-10
37. Ramirez JD, Guhl F, Umezawa ES, Morillo CA, Rosas F, Marin-Neto JA, et al. Evaluation of adult chronic chagas' heart disease diagnosis by molecular and serological methods. *Journal of clinical microbiology*. 2009;47:3945-3951
38. Otani MM, Vinelli E, Kirchhoff LV, del Pozo A, Sands A, Vercauteren G, et al. Who comparative evaluation of serologic assays for chagas disease. *Transfusion*. 2009;49:1076-1082
39. Camargo ME, Segura EL, Kagan IG, Souza JM, Carvalheiro Jda R, Yanovsky JF, et al. Three years of collaboration on the standardization of chagas' disease serodiagnosis in the americas: An appraisal. *Bulletin of the Pan American Health Organization*. 1986;20:233-244
40. Maguire JH, Hoff R, Sherlock I, Guimaraes AC, Sleigh AC, Ramos NB, et al. Cardiac morbidity and mortality due to chagas' disease: Prospective electrocardiographic study of a brazilian community. *Circulation*. 1987;75:1140-1145
41. Rassi A, Jr., Rassi A, Rassi SG. Predictors of mortality in chronic chagas disease: A systematic review of observational studies. *Circulation*. 2007;115:1101-1108
42. Andrade JP, Marin Neto JA, Paola AA, Vilas-Boas F, Oliveira GM, Bacal F, et al. I latin american guidelines for the diagnosis and treatment of chagas' heart disease: Executive summary. *Arquivos brasileiros de cardiologia*. 2011;96:434-442
43. Barros MV, da Costa Rocha MO, Ribeiro AL, Machado FS. Tissue doppler imaging enables the identification of diastolic dysfunction of pseudonormal pattern in chagas' disease. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*. 2001;14:353-359
44. Barros MV, Machado FS, Ribeiro AL, Rocha MO. Diastolic function in chagas' disease: An echo and tissue doppler imaging study. *Eur J Echocardiogr*. 2004;5:182-188
45. Viotti RJ, Vigliano C, Laucella S, Lococo B, Petti M, Bertocchi G, et al. Value of echocardiography for diagnosis and prognosis of chronic chagas disease cardiomyopathy without heart failure. *Heart*. 2004;90:655-660
46. Pazin-Filho A, Romano MM, Almeida-Filho OC, Furuta MS, Viviani LF, Schmidt A, et al. Minor segmental wall motion abnormalities detected in patients with chagas' disease have adverse prognostic implications. *Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas / Sociedade Brasileira de Biofisica ... [et al.]*. 2006;39:483-487
47. Barros ML, Ribeiro A, Nunes Mdo C, Rocha MO. [association between left ventricular wall motion abnormalities and ventricular arrhythmia in the indeterminate form of chagas disease]. *Revista da Sociedade Brasileira de Medicina Tropical*. 2011;44:213-216
48. Acquatella H. Echocardiography in chagas heart disease. *Circulation*. 2007;115:1124-1131
49. Nunes MC, Barbosa MM, Ribeiro AL, Colosimo EA, Rocha MO. Left atrial volume provides independent prognostic value in patients with chagas cardiomyopathy. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*. 2009;22:82-88
50. Amundsen BH, Helle-Valle T, Edvardsen T, Torp H, Crosby J, Lyseggen E, et al. Noninvasive myocardial strain measurement by speckle tracking echocardiography:

Validation against sonomicrometry and tagged magnetic resonance imaging. *Journal of the American College of Cardiology*. 2006;47:789-793

51. Hasselberg NE, Haugaa KH, Bernard A, Ribe MP, Kongsgaard E, Donal E, et al. Left ventricular markers of mortality and ventricular arrhythmias in heart failure patients with cardiac resynchronization therapy. *European heart journal cardiovascular Imaging*. 2016;17:343-350
52. Gomes VA, Alves GF, Hadlich M, Azevedo CF, Pereira IM, Santos CR, et al. Analysis of regional left ventricular strain in patients with chagas disease and normal left ventricular systolic function. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*. 2016
53. Barros MV, Leren IS, Edvardsen T, Haugaa KH, Carmo AA, Lage TA, et al. Mechanical dispersion assessed by strain echocardiography is associated with malignant arrhythmias in chagas cardiomyopathy. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*. 2016
54. Nunes MC, Barbosa MM, Ribeiro AL, Barbosa FB, Rocha MO. Ischemic cerebrovascular events in patients with chagas cardiomyopathy: A prospective follow-up study. *Journal of the neurological sciences*. 2009;278:96-101
55. Nunes Mdo C, Barbosa MM, Rocha MO. Peculiar aspects of cardiogenic embolism in patients with chagas' cardiomyopathy: A transthoracic and transesophageal echocardiographic study. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*. 2005;18:761-767
56. Carod-Artal FJ, Gascon J. Chagas disease and stroke. *Lancet Neurol*. 2010;9:533-542
57. Nunes MC, Kreuser LJ, Ribeiro AL, Sousa GR, Costa HS, Botoni FA, et al. Prevalence and risk factors of embolic cerebrovascular events associated with chagas heart disease. *Global heart*. 2015;10:151-157
58. Higuchi ML, Fukasawa S, De Brito T, Parzianello LC, Bellotti G, Ramires JA. Different microcirculatory and interstitial matrix patterns in idiopathic dilated cardiomyopathy and chagas' disease: A three dimensional confocal microscopy study. *Heart*. 1999;82:279-285
59. Marin-Neto JA, Simoes MV, Rassi Junior A. Pathogenesis of chronic chagas cardiomyopathy: The role of coronary microvascular derangements. *Revista da Sociedade Brasileira de Medicina Tropical*. 2013;46:536-541
60. Rochitte CE, Oliveira PF, Andrade JM, Ianni BM, Parga JR, Avila LF, et al. Myocardial delayed enhancement by magnetic resonance imaging in patients with chagas' disease: A marker of disease severity. *Journal of the American College of Cardiology*. 2005;46:1553-1558
61. Rassi A, Jr., Rassi A, Rassi SG. Predictors of mortality in chronic chagas disease: A systematic review of observational studies. *Circulation*. 2007;115:1101-1108
62. Nunes MC, Carmo AA, Rocha MO, Ribeiro AL. Mortality prediction in chagas heart disease. *Expert Rev Cardiovasc Ther*. 2012;10:1173-1184
63. Rochitte CE, Nacif MS, de Oliveira Junior AC, Siqueira-Batista R, Marchiori E, Uellendahl M, et al. Cardiac magnetic resonance in chagas' disease. *Artif Organs*. 2007;31:259-267
64. Regueiro A, Garcia-Alvarez A, Sitges M, Ortiz-Perez JT, De Caralt MT, Pinazo MJ, et al. Myocardial involvement in chagas disease: Insights from cardiac magnetic resonance. *Int J Cardiol*. 2013;165:107-112
65. Mello RP, Szarf G, Schvartzman PR, Nakano EM, Espinosa MM, Szejnfeld D, et al. Delayed enhancement cardiac magnetic resonance imaging can identify the risk for ventricular tachycardia in chronic chagas' heart disease. *Arquivos brasileiros de cardiologia*. 2012;98:421-430

66. Marin-Neto JA, Romano MMD, Maciel BC, Simões MV, Schmidt A. Cardiac imaging in latin america: Chagas heart disease. *Current Cardiovascular Imaging Reports*. 2015;8:1-15
67. Nascimento CA, Gomes VA, Silva SK, Santos CR, Chambela MC, Madeira FS, et al. Left atrial and left ventricular diastolic function in chronic chagas disease. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*. 2013;26:1424-1433
68. Barbosa MM, Costa Rocha MO, Vidigal DF, Bicalho Carneiro Rde C, Araujo RD, Palma MC, et al. Early detection of left ventricular contractility abnormalities by two-dimensional speckle tracking strain in chagas' disease. *Echocardiography*. 2014;31:623-630
69. Pazin-Filho A, Romano MM, Gomes Furtado R, de Almeida Filho OC, Schmidt A, Marin-Neto JA, et al. Left ventricular global performance and diastolic function in indeterminate and cardiac forms of chagas' disease. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*. 2007;20:1338-1343
70. Barbosa MM, Nunes Mdo C, Ribeiro AL, Barral MM, Rocha MO. N-terminal probnp levels in patients with chagas disease: A marker of systolic and diastolic dysfunction of the left ventricle. *Eur J Echocardiogr*. 2007;8:204-212
71. Oliveira BM, Botoni FA, Ribeiro AL, Pinto AS, Reis AM, Nunes Mdo C, et al. Correlation between bnp levels and doppler echocardiographic parameters of left ventricle filling pressure in patients with chagasic cardiomyopathy. *Echocardiography*. 2009;26:521-527
72. Garcia-Alvarez A, Sitges M, Pinazo MJ, Regueiro-Cueva A, Posada E, Poyatos S, et al. Chagas cardiomyopathy: The potential of diastolic dysfunction and brain natriuretic peptide in the early identification of cardiac damage. *PLoS neglected tropical diseases*. 2010;4
73. Marin-Neto JA, Marzullo P, Sousa AC, Marcassa C, Maciel BC, Iazigi N, et al. Radionuclide angiographic evidence for early predominant right ventricular involvement in patients with chagas' disease. *Can J Cardiol*. 1988;4:231-236
74. Marin-Neto JA, Bromberg-Marin G, Pazin-Filho A, Simoes MV, Maciel BC. Cardiac autonomic impairment and early myocardial damage involving the right ventricle are independent phenomena in chagas' disease. *International journal of cardiology*. 1998;65:261-269
75. Nunes MP, Colosimo EA, Reis RC, Barbosa MM, da Silva JL, Barbosa F, et al. Different prognostic impact of the tissue doppler-derived e/e' ratio on mortality in chagas cardiomyopathy patients with heart failure. *J Heart Lung Transplant*. 2012
76. Nunes Mdo C, Barbosa Mde M, Brum VA, Rocha MO. Morphofunctional characteristics of the right ventricle in chagas' dilated cardiomyopathy. *International journal of cardiology*. 2004;94:79-85
77. Nunes Mdo C, Rocha MO, Ribeiro AL, Colosimo EA, Rezende RA, Carmo GA, et al. Right ventricular dysfunction is an independent predictor of survival in patients with dilated chronic chagas' cardiomyopathy. *International journal of cardiology*. 2008;127:372-379
78. Marin-Neto JA, Andrade ZA. [why is there predominance of right heart failure in chagas' disease?]. *Arquivos brasileiros de cardiologia*. 1991;57:181-183
79. Nunes MC, Reis RC, Colosimo EA, Ribeiro AL, Barbosa FB, da Silva JL, et al. Risk estimation approach in chagas disease is still needed. *International journal of cardiology*. 2011;147:294-296

80. Nunes Mdo C, Beloti FR, Lima MM, Barbosa MM, Pinto Filho MM, de Barros MV, et al. Functional capacity and right ventricular function in patients with chagas heart disease. *Eur J Echocardiogr*. 2010;11:590-595
81. Abstracts of the 2015 scmr/eurocmr joint scientific sessions, february 4-7, 2015, nice, france. *Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance*. 2015;17 Suppl 1:M1-W36
82. Vianna LG, Campos GP, de Magalhaes AV. [myocardial infarct without coronary obstruction associated with chronic chagas cardiopathy]. *Arquivos brasileiros de cardiologia*. 1979;33:41-47
83. Torres FW, Acquatella H, Condado JA, Dinsmore R, Palacios IF. Coronary vascular reactivity is abnormal in patients with chagas' heart disease. *American heart journal*. 1995;129:995-1001
84. Marin-Neto JA, Simoes MV, Ayres-Neto EM, Attab-Santos JL, Gallo L, Jr., Amorim DS, et al. Studies of the coronary circulation in chagas' heart disease. *Sao Paulo medical journal = Revista paulista de medicina*. 1995;113:826-834
85. Rabelo DR, Rocha MO, de Barros MV, Silva JL, Tan TC, Nunes MC. Impaired coronary flow reserve in patients with indeterminate form of chagas' disease. *Echocardiography*. 2014;31:67-73
86. Acquatella H, Perez JE, Condado JA, Sanchez I. Limited myocardial contractile reserve and chronotropic incompetence in patients with chronic chagas' disease: Assessment by dobutamine stress echocardiography. *Journal of the American College of Cardiology*. 1999;33:522-529
87. Kuschnir E, Kustich F, E[elman M, Santamarina N, Podio RB. Valoration de fluxo miocardico con rb 86 en pacientes con cardiopatia chagasica con insuficiencia coronaria y en controles normales. Parte 1: Estudios basales. *Arquivos brasileiros de cardiologia*. 1974;27:9
88. Kuschnir E, Kustich F, Epelman M, Santamarina N, Podio RB. Valoration de fluxo miocardico con rb 86 en pacientes con cardiopatia chagasica con insuficiencia coronaria y en controles normales. Parte 2: Respuesta al ejercicio y a la cardiotonificacion aguda. *Arquivos brasileiros de cardiologia*. 1974;27:11
89. Hagar JM, Rahimtoola SH. Chagas' heart disease in the united states. *The New England journal of medicine*. 1991;325:763-768
90. Marin-Neto JA, Marzullo P, Marcassa C, Gallo Junior L, Maciel BC, Bellina CR, et al. Myocardial perfusion abnormalities in chronic chagas' disease as detected by thallium-201 scintigraphy. *The American journal of cardiology*. 1992;69:780-784
91. Peix A, Garcia R, Sanchez J, Cabrera LO, Padron K, Vedia O, et al. Myocardial perfusion imaging and cardiac involvement in the indeterminate phase of chagas disease. *Arquivos brasileiros de cardiologia*. 2013;100:114-117
92. Simoes MV, Pintya AO, Bromberg-Marin G, Sarabanda AV, Antloga CM, Pazin-Filho A, et al. Relation of regional sympathetic denervation and myocardial perfusion disturbance to wall motion impairment in chagas' cardiomyopathy. *The American journal of cardiology*. 2000;86:975-981
93. Hiss FC, Lascala TF, Maciel BC, Marin-Neto JA, Simoes MV. Changes in myocardial perfusion correlate with deterioration of left ventricular systolic function in chronic chagas' cardiomyopathy. *JACC. Cardiovascular imaging*. 2009;2:164-172
94. Mott KE, Hagstrom JW. The pathologic lesions of the cardiac autonomic nervous system in chronic chagas' myocarditis. *Circulation*. 1965;31:273-286
95. Köberle F. Pathogenesis of chagas' disease. *Ciba Found Symp*. 1974;20:21
96. Miranda CH, Figueiredo AB, Maciel BC, Marin-Neto JA, Simoes MV. Sustained ventricular tachycardia is associated with regional myocardial sympathetic denervation

assessed with 123i-metaiodobenzylguanidine in chronic chagas cardiomyopathy. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*. 2011;52:504-510

97. Landesmann MC, da Fonseca LM, de BPB, do Nascimento EM, Rosado-de-Castro PH, de Souza SA, et al. Iodine-123 metaiodobenzylguanidine cardiac imaging as a method to detect early sympathetic neuronal dysfunction in chagasic patients with normal or borderline electrocardiogram and preserved ventricular function. *Clin Nucl Med*. 2011;36:757-761
98. Pereira Junior Cde B, Markman Filho B. Clinical and echocardiographic predictors of mortality in chagasic cardiomyopathy--systematic review. *Arquivos brasileiros de cardiologia*. 2014;102:602-610
99. Viotti R, Vigliano C, Lococo B, Petti M, Bertocchi G, Alvarez MG, et al. [clinical predictors of chronic chagasic myocarditis progression]. *Rev Esp Cardiol*. 2005;58:1037-1044
100. Benchimol Barbosa PR. Noninvasive prognostic markers for cardiac death and ventricular arrhythmia in long-term follow-up of subjects with chronic chagas' disease. *Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas / Sociedade Brasileira de Biofisica ... [et al.]*. 2007;40:167-178
101. Theodoropoulos TA, Bestetti RB, Otaviano AP, Cordeiro JA, Rodrigues VC, Silva AC. Predictors of all-cause mortality in chronic chagas' heart disease in the current era of heart failure therapy. *International journal of cardiology*. 2008;128:22-29
102. Issa VS, Amaral AF, Cruz FD, Ferreira SM, Guimaraes GV, Chizzola PR, et al. Beta-blocker therapy and mortality of patients with chagas cardiomyopathy: A subanalysis of the remadhe prospective trial. *Circ Heart Fail*. 2010;3:82-88
103. Sarabanda AV, Marin-Neto JA. Predictors of mortality in patients with chagas' cardiomyopathy and ventricular tachycardia not treated with implantable cardioverter-defibrillators. *Pacing and clinical electrophysiology : PACE*. 2011;34:54-62
104. Ribeiro AL, Rocha MO, Terranova P, Cesarano M, Nunes MD, Lombardi F. T-wave amplitude variability and the risk of death in chagas disease. *J Cardiovasc Electrophysiol*. 2011;22:799-805
105. Bestetti RB, Otaviano AP, Cardinalli-Neto A, da Rocha BF, Theodoropoulos TA, Cordeiro JA. Effects of b-blockers on outcome of patients with chagas' cardiomyopathy with chronic heart failure. *International journal of cardiology*. 2011;151:205-208
106. Duarte Jde O, Magalhaes LP, Santana OO, Silva LB, Simoes M, Azevedo DO, et al. Prevalence and prognostic value of ventricular dyssynchrony in chagas cardiomyopathy. *Arquivos brasileiros de cardiologia*. 2011;96:300-306
107. Rassi Ddo C, Vieira ML, Arruda AL, Hotta VT, Furtado RG, Rassi DT, et al. Echocardiographic parameters and survival in chagas heart disease with severe systolic dysfunction. *Arquivos brasileiros de cardiologia*. 2014;102:245-252
108. Uellendahl M, Siqueira ME, Calado EB, Kalil-Filho R, Sobral D, Ribeiro C, et al. Cardiac magnetic resonance-verified myocardial fibrosis in chagas disease: Clinical correlates and risk stratification. *Arquivos brasileiros de cardiologia*. 2016;107:460-466
109. Torreao JA, Ianni BM, Mady C, Naia E, Rassi CH, Nomura C, et al. Myocardial tissue characterization in chagas' heart disease by cardiovascular magnetic resonance. *Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance*. 2015;17:97
110. Dias JC, Ramos AN, Jr., Gontijo ED, Luquetti A, Shikanai-Yasuda MA, Coura JR, et al. 2 nd brazilian consensus on chagas disease, 2015. *Revista da Sociedade Brasileira de Medicina Tropical*. 2016;49Suppl 1:3-60

TABLES

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.

Reference number: 42

Table 2: Score for predicting all-cause mortality in Chagas disease (Rassi's score) [34]

Predictors			**Points**
New York Heart Association class III or IV			5
Cardiomegaly (chest x-ray)			5
Segmental or global wall motion abnormality (echo)			3
Nonsustained ventricular tachycardia (24h 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

Table 3: Echocardiographic predictors of outcomes in Chagas disease

Author/year	Nº of patients	Characteristics of Chagas disease patients	Follow-up duration	Outcomes	Echocardiography predictive variables*	Other prognostic factors
Viotti (2005)[99]	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 benznidazole treatment
Rassi Jr. (2006)[34]	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 (2007)[100]	50	Indeterminate form and heart disease	84.2 ± 39 m	Cardiac death or documented ventricular tachycardia	Apical aneurysm and LVEF	Isolated PVC count
Theodoropoulos (2008)[101]	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 (2010)[102] †	68	Irreversible chronic heart failure	1326 ± 39 d	Death or heart transplant	LV end-diastolic diameter	BB therapy
Sarabanda (2011)[103]	56	Heart disease with either sustained VT or NSVT	38 ± 16 m	All cause-mortality and sudden death	LVEF < 40%	None
Ribeiro (2011)[104]	113	Indeterminate form and heart disease	106 ± 28 m	Cardiovascular death	LVEF	T-wave variability, NSVT and QSR > 130 ms
Bestetti (2011)[105]	231	Chronic heart failure	19 m	Death or heart transplant	LV end-systolic diameter	No BB therapy and inotropic support
Duarte (2011)[106]	56	Dilated cardiomyopathy	21 ± 14 m	Death or hospitalizaton	Rassi's score	LV dyssynchrony was not associated with events
Nunes (2012)[75]	232	Dilated cardiomyopathy	3.4 y	Death or heart transplant	LVEF, RVMPI, LA volume and E/e' ratio	NYHA class
Nascimento (2013)[67]	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
Carmo Rassi (2014)[107]	60	Heart failure with severe LV systolic dysfunction	24 m	Cardiovascular death	Indexed LA volume	None

*multivariate analysis

†Clinical trial; 456 patients with heart failure were enrolled, and Chagas cardiomyopathy was present in 68 patients. 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 = nonsustained ventricular tachycardia, VT = ventricular tachycardia, Y = years

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

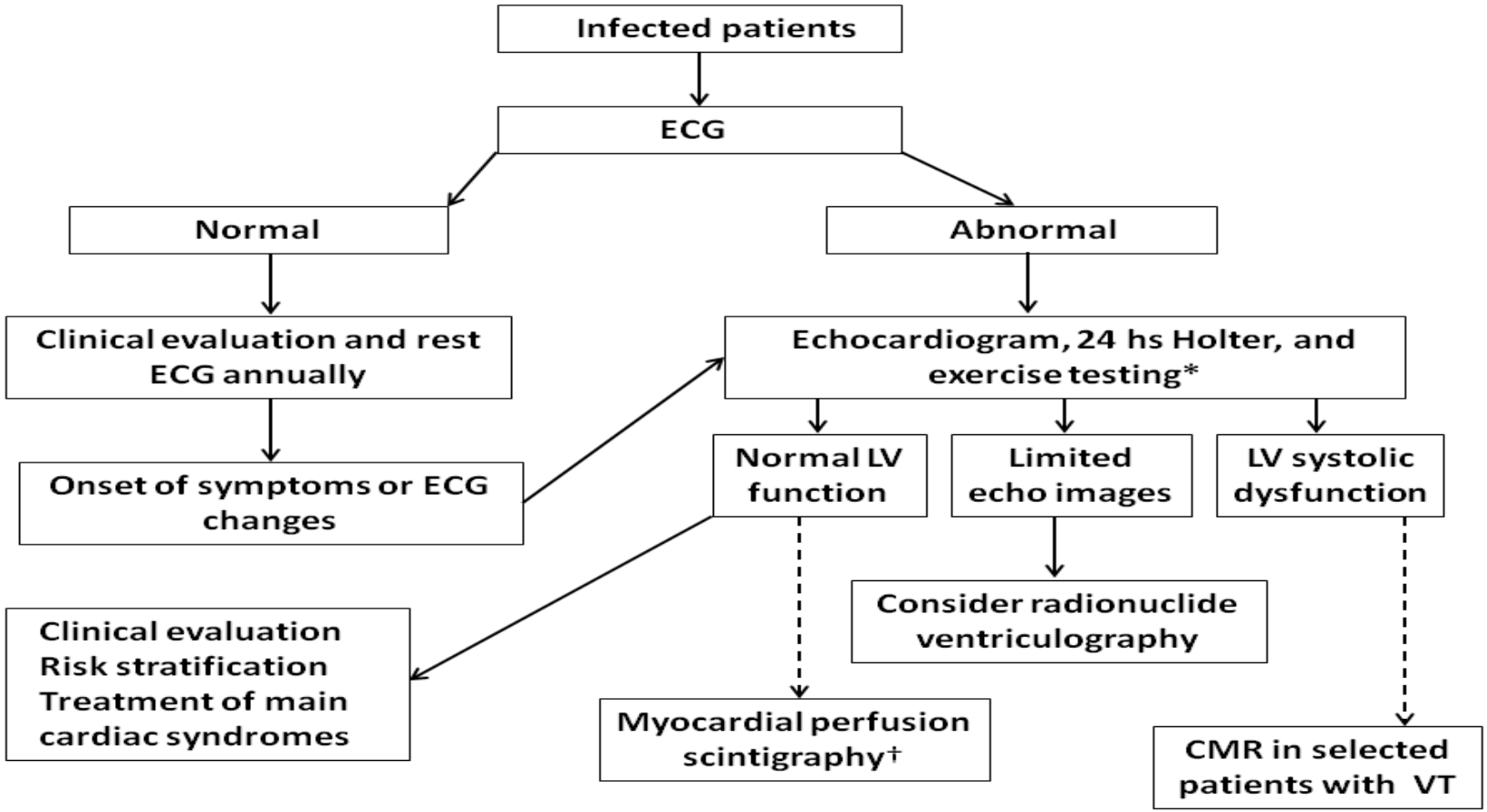
Epidemiological profile	Individuals who were born in, or have lived in endemic areas or a child of a mother from endemic country.
Clinical features	Cardiac rhythm disorders, heart failure, thromboembolic events, chest pain without evidence of epicardial coronary artery disease. Association with megaoesophagus 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.
Cardiac magnetic resonance (CMR) and nuclear imaging methods	Myocardial fibrosis, regional myocardial perfusion defects and sympathetic denervation.

Table 5: Advantages and disadvantages of each imaging modality in Chagas disease

Imaging modality	**Advantages**	**Disadvantages**
Echocardiography	- Widely available, relatively low cost, potentially portable - Allows evaluation of global and regional left ventricular systolic function, diastolic function, right ventricular involvement, atrioventricular valve regurgitation, recognition of intracardiac thrombus, and ventricular aneurysms - Sensitive to mild cardiac involvement, may detect cardiac involvement even in those with normal ECG - Many studies showing that can predict progression of the disease, risk of malignant arrhythmias and death - Speckle tracking longitudinal strain and 3D echocardiography is superior to conventional echo to assess more accurately and reproducibly left ventricular systolic function	- Relatively low reproducibility of measurements - Highly dependent on the expertise of the examiner
Cardiac magnetic resonance	- Allows full evaluation of cardiac structure and function, including most aspects covered by the echo - Allows non-invasive tissue characterization, including myocardial edema and fibrosis - Very sensitive to early cardiac involvement - Predictive of severe ventricular arrhythmias, heart failure, and sudden death	- Not widely available in endemic regions, high cost, non-portable - Highly specialized personnel required - Limited data on right ventricular function available - Limited data on the predictive value for progression of the disease and death
Radionuclide ventriculography	- Alternative method for global biventricular function assessment, as well as the recognition of ventricular aneurysms	- Not widely available, high cost, non-portable - Highly specialized personnel required - No information about the cardiac muscle/walls
Stress echocardiography	- May detect stress-induced wall motion abnormalities and impaired coronary flow reserve early in the indeterminate form, in the absence of angiographic coronary artery disease	- Uncertain clinical value of the findings - Dependent of examiner with high expertise

Myocardial Perfusion Scintigraphy	- May detect cardiac perfusion abnormalities with normal coronary arteries, early in the indeterminate form, that can predict the presence of fibrosis and the deterioration of LV function	- Not widely available in endemic regions, high cost, non-portable - Highly specialized personnel required - Limited data on the predictive value for progression of the disease and death
Myocardial sympathetic innervation	- May detect early sympathetic denervation in the indeterminate form - may be a marker of ventricular arrhythmias with potential for risk stratification of sudden death	- Not widely available in endemic regions, high cost, non-portable - Highly specialized personnel required - Not routinely available in most centers

Panel A: Diagnostic flow chart and suggested periodicity of assessment [110]



*Echocardiography should be repeated every 3 to 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. 24 hs Holter monitor is specially recommendaded 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 arrythmia; 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.

† It 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.