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ORIGINAL RESEARCH

Left Atrial Dynamics Is Altered in Young Adults With Cryptogenic Ischemic Stroke: A Case-Control Study Utilizing Advanced Echocardiography

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BACKGROUND: Ischemic stroke in young individuals often remains cryptogenic. Some of these strokes likely originate from the heart, and atrial fibrosis might be one of the etiological mechanisms. In this pilot study, we investigated whether advanced echocardiography findings of the left atrium (LA) of young cryptogenic stroke patients differ from those of stroke-free controls.

METHODS AND RESULTS: We recruited 30 cryptogenic ischemic stroke patients aged 18 to 49 years and 30 age- and sex-matched stroke-free controls among participants of the SECRETO (Searching for Explanations for Cryptogenic Stroke in the Young: Revealing the Etiology, Triggers, and Outcome) study (NCT01934725). We measured basic left ventricular parameters and detailed measures of the LA, including 4-dimensional volumetry, speckle tracking epsilon, strain rate, and LA appendix orifice variation. Data were compared as continuous parameters and by tertiles. Compared with controls, stroke patients had smaller LA reservoir volumes (10.2 [interquartile range, 5.4] versus 13.2 [5.4] mL; P=0.030) and smaller positive epsilon values (17.8 [8.5] versus 20.8 [10.1]; P=0.023). In the tertile analysis, stroke patients had significantly lower left atrial appendage orifice variation (3.88 [0.75] versus 4.35 [0.90] mm; P=0.043), lower LA cyclic volume change (9.2 [2.8] versus 12.8 [3.5] mL; P=0.023), and lower LA contraction peak strain rate (–1.8 [0.6] versus –2.3 [0.6]; P=0.021). We found no statistically significant differences in left ventricular measures.

CONCLUSIONS: This preliminary comparison suggests altered LA dynamics in young patients with cryptogenic ischemic stroke, and thus that LA wall pathology might contribute to these strokes. Our results await confirmation in a larger sample.

Key Words: brain infarction ■ case-control study ■ echocardiography ■ stroke ■ young, stroke in

Ischemic stroke can occur because of cardioembolism. Some cardiac diseases are categorized as high-risk sources because of an >2% annual ischemic stroke risk.[1] A portion of ischemic strokes remain cryptogenic, that is, with undetermined etiology despite intensive diagnostic investigations. Stroke at younger ages is particularly prone to be of a cryptogenic nature,[2] when there is limited evidence for targeted secondary prevention and counseling on prognosis.

Embolic stroke of undetermined source (ESUS) is a new concept of stroke etiology and represents a defined subgroup of cryptogenic stroke, in which the patient has a neuroimaging pattern typical for embolic strokes, which excludes deep, that is, lacunar, infarctions. In ESUS, no definite source of embolism may be found, which also excludes high-risk sources of cardioembolism.[3] Intensive research has been focused on the possibility of at least part of the ESUS cases being of cardiac origin, whereas ESUS remains

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CLINICAL PERSPECTIVE

What Is New?

- Left atrial dynamics differ between young cryptogenic ischemic stroke patients and healthy controls.
- This finding supports the hypothesis that underlying pathophysiology is cardioembolism in part of the early-onset cryptogenic strokes.

What Are the Clinical Implications?

- Although the results give a clue regarding disease mechanism, more research is needed to explore whether altered left atrial dynamics should alter current secondary prevention options.

Nonstandard Abbreviations and Acronyms

ACE	angiotensin converting enzyme
AF	atrial fibrillation
ATR	angiotensin receptor
BMI	body-mass index
ESUS	embolic stroke of undetermined source
LA	left atrium
LAA	left atrial appendage
LAMDV	left atrial mid-diastolic volume
LALDV	left atrial late diastolic volume
LASV	left atrial stroke volume
LAVmax	left atrial volume, maximum
LAVmin	left atrial volume, minimum
LV	left ventricular
SR	strain rate

a heterogeneous patient group.[4] Also, there is no hard evidence that some lacunar infarctions could not originate from cardioembolic sources.[5] Silent atrial fibrillation (AF) is also thought to be the embolic source for part of the ESUS patients, although symptom severity of ESUS and AF-related strokes does not match.[6] However, AF is rare in young people, and hence most cryptogenic strokes in the young, including ESUS cases, are most likely not attributable to silent AF.[7] Studies suggest that some ESUS patients have slight differences in cardiac structure and function, compared with stroke patients with an established noncardiac stroke etiology. These include left atrial (LA) appendage (LAA) morphology, *P*-wave terminal force on ECG, and LA enlargement.[8,9] A theory on atrial cardiopathy has emerged, and a pathological thrombogenic atrial substrate is thought to be one of the factors in ESUS pathogenesis.[8] Atrial cardiopathy can be principally a reflection of the same pathology as AF, that is, LA remodeling occurring in patients with AF.[10] However, cardiac findings in particularly young ESUS and cryptogenic stroke patients (aged <50 years) have been described very scarcely in the literature—one of the findings being thicker epicardial fat.[11]

We sought to evaluate whether advanced echocardiography methods can detect differences in LA mechanical function between young cryptogenic stroke patients and stroke-free controls and hence signs of atrial cardiopathy even at a young age.

METHODS

Study Population

The data that support the findings of this study are available from the corresponding author upon reasonable request. All participants in this study were recruited among those enrolled into the SECRETO (Searching for Explanations for Cryptogenic Stroke in the Young: Revealing the Etiology, Triggers, and Outcome) Trial (NCT01934725), which is an international, prospective, multicenter, case-control study of young adults (aged 18–49 years) presenting with an imaging-positive first-ever ischemic stroke of undetermined etiology. The study protocol has been published in more detail.[12] Patients were included after standardized diagnostic procedures, including brain magnetic resonance imaging, imaging of intra- and extracranial arteries with either computed tomography angiography or magnetic resonance angiography, and cardiac imaging to rule out established causes of ischemic stroke. Hence, no patients with causally relevant aortic or carotid pathology were included. Cardiac imaging included standardized transthoracic and -esophageal echocardiography.[13] We screened for AF with ≥24-hour Holter monitoring. Patients were classified according to ESUS criteria[3] as ESUS (+) and ESUS (–).

Patients were age and sex matched to stroke-free controls in a 1:1 fashion. A list of 20 potential controls per 1 patient were randomly identified from the Population Registry, with an invitation letter sent to controls 1 by 1. If this strategy did not result in a fit, willing control person, patients' nonrelated proxies or proxies of the study personnel were recruited. Detailed clinical history was recorded from all study subjects, including arterial blood pressure, height, weight, alcohol consumption, and presence of right-to-left shunt. The definition of right-to-left shunt was a positive finding on either transesophageal echocardiography or transcranial Doppler bubble test, and each patient and control

underwent at least one of these tests. Participants were dichotomized according to their right-to-left shunt status. Patients with previous patent foramen ovale closure were excluded from this substudy.

The inclusion period for this substudy was from December 2013 to May 2017. Written informed consent was obtained from all study subjects. The SECRETO has been approved by the ethics committee of Helsinki and Uusimaa Hospital District.

Echocardiography Methods

The same echocardiographist (J.Pi.) examined all patients and control subjects blinded to the case-control status with a General Electric Vivid E9 version 113 cardiac ultrasound device, using M5Sc and 4V probes (General Electric, Horten, Norway). Basic left ventricular (LV) measurements were obtained from the parasternal long-axis view. Measurements of mitral inflow E wave and A wave were obtained from the apical 4-chamber view using the pulsed wave Doppler, and e' velocity was measured using tissue Doppler imaging. Tricuspid regurgitation velocity was assessed from a projection optimized to the regurgitation jet. Diastolic function of patients and controls was evaluated using the American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines, with a modification of LA volume (LAV) index, which was measured with 4-dimensional (4D) volumetry and not using the Simpson method, given that it is more sensitive using the same cut-off value of 34 mL/m^2.[14]

From the apical view, both LV and LA 2-dimensional measurements and 4D measurements were obtained. A true apical view was verified using the triplane mode. The apical 4-chamber view was defined as long-axis trans-secting the LV apex and the mitral orifice and maximizing the LV and right ventricular area. The 2-chamber view was defined as a counterclockwise virtual rotation of 60 degrees, hence viewing the LV and LA. The 3-chamber view was defined as a further counterclockwise virtual rotation of 60 degrees, hence viewing the LV, ascending aorta, and LA. In addition to these 3 planes, a fine-tuned virtual rotation was used to obtain an apical view where the LAA orifice was as large as possible, used only for the LAA orifice minimum and maximum measurements. LAA orifice variation was defined as (LAA orifice maximum)–(LAA orifice minimum) and LAA orifice relative variation as (maximum-minimum)/maximum (Figure 1).

LV 4D measurements were obtained from an apical view using multibeat acquisition of 6 cardiac cycles, zoomed in for only the LV, obtaining ≈50 volumes per second. The LV stroke volume was used for calculation of the LA conduit volume.[15] LAV was

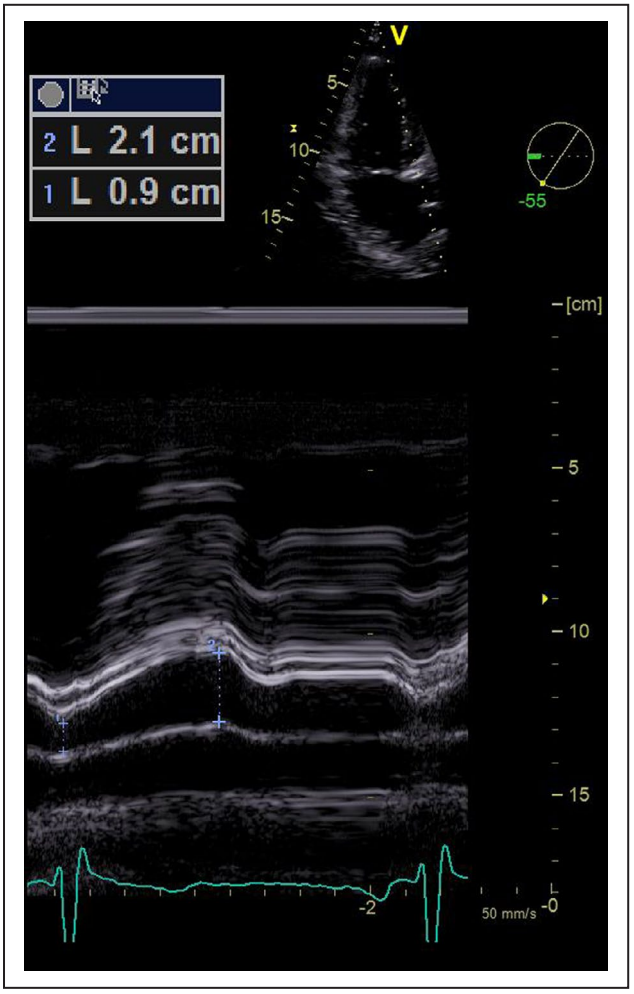

Figure 1. Rotation angle optimized for left atrial appendage orifice measurement.
In this case, the optimal angle was at −55 degrees (compare: 4-chamber view is 0 degrees and 2-chamber view is −60 degrees). Measurement at end of ventricular diastole was 9 mm and at end of ventricular systole 21 mm. Hence, the variation was 12 mm and the relative variation 57%.

determined using the 4D method, zoomed in for only the LA, and using a 4-cycle multibeat method with a volume rate of ≈50 volumes per second. LAV was analyzed in 4 stages of the cardiac cycle, from the volume-time curve: maximum volume (LAVmax) at the end of ventricular systole, mid-diastolic volume after the passive emptying phase, late diastolic volume just before atrial contraction, and minimum volume (LAVmin) after atrial contraction, at the end of ventricular diastole. LA reservoir volume was defined as the volume difference between LAVmax and LA mid-diastolic volume.[15] LA stroke volume was defined as (LA late diastolic volume–LAVmin), and LA ejection fraction was defined as (LA stroke volume/LA late diastolic volume). LA cyclic volume change was defined as LAVmax–LAVmin (Figure 2). LA passive emptying percentage was defined as

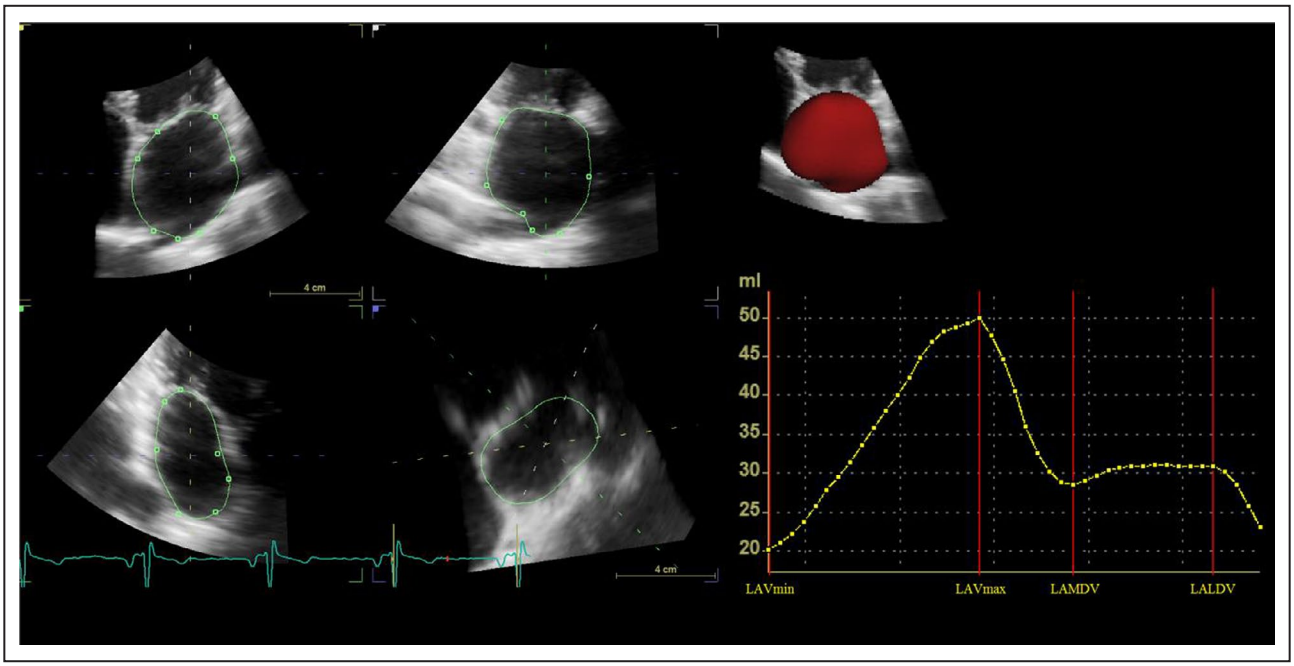

Figure 2. 4D analysis of left atrial volume cycle and definitions of the 4 volumetric measurement points: left atrial minimum volume (LAVmin), left atrial maximum volume (LAVmax), left atrial mid-diastolic volume (LAMDV), and left atrial late diastolic volume (LALDV).
In this patient, LAVmin was 20 mL and LAVmax 50 mL; hence, left atrial cyclic volume change was 30 mL. LAMDV was 28 mL, and hence LA reservoir volume was 22 mL. LALDV was 31 mL, and hence LA stroke volume was 11 mL and LA ejection fraction 11/31 mL=35%. Given that this patient had a left ventricular stroke volume (LVSV) of 87 mL, the left atrial conduit volume was 54 mL (LVSV – LA reservoir volume – LA stroke volume). 4D indicates 4-dimensional; and LA, left atrium.

100*(LAVmax–LA late diastolic volume)/(LAVmax–LAVmin).[16] LA conduit volume, as a measurement of blood flow passing through the LA without affecting its volume, was defined as LV stroke volume–LA reservoir volume–LA stroke volume, which was adequate, given that none of the patients had significant mitral regurgitation or continuous left-to-right or right-to-left shunts.[15] LA sphericity index was analyzed using the LV sphericity index function of EchoPAC version 113 (GE Healthcare 2013).

We also studied LA longitudinal strain using the *P* wave for ECG gating, a method known as epsilon (Figure 3).[17] We measured LA strain rate using tissue Doppler imaging in accordance with Safir-Mardanloo's method for each wall in all 3 apical projections, although only at mid-level (Figure 4).[18] We performed body surface area indexing for LAVs and LAA orifice measurements using the Mosteller formula.[19]

Statistical Analysis

We used the Wilcoxon signed-rank test for examining differences between groups. Maximum tertile was defined as the highest tertile of measurements for both patient and control groups and minimum tertiles as the lowest tertile of measurements for both patient and control groups. Tertiles were analyzed comparing the most pathological tertile of the patient group and control group, for each parameter. For dichotomous baseline parameters, we used the McNemar test. We did a sensitivity analysis based on right-to-left shunt status using the Mann–Whitney *U* test. All analyses used IBM SPSS (version 22; IBM Corp., Armonk, NY) or RStudio software (version 1.2.1335; RStudio, Boston, MA).

RESULTS

We included a total of 30 patients, of which 22 (73.3%) fulfilled criteria for ESUS. Of the 30 controls, 23 were identified from the Population Registry. Compared with controls, patients had a higher body weight and body mass index and a larger body surface area. We found no significant differences between patients and controls regarding other established cardiovascular risk factors. Patients had a higher prevalence of right-to-left shunt (Table 1). None of our patients or controls had chronic kidney disease. Patients had significantly higher usage of antiplatelets, statins, and angiotensin-converting enzyme inhibitors/angiotensin-converting enzyme blockers than controls (Table 1).

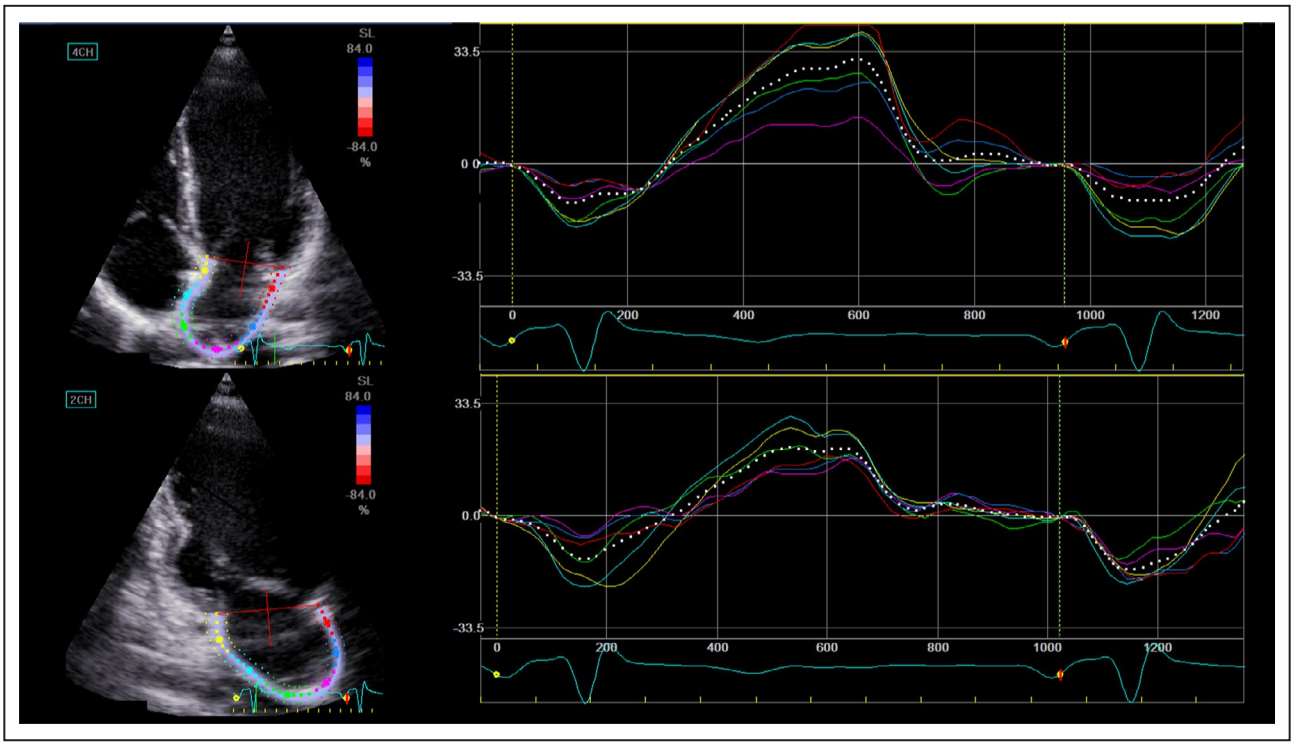

Figure 3. LA epsilon analysis. Note the ECG gating set at the *P* wave.
Following the dotted white line, expressing the epsilon of the entire left atrium, a negative maximum of 12.5 can be noted in the 4-chamber view and a negative maximum of 12.6 in the 2-chamber view. The positive maximums are 33.8 and 20.6, respectively. Hence, the global negative epsilon peak was 12.6 and the global positive epsilon peak 27.2, calculated as means of the 2 views. LA indicates left atrium.

Performance of Measurements

LV basic measurements could be obtained in all study subjects, as were the diastolic measures of mitral inflow E and A. Also, septal and lateral e', as well as LAV index, could be obtained in all subjects. Tricuspid regurgitation velocity measurement was successful in 23 patients and 23 controls (both 76.7%). LAA orifice diameter measurements were successful in 29 case-control pairs, LA volumetry in 30 pairs, LA speckle tracking epsilon analyses in 26 pairs, and tissue Doppler strain rate in 28 pairs.

Analysis of LV Systolic and Diastolic Function

LV basic measurements did not differ significantly between the 2 groups (Table 2). No study subjects had an average E/e' >14. Three patients and 6 controls had impaired e' velocity of either the septal or lateral mitral annulus. One control subject and no patients had tricuspid regurgitation velocity of >2.8 m/s. Five patients and 6 controls had enlarged LAV index, using the 34-mL/m^2 cut-off value. None of the participants fulfilled more than one of the aforementioned criteria for evaluating diastolic function, and hence all patients and controls had a normal diastolic function according to American Society of Echocardiography/European Association of Cardiovascular Imaging criteria.

Analysis of LA Dynamics

LA reservoir volume was significantly lower in the stroke patient group, as was the positive epsilon (Table 2). In analysis by tertiles, stroke patients differed from controls regarding LAA orifice variation (lowest tertile), LA cyclic volume change (lowest tertile), and LA strain rate (highest, ie, least negative, tertile; Table 3). In sensitivity analysis, LA cyclic volume change and LA reservoir volume were smaller in participants with right-to-left shunt than in those without (Table 4). Also, when analyzing the patient and control groups separately, we found no significant differences between patients with or without right-to-left shunt (Tables S1 and S2).

DISCUSSION

To the best of our knowledge, this is the first study to investigate LA functional parameters in young cryptogenic stroke patients with advanced echocardiography. We selected stroke-free young adults for our control group, in order to detect atrial risk factors for cryptogenic

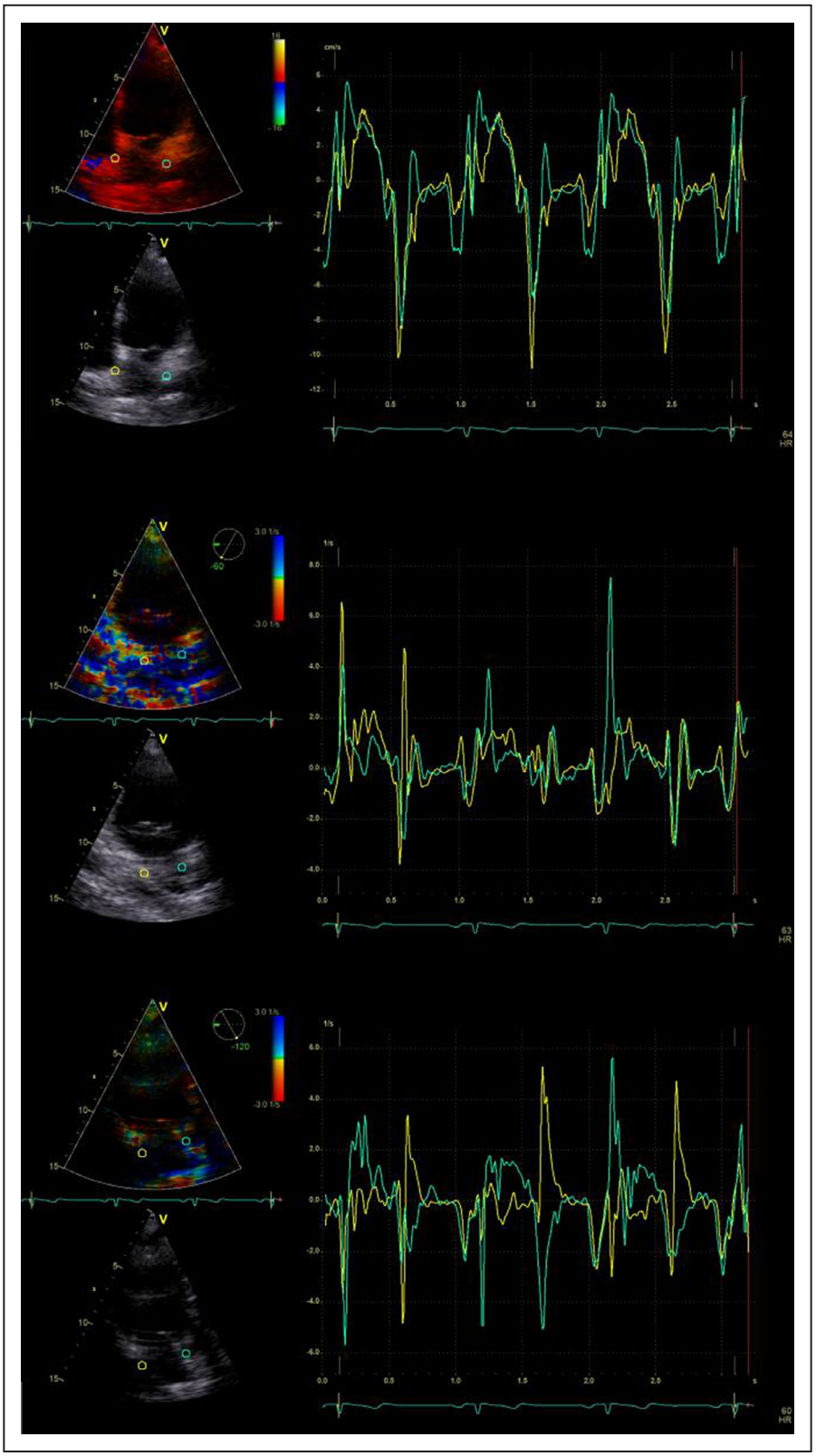

Figure 4. LA strain rate (SR) using tissue Doppler imaging of the 6 mid-level points of the LA, in all 3 the apical projections (upper 4-chamber, middle 2-chamber, and lower 3-chamber).

The 3 SR measurements of the septum are –1.9, –2.6, and –2.2, hence the mean is –1.7. The means of the lateral, inferior, anterior, posterior, and anteroseptal walls are –4.5, –1.7, –1.4, –2.4, and –2.6, respectively. Hence, the global mean is –2.38 for this patient. LA indicates left atrium.

Table 1. Baseline Clinical Data of Patients and Controls

	Patients	Controls	*P* Value
Body measurements			
Height	172 (14)	168 (16)	0.069
Weight	86.8 (30)	75.5 (27)	0.012
Waist circumference, cm	98.8 (19.8)	88.5 (19.9)	0.015
Body mass index	30.2 (7.2)	26.1 (6.7)	0.026
Body surface area	2.04 (0.44)	1.88 (0.41)	0.007
Systolic blood pressure	128 (21)	129 (21)	0.256
Diastolic blood pressure	86 (14)	82 (15)	0.303
Age at echocardiography, y	43 (12)	44 (13)	0.098
Cardiovascular risk factors			
Male sex	15 (50)	15 (50)	1.000
Hypertension	9 (30)	3 (10)	0.146
Diabetes mellitus, type 1	1 (3.3)	0	N/A
Current smoking	9 (30)	11 (36.7)	0.774
Excessive alcohol use	9 (30)	3 (10)	0.031
Physical inactivity	3 (10)	2 (6.7)	1.000
Right-to-left shunt	22 (73.3)	10 (33.3)	0.002
Cardiovascular medication usage			
Antiplatelets	28 (93.3)	0	<0.001
Statins	21 (70)	0	<0.001
Beta-blockers	3 (10)	0	0.250
ACE inhibitors/ATR blockers	15 (50)	0	<0.001
Spironolactone	1 (3.3)	0	1.000
Other diuretics	2 (6.7)	0	0.500
Anticoagulant	2 (6.7)	0	0.500

Body measurements: numbers are median (interquartile range); cardiovascular risk factors: numbers are n (%). For medication, numbers are n (%). ACE indicates angiotensin-converting enzyme; ATR, angiotensin receptor; and N/A, not applicable.

Table 2. Comparison of Echocardiographic Findings Between Stroke Patients and Controls

	Patients	Controls	*P* Value
LV basic measurements			
LV maximum internal diameter (diastolic), mm	49 (7)	50 (8)	0.413
Interventricular septum diameter (diastolic), mm	10 (2)	10 (2)	0.609
LV posterior wall diameter (diastolic), mm	8 (8–10)	9 (7–10)	0.776
LV maximum internal diameter (systolic), mm	33 (7)	31 (7)	0.306
LV end-diastolic volume (4D), mL/m^2	55.03 (17.40)	56.54 (20.40)	0.131
LV end-systolic volume (4D), mL/m^2	20.97 (8.61)	23.67 (11.65)	0.125
LV stroke volume, mL/m^2 (4D)	32.84 (13.19)	36.65 (12.84)	0.329
LV ejection fraction (4D)	62 (14)	59 (15)	0.462
LAA orifice analysis			
LAA orifice minimum, mm/m^2	2.6 (1.6)	3.0 (1.9)	0.256
LAA orifice maximum, mm/m^2	7.7 (4.0)	9.2 (3.0)	0.294
LAA orifice variation, mm/m^2	5.49 (3.31)	6.64 (2.89)	0.265
LAA orifice relative variation, %	69 (19)	67 (16)	0.964
LA volumetry			
LA minimum volume, mL/m^2	10.6 (6.6)	10.5 (4.3)	0.558
LA maximum volume, mL/m^2	25.9 (9.9)	27.5 (9.9)	0.136
LA mid-diastolic volume, mL/m^2	14.6 (6.3)	15.1 (7.2)	0.644
LA late-diastolic volume, mL/m^2	16.5 (7.0)	17.8 (7.9)	0.417
LA reservoir volume, mL/m^2	10.2 (5.4)	13.2 (5.4)	0.030
LA stroke volume, mL/m^2	4.78 (5.01)	6.32 (5.99)	0.517
LA ejection fraction	37.5 (26)	39.5 (18)	0.888
LA cyclic volume change, mL/m^2	14.5 (8.8)	17.7 (5.8)	0.116
LA conduit volume, mL/m^2	16.72 (13.66)	18.57 (16.74)	0.959
LA passive emptying %	55.9 (28.3)	63.2 (18.3)	0.428
LA sphericity index	0.355 (0.24)	0.29 (0.22)	0.198
LA strain/epsilon analysis			
Negative epsilon peak	12.58 (5.19)	14.13 (2.22)	0.322
Positive epsilon peak	17.8 (8.5)	20.8 (10.1)	0.023
LA epsilon peak values negative/positive	0.68 (0.43)	0.64 (0.23)	0.367
LA strain rate	−2.4 (0.8)	−2.8 (0.8)	0.014

Numbers are median (interquartile range). 4D indicates 4-dimensional; LA, left atrium; LAA, left atrial appendage; and LV, left ventricular.

stroke in the general population, and to study whether atrial findings may play a role in cryptogenic stroke. We found the most obvious differences between patients and controls in early diastolic volume and strain changes, represented by LA reservoir volume and positive peak epsilon value. In analysis by tertiles, we further found that patients differed from controls with respect to LAA orifice variation, LA cyclic volume change, and LA strain rate. Part of the explanation of the difference in LA reservoir volume and LA cyclic volume change might be attributable to right-to-left shunt, given that these parameters reached statistical significance stratified by patent foramen ovale (±). However, this shunt is not continuous, and hence it seems probable that the volume differences are attributable to other reasons.

A recent study including older ESUS patients found that ESUS patients had lower LA emptying fraction and higher LA end-diastolic (ie, minimum) volume, compared with healthy individuals.[20] As in that study, our participants exhibited "supernormal"

Table 3. Most Pathological Tertile Analysis of LA Echocardiographic Parameters Between Stroke Patients and Controls

	Patients	Controls	*P* Value
LAA orifice analysis			
LAA orifice minimum, mm/m^2 (highest)	3.44 (0.90)	3.89 (0.54)	0.123
LAA orifice maximum, mm/m^2 (highest)	10.60 (3.46)	11.15 (0.82)	0.478
LAA orifice variation, mm/m^2 (lowest)	3.88 (0.75)	4.35 (0.90)	0.043
LA volumetry			
LA minimum volume, mL/m^2 (highest)	14.50 (2.26)	14.51 (2.50)	0.797
LA maximum volume, mL/m^2 (highest)	30.95 (4.93)	34.03 (3.35)	0.270
LA mid-diastolic volume, mL/m^2 (highest)	19.72 (7.03)	19.97 (3.02)	0.519
LA late-diastolic volume, mL/m^2 (highest)	21.71 (6.14)	22.91 (3.49)	0.171
LA reservoir volume, mL/m^2 (lowest)	5.61 (3.01)	9.01 (2.57)	0.023
LA stroke volume, mL/m^2 (highest)	10.16 (4.10)	10.57 (4.81)	0.748
LA ejection fraction (lowest)	21.5 (6.5)	26.5 (8.75)	0.362
LA cyclic volume change, mL/m^2 (lowest)	9.17 (2.84)	12.84 (3.52)	0.019
LA conduit volume, mL/m^2 (highest)	23.75 (7.19)	26.53 (4.37)	0.945
LA passive emptying % (lowest)	37.1 (10.2)	39.7 (18.0)	0.326
LA sphericity index (highest)	0.51 (0.14)	0.48 (0.10)	0.165
LA strain analysis			
Negative epsilon peak (highest)	17.35 (3.75)	15.5 (0.90)	0.554
Positive epsilon peak (lowest)	14.23 (0.41)	15.53 (3.08)	0.151
LA epsilon peak values negative/positive (highest)	1.01 (0.10)	0.91 (0.25)	0.148
LA strain rate (highest, ie, least negative)	−1.8 (0.55)	−2.3 (0.55)	0.021

Whether the highest or lowest tertile is considered the most pathological is expressed on each row after the parameter name. Numbers are median (interquartile range). LA indicates left atrium; and LAA, left atrial appendage.

LA maximum volumes (patients, 25.7 mL/m^2 versus controls, 28.6 mL/m^2), given that the upper limit is regarded as slightly over 40/mL/m^2 using the 4D volumetry method.[21,22] The differences in LAV variation can, in our case-control study, be detected by differences in LA reservoir volume and positive epsilon and supported by the analysis by tertiles of LA cyclic volume change. However, unlike in the previous study,[20] we did not find differences in LA sphericity index between patients and controls, which might be attributable to milder LA pathology in our younger population.

Table 4. Comparison of LA Findings in Patients and Controls, Based on Right-to-Left Shunt Status

Patients and Controls	PFO (+)	PFO (–)	*P* Value
LAA orifice minimum, mm/m^2	3.05 (1.63)	2.89 (1.91)	0.513
LAA orifice maximum, mm/m^2	8.72 (3.40)	8.83 (3.61)	0.533
LAA orifice variation, mm/m^2	5.81 (2.59)	6.17 (3.25)	0.369
LAA orifice relative variation, %	66.7 (14.7)	71.4 (19.7)	0.286
LA minimum volume, mL/m^2	9.42 (5.50)	11.08 (5.18)	0.351
LA maximum volume, mL/m^2	25.19 (8.78)	27.21 (8.48)	0.083
LA mid-diastolic volume, mL/m^2	13.94 (7.67)	15.15 (6.14)	0.266
LA late-diastolic volume, mL/m^2	16.73 (8.25)	16.42 (6.11)	0.524
LA reservoir volume, mL/m^2	10.4 (5.3)	13.2 (6.6)	0.042
LA stroke volume, mL/m^2	5.74 (5.83)	5.55 (5.01)	0.790
LA ejection fraction	40.5 (17.25)	39.0 (26.0)	0.947
LA cyclic volume change, mL/m^2	14.7 (7.0)	17.9 (6.1)	0.039
LA conduit volume, mL/m^2	19.4 (10.9)	16.2 (16.9)	0.382
LA passive emptying %	55.1 (29.9)	63.3 (18.1)	0.100
LA sphericity index	0.29 (0.19)	0.35 (0.27)	0.604
Negative epsilon peak	13.7 (5.3)	13.5 (3.2)	0.915
Positive epsilon peak	19.8 (11.6)	20.4 (6.4)	0.762
LA epsilon peak values negative/positive	0.68 (0.37)	0.64 (0.31)	0.922
LA strain rate	−2.6 (1.0)	−2.5 (0.7)	0.939

Numbers are median (interquartile range). LA indicates left atrium; LAA, left atrial appendage; and PFO, patent foramen ovale.

An earlier cardiac magnetic resonance imaging study including older patients found a trend of lower LAV change in stroke patients with undetermined stroke compared with patients with determined noncardiac causes. Interestingly, in that study, patients with undetermined stroke also had more atrial fibrosis detected by magnetic resonance imaging, despite no difference in LA maximum volume.[23] Although all of our tertiles of both stroke patients and controls had normal LV ejection fraction, and no patients or controls fulfilled the criteria for diastolic dysfunction, there still might be differences in LV loading conditions attributed to subclinical diastolic dysfunction. However, a finding pointing strongly toward the altered LA dynamics being attributable to primary LA abnormality is the similarity in LAVmin between the groups, LAVmin being a sensitive marker of diastolic dysfunction.[24] In the lack of knowledge on LV filling pressure and LA fibrosis, we cannot draw conclusions on whether the differences in LA dynamics are

secondary to LV conditions or attributable to primary LA disease. However, because of that study's finding of more LA fibrosis in patients with otherwise similar LA dynamics as in our participants, we think it is likely that also younger cryptogenic stroke patients have slightly abnormal LA dynamics attributable to LA fibrosis (ie, representing primary LA disease).[23] An explanation for why the difference emerged only in the volume change of LA is that atrial fibrosis dampens the LA's ability to stretch and contract and hence change its volume, although, in the lack of LV failure, there is no increased LV filling pressure to stretch the LA.

Another finding of ours that points toward primary atrial disease is the significant difference in the lowest tertiles of LA strain rate. In AF, contractility of the LA is also dampened, detected by strain rate.[25] AF is well known to be associated with atrial fibrosis.[26] Perhaps the lower contractility of atrial tissue in patients with paroxysmal AF is also attributable to atrial fibrosis. However, AF is unlikely in the age group of our patients, and hence it seems more probable that they only have mild atrial fibrosis. Our novel method of LAA orifice analysis from the apical projection has a similar profile as LAV and epsilon values: no differences in maximum values, but the variation between minimum and maximum values was lower in the stroke patient group. Interestingly, a larger LAA orifice diameter has been suggested as a stroke risk factor in general AF patients.[27]

Strengths of our study include a systematic and well-matched case-control participant population, a prospective design, a precise protocol with very few missing data, blinding of the echocardiographist until all measurements were performed, and the use of modern echocardiography methods such as 4D volumetry and epsilon. The similar findings of lower LA variation, in both epsilon and volumetry in the stroke patient group, together with lowered strain rate, are findings that complement each other in the conclusion of altered LA dynamics. Weaknesses, in turn, include the small sample size, possible selection bias and other shortcomings inherent to case-control studies, and lack of invasive LV filling pressure measurements. The small sample size also restricted our possibility to adjust for confounders. Thus, we could not firmly determine whether the differences in LA dynamics were of a primary nature or secondary to differing LV filling conditions.

CONCLUSIONS

Our pilot study showed that LA dynamics differed between young cryptogenic stroke patients and stroke-free controls, when measured with advanced cardiac ultrasound techniques. However, there were only slight differences in some parameters and no differences in the rest. Future studies should include larger patient populations to increase discriminatory power, allow for relevant subgroup analyses (eg, stratified by patent foramen ovale status), and differentiating between primary atrial disease and secondary differences reflecting LV function.

ARTICLE INFORMATION

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Author contributions: Jani Pirinen: planning the imaging protocol, performing echocardiography and image analysis, obtaining data, statistical data analysis, and writing the manuscript; Vesa Järvinen: planning the study, revising the manuscript for intellectual content; Nicolas Martinez-Majander: obtaining data, revising the manuscript for intellectual content; Juha Sinisalo: planning the study, revising the manuscript for intellectual content; Pauli Pöyhönen: statistical data analysis, revising the manuscript for intellectual content; Jukka Putaala: planning the study, obtaining data, revising the manuscript for intellectual content, supervision, and funding.

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Disclosures

None.

Supplementary Materials

Tables S1–S2

REFERENCES

1. Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ. An evidence-based causative classification system for acute ischemic stroke. *Ann Neurol*. 2005;58:688–697.
2. Putaala J, Yesilot N, Waje-Andreassen U, Pitkäniemi J, Vassilopoulou S, Nardi K, Odier C, Hofgart G, Engelter S, Burow A, et al. Etiology of first-ever ischaemic stroke in European young adults: the 15 cities young stroke study. *Stroke*. 2012;43:2624–2630.
3. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, Sacco RL, Connolly SJ; Cryptogenic Stroke/ESUS International Working Group. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol*. 2014;13:429–438.
4. Kamel H, Merkler AE, Iadecola C, Gupta A, Navi BB. Tailoring the approach to embolic stroke of undetermined source: a review. *JAMA Neurol*. 2019;76:855–861.
5. Wessels T, Röttger C, Jauss M, Kaps M, Traupe H, Stolz E. Identification of embolic stroke patterns by diffusion-weighted MRI in clinically defined lacunar stroke syndromes. *Stroke*. 2005;36:757–761.
6. Ntaios G, Papavasileiou V, Lip GY, Milionis H, Makaritsis K, Vemmou A, Koroboki E, Manios E, Spengos K, Michel P, et al. Embolic stroke of undetermined source and detection of atrial fibrillation on follow-up: how much causality is there? *J Stroke Cerebrovasc Dis*. 2016;25:2975–2980.
7. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in

Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114:119–125.
8. Jalini S, Rajalingam R, Nisenbaum R, Javier AD, Woo A, Pikula A. Atrial cardiopathy in patients with embolic strokes of unknown source and other stroke etiologies. *Neurology*. 2019;92:e288–e294.
9. Yaghi S, Chang AD, Hung P, Mac Grory B, Collins S, Gupta A, Reynolds J, Finn CB, Hemendinger M, Cutting SM, et al. Left atrial appendage morphology and embolic stroke of undetermined source: a cross-sectional multicenter pilot study. *J Stroke Cerebrovasc Dis*. 2018;27:1497–1501.
10. Kamel H, Okin PM, Elkind MS, Iadecola C. Atrial fibrillation and mechanisms of stroke: time for a new model. *Stroke*. 2016;47:895–900.
11. Gürdal A, Keskin K, Orken DN, Baran G, Kiliçkesmez K. Evaluation of epicardial fat thickness in young patients with embolic stroke of undetermined source. *Neurologist*. 2018;23:113–117.
12. Putaala J, Martinez-Majander N, Saeed S, Yesilot N, Jäkälä P, Nerg O, Tsivgoulis G, Numminen H, Gordin D, von Sarnowski B, et al. Searching for explanations for cryptogenic stroke in the young: revealing the triggers, causes, and outcome (SECRETO): rationale and design. *Eur Stroke J*. 2017;2:116–125.
13. Saeed S, Gerdts E, Waje-Andreassen U, Sinisalo J, Putaala J. Searching for explanations for cryptogenic stroke in the young: revealing the etiology, triggers, and outcome (SECRETO): echocardiography performance protocol. *Echo Res Pract*. 2019;6:53–61.
14. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF III, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2016;17:1321–1360.
15. Järvinen V, Kupari M, Hekali P, Poutanen VP. Assessment of left atrial volumes and phasic function using cine magnetic resonance imaging in normal subjects. *Am J Cardiol*. 1994;73:1135–1138.
16. Okamatsu K, Takeuchi M, Nakai H, Nishikage T, Salgo IS, Husson S, Otsuji Y, Lang RM. Effects of aging on left atrial function assessed by two-dimensional speckle tracking echocardiography. *J Am Soc Echocardiogr*. 2009;22:70–75.
17. Badano LP, Kolias TJ, Muraru D, Abraham TP, Aurigemma G, Edvardsen T, D'Hooge J, Donal E, Fraser AG, Marwick T, Mertens L, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging*. 2018;19:591–600.
18. Safir-Mardanloo A, Khorsand Askari M, Lotfi Tokaldany M, Ashrafi MM, Sadeghian H. Normal values for tissue velocity and strain rate imaging parameters of left and right atrial myocardium in normal subjects. *Echocardiography*. 2019;36:521–527.
19. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med*. 1987;317:1098.
20. Meisel K, Yuan K, Fang Q, Bibby D, Lee R, Schiller NB. Embolic stroke of undetermined source: a population with left atrial dysfunction. *J Stroke Cerebrovasc Dis*. 2019;28:1891–1896.
21. Aune E, Baekkevar M, Roislien J, Rodevand O, Otterstad JE. Normal reference ranges for left and right atrial volume indexes and ejection fractions obtained with real-time three-dimensional echocardiography. *Eur J Echocardiogr*. 2009;10:738–744.
22. Sugimoto T, Robinet S, Dulgheru R, Bernard A, Ilardi F, Contu L, Addetia K, Caballero L, Kacharava G, Athanassopoulos GD, et al. Echocardiographic reference ranges for normal left atrial function parameters: results from the EACVI NORRE study. *Eur Heart J Cardiovasc Imaging*. 2018;19:630–638.
23. Fonseca AC, Alves P, Inácio N, Marto JP, Viana-Baptista M, Pinho-E-Melo T, Ferro JM, Almeida AG. Patients with undetermined stroke have increased atrial fibrosis: a cardiac magnetic resonance imaging study. *Stroke*. 2018;49:734–737.
24. Hedberg P, Selmeryd J, Leppert J, Henriksen E. Left atrial minimum volume is more strongly associated with N-terminal pro-B-type natriuretic peptide than the left atrial maximum volume in a community-based sample. *Int J Cardiovasc Imaging*. 2016;32:417–425.
25. Tan C, OuYang M, Kong D, Zhou X. Association between the left atrial and left atrial appendages systole strain rate in patients with atrial fibrillation. *Med Sci Monit*. 2016;22:4974–4977.
26. Hirsh BJ, Copeland-Halperin RS, Halperin JL. Fibrotic atrial cardiomyopathy, atrial fibrillation, and thromboembolism: mechanistic links and clinical inferences. *J Am Coll Cardiol*. 2015;65:2239–2251.
27. Tang B, Zhang H, Jiang L. The correlation between the mouth diameter of left atrial appendage and stroke risk score in patients with atrial fibrillation. *Eur Rev Med Pharmacol Sci*. 2015;19:790–794.

SUPPLEMENTAL MATERIAL

Table S1. Comparison of left atrial echocardiographic findings between stroke patients with PFO and without PFO.

LAA orifice analysis	**PFO (+)**	**PFO (-)**	***P-value***
LAA orifice minimum, mm/m^2	3.04 (1.37)	1.87 (2.33)	0.135
LAA orifice maximum, mm/m^2	7.73 (3.69)	7.45 (7.48)	0.862
LAA orifice variation, mm/m^2	5.58 (2.68)	4.95 (8.27)	1.000
LAA orifice relative variation, %	67 (16)	79 (30)	0.199
LA volumetry			
LA minimum volume, ml/m^2	8.98 (7.67)	11.61 (5.20)	0.344
LA maximum volume, ml/m^2	23.66 (8.10)	25.94 (10.77)	0.256
LA mid diastolic volume, ml/m^2	14.25 (6.09)	14.98 (3.99)	0.420
LA late diastolic volume, ml/m^2	16.36 (6.89)	16.01 (5.04)	0.597
LA reservoir volume, ml/m^2	9.49 (6.89)	11.40 (10.78)	0.185
LA stroke volume, ml/m^2	5.58 (5.92)	4.12 (3.79)	0.836
LA ejection fraction	42 (21)	24.5 (30)	0.696
LA cyclic volume change, ml/m^2	15.28 (8.06)	14.51 (9.15)	0.277
LA conduit volume, ml/m^2	19.54 (11.18)	14.57 (14.03)	0.156
LA passive emptying %	55.0 (33.7)	69.8 (19.1)	0.097
LA sphericity index*	0.33 (0.20)	0.35 (0.51)	0.909
LA strain/epsilon analysis			
Negative epsilon peak	13.55 (5.70)	12.58 (6.73)	0.651
Positive epsilon peak	17.45 (8.00)	20.78 (8.71)	0.735
LA epsilon peak values negative/positive	0.70 (0.44)	0.59 (0.46)	0.651
LA strain rate	-2.50 (1.50)	-2.35 (0.50)	0.909

LAA, Left atrial appendage

LA, Left atrium

Table S2. Comparison of left atrial echocardiographic findings between controls with PFO and without PFO.

LAA orifice analysis	**PFO (+)**	**PFO (-)**	***P-value***
LAA orifice minimum, mm/m^2	3.08 (2.02)	2.95 (1.88)	0.779
LAA orifice maximum, mm/m^2	10.51 (3.57)	9.10 (3.14)	0.983
LAA orifice variation, mm/m^2	6.85 (2.53)	6.52 (2.49)	0.846
LAA orifice relative variation, %	65 (11)	68 (17)	0.619
LA volumetry			
LA minimum volume, ml/m^2	11.41 (3.69)	10.48 (5.90)	0.880
LA maximum volume, ml/m^2	27.19 (9.25)	28.65 (8.45)	0.619
LA mid diastolic volume, ml/m^2	12.72 (8.95)	15.15 (6.38)	0.559
LA late diastolic volume, ml/m^2	18.57 (9.38)	16.99 (8.11)	1.000
LA reservoir volume, ml/m^2	11.06 (4.29)	13.60 (5.90)	0.530
LA stroke volume, ml/m^2	6.67 (6.42)	5.77 (6.53)	0.914
LA ejection fraction	32.0 (16.5)	39.5 (21.8)	0.779
LA cyclic volume change, ml/m^2	14.41 (5.19)	17.99 (4.95)	0.214
LA conduit volume, ml/m^2	19.36 (11.55)	16.43 (17.53)	0.846
LA passive emptying %	61.9 (24.2)	63.3 (20.9)	0.713
LA sphericity index	0.29 (0.08)	0.33 (0.25)	0.155
LA strain/epsilon analysis			
Negative epsilon peak	15.00 (4.03)	13.75 (3.15)	0.350
Positive epsilon peak	26.00 (10.17)	20.40 (7.81)	0.530
LA epsilon peak values negative/positive	0.57 (0.25)	0.70 (0.28)	0.880
LA strain rate	-3.00 (0.95)	-2.75 (0.78)	0.390

LAA, Left atrial appendage

LA, Left atrium