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Letter to the Editor

Left Atrial Mechanical Dysfunction Is Associated With Atrial Fibrillation and Recurrent Stroke After Cryptogenic Stroke

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Dear Sir:

Atrial myopathy, characterized by electromechanical atrial remodeling, can lead to development of atrial fibrillation (AF) and is independently associated with embolic stroke.[1] Approximately 20%–40% of all strokes are classified as cryptogenic, which are associated with a 3%–6% risk of recurrent stroke within 1 year.[2-4] AF has been detected in 12%–38% of patients within 1 year of cryptogenic stroke supporting the possibility of a prominent cardioembolic mechanism.[2,5] Oral anticoagulant medications, unfortunately, have not demonstrated superiority to antiplatelet agents in preventing recurrent stroke in all patients with cryptogenic stroke or in enriched populations of patients with cryptogenic stroke and suspected atrial myopathy.[3,4,6,7]

There is no consensus on the optimal markers to detect atrial myopathy clinically for purposes of stroke prediction. We aimed to determine if left atrial (LA) mechanical dysfunction, measured by left atrial emptying fraction (LAEF), is associated with AF and recurrent stroke or transient ischemic attack (TIA) in patients with cryptogenic stroke.

This study was approved by the Pennsylvania State University Institutional Review Board (IRB no. 00017160) and follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[8] Patients with cryptogenic stroke (March 2015–March 2022) who received implantable loop recorders (ILRs) for AF screening with at least 1 year of follow-up and interpretable echocardiograms were included (n=192). Patients were excluded for missing covariate data (n=34) resulting in a final cohort of 158 patients. All 158 patients had ILRs present for at least 1 year or developed AF within 1 year. LAEF (exposure variable) was calculated from echocardiograms by measuring the maximal change in atrial volume over the course of the cardiac cycle. AF (primary outcome) was defined by at least 30 seconds of AF on ILR. Data on recurrent stroke or TIA (secondary outcome), covariates, and medication use were obtained by review of the electronic medical record. The covariates included in this study included age, sex, hypertension, coronary artery disease (CAD), prior stroke or TIA, peripheral artery disease, diabetes mellitus, congestive heart failure, carotid artery stenosis, and left atrial volume index (LAVI).

The relationship between LAEF and AF was evaluated using a restricted cubic spline, cumulative incidence curves, and multivariable Cox proportional hazards models. Model discrimination and calibration were evaluated by calculating the C-statistic and Hosmer-Lemeshow χ^2 statistic. The association between LAEF and recurrent stroke or TIA after cryptogenic stroke was evaluated using Cox proportional hazards models.

Additional details on covariate definitions and statistical analysis are available in Supplementary Methods.

Of the 158 patients (mean age, 70.2 years; 52.5% female) in our cohort, 43 had AF (27.2%) over a mean (standard error [SE]) follow-up time of 282 (10.8) days. Compared to those who did not, patients who developed AF had greater LAVI (36.76 mL/m^2 vs. 31.01 mL/m^2, P<0.01), lower LAEF (48.21% vs. 56.93%, P<0.01), and were less likely to have diabetes (P=0.02). There were no additional significant differences in baseline parameters between groups (Supplementary Table 1).

A restricted cubic spline demonstrated a significant linear association (*P* for non-linearity=0.82, *P* for association=0.05) between decreasing LAEF and an increased incidence of AF after cryptogenic stroke (Figure 1A). The cumulative incidence of AF was lowest in patients with LAEF ≥53% (Figure 1B). LAEF <40% was independently associated with a 2.81-fold (1.09–7.23) increased risk of AF after cryptogenic stroke after adjustment for all covariates. When modeling as a continuous variable per 5% decrease, this association was no longer statistically significant after adjusting for LAVI. The addition of LAEF (Model 3) to a model constructed with all covariates (Model 3') resulted in improved discrimination with acceptable calibration (Table 1).

Recurrent stroke or TIA was identified in 11 of the 158 patients (6.9%) with a mean (SE) time from initial stroke to recurrent stroke of 171 (37.2) days. Compared to those who did not, patients who developed recurrent stroke or TIA had lower LAEF (44.79% vs. 55.28%, *P*=0.02) and were more likely to have CAD and develop AF (*P*=0.03) after the index stroke. Those who were on therapeutic anticoagulation at the time of stroke had reduced stroke

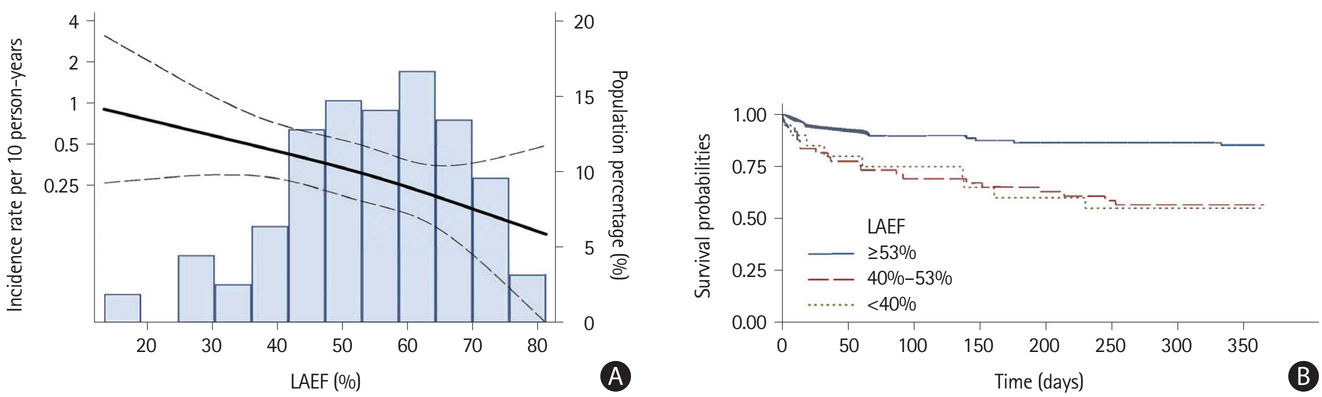

Figure 1. Association of left atrial mechanical dysfunction with atrial fibrillation detected after cryptogenic stroke. (A) Restricted cubic spline with knots at 10%, 50%, and 90%. Adjustments made for age, sex, hypertension, coronary artery disease, stroke or transient ischemic attack, peripheral artery disease, diabetes, carotid artery stenosis, congestive heart failure, and left atrial volume index. (B) Unadjusted cumulative incidence of atrial fibrillation. Categories of left atrial emptying fraction (LAEF) selected by whole number corresponding to the bottom 10%, middle 30%, and remaining 60%.

Table 1. Association of LAEF with AF and recurrent stroke or transient ischemic attack after cryptogenic stroke

	LAEF <40%[§‖] (n=20)	LAEF 40%–53% (n=49)	LAEF ≥53% (n=89)	LAEF per 5% decrease	C-Statistic (95% CI)	χ^2 (*P*-value)[¶]
AF in 1 year, n (%)	9 (45)	21 (43)	13 (15)		-	-
AF burden (%)*, mean (SE)	12.98 (6.32)	8.32 (1.98)	3.09 (0.73)		-	-
Model 1[†]	3.56 (1.48–8.56)	3.48 (1.70–7.09)	1 (Ref)	1.17 (1.06–1.30)	-	-
Model 2	3.32 (1.33–8.34)	2.86 (1.36–6.04)	1 (Ref)	1.17 (1.04–1.31)	-	-
Model 3	2.81 (1.09–7.23)	2.56 (1.20–5.47)	1 (Ref)	1.13 (1.00–1.28)	0.702 (0.625–0.779)	6.89 (0.65)
Model 3'	-	-	-	-	0.689 (0.608–0.770)	4.73 (0.86)
Stroke or TIA in 1 year, n (%)	3 (15)	4 (8)	4 (5)		-	-
Model A[‡]	-	-	-	1.30 (1.07–1.59)		
Model B	-	-	-	1.32 (1.04–1.67)		
Model C	-	-	-	1.28 (0.99–1.65)		
Model D	-	-	-	1.26 (0.96–1.67)		

LAEF, left atrial emptying fraction; AF, atrial fibrillation; N, number; SE, standard error; CI, confidence interval; TIA, transient ischemic attack.
*AF burden at time of diagnosis (minimum 7 days of monitoring depending on available loop recorder reports); [†]Model 1: Cox proportional hazards model including exposure variable (LAEF), age, and sex. Hazard ratios and 95% confidence intervals of LAEF (modeled as a categorical variable or continuous variable) for AF (Models 1–3). Categories correspond to the bottom 10%, middle 30%, and upper 60%. Model 2: Model 1 plus hypertension, coronary artery disease, stroke/TIA, peripheral artery disease, diabetes, carotid artery stenosis, and heart failure. Model 3: Model 2 plus left atrial volume index. Model 3': Model 3 minus left atrial volume index; [‡]Model A: Cox proportional hazards model including exposure variable (LAEF), age, and sex. Hazard ratios (95% confidence intervals) are presented of LAEF for recurrent stroke or TIA (Models A–D). Model B: Model A plus additional adjustment for hypertension, heart failure, stroke/TIA, peripheral artery disease, diabetes, coronary artery disease, carotid artery stenosis, anticoagulation. Model C: Model B plus additional adjustment for left atrial volume index. Model D: Model C plus additional adjustment for AF; [§]Categories selected by whole number of LAEF corresponding to the bottom 10% (LAEF<40%), middle 30% (LAEF 40%–53%), and remaining 60% (LAEF≥53%); [‖]LAEF not evaluated as a categorical variable due to low number of strokes within certain categories; [¶]Hosmer-Lemeshow χ^2 statistic.

severity as determined by the lower National Institutes of Health Stroke Scale. There were no additional significant differences in baseline parameters (Supplementary Table 2). LAEF per 5% decrease was independently associated with an increase in recurrent stroke or TIA. This association was attenuated after adjustment for LAVI and AF (Table 1).

The present study demonstrates that in patients with cryptogenic stroke, reduced LAEF is an independent risk factor for AF and may improve prediction of AF above what can be achieved using established stroke risk factors including LAVI. Our results indicate that the association between reduced LAEF and recurrent stroke or TIA may be mediated by LA size and development of AF.

Oral anticoagulation for the prevention of recurrent stroke in patients with cryptogenic stroke is currently guided by detection of AF post-stroke.[9] Detection of atrial myopathy, an upstream phenomenon independently associated with AF development and embolic stroke, may help refine this strategy. There is no consensus on the best variables for detection of atrial myopathy clinically, although several recent studies have indicated that analysis of LA mechanics is superior to analysis of LA size alone.[10] The four randomized trials evaluating the efficacy of oral anticoagulation for prevention of recurrent stroke in patients with cryptogenic stroke did not incorporate functional LA parameters or LA volume measurements to select candidates for anticoagulation.[3,4,6,7] If our findings are validated, future studies should consider analysis of LA mechanics to guide anticoagulation for prevention or reduction in severity of recurrent stroke after cryptogenic stroke.

There are limitations to be considered in this study. Only 11 of 158 (6.9%) patients suffered recurrent stroke or TIA. Thus, our analysis was largely exploratory for this endpoint. Additionally, despite statistical adjustments being made for potential confounding variables, imperfectly measured and unmeasured variables were not accounted for, as is the case in observational studies.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2024.00584.

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Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: AM. Study design: AM. Methodology: MF, FLN, AM. Data collection: JR, RS, MF, MM. Investigation: AM. Statistical analysis: JR, FLN, AM. Writing—original draft: JR, RS, AM. Writing—review & editing: MF, FLN, GVN, MDG, AM. Approval of final manuscript: all authors.

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Supplementary Methods

Study population

Patients who were diagnosed with cryptogenic stroke and subsequently received an implantable loop recorder (ILR) for screening of atrial fibrillation (AF) at a tertiary care medical center in the United States between March 2015 and March 2022 were eligible for inclusion (n=235). Inclusion criteria consisted of diagnosis of cryptogenic stroke and follow-up for at least 1 year following ILR implantation or diagnosis of AF within 1 year of ILR implantation with interpretable two-dimensional echocardiograms in sinus rhythm. Patients were excluded for missing covariate data (n=34) and lack of adequate follow-up (n=43) resulting in a final cohort of 158 patients.

Exposure variable

All echocardiograms were reviewed by two independent board-certified cardiologists. Phasic left atrial volumes were calculated using biplane method of discs from the apical 2 and 4 chamber views in echocardiograms obtained at time of cryptogenic stroke. Maximum left atrial volume (LAVmax) and minimum left atrial volume (LAVmin) were calculated just before mitral valve opening and mitral valve closure, respectively. The following formula was utilized to calculate left atrial emptying fraction (LAEF): LAEF=[(LAVmax – LAVmin)/LAVmax]×100.

Outcome variables

Development of AF after cryptogenic stroke was the primary outcome of interest and was determined by presence of at least 30 seconds of AF on ILR as noted by independent cardiac electrophysiologists at the author's institution and retrospectively confirmed by the authors. Time to AF development and AF burden were determined retrospectively by the authors. AF burden at the time of AF diagnosis was calculated after a minimum of 7 days and depended on available ILR interrogation reports.

Development of recurrent stroke or transient ischemic attack (TIA) was the secondary outcome of interest and was determined by documentation in the institutional electronic medical record (EMR) by an independent neurology or cardiology provider. Recurrent stroke severity was recorded via the National Institutes of Health Stroke Scale as documented in the institutional EMR. Use of anticoagulation in our cohort included use of apixaban 5 mg twice daily, rivaroxaban 15 mg or 20 mg once daily, dabigatran 110 mg or 150 mg twice daily, or warfarin with a therapeutic international normalized ratio as per EMR review.

Covariates

The covariates included in this study included age, sex, hypertension, coronary artery disease (CAD), prior stroke or TIA, peripheral artery disease, diabetes mellitus, congestive heart failure, and carotid artery stenosis. Comorbid conditions were identified via the following criteria: (1) Hypertension: documented history of hypertension prior to sentinel admission; (2) CAD: documented history of myocardial infarction or presence of coronary artery stenosis >70% on coronary angiography. Coronary calcifications on CT chest were not included as CAD; (3) Prior stroke or TIA: documented history of stroke or TIA prior to sentinel admission. Incidental evidence of prior infarct on computed tomography (CT) or magnetic resonance imaging (MRI) was not included as having history of stroke if the patient did not have clinical symptoms or documentation of stroke prior; (4) Peripheral artery disease: documented history of peripheral arterial disease or history of peripheral arterial stent placement; (5) Diabetes mellitus: documented history of diabetes mellitus or any hemoglobin A1c >6.5%; (6) Congestive heart failure: documented history of heart failure or presence of a left ventricular ejection fraction of <40% on echocardiography prior to sentinel admission; and (7) Carotid artery stenosis: evidence of >70% carotid artery stenosis on CT angiography or carotid Doppler ultrasound. Left atrial maximal volume index was calculated using the following formula: LAVmax/body surface area.

Statistical analysis

Differences between means were determined using the Student's t-test for continuous variables. The chi-squared test or Fisher's exact test were used for categorical variables when appropriate.

The relationship between LAEF and incident AF was explored using a restricted cubic spline adjusted for age, sex, hypertension, CAD, stroke or TIA, peripheral artery disease, diabetes, carotid artery stenosis, congestive heart failure, and left atrial volume index with the knots at 10%, 50%, and 90%.

The association between LAEF and incident AF after cryptogenic stroke was evaluated using Cox proportional hazards models. LAEF was evaluated both as a continuous variable (per 5% decrease) and a categorical variable with categories corresponding to the whole number closest to the bottom 10%, middle 30%, and remaining 60% as reference. Unadjusted cumulative incidence curves were generated for each category. Model 1 included the exposure variable (LAEF) and the following covariates: age and sex. Model 2 added hypertension, CAD, stroke/TIA, peripheral artery disease, diabetes mellitus, carotid artery stenosis, and congestive heart failure. Model 3 added left atrial volume index. Discrimination and calibration for Models 3' (covariates only) and 3 (covariates plus LAEF) were evaluated by calculating the C-statistic and Hosmer-Lemeshow χ^2 statistic.

The association between LAEF and recurrent stroke or TIA after cryptogenic stroke was evaluated using Cox proportional hazards models. Model A was adjusted for age and sex. Model B was additionally adjusted for hypertension, heart failure, stroke/TIA, peripheral artery disease, diabetes, CAD, carotid artery stenosis, and anticoagulation. Model C was additionally adjusted for left atrial volume index. Model D was additionally adjusted for incident AF.

Supplementary Table 1. Baseline characteristics for primary endpoint

Variable	AF (n=43)	No AF (n=115)	*P*
Mean age (yr)	72.46	69.31	0.14
Male sex	21 (48.84)	54 (46.96)	0.83
Hypertension	31 (72.09)	91 (79.13)	0.35
Coronary artery disease	8 (18.60)	16 (13.91)	0.46
Stroke/transient ischemic attack	8 (18.60)	20 (17.39)	0.86
Peripheral artery disease	9 (20.93)	15 (13.04)	0.22
Diabetes	8 (18.60)	44 (38.26)	0.02
Congestive heart failure	2 (4.65)	10 (8.70)	0.39
Carotid artery stenosis	7 (16.28)	17 (15.65)	0.92
Left atrial volume index (mL/m^2)	36.76±11.54	31.01±11.43	<0.01
Left atrial emptying fraction (%)	48.21±14.87	56.93±13.07	<0.01

Values are presented as n (%) or mean±standard error unless otherwise indicated.
AF, atrial fibrillation.

Supplementary Table 2. Baseline characteristics for secondary endpoint

Variable	Recurrent stroke			No recurrent stroke		
	AF (n=6)	No AF (n=5)	Total (n=11)	AF (n=37)	No AF (n=110)	Total (n=147)
Number of recurrent stroke (on anticoagulation)	6 (4)	5 (0)	11 (4)	-	-	-
NIHSS (on anticoagulation)	0±0 (0±0)	3.6±3.6 (-)	1.8±3.1 (0±0)	-	-	-
Left atrial emptying fraction (%)	44.11±20.69	45.62±19.07	44.79±18.98	49.03±13.82	57.47±12.68	55.28±13.45
Left atrial volume index (mL/m^2)	36.56±9.43	39.79±16.52	38.03±12.51	36.30±12.17	30.72±11.07	32.16±11.59
Carotid artery stenosis	2	0	2	5	18	23
Age (yr)	68.0±9.81	70.40±10.97	69.09±9.89	73.19±11.38	69.26±12.44	70.25±12.26
Female sex	3	2	5	19	59	78
Hypertension	5	3	8	26	88	114
Heart failure	0	1	1	2	9	11
Diabetes	3	3	6	5	41	46
Peripheral artery disease	2	1	3	7	14	21
Coronary artery disease	3	1	4	5	15	20
Stroke/transient ischemic attack	2	0	2	6	20	26

Values are presented as mean±standard error or numbers only.
AF, atrial fibrillation; NIHSS, National Institutes of Health Stroke Scale.

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