Brief Report

Patients With Undetermined Stroke Have Increased Atrial Fibrosis

A Cardiac Magnetic Resonance Imaging Study

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Background and Purpose—Some patients with ischemic strokes that are currently classified as having an undetermined cause may have structural or functional changes of the left atrium (LA) and left atrial appendage, which increase their risk of thromboembolism. We compared the LA and left atrial appendage of patients with different ischemic stroke causes using cardiac magnetic resonance imaging.

Methods—We prospectively included a consecutive sample of ischemic stroke patients. Patients with structural changes on echocardiography currently considered as causal for stroke in the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification were excluded. A 3-T cardiac magnetic resonance imaging was performed.

Results—One hundred and eleven patients were evaluated. Patients with an undetermined cause had a higher percentage of LA fibrosis (P=0.03) than patients with other stroke causes and lower, although not statistically significant, values of LA ejection fraction. Patients with atrial fibrillation and undetermined stroke cause showed a similar value of atrial fibrosis.

Conclusions—The LA phenotype that was found in patients with undetermined cause supports the hypothesis that an atrial disease may be associated with stroke. **(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.117.019641.)**

Key Words: atrial fibrillation ■ echocardiography ■ magnetic resonance imaging ■ stroke ■ thromboembolism

A fraction of the ischemic strokes that are currently classified as having an undetermined cause are likely cardioembolic. Patients with a stroke of undetermined cause may have morphological or hemodynamic cardiac changes that are not currently considered as a cause of stroke.

Recent studies suggest that atrial fibrillation (AF) is the final point of a disease characterized by morphological and structural changes in the atria.[1] These changes could increase the probability of formation of thrombi. A decrease in left atrial (LA) ejection fraction could induce stasis, and an increase in atrial fibrosis could lead to both stasis and endocardium changes that favor thromboembolism. Previous studies suggest that specific morphologies of the left atrial appendage (LAA), namely, a cauliflower type, may be associated with an increased risk of thromboembolism by leading to decreased blood velocity.[2]

Warraich et al[3] found that patients with paroxysmal AF had a prothrombotic AF LAA pulse-wave Doppler phenotype even when they were in sinus rhythm as assessed by transesophageal echocardiography.

Cardiac magnetic resonance imaging (CMR) is currently the gold-standard method for assessing cardiac structure and function. We compared the LA and LAA of patients with different ischemic stroke causes using CMR.

Methods

The data that support the findings of this study are available from the corresponding author on request.

This was a prospective, observational, case–control study. We included consecutive patients with ischemic stroke admitted to the stroke units of Hospital Santa Maria (November 2014 to May 2017) and Hospital Egas Moniz (October 2016 to May 2017) in Lisbon, Portugal.

Patients were included if they fulfill the following inclusion criteria: >50 years of age; acute ischemic stroke with a lesion in brain imaging; and complete pathogenic investigation comprised by blood analysis, study of the intracranial and extracranial vessels, heart rhythm (EKG and 24-hour Holter monitoring), cardiac morphology (transthoracic echocardiogram), and evaluation of a right–left shunt (transcranial Doppler with bubble study). Patients were excluded if they had morphological changes considered as a cause of stroke by the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification (ventricular akinesia/hypokinesia, cardiomyopathies, patent foramen ovale with aneurysm of the interatrial septum), moderate or severe valvular disease, and ejection fraction <40%, or if they were unable to perform CMR <3 months of the index stroke.

We used TOAST to classify stroke cause. Patients were further combined into 3 groups: cardioembolism related to AF, undetermined cause, and other specific causes (small vessels, large vessels disease, and other determined causes).

We performed CMR using a Philips Achieva 3 Tesla system (Philips Healthcare, Best, the Netherlands). The following sequences were acquired: steady-state free precession sequence in short-axis and the 3

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long-axis planes for the assessment of left ventricular and LA volumes and ejection fraction; contrast-enhanced angiography; and high-resolution late gadolinium enhancement for fibrosis assessment. The shape of the LAA was categorized into 4 morphologies: chicken wing, cactus, windsock, and cauliflower.[4] Cvi42 software (Circle, Cardiovascular Imaging, Inc, Calgary, Canada) was used for the assessment of left ventricular morphology and function. For LA fibrosis assessment, 3D slicer was applied, appropriately adjusted (www.slicer.og5). The cardiologist was blind to the stroke cause. We compared the obtained values with reference ranges from the UK Biobank.[6] All patients with undetermined stroke and other specific stroke causes were in sinus rhythm when CMR was performed.

We obtained institutional review board approval by the ethical committee of both hospitals (Hospital de Santa Maria and Hospital Egas Moniz). All patients or relatives signed a written informed consent.

Statistical Analysis

The 3 groups of patients were compared using the adequate statistical test (ANOVA, Kruskall–Wallis, and Fisher exact test). A post hoc analysis with Dunn–Bonferroni correction for the 2 prespecified comparisons was done. Adjusted and unadjusted *P* values are presented. Significance level was set at $P \leq 0.05$. Statistical analysis was performed with SPSS 23.

Results

One hundred seventeen patients were included and underwent CMR. Six patients had cardiomyopathies (2 amyloid, 1 noncompaction, and 3 hypertrophic) and were excluded. Therefore, 111 patients were analyzed. These patients had a mean age (SD) of 68.7 (9.4) years. Seventeen patients had cardioembolism associated with AF (7 paroxysmal, 3 persistent, and 7 permanent; in 9 patients, the diagnosis was established during pathogenic investigation), 52 had an undetermined cause, and 42 had other specific causes. Characteristics of these patients are displayed in the Table.

Table. Baseline and CMR Characteristics

	Atrial Fibrillation (n=17)	Undetermined Cause (n=52)	Other Specific Causes (n=42)	*P* Value
Age, y	72.7 (10.3)	69.4 (9.2)	66.2 (8.7)	0.04
Male sex	7 (41.2)	25 (48.1)	31 (73.8)	0.02
Hypertension	14 (82.4)	42 (80.8)	34 (81.0)	0.99
Diabetes mellitus	0 (0)	10 (19.2)	10 (23.8)	0.07
CHA_2DS_2VASC	3 (3)	3 (2)	3 (2)	0.34
Dyslipidemia	9 (52.9)	28 (53.8)	18 (42.9)	0.56
ACEI	3 (17.6)	13 (25.0)	13 (31.0)	0.62
ARA	7 (41.2)	11 (21.2)	11 (26.2)	0.26
β-Blocker	6 (35.3)	15 (28.8)	6 (14.3)	0.13
Diuretic	9 (52.9)	18 (34.6)	12 (28.6)	0.22
CCB	2 (11.8)	12 (23.1)	9 (21.4)	0.70
Antiplatelet	5 (29.4)	13 (25.0)	8 (19.0)	0.65
Anticoagulant	4 (23.5)	0 (0)	1 (2.4)	0.001
Admission NIHSS score	9 (13)	6 (10)	5 (4)	0.06
Atrial appendage shape				0.45
Windsock	14 (82.4)	30 (57.7)	30 (71.4)	
Cauliflower	1 (5.9)	4 (7.7)	1 (2.4)	
Chickenwing	1 (5.9)	10 (19.2)	4 (9.5)	
Cactus	1 (5.9)	8 (15.4)	7 (16.7)	
Indexed atrial volume, mL/m^2	61.0 (35)	39.5 (24)	37 (17)	<0.001
Atrial ejection fraction, %	36.0 (19)	46.0 (13)	50 (8)	<0.001
Atrial appendage fibrosis	14 (82.3)	35 (67.3)	27 (64.3)	0.43
Atrial fibrosis, %	25 (21)	18 (16)	10.5 (16)	0.002
Atrial fibrosis				0.001
<10%	2 (11.8)	13 (25.0)	16 (38.1)	
10–<20%	5 (29.4)	15 (28.8)	18 (42.9)	
20–<30%	4 (23.5)	17 (32.7)	8 (19.0)	
>30%	6 (35.3)	7 (13.5)	0 (0.0)	

Data are represented as n (%), except age that is presented with mean (SD) and the remaining numeric variables that are presented with median (interquartile range). ACEI indicates angiotensin-converting enzyme inhibitor; ARA, angiotensin II receptor antagonists; CCB, calcium channel blockers; and NIHSS, National Institutes of Health Stroke Scale.

Patients with undetermined cause did not differ from patients with AF. When compared with patients with other specific stroke causes, patients with undetermined cause were more frequently females and had higher admission National Institutes of Health Stroke Scale scores.

Patients with an undetermined cause had more LA fibrosis than patient with other specific causes (P=0.03). Atrial fibrosis was similar in patients with AF and in those with undetermined cause (P=0.22; Figure [A]).

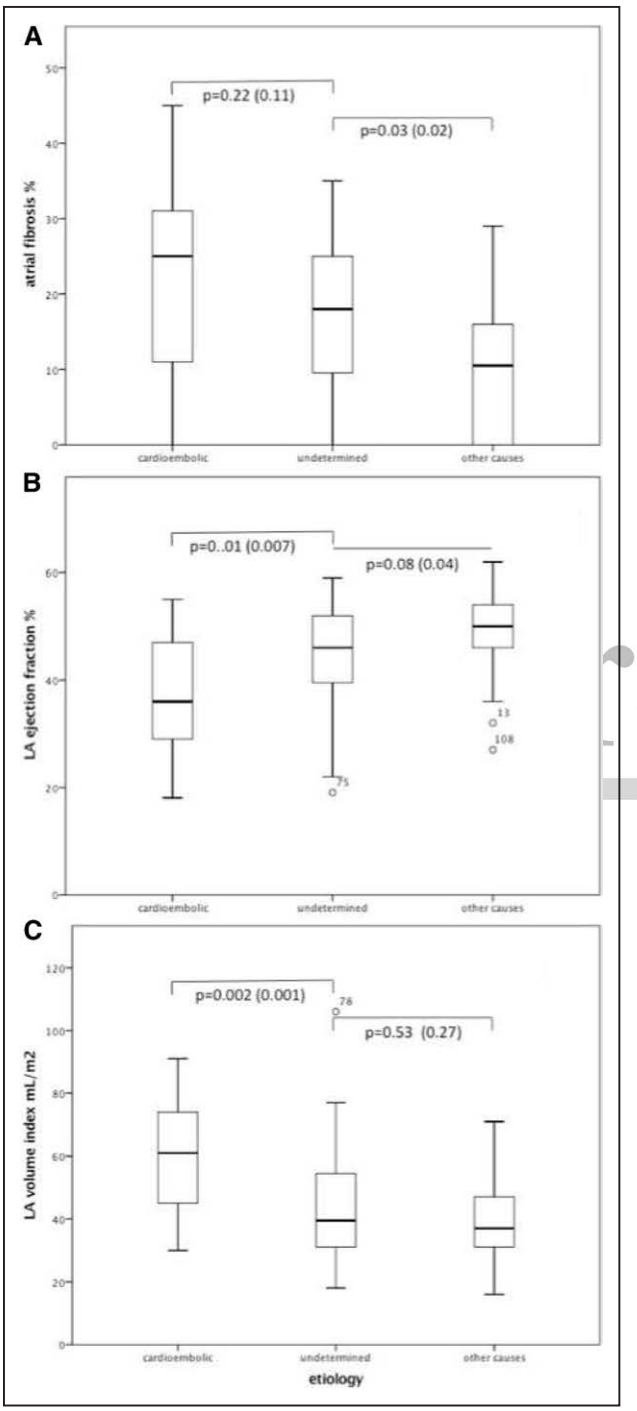

Figure. Box plots of percentage of atrial fibrosis (**A**), left atrial (LA) ejection fraction (**B**), and LA volume index (**C**). *P* values in brackets are unadjusted.

There was no difference across groups regarding the shape or the presence of atrial fibrosis in the LAA.

Patients with an undetermined cause had an LA volume index similar to patients with other stroke causes: 39.5 (24) versus 37 (17) mL/m^2 (P=0.53). Values between 19 and 62 mL/m^2 are within normal range.[6] The LA volume index of patients with AF was larger than that in patients with undetermined cause (P=0.002; Figure [C]).

Patients with undetermined cause had a lower, although not statistically significant, LA ejection fraction (46% [13%]) than patients with other specific stroke causes (50% [8%]; P=0.08). Values between 47% and 73% are considered normal.[6] Patients with AF had an even lower LA ejection fraction (Figure [B]).

Discussion

Patients with undetermined cause showed a higher percentage of atrial fibrosis than patients with other specific causes of stroke and a lower although not statistically significant LA ejection fraction. When compared with patients with AF, they had similar values of atrial fibrosis. These results suggest that some patients with an undetermined stroke cause have an LA phenotype that is intermediate between patients with other stroke causes and patients with AF. This supports the hypothesis of an atrial disease that can worsen and be recognized before ultimately progressing to AF.[7] Atrial hypocontractility and impaired endocardium function could contribute to increased stasis of blood in the LA and to a higher probability of thromboembolism and stroke. Future studies may investigate this phenotype as a target for anticoagulation (or similar) before detection of AF.

Atrial cardiopathy has been suggested as one mechanism of cryptogenic stroke.[7] It is currently accepted that AF leads to atrial remodeling, but there is increasing evidence that a structural atrial condition defined as fibrotic atrial cardiomyopathy[8] can precede the occurrence of AF. AF has been proposed as an arrhythmic manifestation of fibrotic atrial cardiomyopathy.[8]

The LAA is considered the main site of thrombi formation in AF. LAA fibrosis on CMR has been associated with reduced LAA flow velocity in patients with AF.[9] We did not find differences in LAA fibrosis across groups. This can be because of the classification of LAA fibrosis as a binary variable. A previous study concluded that specific LAA morphologies were an independent predictor of thromboembolism in patients with AF.[2] In our study, LAA shape was similar across groups.

We used a classification for undetermined cause different from embolic strokes of undetermined source to increase the homogeneity of the group and to exclude patients who could have a cause for stroke other than that originated from the LA or LAA. However, it is possible that some patients with an undetermined cause have other causes than cardioembolic. This could in part explain the individual variability observed in the CMR data. The follow-up of patients with undetermined cause and other stroke causes will allow determination of who will develop AF in the future and determine whether the phenotype that was found in patients with an undetermined cause is indeed part of a progressive disease of the left atria.

The LA phenotype that was found in patients with undetermined cause supports the hypothesis that an atrial disease may be associated with stroke.

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Disclosures

Dr Ferro received speaker fees from Boheringer Ingelheim and was a consultant for Boheringer Ingelheim. Dr Pinho-e-Melo received speaker fees from Pfizer/Bristol Myers Squibb, Portugal, and a travel grant from Boehringer Ingelhein, Portugal. Dr Viana-Baptista received speaker fees from Boehringer Ingelhein, Portugal, and Daiichi Sankyo, Portugal, is part of an advisory board of Daiichi Sankyo, Portugal and received a travel grant from Boehringer Ingelhein, Portugal. The other authors report no conflicts.

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