Embolic Stroke of Undetermined Source: A Population with Left Atrial Dysfunction

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Background: Cryptogenic stroke, now defined as embolic stroke of undetermined source (ESUS), represents about a quarter of all ischemic strokes and the reoccurrence is high. Understanding this stroke subtype better would likely guide treatment recommendations. In this study, we tested the hypothesis that left atrial (LA) shape and function at rest, as well as with exercise, are abnormal compared to matched normal controls. *Methods:* The study design was prospective enrollment of ESUS subjects who underwent measurement of LA function at rest and exercise by 2D and 3D echocardiograms. The exercise portion of the study was conducted using a ramped supine bicycle protocol during which LA function was measured. Stroke subjects were matched with normal subjects by age, gender, and body surface area. *Results*: Over a 1-year enrollment period, 18 ESUS patients met inclusionary criteria and were studied. Their average age was 58 years old and 44% were female. ESUS subjects have larger LA end-diastolic volume at rest (14 versus 11 mL/m^2, $P = .04$) and with exercise (11 versus 6 mL/m^2, $P = .001$) compared to normal controls. In ESUS, there was a lack of response to maximal exercise of LA function as measured by the LA ejection fraction (61% versus 73% $P = .001$) and the LA function index (.68 versus .82, $P = .02$). The 3D analysis showed spherical remodeling of the LA in ESUS. This remodeling was documented by the sphericity index, which was increased in both diastole (.40 versus .32, $P = .02$) and systole (.63 versus .71 $P = .03$). *Conclusions:* In support of our hypothesis, we found that ESUS subjects have LA dysfunction and remodeling at rest and exercise in comparison to healthy, matched controls. Evaluation of the left atrium in this high-risk stroke subtype has potential to inform stroke prevention strategies and to suggest pathways for research.

Key Words: Cryptogenic stroke—embolic stroke of undetermined source—left atrial dysfunction—echocardiogram

Introduction

The physiology and anatomy of the left atrium (LA) warrant further study because of the increasing realization of its role as a source of ischemic stroke.[1] As an active reservoir, LA contributes to left ventricular (LV) filling through atrial contraction and relaxation.[2] In LV diseases, valvular diseases, arrhythmias and primary atrial diseases, the morphology and function of the left atrium are altered and the chamber enlarges, as its ability to empty is impaired.[3] These changes may be detected by echocardiography and have been shown to be independent predictors of major cardiovascular outcomes.[4] Defining atrial dysfunction may also be important in understanding embolic strokes of undetermined source (ESUSs). ESUS is defined as an ischemic stroke not attributable to small-vessel disease, stenosis of large vessels, known cardiac

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Received December 20, 2018; revision received March 4, 2019; accepted April 4, 2019.

Conflict of interest: None.

This work was supported by UCSF internal Resource Allocation Program grant (N.B.S., Q.F., and D.B.), the Health eHeart Study (all), the Research Cardiac Physiology Laboratory of the CVRI (N.B.S.), and StrokeNet Research Fellowship (K.Y.).

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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.04.004

thrombus/vegetation, or atrial fibrillation (AF).[5,6] ESUS is estimated to account for 20%-25% of all ischemic strokes, about 300,000 strokes annually in the United States and Europe.[5] ESUS patients have an increased recurrence rate compared to noncardioembolic strokes (hazard ratio [HR] 2.36, 95% confidence interval 1.02-5.47; $P = .046$) and cardioembolic strokes with a known source (HR 1.83, confidence interval 1.07-3.14; $P = .028$).[7] There are likely structural markers of left atrial (LA) dysfunction prior to the development of AF since long-term cardiac monitoring showed increasing detection of AF in ESUS patients from 8.6% at 6 months to 30% at 3 years.[8] We hypothesize that quantitating the resting left atrium and its response, in terms of size and function, during graded dynamic exercise would detect LA dysfunction in ESUS.

Methods

In this prospective study, we recruited 120 volunteers through the online Health eHeart study (www.health-eheartstudy.org/study). The Health eHeart is an online community recruitment platform to provide longitudinal cardiovascular information on subjects older than 18 years of age who voluntarily submit their health records. Local participants who were determined to be free of cardiovascular disease based on their health records were invited to participate in this substudy to establish a database of normal echocardiogram values using our exercise protocol. The tools employed included 2-dimensional and 3-dimensional echocardiography for atrial volume and function, Doppler flow signals, a ramped supine bicycle stress protocol to capture the echocardiography, and Doppler stress responses of LV and LA (GE Vivid E9, Horton, Norway).

The stress portion of this study employed an ergometer designed to allow supine exercise in a position optimized for imaging, with increasing resistance in 30-watt increments every 3 minutes (American Medical Positioning, Indianapolis). Images are obtained during low stress (HR 90-100), mid-stress (70% of maximum predicted heart rate), and peak stress (85% maximum predicted heart rate or exhaustion). We measured biplane LA volumes and pulsed waved Doppler LV outflow tract velocity time integral (LVOT VTI) at each stage. LA function index (LAFI)[9] was calculated as LA emptying fraction (LAEF) × LV outflow tract velocity time integral/LA end-systolic volume index (LAESVI), where LAEF was defined as (LA end-systolic volume − LA end-diastolic volume)/LA end-systolic volume.

Subjects with ischemic stroke were identified and invited to participate if they were aged 45-75 with ESUS. ESUS was defined as computed tomography more than 24 hours or magnetic resonance imaging (MRI) less than 5 days from stroke onset that demonstrated a nonsubcortical infarct greater than or equal to 1.5 cm on computed tomography or greater than or equal to 2.0 cm on MRI diffusion-weighted images in largest dimension. Among inclusionary criteria for subjects were being able to tolerate a stress echocardiogram (70% of maximum of age predicted heart rate) within 12 months after stroke onset without exceeding maximum blood pressure of 200 mm Hg systolic and 100 mm Hg diastolic. However, potential subjects were excluded if they were found to have more than 50% extracranial or intracranial atherosclerosis in the vascular territory supplying area of brain ischemia documented on vessel imaging (CT (computed tomography) angiogram (CTA), Magnetic resonance angiogram (MRA), ultrasound, or angiogram). Also if they had known AF during 48 hours of Holter monitoring, major cardioembolic source, other specific cause of stroke identified such as autoimmune arteritis, arterial dissection, or malignancy. Subjects were also excluded if they had a significant morbidity poststroke, defined as modified Rankin score of greater than over equal to 3. In addition, those who might be pregnant or have systolic heart failure determined by an ejection fraction of less than 30% were not enrolled.

ESUS subjects had baseline measurements including blood pressure, hemoglobin A1C, height, weight, waist/hip circumference, and 30-day cardiac event monitor or loop recorder (5 subjects) to exclude AF. A rest echocardiogram was performed with standard 2D and Doppler examination with additional 3D imaging. Within 12 months after incident ischemic stroke, the subject underwent a graded maximal supine bicycle stress echocardiogram performed starting at rest, followed by graded increases of stress from low, mid, and then at 70% of maximum of age predicted heart rate with standard 2D and Doppler examination. Additional 3D datasets were collected. The study was approved by the IRB at University of California San Francisco (UCSF) under the Health eHeart investigation and subjects provided written informed consent.

The image quantitation was performed using standard chamber measurements, as well as novel measurements of left atrium function and 3D sphericity structure (GE EchoPac, Horton, Norway). All raw and processed data were anonymized and archived on UCSF digital research archives. The analysis was performed using a REDCap database using deidentified information. Hypertension, age, gender, ethnicity, body surface area, and clinical data along with echocardiogram variables were recorded. The interpreter of the echocardiograms (NBS) was blinded to the diagnosis of ESUS versus healthy age-matched controls. All analyses were performed using Stata IC 13 (StataCorp LP, College Station, TX). All continuous variables are expressed as mean ± SD. The Shapiro-Wilk test was used to assess the distribution of continuous variables. Comparisons between continuous variables were performed using either *t* tests or Kruskal Wallis test, as appropriate. A 2-way repeated measures ANOVA was performed to compare the differences of ESUS and control during rest and exercise for LA end-diastolic volume index (LAEDVI), LAESVI, LAEF, and LAFI. Categorical variables were compared using χ^2 tests or Fisher's exact tests, as appropriate.

Table 1. *The study subject demographic and baseline comorbidities*

	Matched normal (N = 37)	ESUS (N = 18)	*P* value
Mean age (years)	58 ± 12	58 ± 13	.9
Female	14 (37%)	8 (44%)	.7
Non-Hispanic white	28 (76%)	15 (83%)	.7
BSA (m^2)	1.9 ± .2	1.9 ± .2	.9
History of hypertension	5 (14%)	8 (44%)	.02
History of diabetes	1 (3%)	2 (11%)	.3
MVP without MR	1 (3%)	4 (22%)	.04
PFO	0	5 (30%)	.001

Abbreviations: AF, atrial fibrillation; BSA, body surface area; MR, mitral regurgitation; MVP, mitral valve prolapse; PFO, patent foramen ovale.

Results

In this prospective study, out of 34 patients approached, 18 ESUS subjects agreed to participate over approximately 1 year with an average of age 58. Of the 18 subjects, 44% were female and 83% were Caucasian (Table 1). The age, gender, and body surface area were matched with healthy controls. There was an increased prevalence of hypertension (44% versus 14%, $P = .02$) in the ESUS subjects compared to controls. Mitral valve prolapse without mitral regurgitation was more common in the ESUS subjects (22% compared to controls 3%, $P = .04$, Table 1). There was no difference in LV ejection fraction (65 ± 7 control versus 67 ± 5 ESUS, $P = .30$, Table 2). There were no ESUS subjects with LVEF less than 55%. Five ESUS subjects had loop recorders implanted (Medtronic). Two subjects developed 1%-2% burden of AF after completing the study, which was captured on extended monitoring. In the 2 subjects with AF, one had a LA volume of 32.8 mL/m^2 (mildly enlarged) and the other was normal (26 mL/m^2). Both subjects had normal LAEF and LAFI. The left atrium was evaluated using transthoracic echocardiogram and no thrombi were detected. In 6 young ESUS subjects, a transesophageal echocardiogram was performed but no thrombi were found in the LA appendage.

The standard measure of the left atrium using LAESVI was not different between ESUS and normal controls. However, there is altered LA reservoir function in the ESUS subjects. Table 2 shows that ESUS subjects had a larger LAEDVI at rest (14 versus 11 mL/m^2, $P = .04$). With maximum exercise, the ESUS group continued to have a larger end-diastolic volume than normal (11 versus 6 mL/m^2, $P = .001$). This observation was strengthened with the lack of response of the LA to exercise measured by percent change from rest to peak exercise for LAEDVI (24% decrease in LA size compared to controls 44% decrease, $P = .0001$). Also, maximum exercise in ESUS subjects yielded a significant difference of LA functional index (.68 versus .82, $P = .02$). This blunted response to maximal exercise was supported by comparing the LA ejection fraction in ESUS compared to controls (61% versus 73%, $P = .001$). The percentage change from rest to maximum LA ejection fraction remained significantly different (ESUS 14% versus control 20%, $P = .04$). However,

Table 2. *Left atrial and LV measurements using stress echocardiogram and 3D techniques comparing ESUS to matched normal controls*

	Matched normal (N = 37)	ESUS (N = 18)	*P* value
LVMassI (g/m^2)	69 ± 16	75 ± 18	.2
LVEF at rest (%)	65 ± 7	67 ± 5	.2
LAESVI rest (mL/m^2)	28 ± 6	30 ± 8	.7
LAESVI _max (mL/m^2)	22 ± 6	25 ± 11	.3
LAEDVI rest (mL/m^2)	11 ± 3	14 ± 6	.04
LAEDVI max (mL/m^2)	6 ± 3	11 ± 9	.001
LAFI rest	.52 ± .15	.46 ± .15	.2
LAFI max	.82 ± .21	.68 ± .25	.02
LAEF rest (%)	61 ± 8	54 ± 10	.01
LAEF max (%)	73 ± 10	61 ± 9	.001
Sphericity index of LA end-diastole by 3D	0.32 ± 0.09	.40 ± .14	.02

Abbreviations: LAEDVI, left atrial end-diastolic volume index; LAEF, left atrial emptying fraction; LAESVI, left atrial end-systolic volume index; LAFI, left atrial functional index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index, analog of hypertrophy.

LAFI was normal at rest, but during exercise the ability to improve with exercise is blunted.

the volume index of the LA in ESUS, as typically described at end-systole, did not differ from control subjects (30 versus 28 mL/m^2, $P = .3$). The reproducibility of these LA variables was measured using the coefficient of variability and was 7%.

In healthy control subjects, the 2D echocardiogram demonstrated rapid LA filling during systole, brisk early diastolic atrial emptying, and a significant but smaller contribution to atrial emptying by end-diastolic atrial contraction. Comparatively, the ESUS group had larger end-diastolic volumes, delayed early diastolic relaxation, and a blunted atrial contraction (Fig 1).

Another abnormality in the left atrium of ESUS subjects was remodeling of the left atrium demonstrating an increased spherical shape (sphericity) of the LA from its normal, more ovoid shape, as measured by the 3D sphericity index of the LA at end-diastolic (ESUS .40 versus normal .32, $P = .02$). The 3D echocardiogram technique was used to capture the sphericity index in both systole and diastole. The visually abnormal appearance in ESUS subjects compared to controls suggested by the 2D echocardiogram (Fig 2) was confirmed by the 3D measurements. There was an associated increased sphericity index found in ESUS subjects (.32 versus .40, $P = .02$), which suggests a more spherical shape compared to normal matched controls that showed an elongated LA structure (Fig 3). This increased spherical shape was found in both diastole (Fig 3, A versus B) and in systole (Fig 3, C versus D).

Discussion

In our study, the ESUS subjects have a unique LA profile suggestive of dysfunction and altered shape (remodeling). We hypothesized that ESUS subjects would demonstrate LA dysfunction because prior literature found that AF is not present relative to the time of ischemic stroke event in subjects with continuous cardiac monitoring devices. AF was not present for 30 days prior to ischemic stroke in 73% of subjects. Those subjects known to have AF, 70% were not in AF at the time of their stroke, and were on average 168 days from their last AF event.[10] This suggests there is likely a range of subtler LA abnormality that could be detected prior to the ultimate LA dysfunction manifesting as AF. Therefore, our study looked at LA measurements at rest and exercise, and found that although LA end-systolic volume at rest was not different in ESUS (largest volume during systole), the ability of the

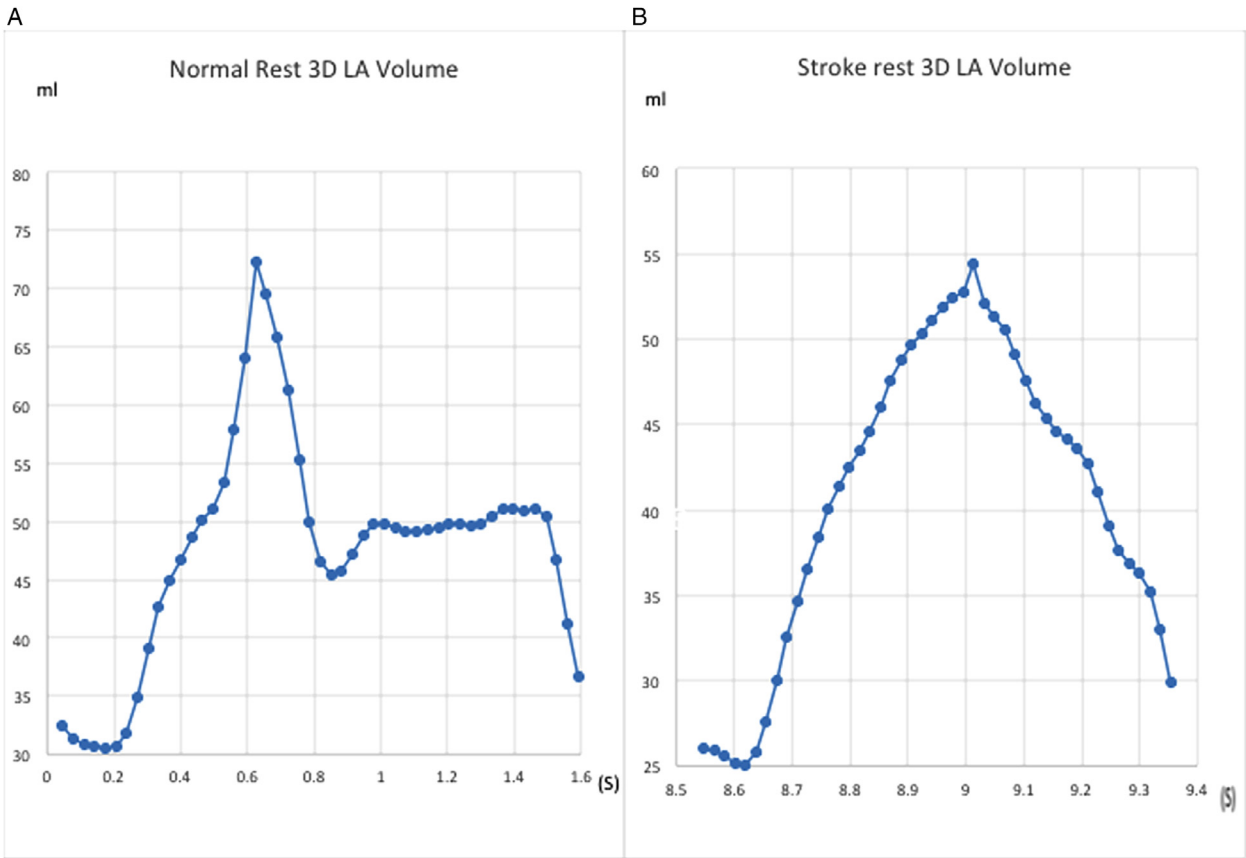

Figure 1. *The 3D echocardiogram graphs the LA volume curve through 1 cardiac cycle. Panel (A) shows a normal subject at rest compared to ESUS subject in panel (B). Note the slower or impaired rate of volume decrease (from maximum to minimum volume) as compared to the normal example. The figure is limited because heart rate variability prevents grouping of multiple subjects in order to graphically depict all ESUS versus normal populations.*

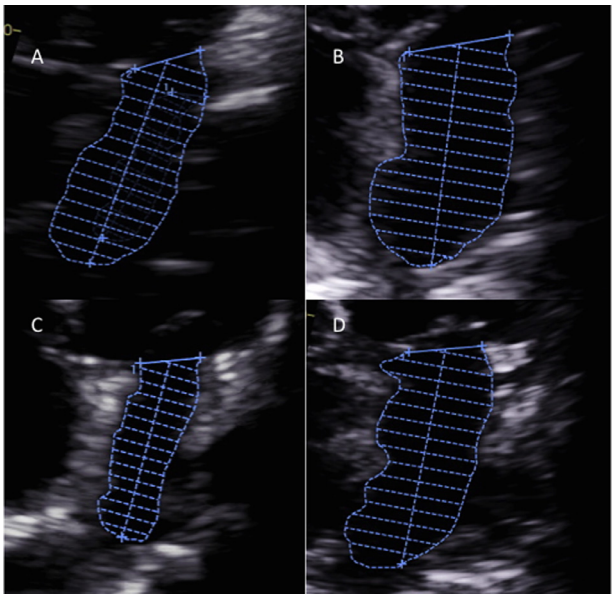

Figure 2. *The 2D echocardiogram with the outline of LA end-diastolic cavity in the 4-chamber view traced to compute volume by the biplane method of discs. In this example, the 2-chamber orthogonal plane used in the computation is not shown. Panel (A) shows a normal subject at rest compared to ESUS subject in panel (B). Panels (C) and (D) compare the normal versus ESUS LA volumes during exercise, respectively.*

LA to empty at stress and rest was impaired. Furthermore, the LA was remodeled to a more spherical shape in the ESUS group. The spherical remodeling shape is described previously in regards to the left ventricle and is associated with congestive heart failure.[11] Also the atrial sphericity index in patients with known AF predicted a poor response to cardioversion and future thromboembolic events in addition to the CHADS2-VASc score.[12,13]

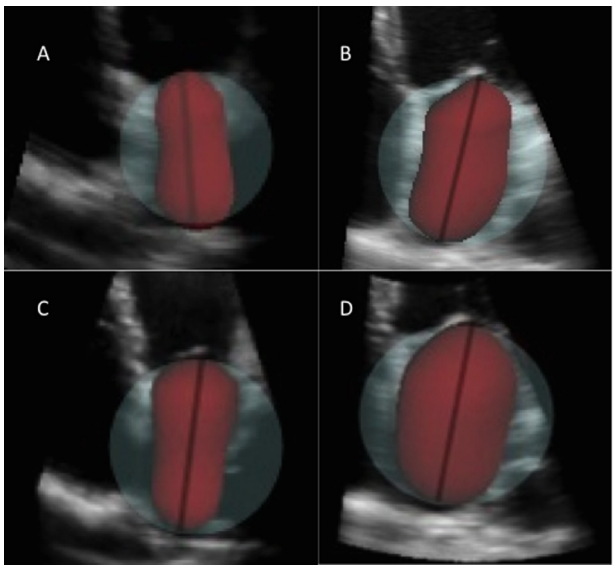

Figure 3. *The 3D LA sphericity measurements in ESUS versus normal matched controls. End-diastole LA sphericity in normal (A) compared to ESUS (B). LA end-systole sphericity in normal (C) compared to ESUS (D).*

Our study is unique because we measure the left atrium in ESUS subjects at rest and exercise, along with characterizing the shape in this important stroke population.

We excluded patients with known AF from our study and subsequently 2 developed AF in 1 year. We acknowledge that longer monitoring of subjects with implantable recorders may yield a higher rate of detection; however, all ESUS subjects underwent guideline recommended 30 days of monitoring. Thus, our study reflects the current evaluation for ESUS patients, which guides clinical management. The profile of LA function and the sensitivity of echocardiography to detect early LA disease are not well established. Unexpectedly, the standard measurement of LA using LAESVI was not associated with ESUS. However, a comprehensive application of sensitive methods found anatomic and physiologic dysfunction. Therefore, additional measurement could be used to define what is considered an abnormal LA. With recent advances in noninvasive echocardiography technology, such as 3D full volume imaging, the ability to accurately measure LA size and function has improved.[14] Because these methods encompass the entire atrium, 3D is validated by MRI as being more volumetrically accurate than 2D methods.[15] Early detection of LA dysfunction may lead to a better understanding of embolic stroke of undetermined source (ESUS), which account for 20% of all stroke patients. It is known that ESUS represents a high-risk population with a 4% annual recurrence rate of ischemic stroke.[16] In patients without known AF, a low LAFI may triple the risk of ischemic stroke.[17,18] However, LAFI and other parameters of the LA in ESUS patients are not well defined either at rest or in exercise. The utility of LA parameters as independent factors in ESUS occurrence and prediction of recurrent embolic strokes is unknown. LA analysis indicating dysfunction in ESUS patient may serve as a clinical tool in determining the best secondary stroke prevention strategy such as anticoagulation rather than the standard antiplatelet medications. The National Institute of Health trial, AtRial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke, is using linear LA size as inclusion criteria. The findings of this study suggest that additional criteria such as end-diastolic LA volume, LAFI, sphericity, and other LA variables may increase the sensitivity of echocardiograms to detect LA dysfunction in ESUS.

Our study is limited by a small sample size, the inability to control for hypertension, mitral prolapse, and patent foramen ovale in our matched controls. Furthermore, there is no assurance that our findings do not represent epiphenomena of an unrecognized abnormality. These results need to be replicated in a larger population. Future directions should include prospective clinical outcomes (stroke reoccurrence, development of AF) and MRI biomarker outcomes of those ESUS patients with abnormal LA physiology.

In conclusion, our study found ESUS subjects had blunted LA function with rest and exercise, decrease in dynamic change from rest to exercise, and remodeling of LA shape in ESUS compared to controls. Stress echocardiography along with sphericity index can reveal new markers of LA dysfunction and perhaps will inform stroke risk. It was an unexpected finding that standard volumetric measurement of LA size LAESVI was not significantly altered in ESUS subjects. We need to use additional LA measurements to detect an important difference in LA dysfunction in ESUS. The research to identify the etiology in ESUS is essential if we are to improve stroke prevention and reduce the burden of this disabling disease.

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