Prevalence and Risk Factors of Embolic Cerebrovascular Events Associated With Chagas Heart Disease

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ABSTRACT

Background: Patients with Chagas disease are at increased risk for stroke that may result in major clinical disability and death. Identification of risk factors involved in the genesis of thromboembolic events related to this disease may lead to improved therapeutic decision making and outcomes.

Objectives: This study sought to assess the prevalence of ischemic cerebrovascular events (ICE) among patients with Chagas heart disease and to identify the risk factors associated with cardioembolism in this population.

Methods: This study involved 330 patients, 193 were men (58%), with a mean age of 49 ± 12 years with Chagas disease classified in the chronic cardiac form of the disease. Comprehensive echocardiography was performed to search a substrate for cardioembolic events, especially apical aneurysm and intracavitary thrombus.

Results: Most of the patients were classified as New York Heart Association classes I or II (75%) with mean left ventricular (LV) ejection fraction of 39 ± 14%. Sixty-seven patients had a previous ICE with the overall prevalence of 20%. Apical aneurysms were detected in 128 patients (39%), whereas LV mural thrombi were found in 48 patients (15%). In multivariate analysis including the potential predictors of ICE, apical aneurysm (adjusted odds ratio [OR]: 2.19, 95% confidence interval [CI]: 1.11 to 4.34; p = 0.024) and LV thrombus (adjusted OR: 2.43, 95% CI: 1.09 to 5.42; p = 0.030) emerged as important determinants of ICE, after adjusting for anticoagulation therapy.

Conclusions: In a selected population referred to a tertiary center for Chagas disease that included patients with different severities of cardiac involvement, the prevalence of ICE was 20%. The presence of apical aneurysm and intracavitary thrombus were independently associated with ICE, after adjustment for other risk factors for stroke.

Chagas disease remains among of the most prevalent infectious diseases in Latin America and has become a health problem in nonendemic countries [1–3]. The chronic cardiac form is the most important manifestation of the disease because of its frequency and severity [4–6]. Chagas disease also represents a risk factor for stroke, which is independent of the severity of myocardial damage and constitutes a leading cause of serious long-term disability [7–12]. Recently, an increase in stroke prevalence is expected with the aging of the population infected with *Trypanosoma cruzi* in Latin America [13].

Cardioembolism is considered to be the main pathophysiological mechanism of ischemic stroke in the setting of Chagas disease, mainly related to apical aneurysm, mural thrombus, and arrhythmias [9,10,14]. However, previous studies have reported significant variability in the frequency of left ventricular (LV) aneurysm and thrombus [10,11,15,16], which affects clinical outcome and therapeutic management.

Transthoracic echocardiography is the cornerstone imaging modality for diagnosis of LV thrombi [17]. Advances in echocardiographic images over the last decades have helped to identify accurately the substrate for thromboembolic events in Chagas disease, leading to improved therapeutic decision making regarding anticoagulation therapy. Therefore, this study sought to assess the prevalence of ischemic cerebrovascular events (ICE) among patients with Chagas heart disease and to identify the risk factors associated with cardioembolism in this population.

METHODS

This is a cross-sectional study that included 330 patients with Chagas heart disease who were referred to Chagas disease outpatient referral center at the Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil, from June 1999 to June 2014. The diagnosis of Chagas disease required ≥2 positive serologic tests for antibodies against *T. cruzi* (indirect hemagglutination, indirect immunofluorescence, or enzyme-linked immunosorbent assay) and the presence of any electrocardiographic (ECG) changes related to Chagas disease [18,19]. ECG findings including nonspecific ST-T wave changes, low voltage, and LV hypertrophy were not considered to be suggestive of Chagas heart disease. Electrocardiographic abnormalities were visually classified using the Minnesota code for Chagas disease.

Patients who had associated heart valve disease were excluded. The protocol was approved by the Universidade Federal de Minas Gerais in Brazil.

Current medication, including taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, amiodarone, beta blockers, digoxin, anticoagulants, and aspirin were assessed and New York Heart Association (NYHA) functional class were obtained. Patients with atrial fibrillation were on anticoagulant therapy at the time of inclusion in the study.

At the initial evaluation of patients with Chagas disease, a complete blood count, urinalysis, serum electrolytes, fasting glycemia, blood lipids, and tests of renal, hepatic, and thyroid function were performed. B-type natriuretic peptide (BNP) levels were measured in 108 patients (33%). The samples for BNP analysis were placed in plastic tubes containing ethylenediamine tetraacetic acid and immediately processed through Triage the BNP Test kits (Biosite Inc., San Diego, CA, USA).

For the purpose of the study, patients who presented with cerebral ischemia, ranging from transient ischemic attack to stroke based on clinical symptomatology and neuroimaging data, mainly computed tomography scan, were considered to have ICE [20]. Magnetic resonance imaging was indicated in a few cases, especially when there was dissociation between clinical and radiological findings as it is not widely available in the public health system.

Echocardiographic evaluation

A standard transthoracic 2-dimensional echocardiogram was performed according to recommendations of the American Society of Echocardiography [21]. LV ejection fraction was calculated according to the modified Simpson rule.

Apical and low parasternal echocardiographic windows were used to acquire zoomed images of the apex, with high-frequency transducers. This procedure improved the quality of the apex images and allowed for the detection of the typical aneurysms. These lesions usually appear in a restricted and small area, characterized by a dyskinetic thin segment at the apex and limited by an area of normal contraction [22]. Thrombus in the apex of the LV was defined by the presence of a distinct mass close to the endocardium of an abnormal contracting wall, which could be visualized throughout the cardiac cycle in ≥2 different echocardiographic views [23]. Examinations were analyzed by a second observer, who was unaware of the patient's clinical status, and a consensus about the diagnosis of aneurysms and thrombus was obtained.

Global right ventricular (RV) function was quantitatively assessed using the RV myocardial performance index (Tei index) [24]. RV tissue Doppler imaging was obtained at the lateral tricuspid annulus in the apical 4-chamber view, where peak systolic (S′) and early (e′) and late (A′) diastolic velocities were measured [25]. The tricuspid regurgitant velocity was recorded with continuous-wave Doppler imaging and used to determine the systolic pulmonary artery pressure using the modified Bernoulli equation.

LV diastolic function was assessed by pulsed Doppler of the mitral inflow and by tissue Doppler imaging measurements, obtained at the medial and lateral border of the mitral annulus in the apical 4-chamber view [26]. Systolic tissue Doppler velocity (S′), and early (e′) and late (A′) diastolic tissue velocities were acquired, and the ratio of the mitral E velocity to the mean e″ was calculated (E/e′).

Left atrial volume was assessed by the biplane area-length method from apical 4- and 2-chamber views [26]. Measurements were obtained in end-systole from the frame preceding mitral valve opening, and the volume was indexed for body surface area.

Statistical analysis

Categorical data were presented as numbers and percentages, and continuous data were expressed as mean ± SD or median (interquartile range). The variables of patients with and without ischemic events were compared using chi-square test, unpaired Student t test or Mann-Whitney U test, as appropriate. Logistic regression analysis was performed to determine characteristics that were independently associated with history of ICE. Clinical and echocardiographic variables that were found to be significantly associated with ICE in univariate analysis were included in the multivariable logistic regression analysis. The potential predictive variables of ICE included in the multivariate analysis were NYHA functional class, atrial fibrillation, anticoagulant therapy, blood pressure, LV ejection fraction, and apical aneurysms and thrombus.

A value of $p < 0.05$ was considered significant. SPSS (version 18, SPSS Inc., Chicago, IL, USA) was used for all analyses.

RESULTS

Characteristics of the study population

The study population consisted of 330 patients, 193 were men (58%), with mean age of 49 ± 12 years (19 to 73 years). The demographical and clinical characteristics of the patients, according to the presence of ICE are summarized in Table 1. Sixty-seven patients had ICE with a

prevalence of 20%. In 10 patients, stroke occurred as the first clinical manifestation of the Chagas disease, even before serologic tests have been performed.

Most of the patients were in NYHA classes I or II (75%), whereas 83 patients were in NYHA classes III or IV (25%). Of note, 26 patients were previously asymptomatic and ICE was the main determinant of symptoms, with disability and cognitive impairment.

At the time of inclusion, all patients were on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 224 (68%) on diuretics, 143 (43%) on amiodarone, 118 (36%) on beta blocking agents, 116 (35%) on digoxin, 87 (26%) on oral anticoagulants, and 72 (22%) on antiplatelet drugs. There was no difference in medication between the patients with ICE versus those without, with the exception of warfarin (Table 1).

Right bundle branch block (RBBB) was the most frequent ECG abnormality, observed in 132 patients (40%). Of the patients with RBBB, 105 patients had associated left anterior fascicular block and 4 had left posterior fascicular block. Left bundle branch block was detected in 27 patients (8%), and 48 patients (15%) had a pacemaker at enrollment. RBBB associated with left anterior fascicular block was more frequent in the patients without ICE than in those with ICE. Other ECG abnormalities were similar between patients with and without ICE. Atrial fibrillation was present in 26 patients (8%), and it was not associated with ICE. All patients with atrial fibrillation were taking anticoagulants.

Echocardiographic characteristics of the patients are shown in Table 2. The mean LV ejection fraction was 39 ± 14% and was similar between patients with and without ICE. The patients were also stratified according to the LV ejection fraction quartiles to evaluate the rate of ICE across the spectrum of ventricular function, and the frequency of ICE was similar among the patients with severe, moderate, or mild LV systolic dysfunction (Fig. 1). Thirty-eight patients (12%) had no systolic dysfunction, of whom 12 (32%) had ICE.

The parameters to assess LV filling pressure and RV function were similar between the groups. Apical aneurysms were detected in 128 patients with the overall prevalence of 39% (Fig. 2). Left ventricular thrombus, mainly apical, was found in 48 patients (15%) (Fig. 3). Of the patients with apical aneurysm, 37 (29%) had mural thrombus associated. The presence of LV apical aneurysms and thrombus were more frequent in the patients with ICE.

Associated factors with ischemic cerebrovascular events

Several clinical, ECG, and echocardiographic variables were tested for a possible independent association with ICE (Table 3). In multivariate logistic regression analysis including the potential predictors of ICE, apical aneurysm (adjusted odds ratio [OR]: 2.19, 95% confidence interval [CI]: 1.11 to 4.34; p = 0.024) and LV thrombus (adjusted

TABLE 1. Demographic and clinical features of the study population according to the presence of ICE

	Patients Without Events (n = 263)	Patients With Previous ICE (n = 67)	p Value
Clinical Parameters			
Age, yrs	50 (41, 58)	54 (43, 59)	0.302
Male	154 (59)	39 (58)	0.959
Body surface area, m^2	1.66 (1.55, 1.78)	1.65 (1.58, 1.76)	
NYHA functional class			
I	88 (34)	26 (38)	0.578
II	106 (40)	27 (40)	
III	39 (15)	10 (15)	
IV	30 (11)	4 (6)	
RV failure*	95 (36)	23 (34)	0.879
Syncope	60 (23)	19 (28)	0.234
Heart rate, beats/min	64 (60, 72)	66 (60, 73)	0.232
SBP, mm Hg	110 (100, 120)	110 (100, 121)	0.481
DBP, mm Hg	70 (60, 80)	76 (70, 80)	0.142
Medications			
Diuretics	183 (70)	41 (61)	0.255
ACE inhibitors	208 (79)	49 (73)	0.413
ARB blockers	59 (22)	14 (21)	0.878
Beta blockers	95 (36)	23 (34)	0.924
Digoxin	94 (36)	22 (33)	0.744
Aspirin	53 (20)	19 (28)	0.149
Anticoagulants	55 (21)	32 (48)	<0.001
Amiodarone	117 (44)	26 (39)	0.483
Electrocardiographic Parameters			
RBBB	18 (7)	9 (13)	0.111
RBBB plus LAFB	90 (34)	15 (22)	0.045
LBBB	21 (8)	6 (10)	0.524
Atrial fibrillation	20 (8)	6 (9)	0.689
First-degree AVB	55 (21)	10 (15)	0.841
Pacemaker	38 (14)	10 (15)	0.867
Ventricular ectopy	128 (49)	37 (54)	0.707
BNP, pg/ml[†]	154 (83, 266)	167 (37, 447)	0.977

Values are median (interquartile range) or n (%).
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; AVB, atrioventricular blocks; BNP, B-type natriuretic peptide; DBP, diastolic blood pressure; ICE, ischemic cerebrovascular events; LAFB, left anterior fascicular block; LBBB, left bundle-branch block; NYHA, New York Heart Association; RBBB, right bundle branch block; RV, right ventricle; SBP, systolic blood pressure.
*Manifestations of right-sided heart failure.
[†]BNP levels were obtained in 116 patients (35%).

OR: 2.43, 95% CI: 1.09 to 5.42; p = 0.030) emerged as associated factors with ICE, after adjusting for anticoagulation therapy. Functional class, presence of atrial fibrillation, LV ejection fraction, and left atrial volume were not associated with previous ICE.

DISCUSSION

This study addresses the prevalence of ICE and potential cardiac embolic source in a wide spectrum of Chagas heart disease severity, including patients with preserved LV systolic function to severe dilated cardiomyopathy. The

TABLE 2. Echocardiographic characteristics according to the presence of ICE

	Patients Without Events (n = 263)	Patients With ICE (n = 69)	p Value
LVDd, mm	63 (57, 69)	61 (55, 69)	0.075
LVDd/BSA, mm/m^2	38 (34, 42)	36 (32, 41)	0.227
LVSd, mm	51 (43, 60)	48 (40, 58)	0.154
LVEF, %	37 (28, 49)	40 (29, 51)	0.203
LA dimension, mm	42 (38, 49)	40 (37, 48)	0.171
LA volume index, ml/m^2	43.6 (31.6, 54.3)	42.3 (29.3, 58.2)	0.991
RV diastolic area, cm^2	17 (13, 24)	16 (11, 21)	0.260
RVMPI	0.38 (0.26, 0,64)	0.42 (0.24, 0.69)	0.868
PASP, mm Hg	33 (28, 39)	31 (28, 41)	0.713
E, cm/s	72 (56, 90)	67 (52, 84)	0.135
A, cm/s	50 (37, 73)	56 (36, 75)	0.634
E/A ratio	1.5 (0.8, 2.4)	1.3 (0.7, 2.1)	0.242
DT, ms	183 (145, 252)	190 (152, 234)	0.785
E/E' ratio	10.4 (7.4, 15.3)	8.6 (6.6, 14.4)	0.325
E'	6.9 (5.5, 8.6)	8.2 (5.5, 10.0)	0.157
Moderate or severe TR	49 (19)	8 (12)	0.186
Moderate or severe MR	75 (29)	14 (21)	0.365
LV apical aneurysm	92 (35)	36 (54)	0.005*
LV thrombus	28 (11)	20 (30)	<0.001*

Values are median (interquartile range) or n (%).
A, late transmitral flow velocity; BSA, body surface area; DT, deceleration time; E, early diastolic transmitral flow velocity; E', early diastolic mitral annular velocity; E/A, ratio of early to late transmitral flow velocity; E/E', ratio of the early diastolic transmitral flow velocity to early diastolic mitral annular velocity; LA, left atrial; LV, left ventricle; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVSd, left ventricular end-systolic diameter; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure; RVMPI, right ventricular myocardial performance index; TR, tricuspid regurgitation; other abbreviations as in Table 1.
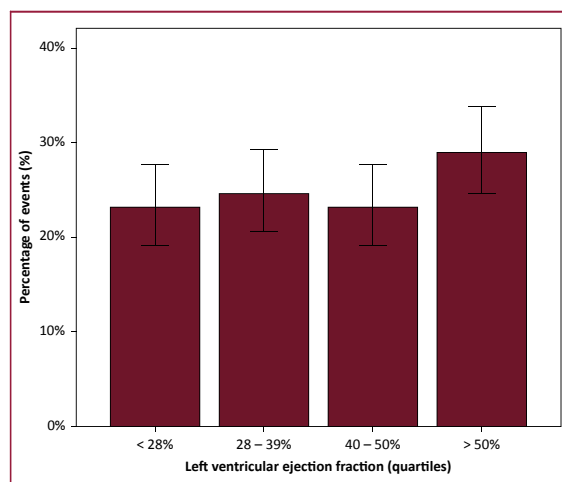*p value < 0.05.

results show that ICE prevalence was 20% in the current era of improvement in echocardiographic images and prophylactic anticoagulation. The presence of apical aneurysm and intracavitary thrombus were independently

FIGURE 1. The rate of ischemic cerebrovascular events according to the left ventricular ejection fraction quartiles in 330 patients with Chagas heart disease. Error bars represent confidence intervals.

associated with ICE, after adjustment for anticoagulation therapy, functional class, and ECG abnormalities.

Stroke in Chagas disease

The studies examining the prevalence of stroke in patients with Chagas disease have yielded varying results. Autopsy studies of patients with severe cardiomyopathy reported that 10% to 35% had cerebral infarction [27–29]. A previous autopsy study showed that cerebral infarction and its complications have been associated with death in 52% of the cases [29]. Furthermore, the evidence reported in autopsy studies suggests a high frequency of systemic embolic events [29,30], in contrast to clinical studies [10,31].

Previous clinical studies addressing the association between stroke and Chagas disease have focused especially on the role of Chagas disease as an independent risk factor of stroke, adjusting for traditional cardiovascular risk factors [8,9,32,33]. In a case-control study including patients with similar cardiovascular risk profiles, T. cruzi infection was more frequent in cases of acute stroke than in acute coronary syndrome [32]. A cross-sectional study showed that classic vascular risk factors, such as hypertension, diabetes mellitus, and smoking, are less common in patients with Chagas disease—related stroke than in those without [34], especially as stroke patients with Chagas disease are younger than nonchagasic patients

are [9]. In other studies, ischemic stroke was more frequent in patients with Chagas disease than in the non-Chagas cardiomyopathies [9,33,35].

However, these previous studies have included patients at different stages of Chagas disease progression, from indeterminate to chronic forms of the disease [13]. Additionally, a few studies have assessed the risk of ischemic stroke in Chagas disease using a comprehensive echocardiographic evaluation to establish the embolic source [9,11,14]. In contrast, the present study encompasses a homogenous population of Chagas disease patients with chronic cardiac form to identify the cardiac source of the embolism. In particular, identification of thrombus has important implications for management of Chagas heart disease. We previously found a prevalence of 23% of LV intracavitary thrombus in a series of 75 patients with Chagas cardiomyopathy [11]. The current study, which included a substantial number of patients, showed a prevalence of 15% of LV thrombus, which is in agreement with previous reports [10,11,36]. Conversely, autopsy studies have detected LV thrombosis in 35% to 44% of patients who died from congestive heart failure or sudden death with chronic Chagas disease [30,37].

The frequency of apical aneurysm assessed by echocardiography was 39% in the study cohort, but in patients with ICE, the prevalence was higher (54%). Our results support the concept that aneurysms are predictors of mural thrombus and stroke [9,11,13,14]. Interestingly, multivariable analysis showed that both the apical aneurysm and the presence of thrombus are independent markers for stroke risk, with the 2 parameters providing additive predictive value.

Although ECG arrhythmia seems to be an important risk factor in the genesis of ischemic stroke related to Chagas disease, in the present study, atrial fibrillation was not associated with stroke. The absence of a significant relation between atrial fibrillation and stroke may in part be explained by the young ages of our cohort and the protection given by anticoagulation. Moreover, due to the cross-sectional design of the study, we cannot determine time exposed to atrial fibrillation as well as the presence of paroxysmal atrial fibrillation.

Additionally, thrombi are more frequently detected in the apex of the LV than in the left atrium. In our previous study, which used transesophageal echocardiography for detection of a cardiac source of emboli in Chagas cardiomyopathy, left atrial thrombi did not associate with ischemic cerebral events [11]. However, the cause-effect relationship between atrial fibrillation and stroke cannot be determined from this present cross-sectional study. A previous study showed that atrial fibrillation has prognostic value for stroke mortality in chronically *T. cruzi*—infected elderly patients [38].

Study limitations

In the present study, silent cerebral infarction was not assessed and some patients who had stroke may not have
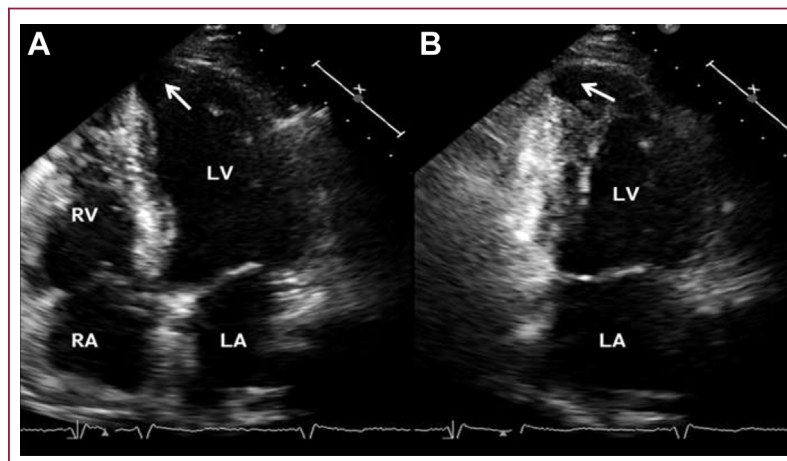
FIGURE 2. Two-dimensional 4-chamber (A) and 2-chamber (B) echocardiogram apical views of a patient with Chagas heart disease with a left ventricular apical aneurysm. There is a distinct limit between the normal contractile myocardium and the dyskinetic apex (arrows). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

been included. Another limitation of our study is that all traditional stroke risk factors were not fully evaluated [13]. Even Chagas disease patients with LV dilation may have experienced a stroke because of an underlying cerebral vessel disease, because potential noncardioembolic causes of stroke may be observed in Chagas disease stroke patients [9]. In addition, this is a cross-sectional study, and the status of anticoagulation therapy at the time of ICE was not known, which does not allow establishing the protective effect of anticoagulation on the incidence of ICE.

As all the echocardiographic studies were performed in a tertiary-care referral center for Chagas disease, a bias
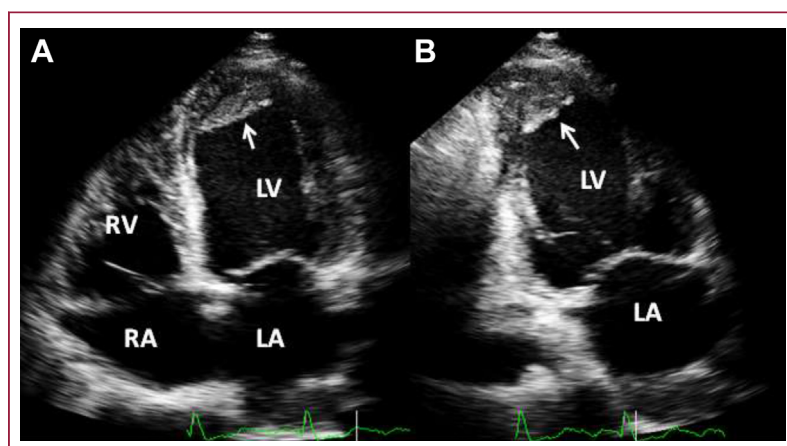
FIGURE 3. Two-dimensional 4-chamber (A) and 2-chamber (B) echocardiogram apical views of a patient with Chagas heart disease showing apical thrombus (arrows). There is a distinct mass close to the endocardium of the apex of the left ventricle, which can be visualized in at least 2 different echocardiographic views. Abbreviations as in Figure 2.

TABLE 3. Factors associated with ICE

Covariates*	Univariate Analysis			Multivariate Analysis[†]		
	OR	95% CI	p Value	OR	95% CI	p Value
Age, yrs	1.01	0.98–1.04	0.333	1.01	0.98–1.04	0.625
NYHA functional class	0.83	0.62–1.11	0.217	0.66	0.42–1.03	0.066
Atrial fibrillation	1.22	0.47–3.16	0.689	0.91	0.22–3.74	0.893
LVEF, %	1.01	0.99–1.03	0.211	0.99	0.97–1.03	0.858
LV apical aneurysm	2.15	1.25–3.70	0.006	2.19	1.11–4.34	0.024
LV thrombus	3.56	1.85–6.84	<0.001	2.43	1.09–5.42	0.030
LAV index, l/m^2	0.99	0.98–1.01	0.888	1.01	0.99–1.03	0.276

CI, confidence interval; LAV, left atrial volume; OR, odds ratio; other abbreviations as in Tables 1 and 2.

*The C-statistic for predicting ICE was 0.70 (95% CI: 0.62 to 0.77).

[†]Multivariate analysis was adjusted for age, NYHA functional class, presence of atrial fibrillation, LVEF, and LAV.

selection about prevalence of apical aneurysm in our population cannot be ruled out. In addition, transthoracic echocardiography may miss the diagnosis of an intracardiac thrombus, especially if the image is foreshortened or if the thrombus is small or attached to the ventricular wall, and any artifact within a cardiac chamber should potentially be considered a thrombus [39].

CONCLUSIONS

In a selected population referred to a tertiary center for Chagas disease, including patients with different disease severity from asymptomatic with normal ventricular function to severe dilated cardiomyopathy, the prevalence of ICE was 20%. The presence of apical aneurysm and intracavitary thrombus were independently associated with ICE after adjustment for anticoagulation therapy, LV systolic function, and arrhythmias.

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