REVIEW ARTICLE

Imaging Techniques in the Diagnosis and Prognosis of Chagas Disease.

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The introduction of cardiovascular imaging methods has substantially improved the diagnostic sensitivity and specificity of structural and functional abnormalities in numerous cardiac disorders. Chagas disease is still a public health problem in Latin America. (1) Various imaging methods have been evaluated in chagasic patients to analyze their usefulness in the diagnosis, follow-up, as predictors of morbidity and mortality and in the therapeutic outcome of this disease. The aim of the present review is to show the most recent findings, particularly those with Doppler echocardiography, as they are the most numerous. It also briefly reviews its use with nuclear and magnetic resonance techniques.

CLINICAL CLASSIFICATION

The initial manifestation of Chagas disease can occur in its acute phase and more commonly in its chronic phase. The acute phase may appear with a nonspecific febrile syndrome lasting 2 to 8 weeks, becoming clinically manifest in less than 1% of infected subjects. (2, 3) Acute chagasic myocarditis is infrequent, and appears in only 1% to 5% of patients developing the acute phase (1 to 5 of every 10000 infected subjects). (2) In general, infestation by Reduvvidae bugs passes unnoticed and evolves to the chronic stage various decades later. Subjects with chronic chagasic cardiomyopathy (CCM) may be symptomatic or asymptomatic. Most investigators combine clinical findings, electrocardiogram (ECG) and presence or absence of cardiomegaly or systolic dysfunction into four groups of increasing cardiac injury (Table 1, Figure 1). Approximately 75% of seropositive subjects are asymptomatic. They are considered to be in the "undetermined" phase of the disease with normal ECG (stage A). ECG abnormalities imply disease progression (stage B). By definition, there is no cardiomegaly or left ventricular (LV) systolic dysfunction in either of these two groups. However, 10% or less of these patients may have LV regional contractile dysfunction. Symptomatic subjects with mild to moderate cardiac injury in NYHA functional class II or III are in stage C, and can present arrhythmias, embolism, sudden death and/or reversible heart failure (HF). (1-8) Most of these patients have an abnormal ECG, a dilated heart and abnormal systolic and diastolic function. Almost half of these patients can have regional contractile dysfunction, particularly of the apex. (1, 3-6, 9, 10) Variable mitral and tricuspid valve regurgitation is common. Ten-year survival of patients with moderate cardiac injury (stage C) may be above 50% and even 85%, but untreated patients with severe damage, in NYHA functional class IV (stage D), have high mortality, more than 50% at 2 years. Coronary angiography in all the groups is almost always normal or shows not significant obstructive lesions.

ACUTE CHAGAS DISEASE

An echocardiographic series involving one of the highest numbers of patients in the acute phase of Chagas disease included 58 patients, over 50% of which had abnormal echocardiogram. (11) Almost half of the patients presented pericardial effusion, (42%) which was moderate to severe in 10 to 12 patients with heart failure. Of notice, almost two-thirds (63%) of patients had normal left ventricular ejection fraction (LVEF) and only 6% presented LV dilation. The ECG was normal in 41% of patients. Five patients died, 4 due to HF. Acute chagasic myocarditis was diagnosed by myocardial biopsy in 26 patients and by necropsy in 3 children. In two other reports (12, 13) pericardial effusion was present in 7 out of 8 patients, three of whom had cardiac tamponade. Oral chagasic infestation may originate a clinically more severe acute phase of the disease owing to the high parasite load. In 107 pupils and teachers of a school in Caracas infested for drinking contaminated guayaba juice, (14) 75% presented symptoms, 59 % ECG changes, 44% parasitemia and 20% needed hospitalization. Only one 5-year old child died due to HF. In 18 echocardigrams performed on these patients, half presented pericardial effusion, which was mostly mild, but 2/18 had cardiac tamponade. Systolic function was normal in all of them. It is probable that early antiparasitic therapy avoided a worse outcome in this group of patients. The image in Figure 2 corresponds to an adult woman with pericardial tamponade who underwent urgent pericardiocentesis. Echocardiographic exploration may be of great value in every symptomatic patient during the acute phase.

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	Asymptomatic		Symptomatic	
NYHA	I		II-III	IV
Stage*	A	B	C	D
ECG**	Normal	Abnormal	Abnormal	
RBBB (%)	-	9-18	34-40	
ILASB (%)	-	9-15	23-39	
VPC (%)	-	3-9	12-75	
AVB 1-2 (%)	-	2-5	9-14	
Heart size	Normal		Increased	
LV aneurysm (%)	1.6-8.6		47-64	
LV posterobasal injury (%)	5.3-22		16-30	
LV ejection fraction	Normal		Decreased	
Diastolic function	NL	NL, PR	PR, PN, RR, IR	
5-year-survival (%)	≈ 98		≈ 85	≈30

Percentages represent the range of mean values of different series. ECG: Electrocardiogram. VI: Left ventricular. RBBB: Complete right bundle branch block. ILASB: Incomplete left anterior subdivision block. PVC: Premature ventricular contractions. AVB 1-2: First degree or second degree atrioventricular block. NL: Normal. PR: Prolonged relaxation. PN: Pseudonormal: RR: Reversible restrictive. IR: Irreversible restrictive. Modified from Acquatella (6). Reproduced with modifications. Copyright 2007 American Heart Association.

Table 1. Clinical, electrocardiographic and echocardiographic findings in chronic chagasic cardiomyopathy.

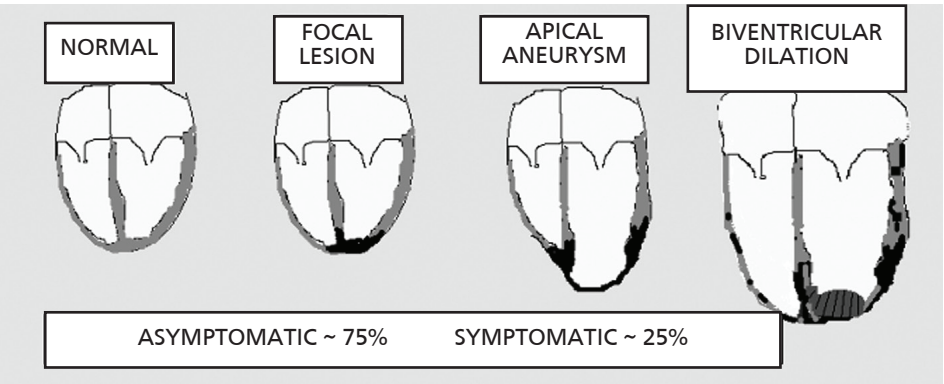

Fig 1. Chronic chagasic cardiomyopathy. Graph depicts the progression per decade of echocardiographic left ventricular structural lesions from the indeterminate, apparently normal phase (left) to biventricular dilation (right), sometimes with apical thrombi. Segments in black indicate scarred fibrous regions. Reproduced with permission. Copyright©2011, Gaceta Médica de Caracas.

CHRONIC CHAGAS DISEASE

Most autopsies of initial series were performed in subjects dying at advanced terminal phases of the disease, with biventricular dilation. (1-4) A pioneer study (15) called the attention on the high frequency of LV chagasic aneurysm in these patients. These results were confirmed by others, (16, 17) including a large series of 1078 autopsies, (18) where apical aneurysm was found in more than half of cases, more frequently in men and with similar rates in all age groups. (18) Eighty two percent had LV ectasia, 9% in the right ventricular (RV) apex. In other series the rates ranged from 30% to 92%. (3, 15, 17) Other LV segmental lesions, as for example in the posteroinferior wall, varied from 21% (16) to 33% (3) (Figure 3). (9)

DOPPLER ECHOCARDIOGRAPHY FINDINGS

In asymptomatic subjects, it may be difficult to differentiate a normally thin apical segment from a thin apical scar. This could explain the different rates of apical abnormality found among different publications. (19-26) Left ventricular chamber opacification with intravenous contrast agent combined with harmonic imaging may be useful in difficult cases. (19) The aneurysm size may range from very small, similar to a "punch", to an aneurysm indistinguishable from that caused by myocardial infarction.

Average prevalence of LV aneurysm by two-dimensional echocardiography in 920 asymptomatic subjects (undifferentiated) or with minimal myocardial injury was 8.5% (range 1.6% to 8.6%) (19, 22, 24) and 55% (range 47% to 64%) (22, 24, 26) in 242 patients with moderate to severe myocardial injury (see Table 1). In a study that included 1053 patients, (25) these rates of were less frequent; 2% in patients with normal ECG and 24% in those with abnormal ECG. Logistic regression analysis revealed that LV aneurysm was an independent predictor of wall thrombus. (25)

An important complication of CCM is cardioembolic events, frequently originated by apical thrombi (Figure 4). In 75 patients (26) studied with surface or transesophageal echocardiography (TEE) with a mean 2-year follow-up, 47% had apical aneurysm and 23% apical thrombi, with a significant association between them for stroke ($p<0.01$). Intracardiac thrombi were most frequent in patients with ventricular dysfunction. Additionally, TEE reveals atrial thrombi.

Cardiac echocardiography may detect LV segmental contractile dysfunction. The most common form appears in the posteroinferior wall. Its mean prevalence was 20% (range 5.3% to 22%) (19, 22, 24, 27) in 1164 asymptomatic subjects or with mild heart injury and 23% (range 16-30%) (22-24) in 280 patients, either symptomatic or with HF (Figure 3).

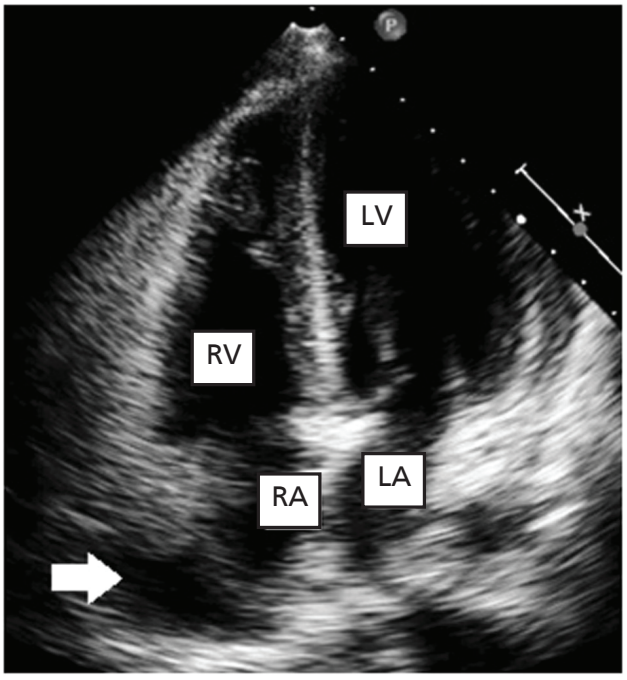

Fig 2. Acute Chagas disease. Four-chamber image of a woman with acute chagasic myocarditis with pericardial effusion and tamponade requiring puncture drainage. Cavity sizes and systolic function were normal. The arrow indicates compression of right atrial free wall. RV: Right ventricle. LV: Left ventricle. RA: Right atrium. LA: Left atrium. Reproduced with permission. Copyright©2011, Gaceta Médica de Caracas.

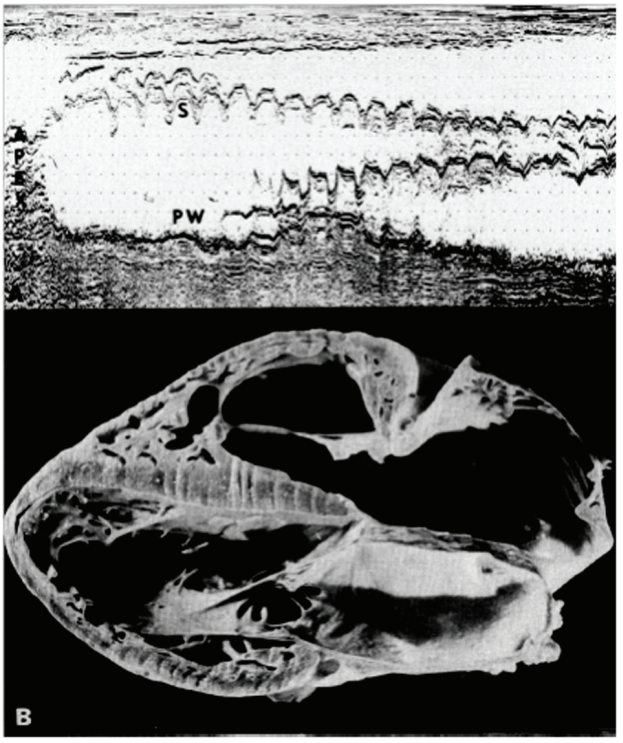

Fig 3. M-mode echocardiography and post mortem cardiac longitudinal section from a 42-year old man with severe heart failure secondary to chronic chagasic cardiomyopathy. A. Low velocity M-mode showing relatively preserved septal (S) contractility contrasting with the noncontractile, thin postroinferior wall (PW). B. Cardiac long axis view showing thin posteroinferior fibrotic scar with relative preservation of the septal wall. The right ventricle is dilated. Coronary arteries were normal. (9) Reproduced with permission. Copyright 1980, American Heart Association.

Systolic function

Patients with the indeterminate form of Chagas disease almost invariably have normal systolic function, (19, 21, 28-30) though some may have abnormal ECGs. (19) Thirteen percent of 505 subjects with normal ECG and a mean LVEF of 67% had segmental lesions and 0.8% systolic dysfunction. Conversely, in a series of 257 subjects with abnormal ECG and average LVEF of 68%, 33% had segmental contractile dysfunction and 8% systolic dysfunction. Both groups had normal end-diastolic biventricular dimensions. (19) Recently, tissue Doppler imaging (TDI) has been incorporated to estimate changes in myocardial velocity during the cardiac cycle. Subjects with normal ECG and echocardiography may, however, have prolonged LV(31, 32) and RV (33) isovolumic contraction as expression of early contractile malfunction. Therefore, a normal ECG does not rule out other abnormalities whose future significance is currently unknown. In patients with abnormal ECG, global systolic function has important prognostic implications. In a cohort of 538 patients (30) grouped in 4 progressive stages of the disease (A to D), (7) survival rates of 98%, 91%, 45% y 13% at 5 years were significantly different, according to whether patients had normal or slightly decreased LVEF or reversible or irreversible HF, respectively.

Systolic dysfunction may become apparent under pharmacological stress, both in asymptomatic as symptomatic patients. Impaired chronotropic, global and regional contractile response has been seen during dobutamine stress echocardiography. (34) Some patients present a biphasic behavior (initial contractile increase followed by hypokinesia at higher dobutamine doses), predominantly in the LV posteroinferior segments, suggestive of viable but dysfunctional myocardium. There are several and complex possible mechanisms to explain this response, including beta-adrenergic dysfunction, endothelial dysfunction, ischemia and structural myocardial damage. (34). Other studies have found a lower slope of the end systolic pressure- dimension relation during adrenaline infusion, (35) indicating reduced LV contractility in subjects with the indeterminate form of Chagas disease, mild myocardial involvement or in carriers of the digestive form of the disease.

Diastolic function

Chronic myocardial injury (1, 3, 4, 22) may impair ventricular relaxation and diastolic filling. The decrease in LV distensibility leads to increased left atrial (LA) pressure, changes in transmitral venous flow and pulmonary flow velocities, and prolonged systolic and diastolic time intervals (Figure 5). The combination of diastolic dysfunction and increased brain natriuretic peptide (BNP) levels is able to detect initial myocardial injury in chagasic patients. (36) Moreover, the combination of pulsed wave Doppler (PW) mitral valve inflow with TDI of mitral annulus velocities (E/E´ratio) is used to classify patients into four progressive stages of diastolic dysfunction: abnormal and pseudonormal relaxation and reversible and non-reversible restrictive filling. (37)

In a group of 169 patients with CCM, divided according to these four stages, diastolic dysfunction was found in one fifth of the patients, with a strong correlation between worsening diastolic function and increased atrial and LV dimensions and decreased LVEF. A reduced TDI septal E´

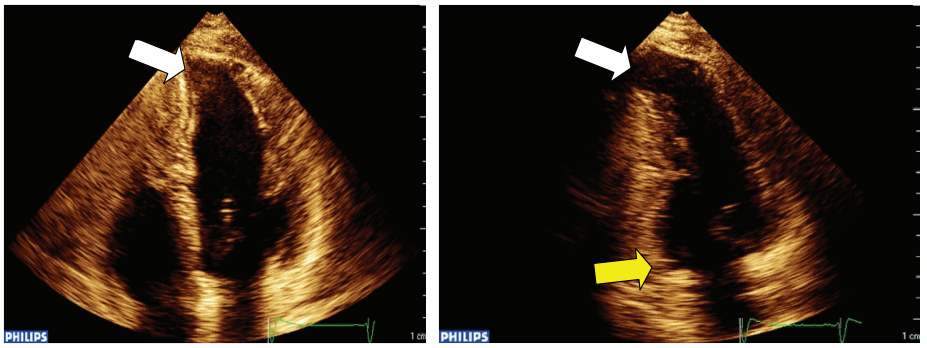

Fig 4. A. Real-time four-chamber window showing apical dyskynesia (arrow) with contractile preservation of the medial and basal portions of the septum and the left ventricular lateral wall. **B.** Two-chamber apical window showing a typical apical aneurysm with a big thrombus (white arrow). The inferobasal segment (yellow arrow) was akynetic. The inferomedial segment and the anterior wall showed normal contraction. The two-chamber apical window offers an improved view of the left ventricular apical aneurysm. The patient suffered right arm embolism as initial manifestation. Modified with permission. Copyright©2011, Gaceta Médica de Caracas.

wave of 11 cm/s and a septal E/E´ratio with a cut-off point of 7.2, were highly sensitive, moderately specific and with high negative predictive value for detecting any kind of diastolic dysfunction (Figure 5). In another study of 89 patients, (38) patients with pseudonormal diastolic function had larger end-diastolic and end-systolic dimensions, worse LV segmental motility score and lower LVEF compared with the normal filling group. Tissue Doppler imaging was able to differentiate patients with CCM and normal diastolic function from those with a pseudonormal pattern and increased LV filling pressures. In other studies using simultaneous M-mode echocardiogram, phonocardiogram and apex cardiogram tracings, (39. 40) significantly prolonged isovolumic relaxation and ventricular filling were found both in asymptomatic subjects with normal systolic function as in symptomatic patients. Actually, diastolic abnormalities usually precede systolic dysfunction. (38-40)

Other techniques

The myocardial performance index (MPI) or Tei index evaluates global ventricular function combining systolic and diastolic time intervals using pulsed Doppler echocardiography. (41) A MPI study comparing 88 patients with CCM and 45 non-chagasic controls (42) showed abnormally high LV MPI values (> 0.32) in 36% asymptomatic, 100% symptomatic and only 2% control subjects. Asymptomatic chagasic subjects with abnormal ECG presented abnormal MPI, but healthy control subjects with the same abnormal ECG changes had normal MPI. Symptomatic patients had markedly increased RV and LV MPI suggestive of severe myocardial dysfunction. In another work, (43) myocardial strain rate (Figure 6) was used to assess LV radial and longitudinal contractile function in subjects with the indeterminate form of Chagas disease, in patients in the chronic stage with LVEF above or below 50% and in normal control subjects. Percent myocardial radial and longitudinal segmental shortening were significantly higher in healthy controls than in subjects in the chronic stage. Patients with the indeterminate form of the disease had higher values than CCM patients with decreased LVEF, but the difference was not statistically significant compared with healthy control subjects. This technique thus allows measurement of slight changes in contractile dysfunction, which cannot be visually detected.

The recent introduction of three-dimensional echocardiography has improved the simultaneous contractile evaluation of each LV segment, detecting synchrony impairment (Figure 7).

Right ventricle

Biventricular radioisotope angiography was able to reveal systolic dysfunction limited to the right ventricle as the only anomaly (44, 45) In 74 patients with two-dimensional Doppler echocardiography RV dysfunction was secondary to the severity of LV injury and to the elevated levels of pulmonary pressure, rather than to RV intrinsic injury. (46) Additionally, RV function was evaluated by the Tei index in 158 dilated patients with LV end-diastolic dimension > 31 mm/body surface area and LVEF < 55%. (47) Multivariate analysis showed that after adjusting for LVEF and NYHA functional class, the RV Tei index was an independent predictor of death. (47) It was concluded that severe RV dysfunction entails poor prognosis in CCM. (47)

As previously indicated, RV TDI may identify myocardial damage in subjects with the indeterminate form having normal systolic function. (33) In general, patients with CCM initially develop LV HF symptoms and in advanced stages these symptoms extend to both ventricles.

Echocardiographic prognostic variables

Selected publications of echocardiographic studies in CCM patients estimating the prognostic value by Cox multivariate survival analysis were used (Table 2 and Figure 8). Studied populations included subjects with a wide range of Chagas disease severity, varying from none (19, 29) to mild-moderate (19, 20, 25, 48, 49) and severely symptomatic. (50, 51)

No mortality occurred in the two series that included asymptomatic subjects with normal ECG at study entry. In the series with 159 patients there were no events, (29) LVEF remained normal in all patients and the ECG showed no changes in nearly 80%. In the other series of 505 asymptomatic subjects with normal ECG, (19) no deaths occurred and only 8% of subjects presented adverse events. However, among 257 asymptomatic subjects with initially abnormal ECG, mortality was 1% and 26% of patients had clinical events. In the remaining 87 patients with initially abnormal ECG, cardiomegaly and no HF, mortality was 14% and 52% had clinical events. Univariate and multivariate analysis (19) showed that changes in the clinical group, LV end-systolic dimension and LVEF were predictors of mortality, while Chagas-related ECG abnormalities, LV systolic and diastolic dimensions and LVEF were predictors of adverse events.

The following studies include patients with HF. In a series of 738 patients, (48, 49) univariate survival Cox analysis showed significant differences between surviving and non-surviving patients in end-diastolic and end-systolic dimen-

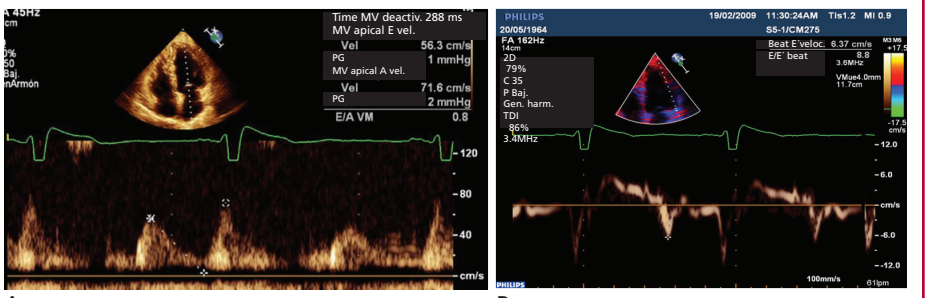

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Fig 5. A. Mitral valve pulsed Doppler echocardiography showing a prolonged relaxation left ventricular filling pattern, suggestive of mild diastolic dysfunction; E/A = 0.8. **B.** Tissue Doppler image at the most basal level of the lateral wall showing prolonged relaxation and isovolumic contraction, and decreased E´ filling wave for E/E´=8. Modified with permission. Copyright©2011, Gaceta Médica de Caracas.

sions, LVEF, LV mass, moderate to severe systolic dysfunction and apical aneurysm. In the multivariate analysis, ECG QT interval dispersion (QTd) and LV end-systolic dimension were the most significant independent predictors for all endpoints. (48, 49) In another study including 1053 subjects, classified according to the presence of apical aneurysm, (25) univariate analysis revealed that patients with aneurysm had significantly greater mortality rates (total, cardiac, sudden), HF, X-ray cardiomegaly, abnormal ECG, LVEF < 45%, apical thrombus and increased LVend-systolic and end-diastolic dimensions, but in the multivariate analysis, only LVEF predicted death. Apical aneurysm did not reveal significant differences after adjusting for LVEF.

The following series included patients with advanced HF. In a series of 56 patients in NYHA functional class III and IV, (50) univariate analysis showed that LVEF, LV diastolic dimension, NYHA functional class IV and use of digitalis were predictors of mortality, but in the multivariate analysis, LVEF was the only risk factor. In another study (20) of 283 patients grouped according to whether they were asymptomatic or symptomatic, LV end-diastolic and end-systolic dimensions, LV percent shortening fraction, mitral E-point septal separation, LV radius to wall thickness ratio, LV mass and other non-echocardiographic variables were mortality predictors by univariate analysis. On the other hand, initial NYHA functional class, mitral E point septal separation and LV shortening fraction were mortality risk predictors by multiple regression analysis. Finally, two series studied only patients with HF. In one series of 56 patients with NYHA functional class III-IV, (50) LVEF was the only significant predictor of mortality. In another series of 104 male patients (51) in NYHA functional class II, III and IV, statistically significant differences between survivors and nonsurvivors on multivariate analysis were found for LVEF and maximal O2 uptake (VO2max). Therefore, in these series, systolic dysfunction and increased cardiac dimensions emerged as the most significant predictors of morbidity and mortality.

A score combining clinical and echocardiographic variables has been recently proposed. (52) In 424 ambulatory patients followed-up for an average of 7.9 years, 130 deaths occurred. Cox analysis identified six prognostic factors of risk of death and each was assigned a score according to the regression coefficient: 5 points to NYHA functional class III-IV and or X-ray cadiomegaly, 3 points to low echocardiographic ejection fraction and/or nonsustained ventricular tachycardia in 24-hour Holter and 2 points to low voltage QRS and/or male gender. Low risk was 0-6 points, intermediate risk: 7-11 points, and high risk: 12 to 20 points. Ten-year mortality was 10%, 44% and 84%, respectively. In a comparative study of mortality predictors in 224 patients with CCM

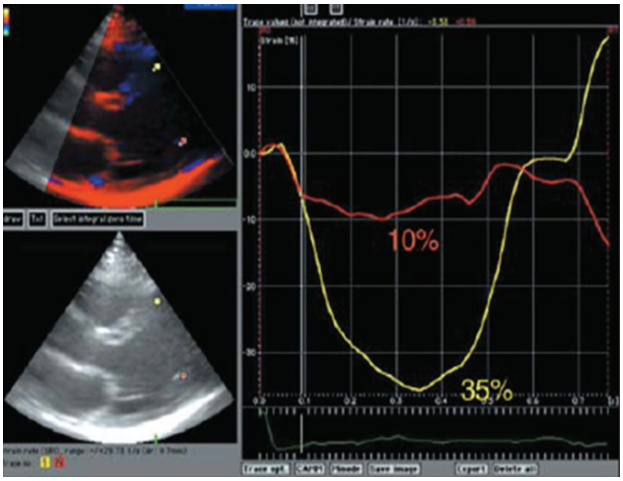

Fig 6. Strain analysis of myocardial contractility. The septal wall (yellow tracing) shows normal systolic shortening, while the posterior wall (red tracing) has contractile dysfunction. This and other recent techniques offer the opportunity of detecting abnormalities before systolic dysfunction. (43) Reproduced with permission. Copyright 2005 Arquivos Brasileiros de Cardiologia.

and 63 patients with idiopathic dilated cardiomyopathy (DC) (53) followed-up for nearly 40 months, 104 patients died and 9 underwent cardiac transplantation. Cox multivariate analysis showed that NYHA functional class, LVEF, RV Tei index, LA volume index in ml/m2 and chagasic ethiology were independent predictors of cardiac events. In a subgroup with severe reduction of LVEF to < 30%, survival in patients with CCM was 55% and 26% at one and 3 years, while in subjects with DC it was 82% and 67%, respectively.

Left atrium

Increased LA volume, a marker of chronically elevated LV filling pressure, has been shown to be a predictor of prognosis in HF caused by several cardiomyopathies. In a series of 192 patients with CCM with an average follow-up of 2.5-years, (54) LA volume independently increased the prognostic predictive value together with NYHA functional class, LVEF, RV function and the E/E´ Doppler ratio. The cut-off point associated with excess mortality was 51 ml/m2 ($p<0.001$).

In a recent comparative study (55) LA function was evaluated by three-dimensional echocardiography in 30 CCM patients, 30 patients with DC and 20 normal subjects. Maximum (Volmax/m2) and minimum (Volmin/m2) LA volumes

and preatrial contraction volumes were estimated to calculate total and active LA emptying fractions. Left ventricular ejection fraction and mitral regurgitation severity were similar in both cardiomyopathy groups. Patients with CCM had significantly larger LA Volmax/m2 than patients with DC, and both had larger values than the control group. Total LA emptying fraction was significantly lower in the CCM group than in the DC group, and both lower than control. A similar response was found for the active LA emptying fraction. In addition, the E/E´ratio was greater in patients with CCM than in those with DC. Multiple regression analysis showed that E/E´ratio was the only independent predictor of a worsening active LA emptying fraction. These findings suggest that there is greater degree of atrial impairment in CCM, probably associated with higher increase of LV filling pressure. (55)

OTHER IMAGING TECHNIQUES

Nuclear

In a radioisotopic angiography study (56) performed in 30 patients with CCM, dipiridamol 20 mg IV, increased LVEF and RV ejection fraction and improved contractile dysfunction of hypokinetic segments, especially in apical regions and the LV and RV inferior wall. Chronic administration of oral dipiridamol might preserve this response.

A myocardial perfusion study with Tl-201 scintigraphy (57) showed the correlation between myocardial perfusion abnormalities and LV systolic dysfunction severity, even in the first stages of the disease with normal echocardiographic LVEF. 123I-mIBG single photon emission computed tomography (SPECT) revealed segmental uptake defects in 33% of the 12 asymptomatic patients, in 77% of 13 patients with abnormal ECG and echocardiographic segmental abnormali-

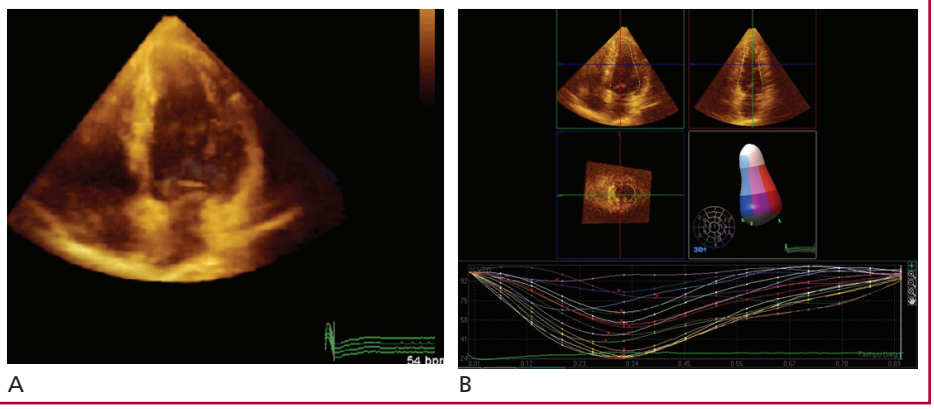

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Fig 7. **A.** Three-dimensional echocardiography of the patient shown in Figure 5. Electronic processing allows cropping to study other views. **B.** Regional contractility. Temporal segment contractility can be measured and asynchrony can be detected with this technique.

Author	Patients (n)	Mean follow-up (months)	Mortality %	Event (%) SD	HF	EM	Mortality predictors* p < 0.05
Ianni (29)	159	99	0	0	0	0	-
Viotti (19)	849	118	0,6	-	-	-	LVSD, LVEF, Group
Salles (48, 49)	738	58	8	74	22	4	LVSD, QTd
Xavier (25)	1.053	66	10	57	22	4	LVEF
Bestetti (50)	56	24	28	69	31	-	LVEF
Rodríguez Salas (20)	283	48	38	37	44	6	Group, SF, EPSS
Mady (51)	104	30	48	64	36	-	LVEF, $VO_{2máx}$
Rassi (52)	424	95	31	63	15	9	NYHA, CARD LVEF, NSVT QRS, M

Table 2. Survival analysis from echocardiographic series

SD: Sudden death. HF: Heart failure. EM: Embolism. LVSD: Left ventricular systolic dimension. LVEF: Left ventricular ejection fraction. Group: Clinical group of each series. QTd: Electrocardiographic QT dispersion. SF: M-mode shortening fraction. EPSS: M-mode mitral E-point septal separation.. VO2máx: Maximum oxygen consumption in treadmill exercise test. CARD: Cardiomegaly. NSVT: Non-sustained ventricular tachycardia. QRS: Low voltaje QRS. M: Male gender. Decimals are rounded. * Multivariate analysis. Modified from Acquatella. (6) Reproduced with permission. Copyright 2007 American Heart Association.

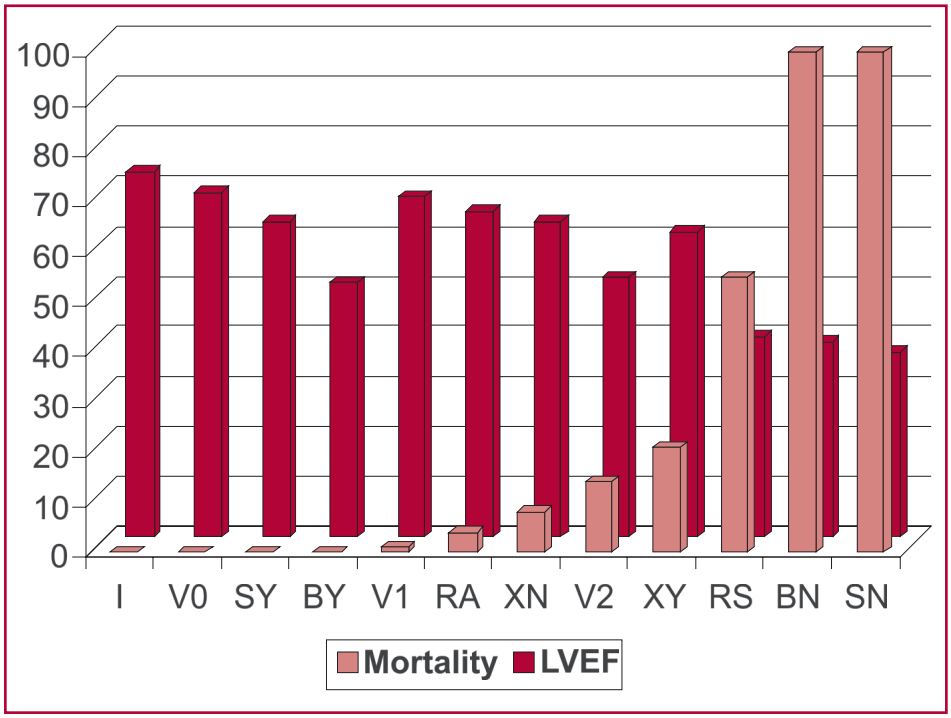

Fig. 8. Statistically significant inverse correlation between left ventricular ejection fraction (LVEF) and mortality in 3138 patients from six echocardiographic series detailed in Table 2. The first letter indicates author´s initial, and the second letter the clinical group. I = Ianni (29); V = Viotti (19), groups 0, 1, and 2; S = Salles (48,49), groups Y (alive) and N (deceased); B = Bestetti (50), groups Y (alive) and N (deceased); R = Rodríguez-Salas (20), groups A (asymptomatic) and S (symptomatic); X = Xavier (25), groups Y and N (aneurysm yes or no) (6). See text for other details. (6) Reproduced with permission. Copyright 2007, American Heart Association.

ties, and in 92% of 12 patients with severe cardiac injury. In addition, there was marked topographic association between perfusion, innervation and contractile abnormalities in all the groups. Defects predominated in the inferior, posterolateral, and apical LV regions.

A follow-up study with Tl-201 SPECT was performed in 36 patients at rest and under stress to detect myocardial perfusion abnormalities (59) (Figure 9). A prospective new evaluation carried out at 5.6 ± 1.5 years to assess changes in LVEF and perfusion area revealed deterioration of left ventricular function and a significant correlation between reduced LVEF from 55% to 50% and increased perfusion defect from 19% to approximately 27%. Moreover, 20 patients with normal coronary angiography showed LV reversible perfusion defects. In two-thirds of the patients, there was progression of initially reversible segmental defects to defects at rest, whereas in segments without initial reversible defects only 9% had the same progression. Of interest, affected segments were predominantly those of the LV inferior wall and apex, similarly to echocardiographic observations. (6, 19, 22-24, 27) These findings support previous studies (34) with intracoronary acetylcholine infusion that implicate CCM microcirculatory abnormalities probably due to endothelial dysfunction.

Magnetic resonance

Ten patients underwent gallium-67 myocardial uptake and magnetic resonance imaging (MR) (60) to assess myocardial inflammation, together with RV endomyocardial biopsy and echocardiographic LVEF. The results of this group were compared with those of 10 patients with DC. Eight of the 10 patients with CCM showed higher signal intensity, suggesting myocardial inflammatory process and two had borderline evidence of this process. Only one patient in the control group with DC had abnormal uptake that was positive for inflammation.

The degree of myocardial fibrosis (MF) using delayed gadolinium-enhanced magnetic resonance imaging (61) was studied in 51 patients, classified in three groups. Group I: 15 asymptomatic patients (indeterminate phase), group II: 26 patients with cardiac injury and group III: 10 patients with ventricular tachycardia (Figure 10). Myocardial fibrosis was observed in 68.6% of all cases. The severity differed in each group: 20% in group I, 84.6% in group II and 100% in group III, and the extent of fibrosis varied from 0.9 ± 2.3% to 16.0 ± 12.3% up to 25.4 ± 9.8% in each group, respectively. A significant correlation was found with NYHA functional class and between LVEF and segmental contractile abnormality. Assessment of the extent and severity of MF by magnetic resonance allows the early detection of CCM evolution and correlates with other parameters that affect the myocardium in this disease.

Applications in patient management

Doppler echocardiography of the heart has been incorporated to clinical studies of Chagas disease. Thus, LVEF has been shown to have great prognostic power in patient survival analysis, (19, 20, 25, 29, 48-51) in combination with nuclear studies (57-59) or magnetic resonance con gallium-67 to identify myocardial inflammation, (60) or with contrast with gadolinium to detect MF. (61) Echocardiographic assessment of systolic and diastolic dysfunction has shown correlation with BNP levels in patients with CCM with or without HF. (36, 62) It has also been used in the follow-up of patients with pacemaker implantation (63) or defibrillator implantation with automatic cardioversion (64), in the study of the effect on diastolic function of medications as enalapril, (65) or the antiparasitic agent benznidazol. (66) Assessment of benznidazol in a non-randomized trial of 566 chagasic subjects (66) showed decreased mortality rate in treated patients compared to non-treated ones (1.1% vs. 4.2%, respectively). The only independent predictive values of clinical deterioration were low echocardiographic LVEF and higher LV end- diastolic dimension, though this last variable was

not significant when it was adjusted by LVEF. Currently, an ongoing large, randomized study is evaluating the effect of benznidazol in CCM. (67)

Limitations

Several echocardiographic and imaging findings described here are nonspecific and can be found in other cardiomyopathies (ischemic and non-ischemic). More comparative studies are needed to estimate the sensitivity and specificity of these abnormalities. Studies with the new strain rate, speckle tracking and especially three-dimensional echocardiography techniques might provide new information of diagnostic and prognostic utility. On the other hand, LVEF should be performed ideally by two-dimensional or three-dimensional echocardiography instead of the traditional M-mode echocardiography which does not assess the frequently abnormal apex of these patients. There are no studies directly comparing differences in cardiac injury between regions to the north or south of the Amazon River, as occurs in the case of digestive injury, which is unknown at the north of South America or in Central America.

CONCLUSIONS

Patients with acute chagasic myocarditis should be routinely evaluated with echocardiography, especially if they present signs and symptoms of HF, to rule out pericardial effusion and specifically cardiac tamponade. In the chronic phase, subjects with normal ECG have a good long-term prognosis. Most of these patients have normal systolic function but may present contractile and diastolic function abnormalities, although the clinical significance in disease progression is currently unknown. Chronic symptomatic patients may have a single ventricular abnormality ranging from a small isolated apical aneurysm to a globally dilated heart without segmental scars. A possible chagasic etiology should be considered in the differential diagnosis of a cardiomyopathy patient with positive epidemiologic history and serology, suggestive ECG abnormalities and apical aneurysm. A depressed LVEF

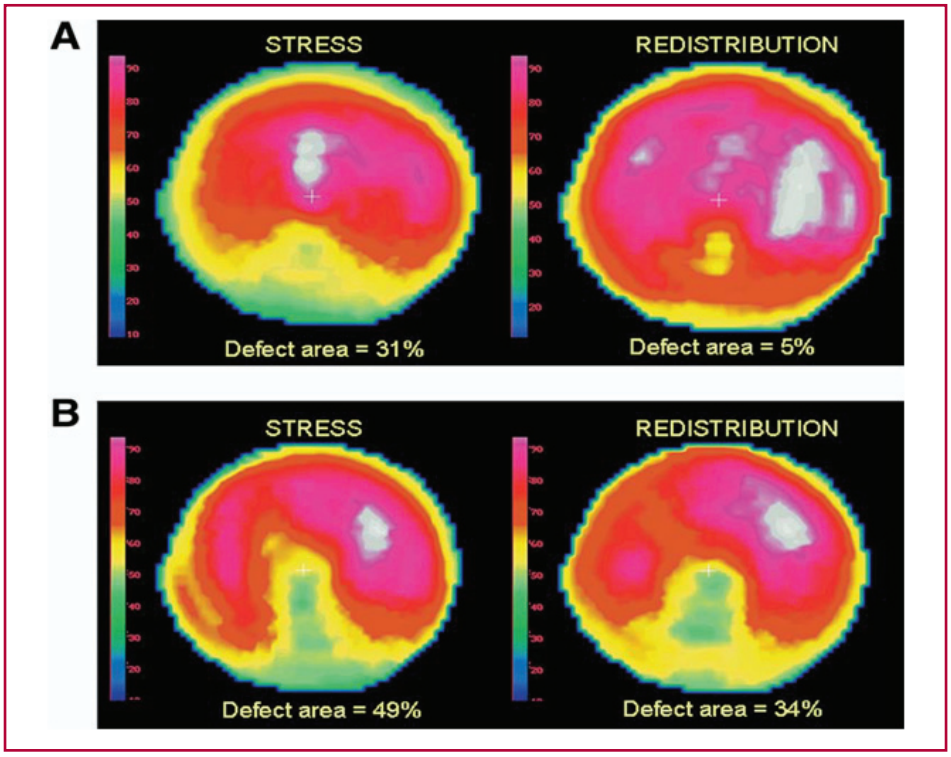

Fig. 9. Initial **(A)** and follow-up at 6.5 years **(B)** thallium-201 myocardial perfusion polar maps during stress and redistribution. Initial ejection fraction decreased from 36% to 31%. Perfusion defects involve the apex and the septal, inferoseptal, inferior and inferolateral wall regions in the initial study. The perfusion defects are more extended in the later study. (59) Reproduced with permission. Copyright 2009, American College of Cardiology.

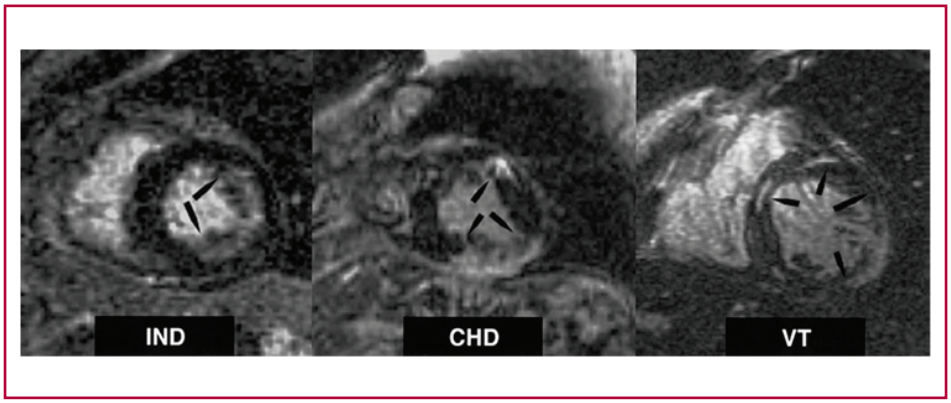

Fig. 10. Myocardial delayed gadolinium-enhanced magnetic resonance (arrows) in left ventricular minor axis slices of chronic chagasic cardiomyopathy patients, (61) indicating areas of myocardial fibrosis. Clinical groups: IND, indeterminate; CHD: Chagas disease; VT: Ventricular tachycardia. Reproduced with permission. Copyright©2005, American College of Cardiology.

and increased LV cavity dimensions have shown predictive value as risk factors of morbidity and mortality in different survival studies. The various imaging modalities mutually complement the diagnosis, prognosis and follow-up of chagasic patients.

Conflicts of interest

None declared.

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