# Recommendations for Multimodality Cardiac Imaging in Patients with Chagas Disease: 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)

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*The American Society of Echocardiography and the writing group sadly note the passing of Dr. Rodolfo Viotti in March 2017, while this document was being written. It was our honor to work with Dr. Viotti on a topic that was very dear to him throughout his long career.



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**Abbreviations**

**2D** = Two-dimensional

**3D** = Three-dimensional

**ASE** = American Society of Echocardiography

**ChD** = Chagas disease

**ChHD** = Chagas heart disease

**CMR** = Cardiac magnetic resonance

**CT** = Computed tomography

**ECG** = Electrocardiographic

**HF** = Heart failure

**LA** = Left atrial

**LGE** = Late gadolinium enhancement

**LV** = Left ventricular

**LVEF** = Left ventricular ejection fraction

**PW Doppler** = Pulsed wave Doppler

**RV** = Right ventricular

**RVEF** = Right ventricular ejection fraction

**TEE** = Transesophageal echocardiography

**TTE** = Transthoracic echocardiography

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## I. INTRODUCTION

Chagas disease (ChD) is a significant public health problem in most Latin American countries. Observed mainly in rural areas, in recent decades it has spread to cities and to nonendemic countries, mostly as a result of migration of infected people. Increasing numbers of cases are now being identified in the United States, Spain, and other countries, which makes its diagnosis and management of increasing interest worldwide.

During an antimalarial campaign in Lassance (Minas Gerais, Brazil) in 1909, Carlos Chagas identified the parasite *Trypanosoma cruzi*, its vector for transmission (triatomine bugs, called differently in each country: kissing bug, *barbeiro*, *vinchuca*, *chinche*, etc.), and described the initial cases of the disease.[1] Transmission occurs mainly through the bite of these vectors but may also occur by blood transfusion, from mother to fetus, oral ingestion of contaminated foods, organ transplantation, and laboratory accidents. Vector control programs have substantially diminished *T. cruzi* and ChD incidence. However, about 70 million people remain at risk for acquiring the infection.[2]

The diagnosis of ChD is made by epidemiologic history and by two or more positive serologic tests. There are two clinical phases of *T. cruzi* infection: acute ChD, seen early after acquiring the infection, and chronic ChD, lasting for decades. About 70% to 80% of individuals with chronic *T. cruzi* infection remain asymptomatic (indeterminate form), while 20% to 30% develop cardiac and/or gastrointestinal disease.[3] Patients with chronic Chagas heart disease (ChHD) are staged according to the severity of myocardial damage and symptoms of congestive heart failure (HF; Table 1).[4,5] Assessment by electrocardiography is mandatory because the earliest signs of ChHD are generally conduction system defects and/or ventricular arrhythmias. The introduction of various cardiac imaging modalities, such as echocardiography, nuclear medicine, computed tomography (CT), cardiac magnetic resonance (CMR), and chest radiography, provides valuable information on cardiac structure and function.

The purpose of this document is to provide recommendations for the use of cardiac ultrasound and other imaging modalities in the diagnosis, classification, and risk assessment of myocardial damage from early to advanced forms of ChHD.

## II. EPIDEMIOLOGY OF ChD: GEOGRAPHIC DISTRIBUTION WORLDWIDE AND IN THE UNITED STATES

ChD is caused by the protozoan parasite *T. cruzi*, transmitted when feces of an infected triatomine vector enters the mammalian host through the bite wound or mucous membranes.[6] Infection is lifelong in the absence of treatment. Vector-borne transmission occurs in parts of North America, Central America, and South America, with geographic distribution determined both by the ecology of the triatomine vectors and factors such as housing conditions that govern contact between vectors and the human population.[7] Transmission can also occur through transfusion of infected blood components, organ and bone marrow transplantation, and from mother to fetus. Outbreaks attributed to contaminated food or drink have been reported in northern South America.[8] In addition, many *T. cruzi*–infected individuals have moved from endemic rural villages to Latin American cities, and hundreds of thousands now live in the

**Table 1** Stages of ChHD

| | Chronic Phase | | | | |
|---|---|---|---|---|---|
| | | Chagas Cardiomyopathy | | | |
| Acute Phase | Indeterminate Form, A | B1 | B2 | C | D |
| Infected by *T. cruzi* and findings of acute ChD | Positive serology<br>Normal ECG findings<br>No heart disease or HF | Structural cardiomyopathy (abnormal ECG or echocardiographic findings) but normal LV function<br>No HF | LV dysfunction<br>No HF | LV dysfunction<br>HF (current or prior) | Refractory HF despite optimal medical therapy |

Modified from Andrade *et al.*[4] and Bern *et al.*[5]

United States, Spain, and other nonendemic countries outside Latin America (Figures 1[2] and 2[9,10]).

*T. cruzi* infects many mammalian species. The vector species responsible for the majority of human infections are considered domestic because they are adapted to living in cracks in mud walls and thatch roofs of rustic rural houses.[11] Inhabitants of infested houses are repeatedly exposed to vectors and parasites over many years. In highly endemic villages, a high percentage of the adult population is infected, with the prevalence rising with increasing age.[12] The prevalence of cardiac morbidity also increases with age.[13] An estimated 20% to 30% of *T. cruzi*–infected individuals eventually develop Chagas cardiomyopathy, but in endemic or previously endemic settings, a much higher percentage of the elderly may have cardiac signs.[3]

Latin America has made substantial progress in decreasing *T. cruzi* transmission, largely through residual insecticide application to control domestic infestation.[14] The estimated global ChD prevalence declined from 18 million in 1991, when the first regional control initiative began, to approximately 6 million in 2010.[2,6,14] The Pan American Health Organization has certified interruption of transmission by domestic vectors in several countries of South America and Central America.[15,16] *T. cruzi* serologic screening is conducted in most blood banks in Latin America and the United States, and some countries have systematic screening for congenital ChD. Nevertheless, ChD remains the most important parasitic disease in the Western Hemisphere.

The southern half of the continental United States has established enzootic transmission cycles, with infected vectors and mammalian hosts such as raccoons, opossums, wood rats, and domestic dogs.[7,17] Nevertheless, the majority of infected residents are Latin American immigrants infected in their home countries, and infected individuals are found in nearly every state. On the basis of the Latin American immigrant population and estimates of prevalence in their home countries, an estimated 300,000 *T. cruzi*–infected immigrants reside in the United States.[9] Locally acquired vector-borne infection has been documented in a handful of cases over the past 60 years and has been inferred in blood donors for whom acquisition of the infection in Latin America has been ruled out or judged unlikely.[7,18,19] Direct assessments of prevalence in the United States are sparse and have been restricted to small-scale surveys or case series in populations chosen because of anticipated high risk (e.g., Latin American immigrants with nonischemic heart disease).[20-22] Because of low provider awareness, cases of Chagas cardiomyopathy likely go unrecognized, and women at risk for vertical transmission to their infants are not screened.[23,24] Thus, more work is needed to raise awareness and improve the knowledge base of providers in the United States. In addition, more extensive epidemiologic studies and better diagnostic and treatment availability are required.

## Key Points

- ChD is a vector-borne zoonotic disease endemic to the Americas, which could be underdiagnosed if aggressive screening campaigns are not pursued.
- Substantial progress has been made in decreasing vector- and blood-borne *T. cruzi* transmission through residual insecticide application and housing improvement, but there remain 6 million infected people and 70 million at risk for infection in the Americas.
- Zoonotic transmission occurs in the southern half of the United States, but *T. cruzi*–infected migrants from Latin America greatly outnumber those infected locally. Patients with ChD are found in nearly every state of the United States and in other countries outside of the Americas.

## III. PATHOPHYSIOLOGY RELATED TO IMAGING AND CLINICAL PRESENTATION

The pathophysiology of myocardial damage in chronic ChHD is complex and multifactorial. ChHD is an acquired inflammatory cardiomyopathy caused by three key pathologic processes: inflammation, cell death, and fibrosis. A consensus is now emerging that parasite persistence and parasite-driven adverse immune response play a pivotal role in the pathogenesis of ChHD.[25]

Because of these underlying pathogenic mechanisms, a variety of structural and functional cardiovascular abnormalities have been shown in patients with ChHD.[26] Cardiac structural cells affected by the inflammatory process include the myocytes, leading to myocytolysis and contraction band necrosis and irreversible lesions of the specialized conduction system and cardiac neural cells. The progressive destruction of normal cardiac constituents leads to a marked reparative and reactive fibrosis, characterized by a dense interstitial accumulation of collagen that encloses fibers or groups of myocardial fibers.[27] This explains the frequent occurrence of atrioventricular and intraventricular blocks, sinus node dysfunction, malignant ventricular arrhythmias, and sudden death in patients with ChHD.[28] Recent studies in the experimental model of chronic *T. cruzi* infection have shown that at early stages, the coalescence of focal areas of myocardial inflammation, necrosis, and fibrosis typically results in the appearance of left ventricular (LV) segmental wall motion abnormalities, a hallmark of ChHD.[29] At later stages, these regional derangements gradually cause progressive impairment of global myocardial contractile function. The ultimate consequence of is dilated cardiomyopathy with biventricular dysfunction and congestive HF.[28]

Derangements of the coronary microcirculation, including increased platelet activity, microthrombi, microvascular spasm, and endothelial dysfunction, have been reported in animal models of *T. cruzi* infection and in studies of humans with ChD.[30] These phenomena precede and may be causally related to the development of segmental wall motion abnormalities. Abnormal reactivity to vasodilator and vasoconstrictor stimuli has also been reported in the epicardial coronary arteries of patients with ChD. Overall, these derangements in the coronary microcirculation are likely to cause ischemic myocytolic necrosis and reparative fibrosis that are clinically expressed as ischemic-like symptoms, electrocardiographic changes, and perfusion defects described in ChHD patients with angiographically normal coronary arteries. In the advanced stages of ChHD, ventricular aneurysms are detected mostly in watershed zones between principal coronary artery branches, such as regions between the left anterior descending and posterior descending coronary arteries and the right coronary and left circumflex coronary arteries, which supply the apex and the basal-posterior wall of the left ventricle, respectively.[31]

Virtually all pathophysiologic aspects of chronic ChHD can be detected using various imaging modalities, which are discussed in the following sections.

## IV. SPECIAL FEATURES OF ELECTROCARDIOGRAPHY AND EACH IMAGING MODALITY IN RELATION TO ChD

### IV.a. Electrocardiography and Continuous Rhythm Monitoring

Electrocardiographic (ECG) abnormalities are often the first indicator of cardiac involvement in ChD. Electrocardiography remains a cost-effective diagnostic test that should be performed routinely once serologic confirmation is obtained. Recent regional guidelines provide a class I recommendation with level of evidence C for the indication of 12-lead electrocardiography in the diagnosis and risk stratification of patients with ChD.[4]

By and large, the acute presentation of ChD is usually mildly symptomatic and manifests as a flu-like event. In approximately 5% of cases, acute myocarditis may clinically manifest with a wide range of ECG abnormalities. The most frequent findings are nonspecific and common to any myocarditis and include sinus tachycardia, diffuse abnormal repolarization, low QRS voltage, and atrioventricular block. With severe myocarditis, higher degrees of atrioventricular block and intraventricular conduction disturbances (bundle branch and fascicular blocks) may occur.[32] In a series of acute Chagas myocarditis cases, ECG alterations were documented in 66% of the patients. Abnormal repolarization was the most common finding (37%), and the most frequent arrhythmia was inappropriate sinus tachycardia (9%), followed by atrial premature complexes (8%). In this series, only 2% developed right bundle branch block.[33] Abnormal ECG findings during the acute phase may have prognostic implications, as reported by Porto[34] in a classic series of patients presenting with acute Chagas myocarditis.

Electrocardiography is instrumental in classifying the stage of disease in patients in the chronic phase of ChD. The lack of ECG abnormalities stages *T. cruzi* carriers in the indeterminate phase of the disease (stage A; Table 1). Normal ECG findings are rare in the presence of moderate or severe LV dysfunction, while a greater number of ECG alterations correlates with worse LV function, especially if left bundle branch block is present. Of note, ECG abnormalities were strongly associated with ChHD in the Retrovirus Epidemiology Donor Study II, with a high negative predictive value (95%) for

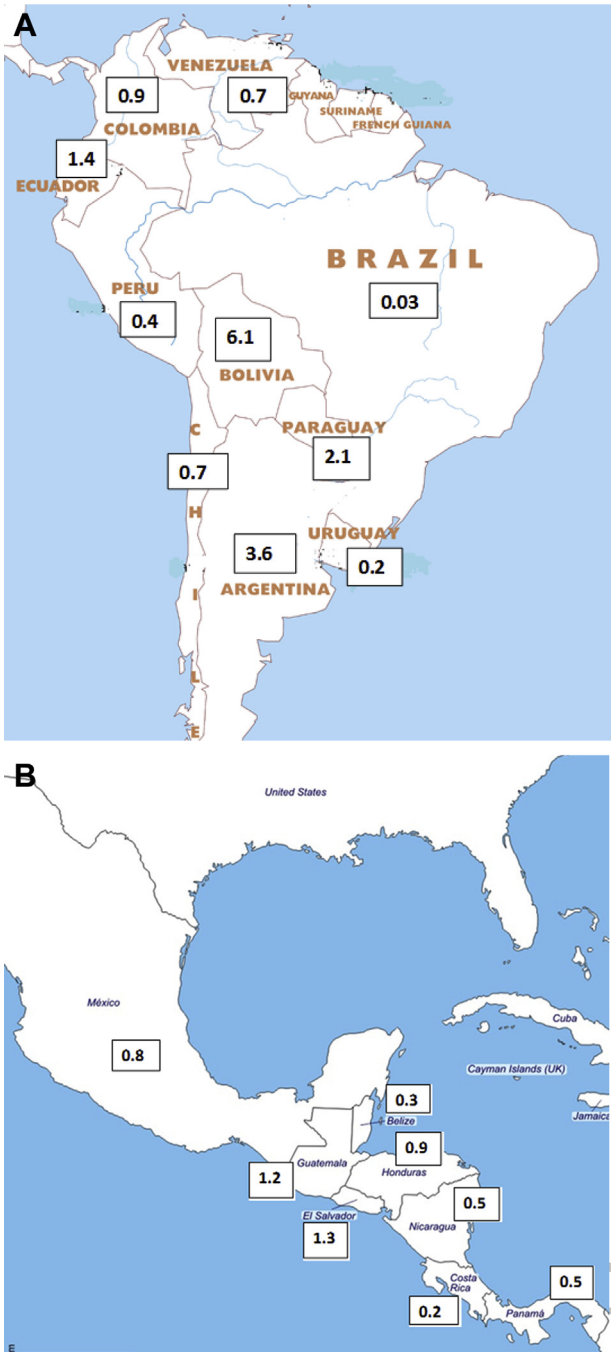


Figure 1 Estimated prevalence of *T. cruzi* infection per 100 habitants per country. **(A)** South America. **(B)** Mexico and Central America.[2]

Chagas cardiomyopathy. This finding suggests that in rural areas with very limited resources, normal ECG findings without other imaging modalities (such as echocardiography) could be sufficient screening in asymptomatic *T. cruzi*–infected individuals.[35]

The earliest ECG abnormalities of ChHD usually involve the conduction system, manifesting most frequently as right bundle branch block and/or left anterior fascicular block. Second- and third-degree atrioventricular block have also been strongly related with Chagas cardiomyopathy in endemic populations. Sinus node dysfunction may present as episodes of sinoatrial block with bradycardia or ectopic atrial tachycardia (Figure 3).

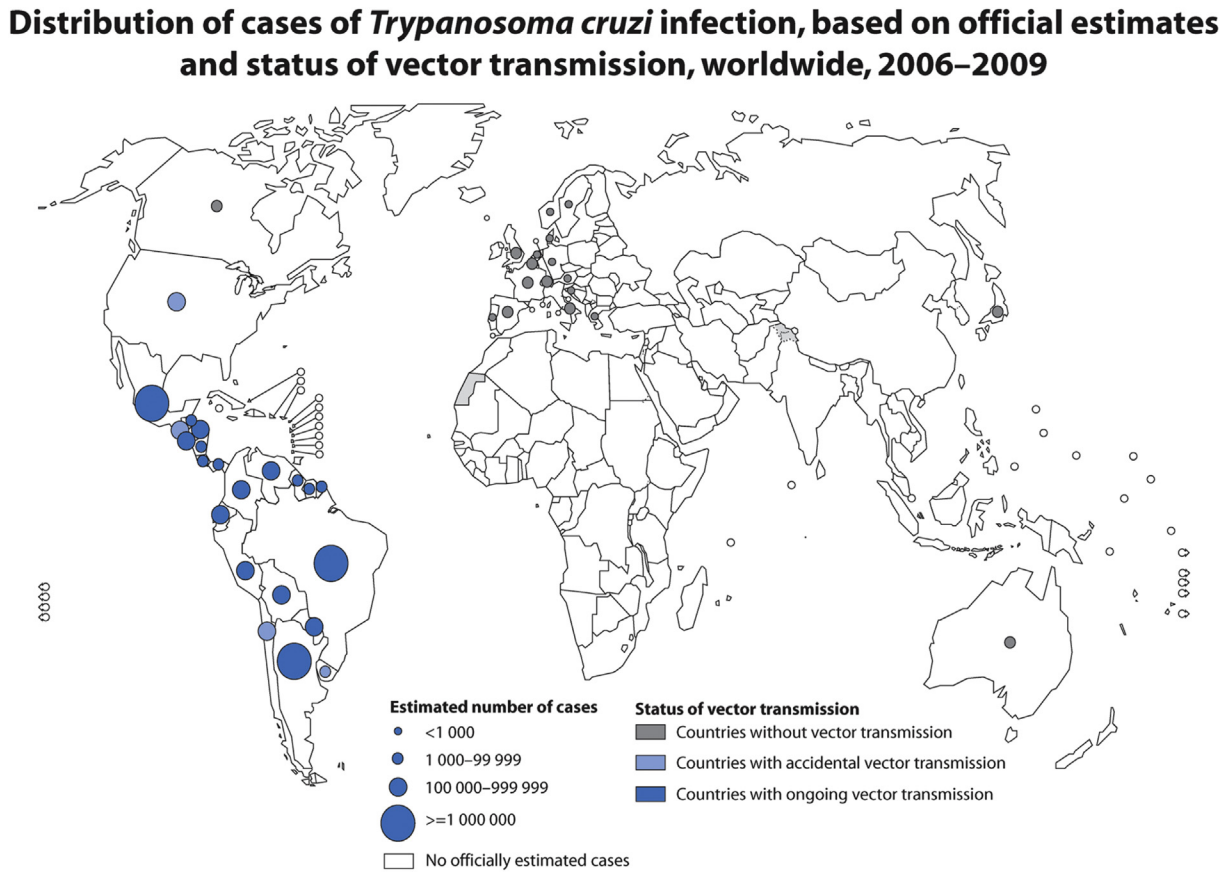


Figure 2 Estimated number of ChD cases per country and their status of vector transmission (2009). Obtained with permission from the World Health Organization (http://gamapserver.who.int/mapLibrary/Files/Maps/Global_Chagas_2009.png).

Complex ventricular arrhythmias such as ventricular tachycardia occur even in patients without overt HF but tend to be associated with more advanced stages of ChHD and worse prognosis.[36,37]

Electrocardiography is also a useful tool for risk stratification. The presence of premature ventricular contractions, increased QT-interval dispersion, low-voltage QRS, QRS fragmentation, and prolonged QRS duration have all been associated with a worse prognosis.[38-40] Once ECG abnormalities arise, they imply disease progression (stage B; Table 1), preceding the appearance of HF symptoms (stages C and D). ECG abnormalities are frequent and related primarily with nonspecific repolarization alterations (30%–40%), right bundle branch block in conjunction with left anterior fascicular block (20%–35%), premature ventricular ectopic beats (5%–10%), and atrial fibrillation (5%–10%).[4,41] These findings have been recently supported by Echeverría *et al.*,[42] who by using electrocardiography for Chagas cardiomyopathy staging predicted disease progression as determined by elevation in N-terminal pro–brain natriuretic peptide and high-sensitivity troponin.

Twenty-four-hour ambulatory ECG monitoring (Holter) is recommended in patients with symptoms suggestive of cardiac arrhythmias (palpitations, presyncope, or syncope) or the presence of certain ECG findings, such as sinus bradyarrhythmias (heart rate $<$ 40 beats/min and/or prolonged sinus pauses), second-degree atrioventricular block, or frequent and/or repetitive (bursts of) ventricular extrasystoles.[4,43]

Holter monitoring may identify patients at risk for sudden death and unmask early signs of cardiac autonomic dysfunction with reduced heart rate variability.[44] In asymptomatic patients or those with rare symptoms, Holter monitoring will have a low diagnostic yield and is usually not routinely indicated. An implantable cardiac monitor may be considered in patients with other markers of risk such as depressed LV or right ventricular (RV) function, regional wall motion abnormalities, or syncope with frequent premature ventricular complexes or palpitations.

In summary, electrocardiography should be performed in all patients identified with positive *T. cruzi* serology. The rationale for this strategy is based on the cost-effectiveness and wide availability of this diagnostic test, in addition to high negative predictive value to rule out cardiomyopathy in *T. cruzi*–infected individuals. Electrocardiography serves two purposes: staging and prediction of disease progression. The appropriate timing and frequency for performing electrocardiography during follow-up remains debatable and is not evidence based. It seems reasonable that in individuals with a normal baseline ECG findings, follow-up ECG testing may be performed at least every 5 to 10 years. Further screening with biomarkers and cardiac imaging may be selectively performed, depending on baseline ECG findings. Patients with frequent premature ventricular complexes, nonsustained ventricular tachycardia, and other bradytachyarrhythmias identified by Holter monitoring should undergo further assessment of LV systolic function.

### IV.b. Echocardiography

#### *IV.b.i. M-Mode and Two-Dimensional Echocardiography.*

ChHD is an inflammatory cardiomyopathy that may affect the myocardium in a segmental or regional manner. On imaging, the heart may appear normal, have localized segmental ventricular

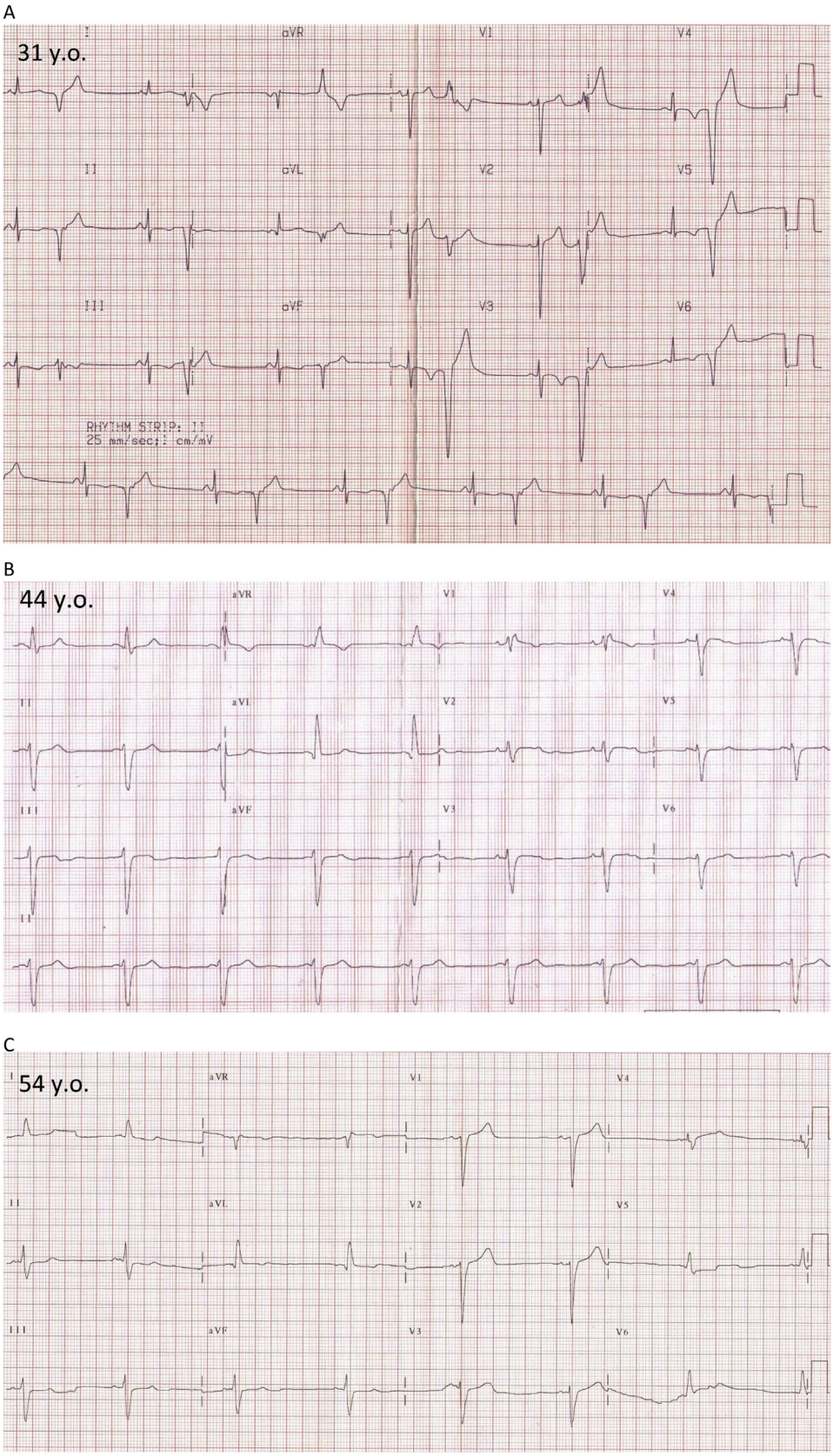


Figure 3 ECG progression of a single patient with ChHD over 23 years of follow-up. **(A)** At 31 years of age, sinus bradycardia, ventricular bigeminy, narrow QRS (0.10 sec), and ST-T convex upward with inverted T wave (suggestive of apical aneurysm, subsequently demonstrated by two-dimensional echo). **(B)** At 44 years of age, sinus rhythm, no extrasystoles, and a new right bundle branch block with left anterior fascicular block (QRS duration increased to 0.134 sec), and precordial R-wave size decreased. **(C)** At 54 years of age, sinus bradycardia, no extrasystoles, left anterior fascicular block is present without right bundle branch block (which appears on exercise), and QRS duration is 0.126 sec. These changes may explain different rates of ECG findings. Corresponding 2D echocardiographic images at 54 years of age are shown in Figure 5.

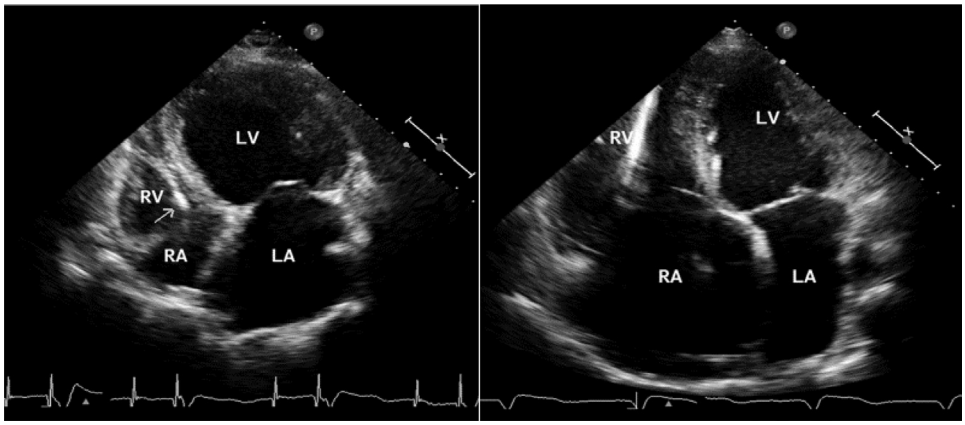


**Figure 4** Dilated ChHD cardiomyopathy (stage D). Four-chamber view echocardiograms of two patients with ChHD in congestive HF with severe global hypokinesis and low ejection fraction, similar to other dilated cardiomyopathies. A pacemaker wire is seen in the right heart chambers *(arrow)*. *(Left)* The left ventricle (LV) and left atrium (LA) are severely dilated with normal size right ventricle (RV). *(Right)* Biventricular and biatrial severe dilatation. *RA*, Right atrium.

abnormalities (wall motion, thinning, aneurysms, etc.), or manifest as a globally dilated cardiomyopathy with associated valvular heart disease (mainly functional mitral and tricuspid regurgitation). In general, echocardiographic evaluation should be performed as suggested by the American Society of Echocardiography (ASE) guidelines on chamber quantification,[45] with a special emphasis on LV function and morphology, RV function, and valvular disease. As previously mentioned, the absence of ECG abnormalities mostly rules out significant cardiomyopathy. However, it is reasonable to perform at least a single echocardiographic examination (baseline evaluation) on every patient with positive serology for ChD and repeat during follow-up if the ECG findings become abnormal to document disease progression (Table 1). Patients with symptomatic ChHD (HF) may present with predominantly hypokinetic, dilated left ventricles with diminished LV ejection fraction (LVEF), or biventricular dilatation (Figure 4). Although infrequent, even asymptomatic subjects may display subtle abnormalities by two-dimensional (2D) and three-dimensional (3D) echocardiography, such as small aneurysms or wall motion abnormalities.

*Global LV Function.* Initial rural surveys using basic M-mode and 2D echocardiography were useful for clinical staging by estimating anatomic and functional damage and assessing LV function.[46,47] Current ASE guidelines recommend routine clinical evaluation using 2D and 3D echocardiography to estimate LV, RV, left atrial (LA) and right atrial volumes and dimensions and for assessment of LV and RV function.[45] Global LV systolic function should be addressed on 2D echocardiography by calculation of LVEF through the biplane method of disks (the Simpson rule). The endocardial border should be traced at the interface of the compacted myocardium and the LV cavity at end-systole and end-diastole in the apical four- and two-chamber views. Although the accuracy of LV volumes and LVEF is higher when using 3D echocardiography (which is therefore preferred whenever available), 2D echocardiography has the advantage of easiness and wider availability. However, the presence of apical LV aneurysms present a challenge to the use of the method of disks, as apical aneurysms frequently cannot be included within the ultrasound field (Figure 5).

*Regional Wall Motion Abnormalities.* LV segmental abnormalities are common in ChHD at any stage of the disease. These are located mainly at the LV apex (Figure 6, Videos 1 and 2, available at www.onlinejase.com) and inferior and inferolateral walls (Figures 7 and 8) but may also affect other LV or RV segments.[48] Technically, it is important to perform a comprehensive examination from multiple windows, as wall motion abnormalities should be demonstrated in at least two different views to avoid false-positive results. The use of ultrasound contrast agents for LV opacification (Figure 9) and wall motion evaluation is recommended when images are suboptimal in at least two contiguous segments.[49,50] In addition, contrast could be particularly useful for the detection of small aneurysms and thrombus, typical of ChHD.[51] In a review of 2D echocardiographic series of patients with ChHD, among 920 asymptomatic patients with mild cardiac damage, the prevalence of LV aneurysm was 8.5%, while it increased to 55% in patients with more advanced cardiac disease.[47] Similarly, LV apical abnormalities had a low prevalence in those with normal ECG findings but increased to 24% in those with abnormal ECG findings. Other common contractile abnormalities involve the inferolateral or inferior walls, with prevalence of up to 23% in symptomatic patients.

*Valvular Disease.* A comprehensive evaluation in patients with ChD should include careful examination of the cardiac valves. Two-dimensional echocardiography is used to evaluate valvular and subvalvular structure and, together with a thorough Doppler examination, provide a good understanding of the severity and etiology of different valvular diseases and dysfunction.[52,53] Functional incompetence of the mitral and tricuspid valves is common as ChHD advances (Figure 10). Ventricular remodeling with progressive dysfunction, dyssynchrony, valvular annular dilation, tethering of the subvalvular apparatus, fibrosis, and atrial enlargement may induce various degrees of valve dysfunction. An understanding of these alterations will help in determining the need and proper strategy for therapeutic interventions.

***IV.b.ii. Three-Dimensional Echocardiography.*** Cardiac chambers are 3D structures with complex anatomy and variable shape. Therefore, the accuracy of 2D echocardiography for evaluation of cardiac structure, shape, and dimensions is limited, as it requires some degree of reconstruction and geometric assumptions. Three-dimensional echocardiography, on the other hand, allows visualization of cardiac chambers in their entirety without geometric assumptions.[45,54-56] Creation of 3D echocardiographic images requires specialized transducers for acquisition of a volume (pyramid) of data rather than a slice (2D echocardiography). The 3D volume could be acquired through a single

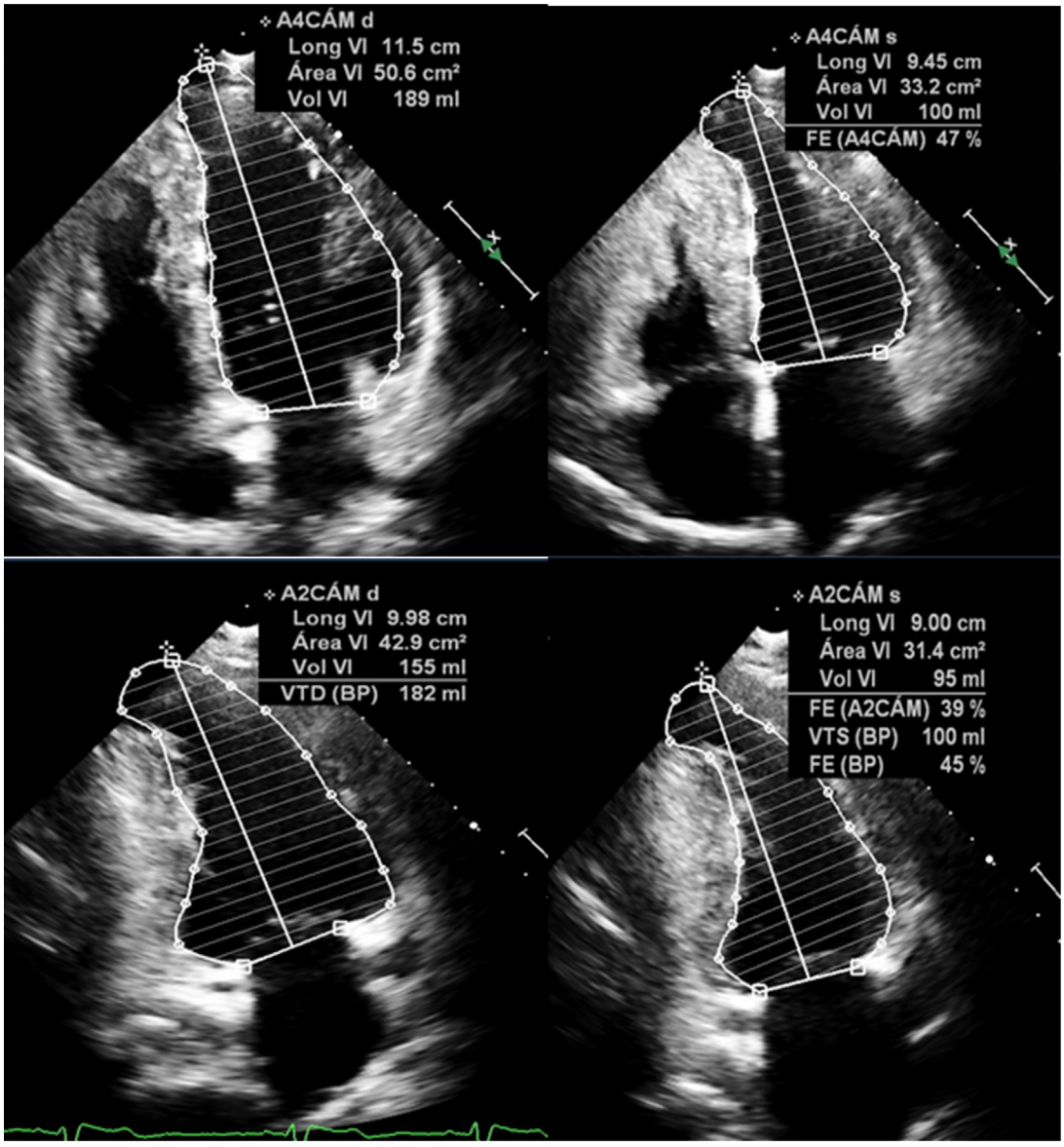


Figure 5 Challenges in 2D echocardiographic LVEF and volume evaluation by the method of disks (Simpson rule) in patients with ChHD with apical aneurysm. Four-chamber and two-chamber apical views (biplane method) in a 54-year-old patient with ChHD. LV volumes are increased, and LVEF is mildly decreased. ECG follow-up is shown in Figure 3C. Notice the LV apical aneurysm, especially in mid-systole *(right)*. As in this case, large apical aneurysms are frequently difficult to contain within the image, and therefore adequate tracing of the cavity/endocardial interface may not be feasible.

heartbeat or by stitching together smaller volumes in consecutive beats. Although 3D echocardiography has significant advantages over 2D echocardiography, as mentioned above, there are limitations, related mostly to lower temporal and spatial resolution or stitching artifact with multibeat acquisition. Nevertheless, by direct visualization of the entire left ventricle, 3D echocardiography avoids foreshortening of the left ventricle from the apical windows and facilitates measurement of LV volumes and LVEF by direct endocardial contour tracing, rather than assumptions of LV shape from 2D apical views with the single or biplane method of disks (Figure 11). Three-dimensional echocardiography is currently well validated compared with other 3D imaging techniques such as CMR and cardiac CT.[45,54,56] This concept also applies to visualization and volume measurements of other cardiac chambers, such as the left atrium and right ventricle (Figure 12).[57,58] As with patients with other forms of cardiomyopathy, 3D echocardiography should be used in patients with ChD to evaluate cardiac chamber size and ventricular function.[45] Currently, LV volumes and LVEF can be measured using a variety of semiautomated software that are less time-consuming and improve reproducibility.[55] In patients with ChHD presenting with HF, it is important to have information concerning RV size and function, which is particularly challenging with 2D echocardiography. The use of 3D echocardiography allows an accurate analysis of RV volumes and RV ejection fraction (RVEF; Figure 12). In addition, the use of 3D or 3D-derived 2D images (biplane, Xplane, etc.) could help in detecting small LV aneurysms that would otherwise be overlooked by 2D echocardiography because of foreshortening.

The analysis of mitral regurgitation severity in patients with chronic Chagas cardiomyopathy should include 3D echocardiography as part

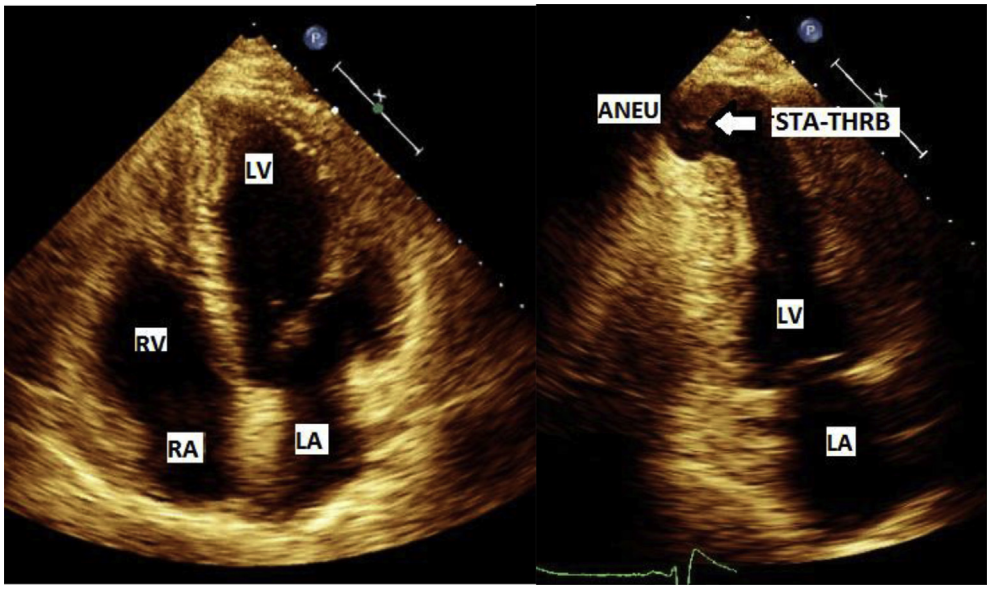


Figure 6 Left ventricular apical aneurysm and thrombus (stage B2). Apical four- and two-chamber views *(left and right)* of a 48-year-old patient with chronic ChHD who presented with a right arm embolic event. A left ventricular apical aneurysm (ANEU) shows blood stasis with small thrombus (STA-THRB). The mid and basal segments of the left ventricle (LV) had normal contractility. LVEF was 45%. Right ventricle (RV), left atrium (LA), and right atrium (RA) were roughly spared from disease.

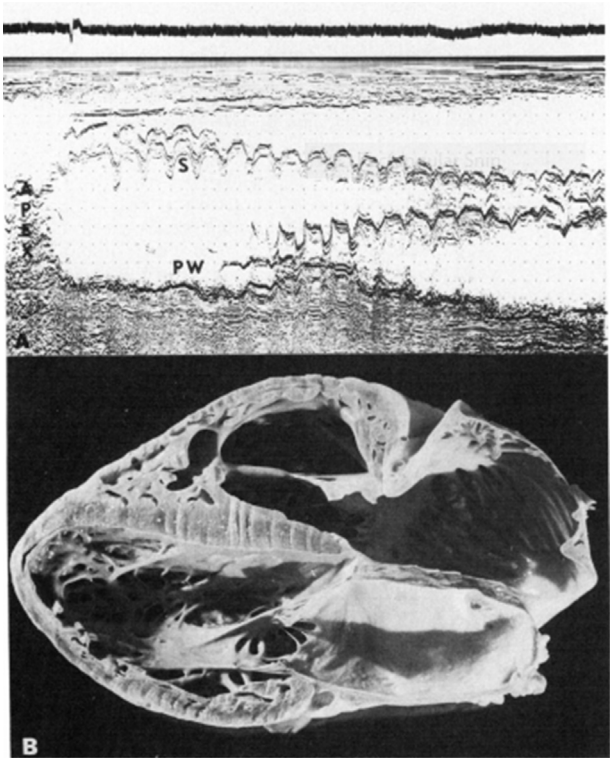


Figure 7 Inferolateral wall fibrosis and akinesis, M-mode, and autopsy specimen. Long-axis slow sweep M-mode echocardiogram **(A)** and cardiac specimen **(B)** from a 52-year-old male patient with ChHD, HF, and arrhythmias, showing extensive scarring and akinetic inferolateral wall (posterior wall [PW]), extensive to apex, contrasting with relatively preserved septal (S) systolic motion and thickening. The coronary arteries were normal at autopsy. (Reproduced with permission from Acquatella *et al.*[46]).

of the comprehensive mitral valve evaluation to assess the structure and morphology of the leaflets and subvalvular apparatus. Although a dilated annulus with tethering of the leaflets from a dilated left ventricle (functional or secondary mitral regurgitation) is the most common finding in ChHD, the examination should evaluate other coexisting valvular abnormalities.[52-54] Therefore, careful attention should be paid to valvular and subvalvular function and structure to evaluate for presence, location, and extent of prolapse, redundant tissue, clefts, rheumatic changes, annular dimensions, cusp separation, and other abnormalities that are not specific for ChHD. Color 3D echocardiography may be used to identify multiple or noncircumferential jets, measure the vena contracta area, or, in combination with continuous-wave Doppler echocardiography, calculate regurgitant orifice area or regurgitant volume and fraction using the proximal isovelocity surface area method. Comprehensive analysis with information derived from 2D, 3D, and Doppler echocardiography may be useful for the prediction of success in future attempts at mitral valve repair (surgical or percutaneous), similar to other etiologies of functional mitral regurgitation.

***IV.b.iii. Strain and Speckle-Tracking Echocardiography.*** Myocardial deformation imaging is a relatively new technique for quantitative assessment of myocardial contractility.[59] Strain is a measure of myocardial deformation, defined as the change in length of the myocardium relative to the original length. Strain rate is the rate of change in strain.[60] Myocardial deformation imaging with echocardiography can be measured using Doppler tissue imaging and 2D and 3D speckle-tracking echocardiography (Figures 13 and 14). Tissue Doppler–derived strain has several limitations, particularly in relation to angle dependency and noise interference. Therefore, strain measurement based on speckle-tracking, which is not angle dependent, has become a method of choice to assess myocardial deformation.

Speckle-tracking echocardiography has allowed the increased recognition of subclinical myocardial dysfunction, particularly in patients with

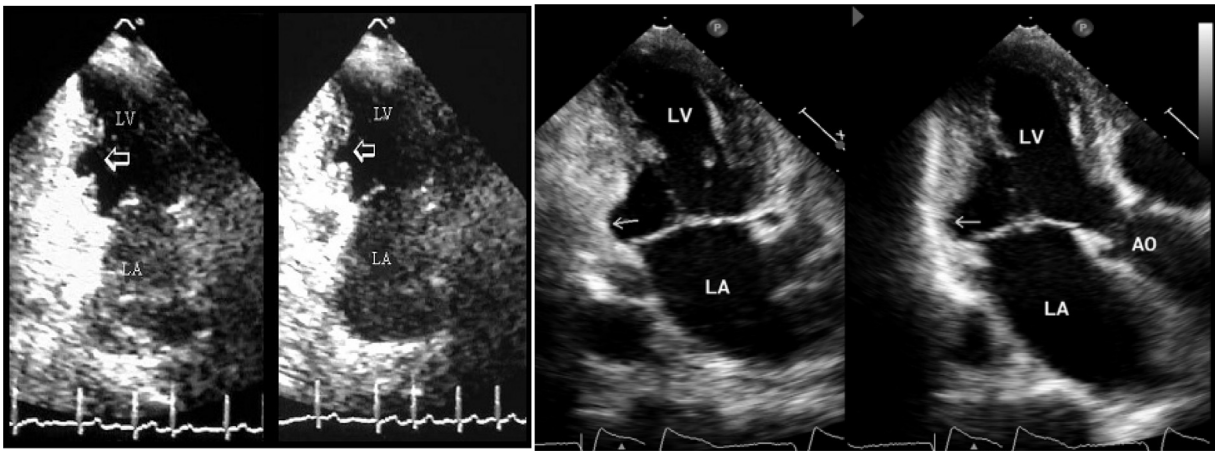


**Figure 8** Left ventricular aneurysms in the inferior and inferolateral walls. Two patients with ChHD with segmental contractile abnormalities at the inferior-posterior-basal left ventricular walls. *(Left)* Two-chamber apical views in diastole and systole, respectively, showing a "punch-type" localized lesion in the midsegment of the inferior wall *(arrows)*. *(Right)* Two- and three-chamber apical views of a localized lesion in the basal segment of the inferolateral wall *(arrows)*. *AO*, Aorta; *LA*, left atrium; *LV*, left ventricle.

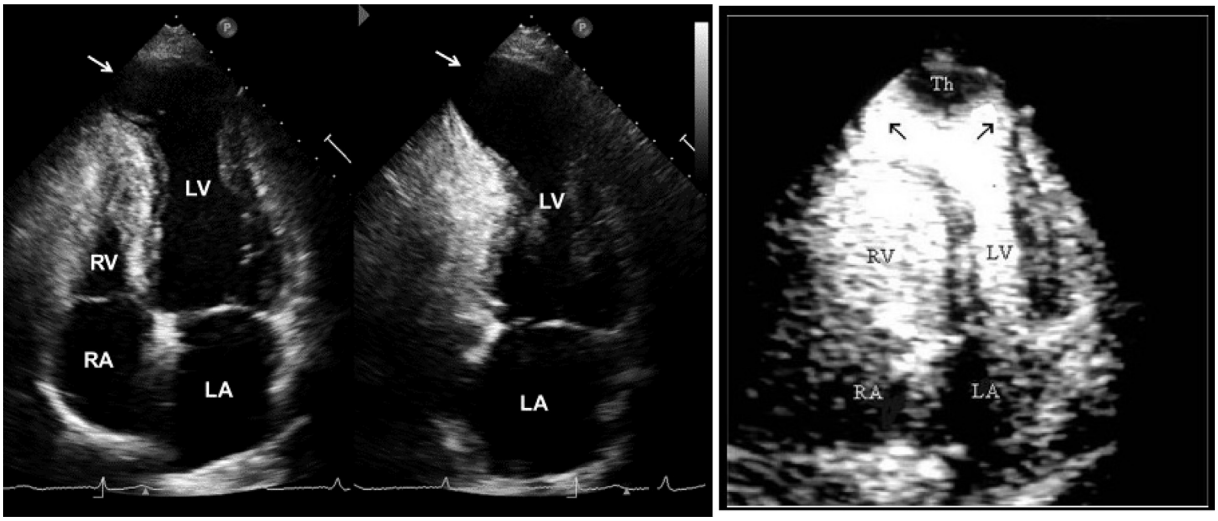


**Figure 9** Left ventricular apical aneurysm *(arrows)* in patients with HF. *(Left)* Apical four- and two-chamber views of a patient with ChHD in stage B2 with a large left ventricular apical aneurysm *(white arrows)*; the right ventricle (RV) has a normal size. *(Right)* Contrast echocardiography for left ventricular opacification in a different patient with ChHD and biventricular damage shows a large apical aneurysm *(black arrows)* with a thrombus (Th). *Arrows* show areas of dyskinesis. Contrast infusion defines the extension of the aneurysm and size of the thrombus. The right ventricle is more dilated than the left ventricle (LV). *LA*, Left atrium; *RA*, right atrium.

the indeterminate form of ChD.[61-63] Global longitudinal strain is the most validated method for the detection of subclinical LV dysfunction in patients with ChHD (and other types of cardiomyopathies) and is highly correlated with the amount of myocardial fibrosis, as detected by CMR.[64] Regional strain is of particular interest in ChHD, given the frequent segmental myocardial involvement described above (apical and inferior or inferolateral walls).

In addition to early detection of myocardial injury in ChD, strain has also been explored as a potential predictor of disease progression signaled by an increase in brain natriuretic peptide and worsening diastolic dysfunction.[62,63,65]

Other uses of myocardial strain are currently being explored, such as for evaluation of mechanical dispersion (Figure 14),[66] as well as LA and RV strain. However, their use is currently experimental.

In conclusion, a growing body of evidence suggests that assessment of cardiac function by echocardiographic myocardial deformation parameters provides incremental information in clinical settings. In the context of ChD, the clinical impact of early myocardial changes assessed by these advanced echocardiographic techniques in predicting disease progression remains to be well defined.

### IV.c. Cardiac Magnetic Resonance and Computed Tomography

***Cardiac Magnetic Resonance.*** The three main aspects involved in the diagnosis, risk stratification, and management of patients with ChD are related to the underlying cardiomyopathy and arrhythmogenic substrate including risk for sudden cardiac death and thromboembolic risk. CMR, although not widely available, has been increasingly shown to be a versatile noninvasive imaging modality for this entity. Given its excellent spatial resolution and unique

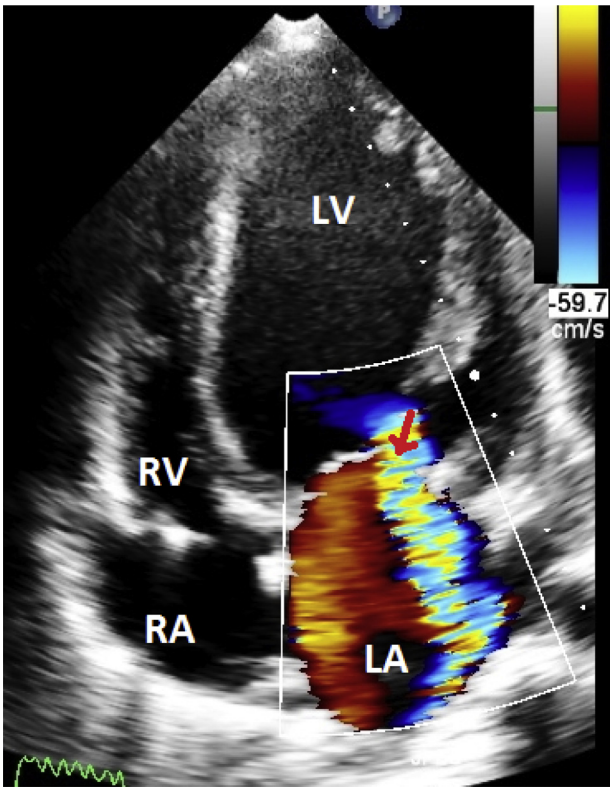


Figure 10 Mitral regurgitation (MR). A 47-year-old woman with ChHD in HF (stage D) and severe MR. The color Doppler image acquired from the apical four-chamber view shows a large eccentric regurgitant color area (*red arrow*) with "wall-hugging" appearance, directed to the left pulmonary veins and reaching the roof of the left atrium (LA), allowing a qualitative visual estimation as severe MR. Regurgitant volume was >50 mL/beat. The left ventricle (LV) is severely hypokinetic and dilated; LVEF was 25%. It is recommended to perform a comprehensive MR evaluation with multiple qualitative and quantitative parameters. *RA*, Right atrium; *RV*, right ventricle.

capability of tissue characterization of myocardial edema and fibrosis, CMR can provide good insight into the pathophysiology of the disease.[67]

CMR protocols begin with cine sequences using steady-state free precession, which allow accurate assessment of the severity and extent of biventricular involvement by accurate calculation of ejection fraction and evaluation of wall motion abnormalities. As mentioned previously, LV systolic dysfunction is the strongest predictor of morbidity and mortality in ChD. Asymptomatic LV systolic dysfunction is even more prevalent than symptomatic HF. Importantly, diagnosis at a subclinical stage may help in preventing or delaying progression of the disease by appropriate therapeutic interventions. Regional wall motion abnormalities, including the typical apical aneurysm, can be readily recognized by this technique without the potential limitations of inadequate echocardiographic windows.

The use of noncontrast T2-weighted sequences allows the evaluation of myocardial edema, which can occur through all phases of the disease and with good correlation with the traditional late gadolinium enhancement (LGE).[68] LGE is assessed using T1-weighted sequences, approximately 10 to 15 min after gadolinium administration. As a paramagnetic extracellular contrast agent, gadolinium will distribute into the areas where there is expansion of the interstitium related to myocardial fibrosis or necrosis. For adequate LGE imaging, the normal or unaffected myocardium signal is nulled (black), whereas the involved myocardial segments will have a prolonged washout from decreased capillary density, causing shortening of T1 and therefore a higher or brighter signal.[69]

Several patterns of LGE have been described in patients with ChHD, including subendocardial and transmural (both are difficult to distinguish from prior myocardial infarction), midwall, or subepicardial. LGE tends to more commonly involve the basal inferolateral segments and LV apex (Figure 15, Video 3; available at www.onlinejase.com). Myocardial fibrosis can be found in up to 8% of patients with positive serology for ChD despite normal ECG and echocardiographic findings.[70] Importantly, the presence and extent of myocardial fibrosis correlate well with the New York Heart Association functional class and likelihood of ventricular arrhythmias, particularly when a transmural pattern is found extending beyond two or more contiguous segments.[71,72] In addition, myocardial fibrosis inversely correlates with LV systolic function.[5] Therefore, assessment of fibrosis by LGE imaging has been shown to be an excellent marker of disease severity.

CMR with LGE imaging can also evaluate thromboembolic risk. Specifically, the high spatial resolution of CMR makes it the best imaging modality to detect intracardiac thrombi related to LV aneurysms. LV thrombus, which carries a high risk for stroke and peripheral embolism, could be missed by echocardiography in patients with limited image quality, even when using ultrasound contrast agents.[73,74]

Although CMR imaging is an excellent tool for the risk stratification and prognosis of patients with ChD, it is not readily available to most patients living in rural endemic areas. In addition, CMR studies in patients who have received prior implantable cardiac devices such as defibrillators, conventional pacemakers, and cardiac resynchronization devices, are at this time relatively contraindicated.

***Cardiac CT.*** The literature on cardiac CT in ChD is limited to isolated case reports. Data acquisition is performed following intravenous iodine contrast injection with ECG synchronization. Different scanning protocols are available that can be restricted to imaging only the diastolic phase (prospective acquisition, less radiation, and commonly used for coronary computed tomographic angiography) or imaging the entire cardiac cycle (retrospective acquisition, more radiation), which allows quantification of cardiac function. The 3D data set is postprocessed offline using multiplanar reconstruction for visualization of the entire cardiovascular anatomy in any given plane, with excellent spatial resolution.

Similar to CMR image acquisition, cardiac arrhythmias such as atrial fibrillation or premature atrial or ventricular contractions can produce image artifacts, making it difficult for study analysis and interpretation. Technological advances with availability of a larger number of detector rows (i.e., ≥256) allows volumetric coverage of the entire heart with one beat, therefore minimizing some of these problems.

Cardiac CT could be considered in three particular clinical scenarios for patients with ChD: (1) To exclude significant coronary artery disease in patients with low to intermediate pretest probability. This differential diagnosis could be particularly challenging in patients with ChHD presenting with cardiomyopathy and/or wall motion abnormalities. Coronary computed tomographic angiography has an excellent negative predictive value to exclude coronary artery disease in patients with low and intermediate pretest probability.[75] (2) In the planning of complex electrophysiologic procedures. Patients with ChHD have larger epicardial compared with endocardial substrate

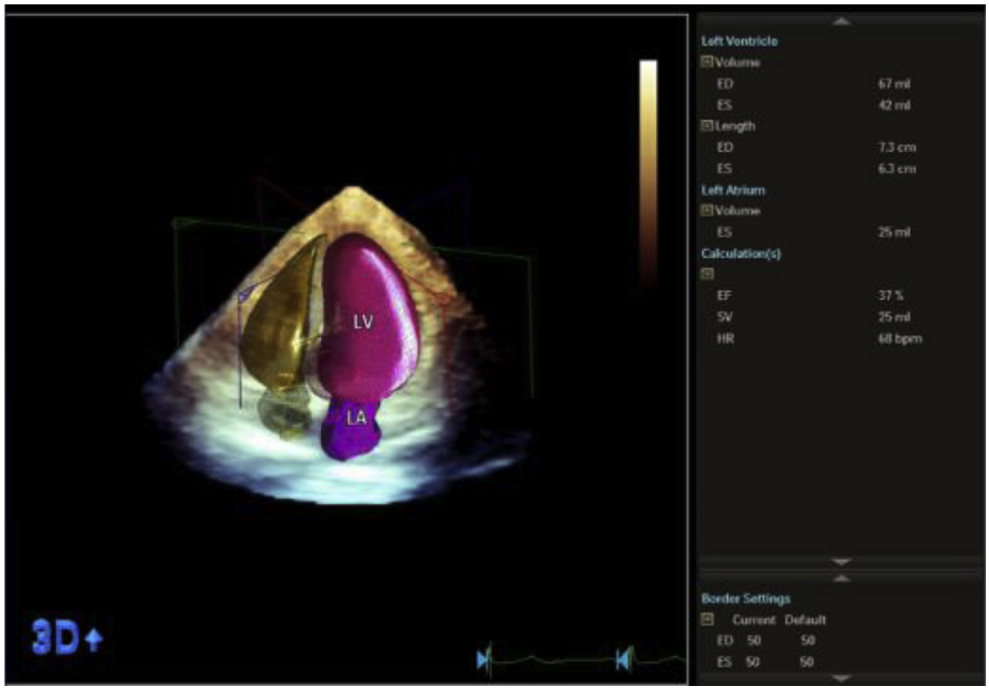


**Figure 11** LVEF by 3D echocardiography. Three-dimensional four-chamber apical view of a 56-year-old man with HF in New York Heart Association functional class III and depressed left ventricular systolic function. Evaluation of left ventricular volumes and LVEF was done by 3D echocardiography using an automated adaptive analytics algorithm for quantification. LV end-diastolic (ED) volume was 67 mL; LV end-systolic (ES) volume was 42 mL; LVEF was 37%; left atrial end-systolic volume was 25 mL. *HR*, Heart rate; *LA*, left atrium; *LV*, left ventricle; *SV*, stroke volume.

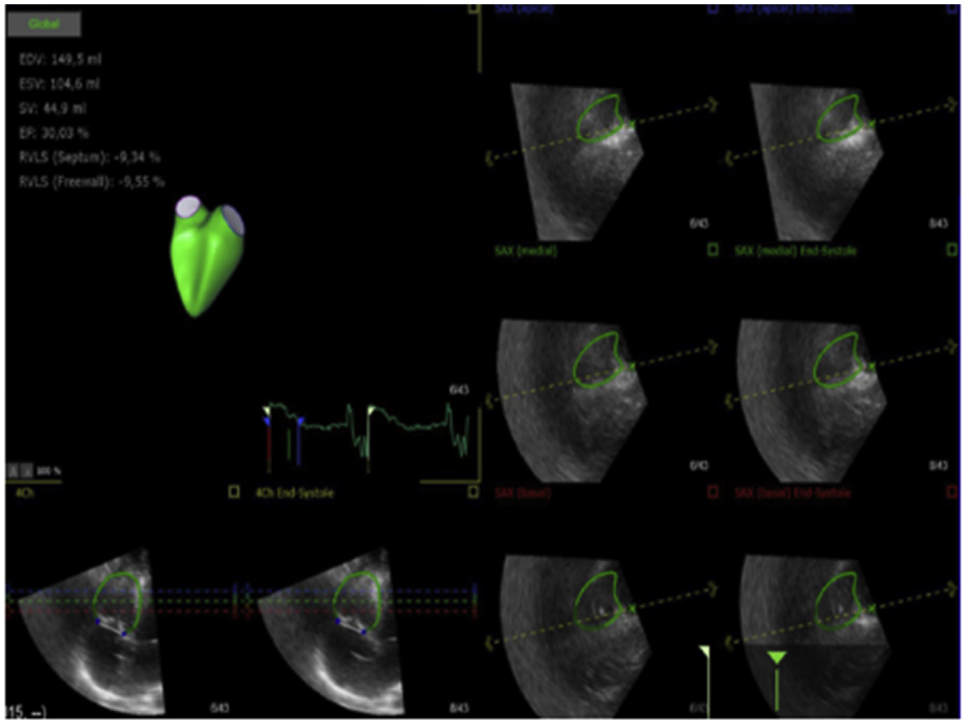


**Figure 12** RV function by 3D echocardiography. RV 3D echocardiography in a 49-year-old patient with ChHD and HF presenting in New York Heart Association functional class III. In addition, the results for RV longitudinal strain (RVLS) by speckle-tracking are shown *(top left)*. RV end-diastolic volume (EDV) was 149.5 ml; RV end-systolic volume (ESV) was 104.6 ml; RVEF was 30%; RV stroke volume (SV) was 44.9 mL; septal RVLS was −9.34%; free wall RVLS was −9.55%.

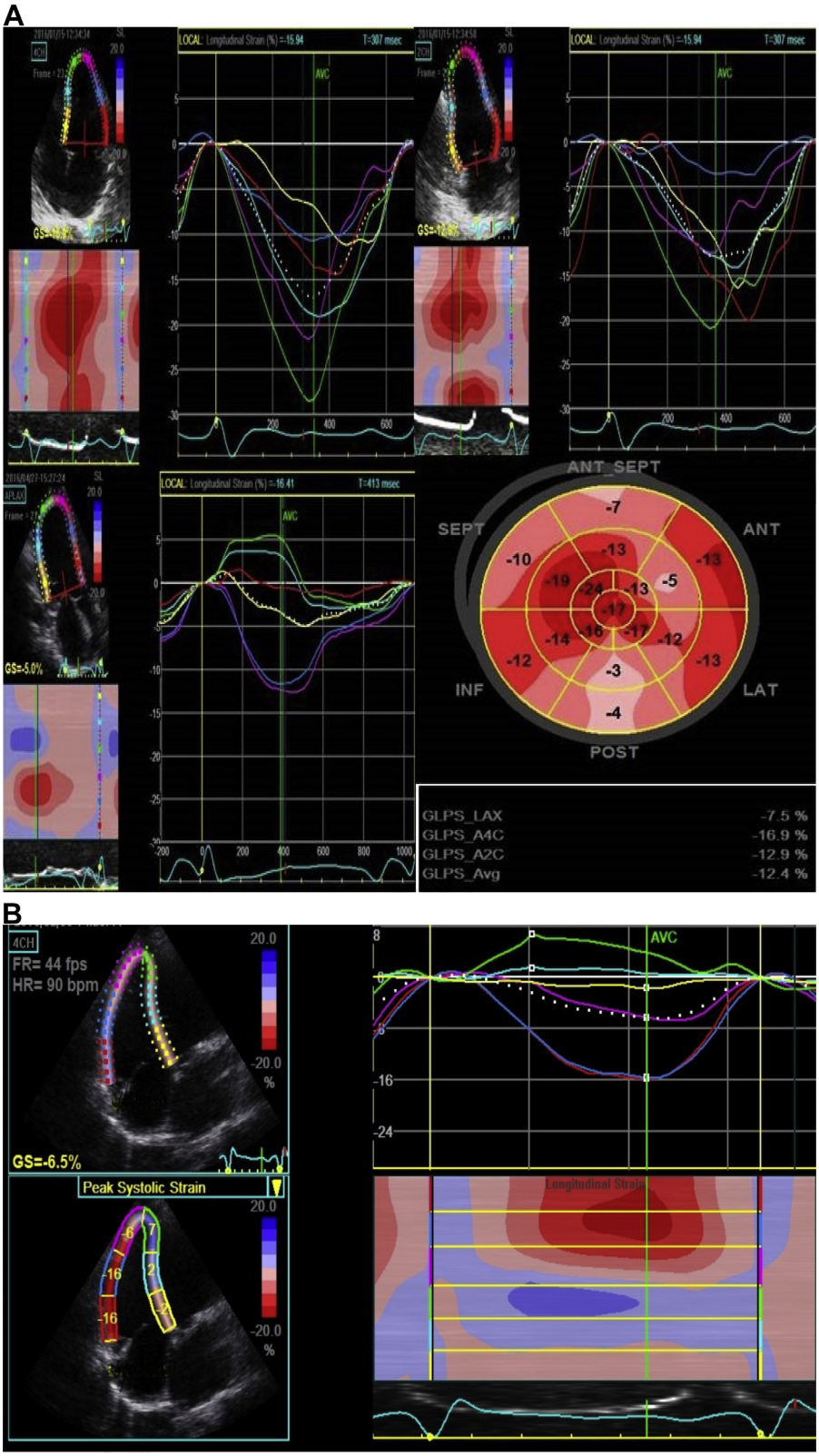


Figure 13 Global longitudinal strain of the left and right ventricles. **(A)** Abnormal LV longitudinal strain findings in a patient with ChHD with right bundle branch block, reduced LVEF, and prior symptoms of heart failure (stage C). *(Top left)* LV longitudinal strain in apical four-chamber view; note the delayed peak strain of the septal segments *(yellow and blue tracings)* typical of right bundle branch block. *(Top right)* Apical two-chamber view. *(Bottom left)* Apical three-chamber view. *(Bottom right)* "Bull's-eye" plot of strain values for each myocardial segment. **(B)** Abnormal findings of RV longitudinal strain (global strain [GS] was −6.5%, free wall strain was −12.6%) in a patient with ChHD (asymptomatic with abnormal ECG findings and decreased LVEF, stage B2). *(Top left)* Apical four-chamber view. *(Bottom left)* Regional strain values. *(Top right)* Time-strain curves. *(Bottom right)* M-mode parametric colorization. *4CH*, Four-chamber; *A2C*, apical two-chamber; *A4C*, apical four-chamber; *ANT*, anterior; *ANT_SEPT*, anteroseptal; *AVC*, aortic valve closure; *Avg*, average; *FR*, frame rate; *GLPS*, global longitudinal peak strain; *HR*, heart rate; *INF*, inferior; *LAT*, lateral; *LAX*, long-axis; *POST*, posterior; *SEPT*, septal.

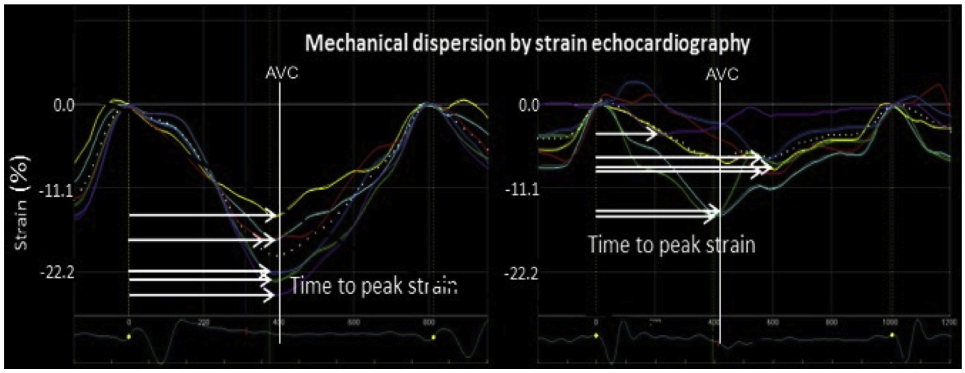


**Figure 14** Mechanical dispersion by myocardial strain imaging. Longitudinal strain curves from apical four-chamber view displaying six of the 18 LV segments used to calculate mechanical dispersion. *(Left)* Mechanical dispersion in a patient with ChHD without ventricular arrhythmias. *(Right)* A patient with ChHD who presented with LV dysfunction and a previous episode of sustained ventricular tachycardia. The time to maximal myocardial shortening of longitudinal strain was markedly dispersed compared to the patient without arrhythmias. *AVC*, Aortic valve closure.

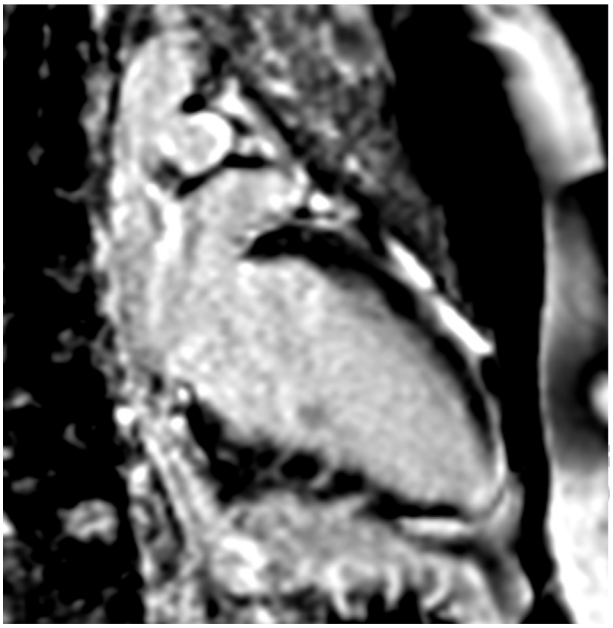

**Figure 15** CMR with LGE. Small, focal LV apical aneurysm in a 25-year-old patient with ChHD presenting with a stroke. Delayed gadolinium enhancement shows an LV aneurysm with myocardial fibrosis (*white* within the apical myocardium). Video 3 with cine noncontrast CMR shows the apical dyskinesis and small aneurysm.

areas for ventricular arrhythmias.[7] This puts patients at risk for coronary artery injury during ablation, a complication that can be avoided by properly planning the procedure with advanced imaging. Coregistration of cardiac computed tomographic 3D data sets with electroanatomic mapping data allows better understanding of the anatomic relationship of the arrhythmia-substrate areas and the coronary arteries, therefore increasing ablation safety.[73] (3) To evaluate LV function and morphology in patients with difficult echocardiographic windows who are unable to undergo CMR because of device incompatibility. Retrospective gated acquisition following intravenous contrast injection can provide quantification of cardiac function as well as detection of regional wall motion abnormalities, apical aneurysms, and intracardiac thrombi.

## Key Points

- CMR is a versatile imaging modality for ChHD, allowing exquisite visualization of heart function, anatomy, and tissue characterization.
- Presence of myocardial fibrosis by CMR with LGE imaging has been associated with increased cardiac arrhythmias and risk for sudden cardiac death.
- Cardiac CT can provide ancillary noninvasive evaluation of coronary artery anatomy and atherosclerosis. Coregistration of 3D data sets with electrophysiologic electrical mapping during ablations might improve procedural safety and outcomes.

### IV.d. Nuclear Medicine

Various nuclear medicine imaging modalities have been used to assess biventricular function, myocardial perfusion, innervation, and inflammation in patients with ChD. Those with proven clinical value are described here.

***Radionuclide Planar Gated Angiography.*** This method can be used for the evaluation of global biventricular function in patients for whom echocardiography is hindered by technical problems, preventing optimal imaging or adequate quantitative evaluation.[76-78] This method was once considered the gold standard for the measurement of LVEF because it allows the averaging of hundreds of cardiac cycles without resorting to any geometric assumptions in the usually distorted LV shape exhibited by patients with ChHD with aneurysms or other wall motion abnormalities.

***Single-Photon Emission Computed Tomographic Myocardial Perfusion Scintigraphy.*** In patients with ChHD, perfusion defects may be related to concomitant epicardial coronary disease or, more frequently, to microvascular disease in the setting of normal results on coronary angiography. More specifically related to ChHD, fixed perfusion defects seen during both stress and rest conditions predominate in LV regions exhibiting advanced wall motion impairment (such as akinesis or dyskinesis) and are interpreted as representing areas of fibrosis. Reversible perfusion defects, on the other hand, denote the occurrence of myocardial ischemia due to microvascular flow disturbances. These ischemic defects have been described even in Chagas patients with the indeterminate form of the disease and are topographically correlated with myocardial areas exhibiting more significant wall motion abnormalities at later stages of the cardiomyopathy.[79,80] Moreover, the increase over time in the extent

of myocardial fibrosis, as denoted by the transformation of previously reversible into fixed perfusion defects, correlates with a decrease in LVEF.[81]

***Myocardial Sympathetic Innervation Imaging.*** Myocardial scintigraphy with $^{123}$I-metaiodobenzylguanidine can be used for the in vivo assessment of cardiac sympathetic innervation integrity in patients with ChHD. Regional sympathetic denervation is an early derangement in the pathophysiology of ChHD, preceding the development of regional LV contraction disturbances. In fact, abnormal metaiodobenzylguanidine uptake has been shown in most Chagas patients with no apparent cardiac involvement.[31,82] Impaired regional myocardial sympathetic innervation has also been associated with the occurrence of sustained ventricular tachycardia in patients with ChHD.[83,84]

## V. VENTRICULAR FUNCTION

### V.a. LV Systolic Function

Echocardiography is the imaging modality of choice to determine LV structure and function in ChD, complementing information provided by clinical status and electrocardiography.[4,47] In selected asymptomatic patients with normal ECG findings, further evaluation with echocardiography may be recommended to classify the presence and severity of myocardial damage, based mainly on detection of subtle regional wall motion defects.[4]

*T. cruzi*–infected patients in the indeterminate form may have subtle changes in LV segmental contractility detected either by conventional or speckle-tracking echocardiography.[61,85] Once the disease progresses to heart damage with development of ECG changes consistent with ChHD, increased LV diameters associated with segmental wall motion abnormalities are usually seen. In more advanced disease with HF, diffuse hypokinesis with enlargement of all cardiac chambers is the predominant characteristic (Figures 4 and 5).[47,86]

Regional LV contractility abnormalities represent a characteristic aspect of ChD and may occur in any stage of the disease. The frequency of these abnormalities varies according to the stage of the disease. In asymptomatic patients with preserved LVEF, wall motion abnormalities can be detected in up to 10% of patients, particularly in inferolateral basal segments (Figures 6–9).[48] As the disease progresses to a dilated cardiomyopathy, the prevalence of regional abnormalities increases to approximately 50% of patients.[47,87] Although segmental wall motion abnormalities are one of the most common findings of cardiac involvement in ChD, the mechanism has not been defined. It has been hypothesized that microvascular involvement leads to ischemia in distal areas of the coronary territories.[88] The diagnosis of LV segmental lesions is essential, because it permits the identification of individuals at risk for worsening of LV function and ventricular arrhythmias.[66,89,90]

Apical aneurysm is a hallmark of ChHD, so the presence of apical aneurysms may help differentiate this disease from idiopathic cardiomyopathy.[37,48] The prevalence of aneurysms varies widely, because of the heterogeneity of the population analyzed and the accuracy of the imaging method used for its diagnosis. Importantly, apical aneurysms may be missed if a detailed echocardiographic examination is not performed. To better identify apical aneurysms, multiple views, often unconventional or foreshortened with the transducer slightly angled to visualize the apex, may be required. An apical aneurysm is usually defined as a well-delineated dyskinetic area with marked wall thinning at the apex involving opposing walls and limited by an area of normal contraction. Aneurysm size is variable (Figures 6, 8, and 9) and is frequently difficult to distinguish from a healed transmural myocardial infarction.[48] LV apical aneurysms are found in 8.5% of asymptomatic patients, but this increases to 55% (ranging from 47% to 64%) in patients with moderate or severe LV systolic dysfunction. RV aneurysms are unusual, but some patients have apical aneurysms affecting both ventricles. An autopsy study showed that 82% of aneurysms were found at the LV apex, 9% in the right ventricle, and 9% in both ventricles.[91]

Mural thrombi can be associated with aneurysms (Figure 6) and are important risk factors for systemic embolisms in patients with ChHD.[91-94] The prevalence of LV thrombus in clinical studies is approximately 20%, but it may be higher in more advanced disease stages, as suggested by autopsy studies that showed LV thrombosis in 35% to 44% of patients with ChHD who died of congestive HF or sudden cardiac death.[95,96]

***Assessment of LV Systolic Function by Echocardiography.*** The quantification of LV size and function constitutes one of the earliest indications for echocardiography. The accuracy of the determination of global and regional LV function with echocardiography has improved dramatically over the past decade with several technological developments.[97]

A pioneering study using M-mode echocardiography demonstrated hypokinesis of the posterior wall with relative preservation of septal motion in patients with ChHD (Figure 7).[46] In advanced ChHD, a diffuse hypokinesis was detected with a nonspecific pattern, indistinguishable from idiopathic cardiomyopathy.[98]

Previous studies have used the change in the M-mode LV dimension from diastole to systole to calculate the percentage of fractional shortening and LVEF. However, this method is no longer recommended in ASE guidelines[45] and is particularly unreliable in patients with ChD with pronounced LV dilation or in those with either marked segmental wall motion abnormalities or aneurysms. Therefore, most recent studies have used 2D echocardiography for the assessment of LV function and to quantify LVEF.

Three-dimensional echocardiography has been shown to quantify LV volumes and function more accurately, as no geometric assumptions are required (Figure 11). Given the frequency of segmental abnormalities and aneurysms, it seems most appropriate to include full volume 3D echocardiography of the left and right ventricles in any echocardiographic examination of patients with suspected ChHD. However, there are limited data to date on the additional value of 3D echocardiography for the evaluation of the left ventricle and left atrium in ChD.[65,99]

Regardless of the parameter used to estimate ventricular systolic dysfunction, the most consistent independent risk predictor of mortality in ChD is impaired LV function.[39] In a systematic review, echocardiographic or cine ventriculographic evidence of decreased contractility, either qualitatively or quantitatively expressed, was found to be strongly associated with an increased risk for mortality in the majority of the studies reviewed.[100] Although LVEF has been the most widely used prognostic variable, other echocardiographic parameters have been reported to be useful in the risk stratification of patients with impaired LV systolic function.[101,102] Additional information about myocardial perfusion and fibrosis from CMR or single-photon emission computed tomographic imaging can help assess prognosis (see specific sections in this document for more details).

## Key Points

- Echocardiography is the most common imaging modality used to detect cardiac involvement in patients with ChD, even in those with normal ECG findings.
- Segmental LV wall motion abnormalities may be found in early stages of the disease, especially at the apex and in the inferior and inferolateral walls.
- Apical aneurysms are the hallmark lesion in ChD, which is helpful in distinguishing ChHD from other cardiomyopathies.
- Late manifestation of ChD is characterized by diffuse LV hypokinesis with enlargement of all cardiac chambers.
- LV systolic dysfunction is a powerful predictor of mortality in ChD.

### V.b. LV Diastolic Function

Assessment of diastolic function includes evaluation of myocardial relaxation, ventricular stiffness, and estimation of LV filling pressures. As in other cardiomyopathies, diastolic dysfunction usually precedes systolic dysfunction.[103,104] Therefore, it is reasonable to assume that most patients with myocardial disease also have diastolic dysfunction. As recommended by the updated ASE and European Association of Cardiovascular Imaging guidelines, evaluation of diastolic function and LV filling pressures is based mostly on four parameters: LA volume index, peak tricuspid regurgitation velocity, mitral annular tissue Doppler velocity (e′), and E/e′ ratio.[105] Diastolic dysfunction is initially manifested by impaired relaxation, an energy-dependent process that leads to a reduction in early passive filling of the left ventricle and increase in active filling (low E and high A waves in mitral inflow, grade I diastolic dysfunction).[106] With the development of systolic dysfunction, the increase in diastolic volume produces a rise in diastolic pressures that results in a decrease in atrial contribution to ventricular filling, an increase in LA pressure, and LA dilatation (grade II). Patients with HF typically show grade II or III diastolic dysfunction with a decrease in atrial function (high E and low A waves).

***Doppler Tissue Imaging.*** Peak e′ velocity obtained by pulsed Doppler tissue imaging is decreased in patients with ChD with ECG abnormalities, systolic dysfunction, and HF but is frequently normal in the indeterminate form. The combined use of peak velocity of the E wave of mitral flow and e′ (E/e′ ratio) is a surrogate for LV end-diastolic filling pressures (E/e′ $<$ 8 reflects normal pressures, and E/e′ $\geq$ 15 reflects elevated pressures).[105] E/e′ is gradually increased from indeterminate to more advanced forms of ChHD.[107-109] An elevated E/e′ ratio $>$ 15 is a strong predictor of poor outcomes in patients with ChHD with mild to moderate LV dysfunction,[102] and it correlates with functional class, brain natriuretic peptide level, and detection of fibrosis by gadolinium delayed enhancement with CMR.[110] However, patients with ChHD may present with some confounding factors, including atrial fibrillation or RV pacing, that limit the accuracy of mitral annular velocities and E/e′ ratio in the assessment of diastolic function.

***Color M-Mode Flow Velocity Propagation.*** Flow velocity propagation is decreased in patients with ChD with systolic dysfunction and HF but may be normal in patients without ECG and regional contraction abnormalities.[47] The apical contractility abnormality may contribute to a diminished diastolic suction in patients with ChHD, showing a decreased slope of flow propagation velocity.

## Key Points

- LV diastolic dysfunction is a common finding in early stages of Chagas cardiomyopathy because of extensive fibrotic changes in the myocardium.
- Evaluation of diastolic function by means of E/e′ and LA volume index has additional, independent prognostic value in patients with systolic dysfunction and HF.
- The accuracy of some variables used to assess diastolic function (such as E and e′) is reduced in the presence of arrhythmias and RV pacing, which is common in patients with ChHD.

### V.c. RV Function

The right ventricle is composed of three parts, inlet, main cavity, and outlet (infundibulum), giving it a complex geometry that is difficult to analyze in a single biplane view and making its volume calculation impossible by the use of 2D geometric assumptions. In addition, the thin walls, prominent trabeculations, and presence of the moderator band further contribute to the difficult task of defining the RV endocardial borders. Thus, as opposed to the left ventricle, RVEF by 2D echocardiography is not recommended. Although 3D echocardiography seems to be a promising technique, it is still difficult to obtain adequate RV images to allow a routinely useful RVEF calculation in clinical practice. Instead, other easier to obtain parameters have been shown to be clinically useful and are recommended by recent ASE guidelines.[45,111,112] These parameters are tricuspid annular plane systolic excursion (obtained by M-mode echocardiography of the tricuspid valve annulus), fractional area change (obtained by the difference between the end-diastolic and end-systolic RV areas, divided by the diastolic area times 100), tissue Doppler systolic velocity of the tricuspid annulus (RV s′), and RV myocardial performance index (Tei index, which expresses both RV systolic and diastolic function). Although indices such as tricuspid annular plane systolic excursion and RV s′ express basal, longitudinal contractility, they have good correlation with RV global systolic function and may be useful for assessing RV systolic function in a variety of clinical scenarios. More recently, strain has emerged as an echocardiographic tool for the mechanical evaluation of the ventricles, allowing the detection of subclinical dysfunction, while traditional indices of systolic function, such as ejection fraction, are still preserved. RV free wall strain (Figure 13B) is a novel technique for evaluating RV systolic function in ChD.[113]

***The Right Ventricle in ChD.*** RV involvement is common in ChHD and has been described even in the indeterminate form by nuclear and biopsy studies.[98,114,115] However, in clinical practice, RV dysfunction assessed by traditional methods of echocardiography is usually not seen in the absence of LV dysfunction.

RV dysfunction in ChHD seems to be multifactorial and could be generated by the burden of chronic pulmonary hypertension secondary to LV systolic dysfunction or, most importantly, by direct damage to the RV myocardium with chronic myocarditis with progressive fibrosis that affects the myocardium of both ventricles. Chagas patients with RV dysfunction may have low cardiac output without clinical evidence of elevated LV filling pressures or pulmonary congestion, so they can be surprisingly stable clinically without acute symptoms of dyspnea. However, RV dysfunction is still related to an ominous prognosis.[116]

***RV Evaluation by Echocardiography in ChD.*** Few studies have systematically analyzed the RV in the context of ChD. However, early abnormalities have been described even in the indeterminate form, such as shortening of the RV isovolumetric contraction time or low RV s′ on Doppler tissue imaging.[117,118] Moreover, RV Tei index

provides incremental prognostic information to that of more traditional risk factors, such as New York Heart Association functional class and LV function.[116] The value of RV strain is still unclear in ChD.[61,113] Occasionally, RV apical aneurysm is the only detectable abnormality.[91]

***RV Evaluation by CMR.*** CMR in ChD has been used almost exclusively for LV evaluation. However, the incremental value of CMR to other traditional imaging modalities in structural and functional evaluation of the right ventricle has been recently highlighted.[119] Although less commonly present, similar features to those described for the left ventricle can be explored and described in the right ventricle (RVEF, aneurysms, thrombus, fibrosis, and inflammation patterns).[113,119] Advanced RV dysfunction is frequently present in ChHD once severe LV dysfunction has developed.

### Key Points

- RV dysfunction is a typical feature of chronic Chagas cardiomyopathy.
- Although more frequently found in the presence of LV dysfunction, RV dysfunction has been described in patients with the indeterminate form of ChHD.
- Because of inherent anatomic and functional peculiarities linked to the morphology of the right ventricle, diagnosis of early RV dysfunction in ChHD is sometimes challenging using most echocardiographic approaches and is more amenable to methods such as CMR or radionuclide angiography.

## VI. RECOMMENDATIONS FOR THE USE OF IMAGING MODALITIES ACCORDING TO THE STAGE OF THE DISEASE: DIAGNOSTIC, MONITORING, AND PROGNOSTIC IMPLICATIONS

### VI.a. Acute ChD

As stated previously, acute ChD is frequently unrecognized, and most patients with chronic ChD do not remember having been acutely ill. Therefore, reports of acute disease are very limited and reflect the findings of patients who were particularly symptomatic and more likely to seek medical attention. Electrocardiography has been used extensively for the detection of cardiac abnormalities in acute ChD, partly because of its low cost and portability. In contrast, echocardiography has been incorporated only more recently. The largest published echocardiographic series on acute ChD included 58 subjects, with a prevalence of abnormal echocardiographic findings slightly higher than 50%.[120] Pericardial effusion was the most common abnormal finding on echocardiography (42% of cases), while decreased LVEF was present in 37%. Apical or anterior dyskinesis was found in 21%, and only 6% had LV dilation. Abnormal ECG findings were present in 41%. Acute myocarditis was documented by myocardial biopsy or necropsy in half of the patients.

There have been a few reports of groups with orally transmitted Chagas infection.[121,122] In these patients, beverages or food were contaminated either by infected triatomines or their feces. The absence of contact with the vector and of traditional cutaneous and Romaña signs (eye swelling) may confuse the diagnosis of orally transmitted ChD with other more common infections. The clinical presentation may be severe because of the massive load of parasites. The majority of patients were symptomatic and 59% showed ECG abnormalities. Echocardiographic findings were similar to those described in the previous paragraph. Importantly, as its presentation is frequently vague in symptoms and ECG and echocardiographic findings, the likelihood of suspecting acute ChD in nonendemic areas is actually very low.

ChD reactivation could happen in the setting of immunosuppression and may present similarly to acute ChD. Sporadic case reports exist in patients with human immunodeficiency virus or with drug-induced immunosuppression such as after transplantation.[123]

In summary, among the few series reported of acute ChD with echocardiographic examination, symptoms were present in 98% of patients.[120,121,124-126] The most common echocardiographic finding was mild to moderate pericardial effusion, with some cases of tamponade requiring pericardial drainage. Signs of congestion due to HF or cardiac tamponade were observed in 24%, diminished LVEF in 35%, and regional wall motion abnormalities in 28%, while ECG abnormalities were the most frequent finding.

### Recommendations

- Echocardiography should be performed whenever acute ChD is suspected.
- A febrile illness accompanied by myocarditic findings on echocardiography and/or pericardial fluid should raise suspicion for acute ChD in endemic countries and in Latin American immigrants with immunosuppressed states living in nonendemic countries.
- As acute myocarditis is a common cardiac presentation, assessment of ejection fraction and wall motion abnormalities is of critical importance.
- Hypotension may be a sign of hemodynamically significant pericardial effusion leading to cardiac tamponade.

### VI.b. Chronic ChD

The spectrum of chronic ChD spans from the indeterminate form to overt HF (Figure 1). Stages A and B are silent or asymptomatic and can last for many years or decades. Indeed, in most patients the disease never progresses to the more advanced symptomatic stages C and D. The role of cardiac imaging and the frequency of examinations is different for each of these stages.

***VI.b.i. Silent or Asymptomatic ChD (Stages A, B1, and B2): Monitoring of LV Function and Myocardial Damage.*** Chronically infected individuals become an intermediate-phase reservoir of *T. cruzi* infection known as the indeterminate phase. This is defined by the presence of two general criteria: (1) at least two positive serologic tests based on the detection of a specific immunoglobulin G antibody or a positive direct demonstration of the parasite in blood or tissue and (2) the absence of signs and symptoms of ChD.[127,128] More than two thirds of *T. cruzi*–infected individuals remain in the clinically indeterminate phase throughout their lives.[129] However, some of these patients evolve to a chronic form with clinically evident heart involvement. Conversion to ChHD with new ECG abnormalities or evidence of definite cardiomyopathy has been reported at rates of 1.8% to 5% per year.[35,129] This rate of conversion may be higher if cardiac examination is performed with more sensitive imaging techniques for detection of early myocardial damage, such as advanced echocardiography (strain) or CMR (for fibrosis and inflammation).[4,61,70] Indeed, anatomopathologic studies with endomyocardial biopsy have demonstrated fibrosis or inflammatory cardiac damage in patients with ChD with no otherwise apparent cardiomyopathy.[130]

Electrocardiography has been the traditional modality of choice for ChD, both because of the specificity of its findings in endemic areas and because of the excellent prognosis associated with normal ECG findings. Echocardiography, although more difficult to provide in a resource-limited environment, is the most useful imaging tool

for the evaluation, classification, and follow-up of patients with ChHD, including those with the indeterminate form.[4] In early stages of cardiac involvement, echocardiography may demonstrate segmental LV wall motion abnormalities (anywhere in the spectrum from hypokinesis to dyskinesis or aneurysms) and diastolic dysfunction, even when ECG findings are normal.[47,131,132] The LV areas most commonly involved are inferior, inferolateral, and apex and frequently do not respect the distribution of coronary artery territories.[48] These segmental abnormalities could identify individuals at risk for ventricular function deterioration or ventricular arrhythmia on Holter[89,90] and should, in fact, reclassify the patient to the chronic stage of ChHD (stage B1).

ChD also leads to impairment of LV diastolic function, which can occur early in the process, including in patients without LV systolic dysfunction. The prevalence and severity of diastolic dysfunction gradually increase as the disease progress from the indeterminate form (present in 10% of cases) to more advanced stages, in which it is found in nearly all patients.[65,108,110]

The use of advanced imaging modalities such as CMR in the early, subclinical stages of ChD is limited by their cost and availability. Although there is additive value compared with electrocardiography and echocardiography, the clinical significance of CMR-specific findings during these early stages is still unclear. In patients with the indeterminate form, the presence of myocardial fibrosis (by LGE), edema (hyperintensity in T2-weighted sequences), and hyperemia (T1-weighted myocardial early gadolinium enhancement sequences) has been demonstrated in 12%, 31%, and 25% of cases, respectively.[68] Whether early therapeutic interventions would be justified on the basis of these findings seems to be unlikely, as patients with the undetermined form of the disease have an excellent prognosis, and their life expectancy is similar to individuals without ChD.[129]

Evaluation of LV function is of great value in determining ChD prognosis because LV dysfunction is one of the most consistent independent predictors of death identified in most series.[37] Given the wide availability, low cost, and high accuracy in cardiac function evaluation, it is recommended to consider performing echocardiography as part of the initial evaluation of patients with positive serology and whenever there are changes in clinical or electrocardiographic status.

## Recommendations

- Electrocardiography and echocardiography should be performed as part of the initial evaluation of all patients with newly diagnosed ChD, to exclude LV dysfunction and aneurysms as well as conduction abnormalities (right bundle branch, left anterior fascicular, and atrioventricular block) or arrhythmias.
- ECG follow-up is reasonable at least every 2 to 5 years in patients with ChD with the indeterminate form.
- Echocardiography should be performed if any changes in ECG findings or clinical condition suggesting possible HF are noted.
- The use of advanced imaging modalities to detect silent myocardial damage (such as strain imaging or CMR) in the indeterminate stage is currently not recommended, as it has limited clinical value.

***VI.b.ii. Symptomatic Chronic ChHD (Stages C and D).*** Morbidity and prognosis of patients with advanced ChHD is almost exclusively related to three conditions: HF, thromboembolism, and cardiac arrhythmias. The goals of imaging are to identify the substrate for these conditions to occur, that is, the presence of LV dysfunction and mitral regurgitation, LV aneurysms or mural thrombus, and myocardial fibrosis and/or inflammation. To achieve these goals, a comprehensive echocardiographic examination should be done according to the ASE chamber quantification and valvular regurgitation guidelines, which would include 2D, Doppler, and preferably more advanced novel techniques such as 3D echocardiography and strain.[45,53] CMR can also achieve all these goals and should be considered an alternative to echocardiography or in some cases as a complementary technique.

***VI.b.ii.1. LV Function and HF.*** As previously stated, a prominent feature of HF due to ChHD involves the inflammation with subsequent necrosis and reparative fibrosis of the myocardium in both atria and ventricles and the specialized intracardiac conduction system. HF in chronic Chagas myocarditis can present with regional wall motion abnormalities or LV global systolic dysfunction (typically in more advanced stages of the disease).

Although in essence the clinical presentation has similar characteristics to other dilated cardiomyopathies, a worse prognosis for patients having HF of Chagas etiology has been suggested.[133]

Basic Imaging Goals for Patients at Risk or Presenting with HF:. Although echocardiography is the preferred method, CMR or other imaging modalities could achieve most or some of these goals:

- Determine the LVEF by 3D echocardiography or the method of disks and grade as normal, mild, moderate, or severe global LV systolic dysfunction.
- Evaluate the presence, location, and grade of regional wall motion abnormalities using a 16-segment model of the left ventricle, including description of aneurysms.
- Estimate LV remodeling by measuring LV dimensions and volumes.
- Evaluate RV dimensions and function by fractional area change, tricuspid annular plane systolic excursion, and RV s′.
- Evaluate the presence and grading of LV diastolic dysfunction by using E/A mitral inflow ratio, mitral annular e′, tricuspid regurgitation velocity, and LA volume index. In addition, estimate LV filling pressures by using the E/e′ ratio.[105]
- Estimate systolic pulmonary artery pressure by peak tricuspid regurgitation velocity (if tricuspid regurgitation is present).
- Estimate right atrial pressure by measuring the inferior vena cava diameter during expiration and the percentage of reduction in the inspiratory phase.
- Evaluate for the presence, severity, mechanism, and etiology of mitral and tricuspid regurgitation.
- Evaluate for the presence of thrombi in the atria and ventricles.

***VI.b.ii.2. Thromboembolism.*** Thromboembolic events are relatively frequent in ChD and represent the third most common cause of death in this entity.[92,134,135] Even early stages of the disease may present with dyskinetic segments or ventricular aneurysms, predisposing to thromboembolism.[93] Although aneurysms are the most significant source of thrombus, advanced cardiomyopathy also predisposes to other embolic sources such as atrial fibrillation or venous stasis. Therefore, careful examination of the LA appendage (in patients with atrial fibrillation or flutter), pacemaker or implantable cardioverter-defibrillator leads, and so on, by transesophageal echocardiography may be warranted. Importantly, embolic events could present both as systemic and as pulmonary embolism. Stroke is the most common clinically recognized form of embolism, followed by limb ischemia and pulmonary embolism. Ventricular dysfunction, apical aneurysms (Figure 6), mural thrombus, LA enlargement with blood stasis, and cardiac arrhythmias are important risk factors for thrombosis in ChD that should be evaluated in patients with ChHD presenting with thromboembolism.[93]

Basic Imaging Goals for Patients at Risk or Presenting with Thromboembolism:.

- Determine the presence, location, and size of potential sources of embolism (left ventricle, right ventricle, LA appendage, cardiac devices, etc.). This evaluation may require advanced imaging modalities such as contrast echocardiography, transesophageal echocardiography, CMR, or cardiac CT.

***VI.b.ii.3. Cardiac Arrhythmias.*** Cardiac arrhythmias play a significant role in the natural history and prognosis of patients with Chagas cardiomyopathy.[136] Sudden cardiac death remains one the leading causes of death in ChHD and is usually triggered by malignant ventricular arrhythmias that are almost invariably related to regional scarring and fibrosis, resulting in regional wall motion abnormalities. As with other cardiomyopathies, 2D echocardiography is the most readily available and cost-effective test for assessment of LV and RV function and detection of wall motion abnormalities and LV aneurysms, all of which are important variables to determine prognosis and disease progression.[4,89,133,137] Wall motion abnormalities, mechanical dispersion, and abnormal global longitudinal strain (Figures 13 and 14) have been associated with a higher frequency of ventricular arrhythmias even in the presence of preserved global LV systolic function.[47,66,89]

CMR provides additional information that may improve prediction of malignant ventricular arrhythmias and sudden cardiac death. ChHD is characterized by diffuse myocardial fibrosis that can be detected by delayed enhanced gadolinium techniques, defining the substrate for ventricular tachycardia.[72] These malignant rhythm disturbances may also be detected in association with irreversible perfusion defects seen with myocardial scintigraphy or with regions of ventricular sympathetic denervation as shown by metaiodobenzylguanidine myocardial scintigraphy.

### Basic Imaging Goals for Patients at Risk for or Presenting with Malignant Arrhythmias:.

- Two-dimensional echocardiography is recommended as the preferred imaging tool in patients with Chagas cardiomyopathy, as it provides information on prognostic variables such as LVEF and segmental wall motion abnormalities.
- CMR can provide detailed insight into the myocardial substrate for malignant arrhythmias by accurate assessment of LVEF, regional wall motion abnormalities, and detection of myocardial fibrosis and edema.
- Nuclear medicine methods constitute alternative ways to stratify risk for malignant arrhythmia in patients with ChHD by detection of perfusion defects, myocardial fibrosis, and regional sympathetic denervation.

## Recommendations for Imaging in Symptomatic Stages of ChHD

- The overall goals of imaging are to identify the substrate for HF, thromboembolism, and malignant arrhythmias such as the presence of LV dysfunction, LV aneurysms or thrombus, myocardial fibrosis or inflammation, and regional sympathetic denervation.
- Although echocardiography is in general the preferred method, CMR is a valuable alternative and could achieve most of these goals. Nuclear angiography is valuable for evaluation of LV and RV function, while nuclear scintigraphy is helpful in detecting myocardial perfusion defects, fibrosis, or denervation.
- Monitoring of cardiac structure and function by echocardiography (and/or CMR) should be performed at least yearly in patients at stage B or higher, as it provides important prognostic information and could assist in making therapeutic decisions.
- In patients at stage B or higher, the imaging report should always include
  - LVEF,
  - Regional wall motion abnormalities and aneurysms,
  - LV diastolic function,
  - RV function,
  - Mitral and tricuspid regurgitation,
  - Pulmonary artery systolic pressure,
  - Presence of intracardiac thrombus, and
  - Myocardial edema or fibrosis.

## VII. SUMMARY AND CONCLUSIONS

Although prevalent mostly in Latin America, ChD is nowadays present in traditionally nonendemic areas such as the United States and Europe. Therefore, physicians around the globe should be aware of the presence of this disease and have a basic understanding of how to diagnose and treat it. This document seeks to provide a deep understanding of the potential role that each cardiac imaging modality plays in the management of patients at risk and those already diagnosed with ChD.

The diagnosis of ChHD is based on epidemiology, positive serology, and clinical and imaging findings. Staging is based on the presence of cardiac involvement and symptoms of HF. As an inflammatory cardiomyopathy, ChHD may affect the myocardium in a global or focal manner. The typical findings are focal hypokinesis, aneurysms, fibrosis or mural thrombus, most commonly affecting the LV apex. More advanced stages could be difficult to distinguish from other dilated cardiomyopathies.

Screening for heart disease with electrocardiography (conduction abnormalities such as right bundle branch block and arrhythmias) is widely accepted because of its low cost and wide availability. More advanced cardiac evaluation with echocardiography, CMR, CT, or nuclear modalities has incremental value and is critical in determining the best treatment options and in predicting prognosis. Among all current imaging options, echocardiography should be the initial imaging modality given its low cost, safety, and availability.

## SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2017.10.019.

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