Abstract

Chagas disease (CD) is a neglected tropical disease (NTD) caused by *Trypanosoma cruzi*, a hemoflagellate protozoa. CD is diagnosed by epidemiologic history and two positive serological tests. The infection has two main clinical phases: acute, early after acquiring the infection, and chronic. The electrocardiogram (ECG) is the first tool to diagnose chronic Chagas heart disease (CCD) after CD serological diagnosis. In addition, the different cardiac imaging modalities, including chest X-ray, echocardiography, single photon emission computed tomography (SPECT), computed tomography (CT), and magnetic resonance, play a crucial role in detecting the cardiac involvement, establishing the prognosis, stratifying patient risk, and addressing the management of CD patients. In this review of the current literature, we summarize the epidemiology, pathophysiology, and clinical presentation of CD. We also discuss the indications, advantages, and limitations of the different cardiac imaging modalities. We also present some case examples, where cardiac imaging proved helpful in cardiac CD (CCD). The early mortality and substantial disability caused by CD represents a health, social and economic burden, particularly in the Latin America. To harness the full potential of medical imaging for the effective management of patients with CD, a comprehensive approach is essential. This involves a concerted effort to invest in the education of medical providers and to facilitate widespread access to diagnostic tools. Accessible and timely diagnosis is crucial for initiating prompt and targeted interventions. Finally, continuous investment in research is vital to advance our understanding of CD and develop innovative solutions for improved patient care.

Introduction

Chagas disease (CD), caused by *Trypanosoma cruzi* (*T. cruzi*), was first described by Dr. Carlos Justiniano Oswaldo Ribeiro das Chagas in 1909. The World Health Organization (WHO) defined CD as a “Neglected Tropical Disease” (NTD). By 2025, it is estimated that approximately 200,000 global cardiovascular deaths will be caused by CD. The main transmission route in endemic zones is vectorial, although the non-vectorial ways including blood transfusion, mother-to-child, food-borne, contamination and organ transplantation should also be considered.

CD is diagnosed by epidemiologic history and two positive serological tests. The infection has two main clinical phases: acute and chronic. Approximately 70% to 80% of individuals with chronic CD remain asymptomatic, while 20% to 30% develop cardiac and/or gastrointestinal disease.

The electrocardiogram (ECG) is the first diagnostic tool to consider for clinical diagnosis since the earliest signs of cardiac CD (CCD) are generally conduction system disorders and/or ventricular arrhythmias. In addition, the different cardiac imaging modalities: chest X-ray, echocardiography, nuclear medicine, computed...
Tomography (CT), and cardiac magnetic resonance (CMR) play an essential role in the diagnosis and management of CD. Thus, in the present multimodality imaging era, and considering that CCD is a NTD, more prevalent in low-and-middle income countries (LMICs) with limited resources, it is mandatory to wisely use the different imaging tools in the best possible way, considering the characteristics of the individual patient.

To harness the full potential of medical imaging for the effective management of patients with CD, a comprehensive approach is essential. This involves a concerted effort to invest in the education of medical providers. Moreover, facilitating widespread access to diagnostic tools, particularly medical imaging modalities, is imperative. Accessible and timely diagnosis is crucial for providing prompt and targeted interventions, thereby enhancing patient outcomes. Finally, continuous investment in research is vital to advance our understanding of CD, refine imaging modalities and develop innovative solutions for improved patient care.

In this review of the literature, we summarize the main characteristics of CCD regarding epidemiology, pathophysiology and clinical presentation. We also review the indications, advantages, and limitations of cardiac imaging techniques in these patients. We further present some clinical cases where cardiac imaging proved helpful in patients with CCD.

### Methods

We conducted a narrative review of articles on CD published on PubMed, SciELO, NCBI, Science Direct, and Embase databases over the last 20 years.

### Epidemiology

Although CD is endemic to Central and South America, patients are also living in non-endemic zones. It has been estimated that around 6–8 million people are infected globally, 65–100 million are at risk of infection, and there are 28,000 new cases annually. Specifically, CCD is the cause of 10,000–14,000 deaths per year. Disease burden of CD, measured by disability-adjusted life years (DALYs), is 7.5 times higher than malaria, which has the highest disease burden among parasitic diseases in the Western Hemisphere.

Regarding the economic impact of CD, Lee et al. reported that the disease reduces 0.51 DALYs, with an individual cost of 474 USD annually. It accounts for over 627 thousand USD in healthcare expenditures and a loss of 382,250 DALYs worldwide.

The loss of DALYs and the socioeconomic impact of CD are caused by incomplete diagnosis and clinical follow-up; lack of funding and access to health care; insufficient knowledge about CD by primary care
physicians and even by cardiologists from non-endemic countries; shortage of financial resources for education and research; as well as inadequate diagnostic tools and treatment.

Pathophysiology

The pathophysiology of the cardiac damage in CD is complex and involves several mechanisms that lead to inflammation, cell death and fibrosis, including damage to the conduction tissue and categorized into: 1) parasite persistence-dependent myocardial damage, with related myocarditis; 2) parasite-driven adverse immune response; 3) neurogenic disorders, and 4) microvascular disturbances causing myocardial ischemia with normal epicardial coronary arteries. Myocardial inflammation, necrosis and fibrosis may result in left ventricular (LV) segmental wall motion abnormalities and congestive heart failure.

The risk of sudden cardiac death (SCD) in CCD patients is increased by the presence of severe ventricular dysfunction and malignant ventricular arrhythmias. Reentrant circuits initiating from areas with heterogeneous distribution of electrically inert scar tissue surrounded by gray zones with normal cardiomyocytes are linked to the appearance of ventricular tachyarrhythmia. In addition, the loss of neuronal cells of the cardiac autonomic nervous system, mainly parasympathetic, can also contribute to SCD.

Clinical scenario

CD presents in three clinical phases: acute, indeterminate (or chronic without overt disease), and chronic. The acute phase appears after an incubation period of 1-2 weeks and lasts 6-8 weeks. Clinical presentation may vary from asymptomatic to non-specific symptoms and signs such as fever, discomfort, muscle pain, hepatosplenomegaly, anorexia, vomiting, diarrhea, Romániga sign and chagoma at the infection site. Meningoencephalitis and myocarditis can occur in less than 1% of patients with severe disease.

Generally, the acute phase resolves spontaneously in few weeks or months. Sixty to seventy percent of patients may be cured with early specific antiparasitic treatment. After the acute phase, most individuals with the infection pass through a long stage of the disease called the indeterminate form (or chronic without overt disease), that is generally without symptoms or signs of cardiac or gastrointestinal tract involvement. In the indeterminate form, patients are seropositive for T. cruzi and, despite normal ECG and chest X-ray findings, that 25- 30% of chagasic patients in this phase have some degree of heart damage.

Less than half of patients develop the cardiac and/or gastrointestinal involvement that characterizes the chronic stage of CD years after the acute and indeterminate phases, with unnoticeable parasitemia levels. Genetic predisposition, geographical area (endemic areas), type of infection, immunosuppression status, concomitant chronic diseases, and other factors like age, male sex, alcoholism, persistence of high parasitemia, and severity of the disease in the acute phase have been associated with disease progression.

To identify predictors of the development of cardiac and digestive disorders in CD, Nunes da Costa et al. studied 379 CD patients and found that cardiac damage was positively associated with previous coronary syndrome (hazard ratio [HR], 2.42; 95% confidence interval [CI], 1.53–3.81), and were negatively associated with Benznidazole therapy (HR, 0.26; 95%CI, 0.11–0.60). Female gender was the only independent predictor of progression to the gastrointestinal form (HR, 1.56; 95%CI, 1.03–2.38); 15-20% of patients may develop dilatation of the gastrointestinal tract, mainly the esophagus and colon.

Chronic Chagas cardiomyopathy (CCCM) affects approximately 20-30% of infected individuals. It develops in a segmental pattern, causing dilated cardiomyopathy, thromboembolic phenomena (both systemic and pulmonary), and arrhythmias that may lead to SCD. Fifty to 65% of the CD deaths are due to SCD, 25% to 30% are caused by heart failure, and 10% to 15% by thromboembolic phenomena.

According to the Latin American guidelines for diagnosing and treating Chagas heart disease (Table 1), cardiovascular involvement in the chronic phase of CD can be classified according to the presence of ventricular dysfunction and heart failure symptoms. CCCM is characterized by more intense and extensive inflammation and fibrosis, autonomic dysfunction, higher frequency of atrioventricular and intraventricular blockage, multifocal ventricular extrasystoles. It is also marked by autoimmunity with production of antibodies against myocytes, beta-adrenergic receptors, and neurons, in comparison with other dilated cardiomyopathies.

Atypical angina pectoris, often unrelated to exertion
and unresponsive to nitrates, is common in patients with CCD. This occurs even in the presence of transient or definite ST-T changes on ECG, abnormal Q waves, and segmental LV wall motion abnormalities, mimicking coronary artery disease (CAD). However, there is no significant epicardial obstructive CAD. Microvascular disturbances and inflammation have been suggested as possible explanations.

Patients with Chagas heart disease have a worse prognosis than other cardiomyopathies. Male gender has been associated with higher mortality rates. Assunção et al., in a study including 62 Chagas heart disease patients, found that heart failure symptoms were significantly more frequent and severe among male than female patients (54% vs. 29% New York Heart Association [NYHA] class > I, p = 0.04). In addition, LV and right ventricular (RV) remodeling were also more pronounced in males, who showed significantly higher LV / RV dilation, LV mass, and lower LV/RV ejection fraction than females.

**Diagnosis / Multimodality Imaging**

Diagnosis of CD is made by detecting the parasite in the acute phase, with high levels of parasitemia by one of three methods: direct (confirmation of the presence of *T. cruzi*), indirect methods, and molecular tests. In the chronic phase, parasitemia is low and, consequently, the most effective diagnostic methods involve identifying antibodies against the etiologic agent. At least two serological methods must be used to confirm the diagnosis. The most used are enzyme-linked immunosorbent assay, indirect immunofluorescence, and indirect hemagglutination. An adequate follow-up allows the identification of those patients who develop CCD. Electrocardiographic changes, often right bundle branch block (RBBB) with or without left anterior hemiblock, indicate the transition from the indeterminate to the chronic cardiac form.

Chagas cardiomyopathy is usually considered a dilated cardiomyopathy. However, the typical distribution of fibrosis to the LV posterior, apicolateral, and apical regions, and the involvement of the sinus node and electric conduction system help distinguish it from other cardiomyopathies.

**ECG**

The more frequent ECG alterations are RBBB, left anterior fascicle block (LAFB), non-sustained ventricular tachycardia (VT), atrioventricular block of variable degree, sinus bradycardia, atrial fibrillation (AF), and changes in the ST segment and T-wave.

**24h Holter**

When available, 24-h Holter monitoring is recommended in the first evaluation of all patients with the cardiac form of CD and whenever new symptoms suggestive of cardiac arrhythmias appear. This recording helps to detect an increased risk of SCD and unmask signs of autonomic dysfunction, such as a reduced heart rate variability.

**Chest X-ray**

Cardiomegaly with enlargement of the right and left heart chambers may appear in advanced stages of CD, but pulmonary congestion is usually mild or absent.

**Exercise test**

When available, an exercise test should be performed to detect ventricular arrhythmias, assess functional capacity, and evaluate the autonomic dysfunction through the chronotropic response and heart rate in the first minute of recovery. It is also possible to assess ST changes in differential diagnosis in patients with chest pain to exclude CAD. However, it is important to consider that ECG-based methods for detecting
myocardial ischemia are of limited value in the general population with CD presenting with precordial pain, due to the high prevalence of baseline ST changes.

**Echocardiogram**

The echocardiogram is the most used imaging modality for diagnosing and following-up CD patients due to its wide availability and information on ventricular function. Three-dimensional echocardiography can quantify LV volumes and function more accurately, as no geometric assumptions are required. Regional strain is beneficial in CCD due to the segmental myocardial pattern of damage, mainly for recognition of subclinical myocardial dysfunction during the indeterminate phase. The most frequent findings in the acute phase of CD are pericardial effusion and wall motion alterations due to myocarditis.

Segmental wall motion abnormalities (from hypokinesia to aneurysm formation) can be seen since the early stages of the chronic phase, mainly in the apex and in basal segments of the inferior and inferolateral wall. LV apical aneurysm is a pathognomonic finding of CCD, frequently associated with intraventricular mural thrombi. LV diastolic dysfunction can also occur, even in asymptomatic forms of the chronic disease, with a prevalence of up to 10%. LV systolic dysfunction predicts mortality in CCC. The early impairment of RV function and consequent cardiac failure causes a predominant systemic congestion.

The “Recommendations for Multimodality Cardiac Imaging in patients with CD: A Report from the American Society of Echocardiography in Collaboration With the InterAmerican Association of Echocardiography (ECOSIAC) and the Cardiovascular Imaging Department of the Brazilian Society of Cardiology (DIC-SBC)” advised that in patients with CD:

- ECG and echocardiogram should be performed as part of the initial evaluation of all patients with newly diagnosed CD to exclude LV dysfunction, aneurysms, and conduction abnormalities or arrhythmias;
- ECG follow-up is reasonable every two to five years in the indeterminate form.
- Echocardiography should be performed if any changes in ECG findings or clinical condition suggesting possible HF are noted.

**CMR Imaging**

CMR provides very accurate and reproducible information of the LV and RV function, with high spatial resolution, and not dependent on geometric assumptions. It can identify myocardial fibrosis using late gadolinium enhancement (LGE). LV apical aneurysms can be detected in 20–28% of CCD patients on CMR, with no sex-based difference.

CMR allows to identify the consequences of inflammation due to cardiac cell injury caused by T. cruzi and its related immune reactions using T2-weighted and LGE sequences for detecting myocarditis.

Up to 20% of asymptomatic chronic-stage patients without LV segmental motion abnormalities have signs of fibrosis on CMR, whose extent relates to the severity of LV systolic dysfunction and the presence of ventricular arrhythmias, and may contribute to the indication for implantable cardioverter defibrillator (ICD) in patients with CCC. LGE can be transmural (44%), intramyocardial (32%), subendocardial (11%), epicardial (11%), or subepicardial, mainly affecting the inferolateral wall and apex.

Other findings throughout all phases of CCD are myocardial edema (increase in T2-weighted -T2W-myocardial signal intensity) and hyperemia (T1-weighted myocardial early gadolinium enhancement –MEGE), similar to myocardial fibrosis (LGE) in extent and location and also associated with the clinical severity. It has been suggested that CD patients in the indeterminate phase of the disease may have myocardial fibrosis and T2W in such a low degree that does not lead to myocardial dysfunction or remodeling and cannot be detected by echocardiogram. Figure 1 (Case 1) shows an example of a patient living in an endemic zone of CD in whom the multimodality (echo and CMR) allowed the diagnosis, which was later confirmed by the serological test.

CMR confirms the tendency for more extensive disease in men. Assunção et al. found a strong negative correlation between LV ejection fraction (LVEF) and myocardial fibrosis (male $r = 0.64$, female $r = 0.73$, both $p < 0.001$) in 62 seropositive Chagas heart disease patients. Males developed greater myocardial fibrosis ($p = 0.002$) and lower LVEF ($p < 0.001$) than females, with more frequent transmural (23.6 vs. 9.9%, $p < 0.001$), subepicardial (14.1 vs. 9.2%, $p = 0.02$) and midwall patterns (23.8 vs. 15%, $p < 0.001$) of myocardial fibrosis.

Although myocardial fibrosis was similarly prevalent in female and male patients (87% vs. 71%, $p = 0.21$), the
amount was significantly higher in males. Furthermore, in both sexes, fibrosis distribution was similarly frequent in lateral and inferior LV segments, but significantly higher in the septal and apical segments in male patients.\(^{29}\)

**Nuclear cardiology**

**Multigated Acquisition (MUGA) scan**

MUGA scan acquisition and processing are reproducible, providing more precise information on ventricular function in patients with CD than echo. In contrast to M-mode and 2D echo, MUGA averages hundreds of cardiac cycles and does not depend on geometric assumptions for LVEF calculation. In addition, it is possible to quantify RV function and to assess ventricular dyssynchrony.\(^{42}\) It helps determine biventricular systolic function in patients with poor acoustic windows and a contraindication for CMR. Figure 2 (Case 2) presents a patient with heart failure and a diagnosis of CD, who was studied with echo and nuclear imaging, as an example of the value of nuclear techniques in these cases.

**Myocardial Perfusion Image (MPI)**

In CCD, MPI with Single-Photon Emission Computed Tomography (SPECT) can show not only fixed perfusion defects, associated with areas of fibrosis and wall motion abnormality,\(^{43,44}\) but also reversible perfusion defects, even without epicardial coronary lesions. Notably, these perfusion defects worsen as fibrosis increases, with fewer reversible and more fixed areas.\(^{45}\)

It is possible to assess intraventricular synchronism using phase analysis in gated SPECT MPI.\(^{46}\) A group of patients in the indeterminate phase of CD who presented segmental motion abnormalities detected by tissue Doppler imaging (TDI)-derived strain, were studied by MPI and intraventricular synchronism.\(^{44}\) From these, 8% had perfusion defects, while 28% had a
post-stress LVEF reduction of ≥5%. The affected segments coincided with those with motion abnormalities in all cases with reversible defects. Histogram bandwidth and phase-derived standard deviation were significantly different between post-stress and rest, showing minor dyssynchrony at rest that normalized at post-stress. Figure 3 (Case 3) shows an example of a MPI SPECT in a patient with an indeterminate phase of CD.

In a study of 36 patients with CCD assessed with stress-rest MPI SPECT initially and after a mean follow-up of 5.6 years, 20 (56%) showed reversible myocardial perfusion defects. Several initially reversible defects became fixed over time. A topographic association was found between the presence of ischemia in the initial evaluation and the development of wall motion abnormality; 32 (68%) of the 47 segments with initial reversible perfusion defects progressed to perfusion defects at rest, and of the 469 segments not showing reversibility in the initial study, only 41 (8.7%) experienced the same progression. Therefore, the authors concluded that the impairment of LV systolic function over time was related to the presence of reversible defects at the initial assessment, and the increase in the extent of irreversible perfusion defects, indicating regional myocardial fibrosis during follow-up. Although most patients with CD have epicardial coronaries without significant lesions, cardiac catheterization may be necessary in some cases to rule out epicardial CAD, which could coexist with CD. Figure 4 (Case 4) shows a patient with a history of CD and a diagnosis of CAD.

**Myocardial Sympathetic Innervation Imaging**

Abnormalities in sympathetic innervation constitute an early finding in CCD, preceding other cardiac changes in one-third of patients and can be associated with areas that will develop regional wall motion abnormalities and perfusion defects. Miranda et al. found that regional myocardial sympathetic denervation assessed with 123Iodine-metaiodobenzylguanidine (123I-MIBG) scintigraphy was associated with sustained VT in CCD. Even in subjects with early forms of CCD with preserved ventricular function, cardiac autonomic sympathetic modulation can be detected with 123I-MIBG SPECT.
Positron Emission Tomography with $^{18}$F-Fluorodeoxyglucose (FDG)

FDG-PET identifies areas of myocardial inflammation in patients with non-ischemic cardiomyopathies. Although the presentation of sarcoidosis and CD may show similarities, but the basal and mid-ventricular septa are mainly affected in the case of sarcoidosis, while for CD, the apex, inferior, and inferolateral segments are more frequently involved.

Some case reports have described increased uptake of $^{18}$F-FDG PET in patients with CD and VT, indicating that inflammation contributes to the occurrence of arrhythmias.

CT

Cardiac CT could be considered in three scenarios in CD patients:

1. To exclude CAD in patients with low to intermediate pretest probability, due to its high negative predictive value.
2. In planning of complex electrophysiological procedures to avoid coronary arteries injuries during ablation.
3. To assess ventricular function and morphology if there are contraindications for CMR and poor acoustic windows for echo.

A proposal for an algorithm for diagnosing CCD is presented in Figure 5.

Risk Stratification in Chagas Heart Disease

The leading cause of mortality in the chronic phase of CD is SCD, accounting for 50%-65% of deaths. Therefore, identifying which patients are at higher risk of developing SCD is paramount. Some risk scores have been developed to predict adverse outcomes in CCD patients. The more frequently used are the Rassi score and the Sousa score.

The Rassi score for patients with established CCD includes six factors (a combination of clinical symptoms, test results, and demographics) with weighted values to categorize patients by risk of 10-year mortality: low (10%), medium (44%), and high (84%). The Sousa score considers four factors (QT dispersion, syncope, premature ventricular contractions, and LV function) to predict the risk of SCD as low (0–2 points), intermediate (3–4 points), and high (>5 points).
Figure 4 - CASE 4. Male, 68 y.o. Chagas antibodies were positive. Atherosclerotic risk factors: high blood pressure, dyslipidemia. Atypical chest pain at moderate stress. History of episodes of ventricular arrhythmias. Indication of gated-SPECT: stratification of ischemic heart disease. A one-day protocol (rest-stress with dipyridamol) gated-SPECT with $^{99m}$Tc-MIBI was performed. A: perfusion images showing reduced uptake in anterolateral, inferolateral, inferior and apical segments, with a very reduced reversibility at apical and inferior (medium-apical) segments (SSS: 19, SRS: 16, SDS: 2). B: ventricular function. Moderate inferior/inferolateral hypokinesis with systolic thickening reduction. Moderate LV dysfunction (LVEF at rest: 39% and at stress: 38%). Dilated LV.

LV: left ventricle; LVEF: left ventricular ejection fraction; MIBI: methoxy-isobutyl-isonitrile; SSS: summed stress score; SRS: summed rest score; SDS: summed difference score; SPECT: single-photon emission computed tomography; $^{99m}$Tc: technetium 99m

Myocardial scar has been related to sustained VT, cardiovascular death, hospital admission for heart failure, heart transplantation, and appropriate implantable cardioverter-defibrillator therapy. Uellendahl et al. found that the percentage of myocardial fibrosis on CMR was progressively and strongly associated with the clinical severity or Rassi score ($r = 0.76$).

How do we identify and manage patients affected by CD?

CD remains a largely neglected disease with insufficient diagnostic and therapeutic pathways. To properly face this health problem through a multidisciplinary, comprehensive, and timely approach, some points should be considered:

- CD has long-term clinical repercussions and causes high care costs exacerbated by social and economic conditions of the inhabitants of LMICs in endemic areas. Therefore, research and investment in community prevention strategies (pharmacological or non-pharmacological) are important.

- High-quality epidemiological research and investment in education are needed to improve the recognition and care of CD patients both in endemic and non-endemic areas.

- The appropriate and efficient use of cardiac imaging is crucial to detect the cardiac involvement in patients with CD, as well as to stage the disease, stratify patient risk and address management with a personalized approach. Thus, investment in diagnostic methods and medical providers’ education is needed.

- New biomarkers for early detection of the disease and monitoring of therapeutic efficacy are needed. These biomarkers will help to guide risk stratification and treatment guidelines.

Conclusions

The early mortality and substantial disability stemming from CD impose a considerable social and economic burden, particularly in the Latin America Andean region. The complex nature of Chagas heart disease underscores the critical role of cardiac imaging not only in detecting cardiac
involvement but also in accurately staging the disease, stratifying patient risk, and guiding effective management strategies (Central Illustration).

As we confront the challenges presented by Chagas heart disease, it becomes increasingly evident that investment in the education of medical providers is paramount. Providing healthcare professionals with the knowledge and skills to recognize, diagnose, and manage Chagas heart disease is fundamental to improve patient outcomes.

Furthermore, a comprehensive approach requires the development and implementation of accurate diagnostic methods, with a particular emphasis on advanced imaging techniques. These methods play a pivotal role in early detection and intervention, essential components in the effort to alleviate the burden imposed by Chagas heart disease.

Concomitantly, the urgency for investment in research persists. Advancements in understanding the pathophysiology, epidemiology, and treatment modalities are crucial for refining our approach to Chagas heart disease. Appropriate allocation of resources towards research initiatives will undoubtedly contribute to the development of innovative and effective strategies to combat this pervasive health challenge.

**Author Contributions**

Conception and design of the research: Peix A, Paez D; writing of the manuscript: Peix A, Araujo R; critical revision of the manuscript for intellectual content: Peix A, Gomez V, Barreda AP, Dondi M, Brink A, Minoshima E, Paez D; providing cases data: Araujo R, Gomez V, Barreda AP; preparation of figures: Minoshima E.

**Potential Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

**Sources of Funding**

There were no external funding sources for this study.

**Study Association**

This study is not associated with any thesis or dissertation work.

**Ethics Approval and Consent to Participate**

This article does not contain any studies with human participants or animals performed by any of the authors.


