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ORIGINAL ARTICLE

The impact of transthoracic echocardiogram in the indication of long-term anticoagulant therapy after ischemic stroke – a Northeast Brazilian center register

O impacto do ecocardiograma transtorácico na indicação de terapia anticoagulante de longo tempo após AVC isquêmico – um registro de um centro do Nordeste brasileiro

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ABSTRACT

Introduction: To prevent the recurrence of an ischemic stroke or transient ischemic attack (TIA), the mechanism of this event must be defined and adequate secondary prevention must be implemented. Despite its widespread use, the impact of echocardiography in this scenario is still subject to discussion. This study objective to evaluate the role of transthoracic echocardiography (TTE) in the indication of long-term anticoagulant therapy after stroke and transient ischemic attack. The secondary objective was to determine the associations between clinical–demographic variables, echocardiographic changes, and the different mechanisms of ischemic stroke. **Methods:** This is a cohort single-center study conducted over 12 months. The variables were compared using the chi-square, Fisher exact, and Kruskal–Wallis tests. The significant p value was < 0.05. **Results:** 355 cases of ischemic stroke and TIA were analyzed, of which 75 (21.1%) were cardioembolic. In 12 patients (3.4%), there was an indication for anticoagulation based on echocardiographic criteria, with a greater impact in the subgroup of patients with Chagas disease. In another 44 patients (12.4%), TTE identified changes that resulted in therapy optimization. Of the considered variables, the history of heart disease and echocardiographic changes were associated with cardioembolism (p<0.001). **Conclusion:** TTE identified significant alterations in 15.8% of the patients and was fundamental in the indication of anticoagulation in 3.4% of the cases. The history of heart disease and echocardiographic changes were correlated with cardioembolic mechanism.

Keywords: Stroke; Transthoracic echocardiography; Intracranial embolism and thrombosis; Chagas disease.

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RESUMO

Introdução: Para prevenir a recorrência de um acidente vascular cerebral isquêmico ou ataque isquêmico transitório (AIT), o mecanismo desse evento deve ser definido e a profilaxia secundária adequada deve ser implementada. Apesar de sua ampla utilização, o impacto da ecocardiografia nesse cenário ainda é passível de discussão. Este estudo tem como objetivo avaliar a ecocardiografia transtorácica (ECOTT) na indicação de anticoagulação após acidente vascular cerebral isquêmico ou ataque isquêmico transitório. O objetivo secundário foi determinar as associações entre variáveis clínico-demográficas, alterações ecocardiográficas e os diferentes mecanismos de AVC isquêmico. **Métodos:** Trata-se de um estudo de coorte, prospectivo, unicêntrico, realizado e conduzido durante 12 meses. As variáveis foram comparadas usando os testes qui-quadrado, exato de Fisher e Kruskal-Wallis. O valor de significância de p foi <0.05. **Resultados:** Foram analisados 355 casos de AVC isquêmico e AIT, dos quais 75 (21.1%) foram cardioembólicos. Em 12 pacientes (3.4%), houve indicação de anticoagulação com base em critérios ecocardiográficos, com maior impacto no subgrupo de pacientes com doença de Chagas. Em outros 44 pacientes (12.4%), o ECOTT identificou alterações que resultaram em otimização da terapia. Das variáveis consideradas, história de cardiopatia e alterações ecocardiográficas estiveram associadas com cardioembolismo (p<0.001). **Conclusão:** O ECOTT identificou alterações significativas em 15.8% dos pacientes e foi fundamental na indicação de anticoagulação em 3.4% dos casos. A história de cardiopatia e as alterações ecocardiográficas foram correlacionadas com o mecanismo cardioembólico.

Palavras-chave: AVC; Ecocardiografia transtorácica; Trombose e embolia intracraniana; Doença de Chagas.

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Introduction

Although preventable in most cases, stroke is one of the main causes of mortality and disability worldwide, with the ischemic subtype representing up to 87% of all cases[1]. Controlling risk factors and implementing adequate secondary prevention are critical for preventing this event from recurring.

To investigate the mechanisms associated with cerebral ischemia, transthoracic echocardiogram (TTE) has traditionally been used to examine sources of cardiac embolism, which accounts for 15%-30% of all cases.

However, in 2018, the American Heart Association/American Stroke Association (AHA/ASA) recommended against the routine use of TTE in the acute phase of ischemic stroke because there was no evidence that this procedure was cost-effective[2]. The following year, a revised version of the same document recommended echocardiography in some patients with a level of evidence IIb[3].

Many studies disagree on the role of TTE in the management of patients with ischemic stroke. Most of the studies are retrospective and use a variety of heterogeneous criteria[4,5]. While some authors question the usefulness of TTE in the workup of ischemic stroke patients, arguing that the proportion of exams that lead to changes in medical management is minimal[6,7], others defend the routine use of TTE in this scenario, arguing that TTE is a non-invasive, available and easy to perform technique to detect sources of embolism with potential therapeutic implications[8-10].

This prospective study aims to evaluate the role of TTE in the indication of long-term anticoagulant therapy after ischemic stroke and TIA. The secondary objective was to analyze the association of clinical–epidemiological variables and echocardiographic parameters with different stroke mechanisms.

Methods

This is a cohort study that was conducted over 12 months in a tertiary high-complexity hospital localized in Brazil's Central Arid Northeast countryside, an endemic region for Chagas disease.

For a historical average in previous years of 450 admissions for ischemic stroke or TIA, a minimum sample size of 208 participants was calculated for a confidence level of 95% and a margin of error of 0.05.

The inclusion criteria were: established diagnosis of ischemic stroke or TIA based on the clinical picture and imaging examinations; age over 50 years (patients considered not young); to realize the investigation protocol examinations - a study of cardiac rhythm, TTE, studies of extra and intracranial vessels, and biochemical tests including serology for Chagas disease.

Exclusion criteria included the inability to undergo imaging tests, the need to transfer to other services, and the patient's request for early discharge.

The following parameters were analyzed to characterize the sociodemographic and clinical profile: age, gender, schooling, place of residence (rural or urban zone), income level, National Institute of Health Stroke Scale (NIHSS) score at admission (ranging from 0 to 42, with higher values indicating more severe deficits); systemic arterial hypertension (SAH); diabetes mellitus (DM); excessive alcohol consumption; smoking; illicit drug use; excess weight/obesity; previous stroke; sedentary lifestyle; history of heart disease; prior diagnosis of dyslipidemia; and total cholesterol and triglyceride levels measured at admission. The following parameters were considered to define a history of heart disease: heart failure of any degree; valve disease requiring clinical or surgical treatment; arrhythmias requiring treatment; coronary artery disease; and other structural diseases that required specialized monitoring. The definitions described in references[11-14] were used to conceptualize SAH, DM, dyslipidemia, excessive alcohol consumption, smoking, overweight/obesity, and sedentary lifestyle.

The echocardiographic variables selected were: left atrial diameter and volume; left ventricular systolic and diastolic diameters; left ventricular mass index; relative thickness of the left ventricular wall; left ventricular ejection fraction (LVEF); the presence of grade II or III diastolic dysfunction; and the absence of motion in the inferodorsal ventricular wall. These variables were chosen based on data from previous studies that demonstrated some association with ischemic stroke[15-22]. The absence of inferodorsal ventricular motion was included because it is a common alteration in Chagas disease. The values proposed by Lang et al. (2015)[23] were considered normal.

The classification proposed in the Trial of ORG 10172 in Acute Stroke Treatment (TOAST)[24] was used to classify the stroke mechanisms. Additionally, the "embolic stroke of undetermined source" (ESUS) concept was used to categorize a specific subgroup of undetermined cases according to the criteria proposed by Hart et al. (2014)[25].

Patients were monitored for the first 72 hours, including cardiac rhythm, and all underwent TTE by echocardiographists local team during their hospital stay.

The following parameters were considered indications for secondary prevention with anticoagulants: atrial fibrillation (AF); atrial flutter; the presence of a mitral or aortic mechanical prosthetic valve; the presence of a mural thrombus in the left atrium or ventricle; the presence of moderate-to-severe mitral stenosis of rheumatic etiology; dilated or restrictive cardiomyopathy with LVEF <35% with ischemic stroke of an embolic pattern with no other source of embolism; absence of anteroseptal ventricular motion associated with LVEF < 40% in an acute myocardial infarction context; and Chagas cardiomyopathy, with ischemic stroke of an embolic pattern[1,26,27].

The study was carried out as per the ethics recommended in the Helsinki Convention, and it was approved by the institutional ethics committee (CAAE numbers: 26085719.1.0000.5054 e 26085719.1.3001.5684). Consent was obtained before recruitment with permission for data use.

Statistical Analysis

Categorical variables were described in terms of their absolute frequency and percentage. The Shapiro-Wilk test was used to determine the normality of quantitative variables, and, as they did not show normal distribution, they were then described using the median and interquartile range. To analyze the association between categorical variables and stroke mechanisms, the chi-square and Fisher's exact tests were performed. The adjusted residuals of the associations with p less than 0.05 were examined. The analysis of the distribution of quantitative variables between the different groups of stroke mechanisms was performed using the Kruskal–Wallis test, followed by the Dwass-Steel-Critchlow-Fligner test of multiple comparisons. Jamovi version 2.3.21 was used for all analyses.

Results

Three hundred fifty-five patients were included - 330 cases (93%) of ischemic stroke and 25 (7%) of TIA (Figure 1).

The median age was 72 years (63-80), with a predominance of males (56.1%). 94.7% had less than 8 years of schooling, 44.2% were from rural areas, and 68.5% had low income. The most common comorbidity

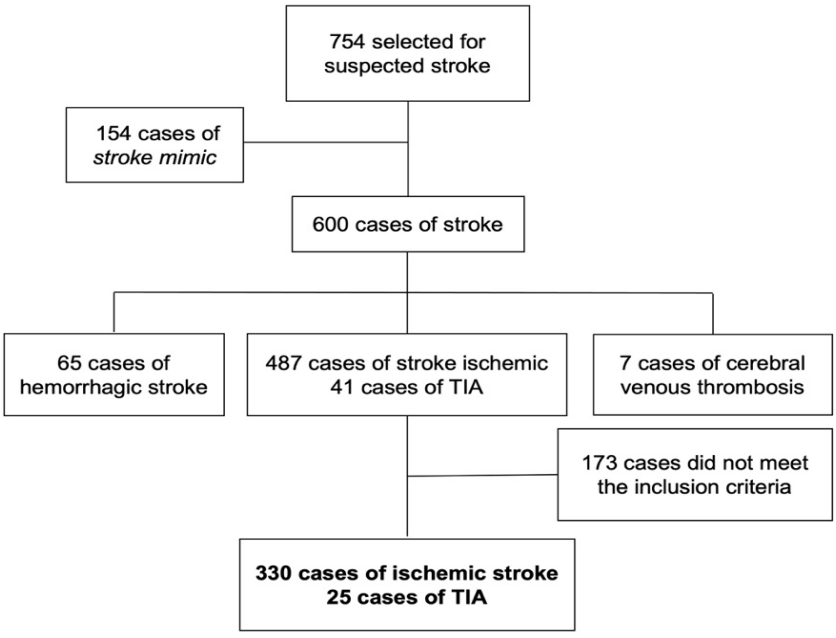


Figure 1. Patient selection flowchart.

at admission was SAH (72.7%). The general characteristics of participants are shown in Table 1.

The most prevalent mechanism was large-artery atherosclerosis, identified in 120 patients (33.8%), followed by undetermined etiology in 103 cases (29%). In the undetermined etiology, 71 (68.9%) cases were ESUS. Embolism of cardiac origin was identified in 75 patients (21.1%) (Graph 1). In relation to cardioembolic events, 62 (82.6%) were related to AF or flutter, and 1 (1.3%) to the presence of a metallic valve prosthesis.

Chagas serology was performed on 300 patients, with 13 positive results (4.3%). Eight of these patients had significant LVEF impairment (38.2% ± 6.4%), of whom 2 had concomitant AF detected during hospitalization, and 1 had symptomatic cervical carotid subocclusion. The remaining 4 patients had either normal TTE or minimal alterations, and 1 patient had valvular alteration (moderate mitral regurgitation) unrelated to Chagas disease.

Based on echocardiographic criteria alone, anticoagulation therapy rather than antiplatelet aggregation therapy was recommended for 12 patients (3.4%), of whom 5 tested positive for Chagas disease (Table 2). Patient number 6 still had an intracavitary thrombus. In 3 cases, an atrial septal aneurysm was identified with no shunt visible on Doppler echocardiography. For them, we opted for antiplatelet therapy. None had AF or flutter detected. There were no other high-risk sources of emboli identified.

For the remaining cardioembolic cases, anticoagulation therapy was recommended to observe the following findings that did not require TTE: AF or flutter detected on the electrocardiogram or a history of metallic valve prosthesis.

In another 44 patients (12.4%), TTE identified findings that, despite not requiring anticoagulation, resulted in an optimization of therapy: 33 Chagas disease-negative patients had LVEF reductions ranging from 35% to 50%, of whom 7 had moderate-severe valvular alterations and 3 moderate-severe pulmonary hypertension; 10 patients had moderate-severe valvular alterations without compromising systolic function; 1 patient had biological aortic valve dysfunction with significant reflux.

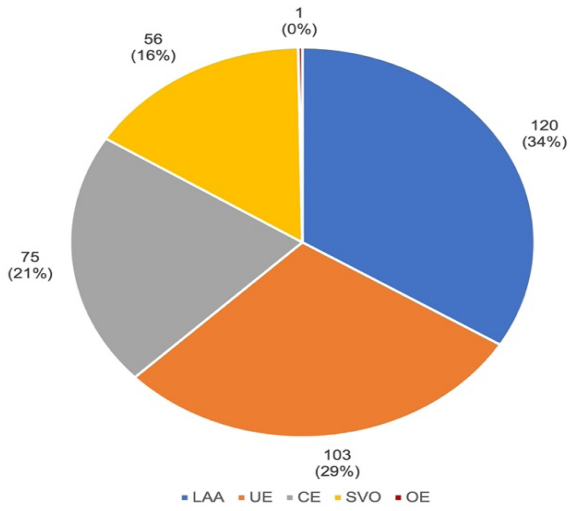
When categorical variables (clinical-epidemiological and echocardiographic) were examined in relation to stroke mechanisms based on the TOAST classification, by *chi-squared* and *Fisher's exact test*, a history of heart disease, identified in 51 patients (14.4%) was associated with cardioembolic mechanism (p<0.001). Others had no statistically significant association with any specific etiology.

The analysis of quantitative variables (clinical–epidemiological and echocardiographic) by *Kruskal-Wallis*, showed that patients with a cardioembolic mechanism had, in relation to the other groups, older age, greater left atrial volumes and diameters, larger left ventricular systolic and diastolic diameters, greater left

Table 1. General characteristics of the sample.

VARIABLES	N (%)	MEDIAN (P25 / P75)#
Age (years)	-	72 (63/80)
Ischemic stroke/TIA	330 (93)/25 (7)	
NIHSS# at admission	-	8 (4/14.5)
Intravenous thrombolysis	81 (22.8)	
Male sex	199 (56.1)	
Schooling		
Illiterate	152 (44.8)	
1–8 years	169 (49.9)	
9–11 years	15 (4.4)	
12 years or more	3 (0.9)	
Place of residence		
Urban area/ Rural area	197 (55.8)/ 156 (44.2)	
Income level		
<1 minimum wage	189 (68.5)	
1–5 minimum wage	87 (31.5)	
Arterial hypertension	258 (72.7)	
Excess weight/ obesity	183 (58.1)	
Sedentary lifestyle	175 (54.9)	
Smoking	98 (27.6)	
Diabetes mellitus	96 (27)	
Previous stroke	53 (14.9)	
Previous heart disease	51 (14.4)	
Excessive alcohol consumption	49 (13.8)	
Dyslipidemia	48 (13.5)	
Use of illicit drugs	1 (0.3)	

Legend: # P25 = 25th percentile; P75 = 75th percentile; NIHSS = National Institutes of Health Stroke Scale; TIA = transient ischemic attack.



Legend: LAA = Large-artery atherosclerosis; CE = Cardioembolism; SVO = Small-vessel occlusion; OE = Other determined etiology; UE = Undetermined etiology.
Graph 1. Mechanisms established according to the TOAST classification. N (%).

ventricular mass indices, and lower LVEFs (p<0.001). The NIHSS score differed between the small-artery occlusion group, in which it was lower, and the cardioembolism and large-artery atherosclerosis groups (p=0.011). Total cholesterol and triglyceride levels were higher in the large-artery atherosclerosis and small-artery occlusion groups, with a significant difference (p<0.001) compared to the cardioembolism and undetermined etiology groups. There was no significant difference in the other comparisons. Table 3 demonstrates the values of each quantitative variable for each group.

Discussion

In this study, TTE increased 3.4% the frequency of cases with the indication of long-term anticoagulant therapy after ischemic stroke and TIA. Furthermore, TTE identified cardiac changes that helped in the treatment of 12.4% of additional patients. The results were obtained in an endemic region for Chagas disease with a population whose sociodemographic characteristics differ from those typically reported in the literature.

The frequency with which TTE modified the management of patients with positive serology findings for Chagas disease is particularly noteworthy. Of the 13 positive patients, 8 (61.5%) had established Chagas cardiomyopathy, and TTE was critical in the indication

Table 2. Description of cases in which transthoracic echocardiography indicated anticoagulation as secondary prophylaxis.

PATIENTS	GENDER	AGE (YEARS)	NIHSS AT ADMISSION	LVEF (%)	SEROLOGY FOR CHAGAS DISEASE
1	M	80	14	38	Positive
2	M	76	0	29	Negative
3	M	54	2	26	Negative
4	M	78	15	29	Negative
5	M	56	16	37	Positive
6	M	72	8	50	Positive
7	M	68	9	23	Negative
8	M	76	22	30	Negative
9	M	63	11	39	Positive
10	M	54	5	36	Positive
11	F	82	5	27	Negative
12	F	71	25	32	Negative

Legend: NIHSS = National Institutes of Health Stroke Scale; LVEF = Left ventricular ejection fraction; M = Male; F = Female.

of anticoagulation as Secondary prevention in 5 of these cases - 2 other patients already had anticoagulation indications due to the presence of AF, and 1 had cervical carotid subocclusion (it was considered the most likely mechanism). The current sample had a higher prevalence of Chagas disease (4.3%) than the most recent estimates for Brazil, which ranged from 1% to 2.4% of the population[28].

The frequency of stroke mechanisms did not differ significantly from what has been reported in other case series[1]. The proportion of ESUS was found to be intermediate between a 2019 Brazilian series[29] and a 2017 Latin American series[30].

Among the risk factors, only a history of heart disease was associated with a specific mechanism, namely cardioembolism. In relation to echocardiographic variables, the correlation between left atrial size[31], structural changes in the left ventricle[15-22], and increased risk of stroke, is well established in the literature. In our sample, these variables differed significantly only when comparing the cardioembolic group with the others.

In relation to AHA/ASA recommendations[3], which advise against the routine use of TTE as an investigative tool for all patients with ischemic stroke, two considerations are necessary. First, despite TTE being decisive in the indication of anticoagulation in only a minority of cases, no other tool was able to define the best therapy in this group of patients. Secondly, aside from aiding in the definition of secondary prevention, TTE may be effective at detecting other relevant structural changes.

As stroke is often the result of inadequate control of risk factors common to other heart diseases, performing TTE may be an opportunity to screen for potential complications. Moreover, TTE is a non-invasive and low-cost examination.

For patients with no established mechanism, examining while still in the hospital is certainly more appropriate. Considering that the impact seems to be more significant in the population with Chagas disease, TTE may be even more relevant in regions with a higher prevalence of the disease, such as Brazil and other Latin American countries. A recent Brazilian study showed that patients who underwent TTE during hospitalization were 3.1 times less likely to be classified as having an undetermined mechanism and had a protective effect by lowering the risk of in-hospital death[32].

The study has several limitations, including being single-center and excluding young patients. Young patients were not included because other conditions commonly researched in this population were not the target of this study. Furthermore, we did not evaluate the additional impact of transesophageal echocardiography, which is generally necessary as a complementary workup for this group of patients. Possibly, the exclusion of young patients may have underestimated the impact of TTE on the indication of long-term anticoagulant therapy in our sample.

Table 3. Distribution of quantitative variables between groups of stroke mechanisms according to the TOAST classification.

VARIABLES	LARGE-ARTERY ATHEROSCLEROSIS median P25/P75#	UNDETERMINED ETIOLOGY median P25/P75	CARDIOEMBOLISM median P25/P75	OCCLUSION OF SMALL ARTERIES median P25/P75	OTHER CAUSES median P25/P75
Age (years)	72 63/79	71 61/79	79 71/83	65 60.8/78.3	73 73/73
NIHSS at admission	9 4/15	8 3/15.8	11 4/15	6 3.75/9.25	5 5/5
Total cholesterol level	215 179/242	186 162/219	179 150/205	222 184/242	141 141/141
Triglyceride level	137 97/200	114 86/157	97.5 75.3/142	166 106/222	141 141/141
LA Diameter (mm)	34 31.5/37	35 32.3/38	41 37/44	33 31/36	32 32/32
LA volume (mL/m^2)	22.5 19.3/29.1	24.7 20.8/38	43.6 34.5/47.2	23.4 17.7/28.7	24.6 24.6/24.6
LV diastolic diameter # (mm)	45 42/48	46 42/49.8	52 44/59	44.5 41/48.3	36 36/36
LV systolic diameter (mm)	29 26/31	29.5 27/33.8	35 26/45	28 27/30.3	22 22/22
LV mass index (g/m^2)	98.6 81.5/126	98.6 80.7/125	128 101/160	95.2 84.9/111	57.5 57.5/57.5
Relative thickness of the LV wall (cm)	0.41 0.38/0.46	0.39 0.35/0.46	0.4 0.33/0.48	0.41 0.38/0.49	0.4 0.4/0.4
LVEF # (%)	64 61/67	63.5 59/68	56 42/61	65.5 61/68	62 62/62

Legend: # P25 = 25th percentile; P75 = 75th percentile; NIHSS = National Institutes of Health Stroke Score; LA = left atrium; LV = left ventricle; LVEF = Left ventricular ejection fraction.

Conclusion

Transthoracic echocardiogram indicated anticoagulation in 3.4% of the cases studied, whereas echocardiographic findings influenced the therapeutic decision in 12.4% of additional cases. The proportion of cases in which TTE modified the course of secondary prevention was more significant in the group of patients with Chagas disease. A history of heart disease was the risk factor most consistently associated with a specific mechanism (cardioembolism). Echocardiographic variables were associated with the cardioembolic stroke group, with no significant differences between the noncardioembolic groups.

Authors' Contributions:

We describe contributions to the papers using the taxonomy (CRediT) (https://casrai.org/credit/) provided below:

Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing: Alan Alves de Lima Cidrão, Antônio Brazil Viana Júnior, Flaviane Melo Araújo, Kleiber Marciano Lima Bonfim, Eduardo Arrais Rocha; *Project administration, Software, Supervision, Validation, Visualization:* Alan Alves de Lima Cidrão, Eduardo Arrais Rocha.

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