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The Role of Left Atrial Strain in Differentiating Embolic Stroke of Undetermined Source From Other Acute Ischemic Stroke Subtypes Related to Large-Vessel Occlusion

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Keywords: embolic stroke of undetermined source | ischemic stroke | large vessel occlusion | left atrial strain

ABSTRACT

Introduction: To evaluate left atrial (LA) function in patients with embolic stroke of undetermined source (ESUS) and other subtypes of acute ischemic stroke (AIS) related to large-vessel occlusion (LVO).

Methods: Consecutive patients with LVO-related AIS were prospectively enrolled from July 2019 to August 2022. To compare LA function with ESUS patients, a control group without prior stroke was sex- and age-matched with ESUS patients in a 1:1 ratio. LA strain was measured within 3 days after stroke. Multivariable logistic regression analysis was performed to assess associations between LA function and stroke subtypes.

Results: This study included 126 patients (mean age 67.7 ± 12.3 year, 39.7% women). Of these, 28 patients met the diagnostic criteria for ESUS, while the remaining were classified as large artery atherosclerosis ($n = 49$) and non-valvular AF-related cardioembolic stroke ($n = 49$). Patients with ESUS had lower left atrial reservoir strain (LASr) and left atrial conduit strain (LAScd) compared to those with large artery atherosclerosis (27.8 ± 7.1% vs. 32.0 ± 5.3%, $p = 0.004$, and 14.3 ± 3.8% vs. 17.3 ± 4.6%, $p = 0.005$, respectively) and the control group (27.8 ± 7.1% vs. 37.6 ± 7.2%, $p < 0.001$ and 14.3 ± 3.8% vs. 21.5 ± 7.9%, $p < 0.001$, respectively). A 5% reduction in LASr and LAScd was associated with a 1.92- and 2.45-fold increase, respectively, in the likelihood of having ESUS compared to large artery atherosclerosis. Lower LASr and LAScd in ESUS patients were prone to be associated with a higher likelihood of cardiovascular events during follow-up.

Conclusions: LA strain is associated with ESUS in stroke patients with LVO. Further studies are needed to explore its utility in identifying specific stroke etiologies.

Yanjuan Zhang and Jincheng Jiao contributed equally.

1 | Introduction

Embolic stroke of undetermined source (ESUS) accounts for approximately 1 in 6 ischemic strokes and carries a high risk of recurrent ischemic stroke (Hart et al. 2017). While theoretically, anticoagulation would be more beneficial for secondary prevention, recent trials failed to demonstrate that anticoagulation treatment could reduce the risk of recurrent stroke in ESUS patients (Hart et al. 2018; Diener et al. 2019; Kamel et al. 2024). Notably, the ARCADIA trial did not show apixaban reduced recurrent stroke in patients with cryptogenic stroke and evidence of atrial myopathy (ACM), characterized by an abnormal electrocardiographic parameter, a high level of natriuretic peptide, or an enlarged left atrium (Kamel et al. 2024). One potential reason for these negative results, aside from the heterogeneous sources of emboli in ESUS (Ntaios et al. 2015), could be the not-well-defined nature of ACM, as ACM has been suggested as a possible mechanistic link to ESUS (Ntaios 2020).

Speckle-tracking echocardiography (STE) is a valid approach of assessing the structure and function of the left atrium (LA) by utilizing transthoracic echocardiographic (TTE) images. Low LA strain assessed by STE may indicate LA mechanical dysfunction even at the early stage when LA volumes are still normal (Pathan et al. 2021). It has been demonstrated that reduced LA strain might be independently associated with ischemic stroke in older individuals (Mannina et al. 2023). Large-vessel occlusion (LVO)-related stroke accounts for slightly over one-third of acute IS (AIS) and significantly increases the likelihood of severe post-stroke outcomes (Malhotra et al. 2017). However, few studies have described LA function in patients with LVO-related ESUS.

This study aims to assess LA function in patients with LVO-related ESUS and other subtypes of AIS and provide some clues for differentiating ESUS in LVO.

2 | Method

2.1 | Study Design and Patients

In this single-center prospective cross-sectional study, consecutive patients with AIS who received endovascular thrombectomy (EVT) were enrolled in the stroke center of the First Affiliated Hospital with Nanjing Medical University between July 2019 and August 2022. The indication and procedure details of EVT have been described in our previous study (Jiao et al. 2022). The inclusion criteria of this study were (1) AIS patients with LVO in the anterior circulation who received EVT and (2) two-dimensional and speckle tracking TTE performed within 1 week of the index stroke. We excluded patients with rheumatic valvular heart diseases, cardiac valve replacement, valvular vegetations, left ventricular dysfunction (left ventricular ejection fraction (LVEF) $\leq 30\%$), intracardiac thrombus, atrial myxoma, recent (within 4 weeks) myocardial infarction, or frequent premature ventricular contractions. We also excluded patients who were unable to cooperate with the TTE examination or had poor ultrasonic images. This study was approved by the Ethics Committee of the First Affiliated Hospital with Nanjing Medical University (2014-SR-113). All enrolled patients provided written informed consent to participate in this study.

2.2 | Definition of ESUS and AF Diagnosis

The subtype of AIS based on the underlying etiology, including large artery atherosclerosis, non-valvular AF-related cardioembolic stroke, small vessel occlusion, and stroke of other determined etiologies. Cryptogenic stroke, according to the Trial of ORG 10172 in Acute Stroke Treatment Criteria (TOAST criteria) (Adams et al. 1993), was adjudicated by the neurologists in the multidisciplinary team of our stroke center.

2.3 | Criteria for ESUS Patients

All ESUS patients met published criteria (Hart et al. 2014). Briefly, ESUS diagnosis required the following assessments: Patients with a prior history of AF or electrocardiographic documentation of an AF episode on admission were not considered to have ESUS. In addition, patients who showed no evidence of AF and no apparent stenosis following recanalization of the occluded vessel underwent 24- to 72-h continuous ECG patch monitoring to detect the presence of AF. Patients with $\geq 50\%$ luminal stenosis due to intracranial atherosclerosis in arteries supplying the ischemic area, as determined by digital subtraction angiography, were also not considered to have ESUS. In this study, all patients considered for ESUS underwent extensive evaluation, including contrast echocardiography of the right heart for patent foramen ovale, coagulation function, and biomarkers in autoimmune rheumatic diseases.

2.4 | Echocardiographic Assessment and LA Strain Analysis

All patients with AIS who underwent EVT received echocardiography using a Philips EPIQ 7C ultrasound instrument with an S5-1 probe. Standard views (parasternal long axis, parasternal short axis, apical 4-chamber, apical 3-chamber, and apical 2-chamber views) recommended by the American Society of Echocardiography were obtained (Lang et al. 2015). All echocardiographic images were ECG-triggered and stored in a cine-loop format with five cardiac cycles. M-mode measurements were performed in the parasternal long-axis view to assess conventional echocardiographic parameters. Right atrial diameter (RAD) and right ventricular dimension (RVD) were measured in apical four-chamber view. LVEF was calculated using biplane Simpson's method in apical four- and two-chamber views. Left ventricular diastolic function was assessed based on parameters including trans-mitral E and A velocities, E/A ratio, average of septal and lateral annular e′ velocities, E/e′, and peak tricuspid regurgitation jet velocity (TRV). Left ventricular diastolic function classification was based on ASE/EHJ recommendation in 2016 (Nagueh et al. 2016).

Left atrial maximal volume (LAVImax), which represents the largest left atrial volume measured during the cardiac cycle, was analyzed in automatic heart model mode (HM ACQ). According to American Society of Echocardiography (ASE) standards,

LAVImax is typically defined based on a biplane measurement. However, our study included some patients with AF, where traditional biplane methods may be less reliable. As reported by Qtani et al., 3D transthoracic echocardiography (TTE) with fully automated quantification software enables more reliable and efficient measurement of the average values of left heart chamber parameters during multiple consecutive beats (Otani et al. 2016). This approach allows for more consistent left atrial volume measurements in AF patients, reducing variability compared to conventional biplane methods.

LA strain, including LA reservoir strain (LASr), LA conduit strain (LAScd), and LA contractile strain (LASct), was assessed by QLAB (13.0) digital workstation using R-R gating (Pathan et al. 2017). LASr represents the peak strain during LV systole, reflecting chamber filling. The value of LASr is positive because LA expands during ventricular systole. LAScd is estimated from the time of mitral valve opening through diastasis until the onset of LA contraction, while LASct is the peak strain during atrial contraction, representing the LV end-diastolic filling contribution by the LA (Figure 1) (Badano et al. 2018). The values of LAScd and LASct are negative due to wall shortening during left atrial conduit and contraction. For this current analysis, these values were transformed and reported as positive. LASr was measured for all patients, while LAScd and LASct were measured for all patients except those in the non-valvular AF-related cardioembolic stroke group due to their lack of P wave.

Left ventricular global longitudinal strain (LV-GLS) was measured using speckle tracking echocardiography (STE) at end-systole from apical four-chamber, apical three-chamber, and apical two-chamber views. LV-GLS was calculated as the average of the 18 segments of the left ventricle (Badano et al. 2018).

2.5 | Observer Variability

We randomly selected 25 cases for intraclass correlation coefficient (ICC) analysis. The intra-observer ICC for LASr, LAScd, LASct, and LV-GLS were 1, 1, 1, and 0.99, respectively; the corresponding inter-observer ICC was 0.99, 0.99, 0.99, and 0.99, respectively.

2.6 | Follow-Up of Patients With ESUS

All patients with ESUS were prospectively followed for 2 years to assess long-term outcomes, including AF, stroke, and death.

2.7 | Statistical Analysis

Continuous variables are presented as mean ± SD, while categorical variables are presented as numbers and frequencies. We compared continuous variables using t-tests between different groups. Logistic regression analysis was performed to compare

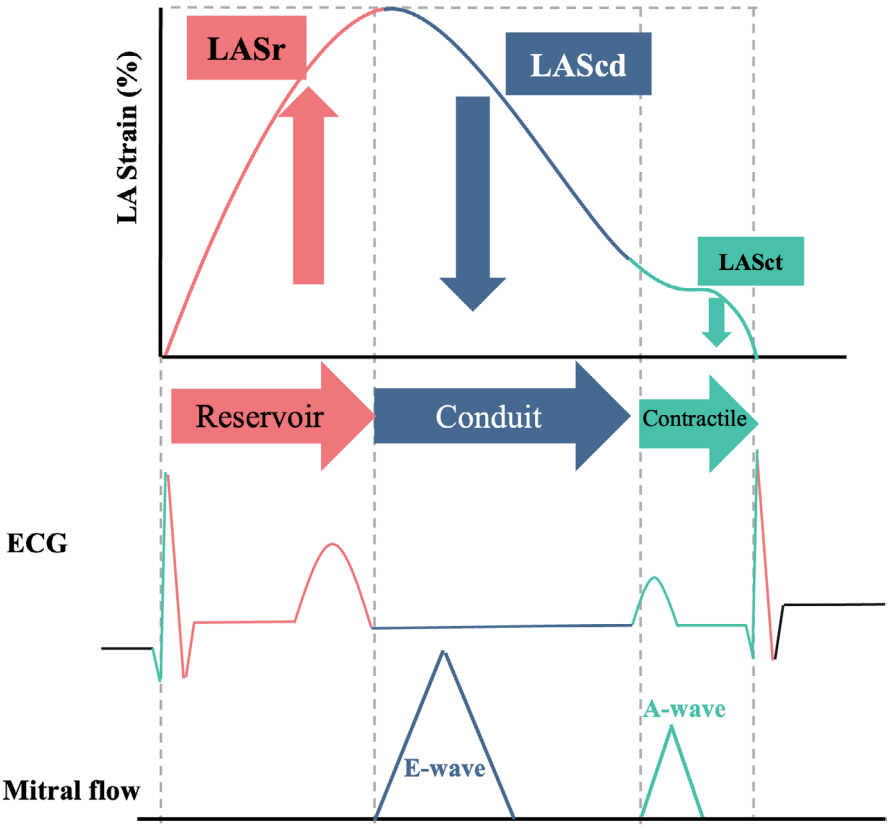

FIGURE 1 | Left atrial strain assessed by speckle-tracking analysis. LASr (left atrial reservoir strain) represents the peak strain of LA during LV systole, reflecting left atrial reservoir function. LAScd (left atrial conduit strain) is measured from the time of mitral valve opening through diastasis until the onset of LA contraction, representing left atrial conduit function. LASct (left atrial contractile strain) is the peak strain during atrial contraction, reflecting left atrial contractile function. The E-wave represents passive left ventricular filling during early diastole. The A-wave represents active atrial contraction during late diastole.

groups controlling for related covariates, including age, sex, body mass index (BMI), LAVImax, E/e′, and LVGLS. Predictive accuracy and cut-offs were defined from receiver operating characteristic (ROC) curve by using Youden index. Data analysis was performed with SPSS statistical package (IBM SPSS Statistics version 25.0, IBM Corporation, Armonk, NY). Statistical significance was defined as a two-sided $p < 0.05$.

3 | Results

3.1 | Study Population

During the study period, a total of 431 AIS patients with LVO-related AIS underwent EVT. 251 LVO-related AIS patients were excluded. Among them, 51 patients refused echo examination, 150 patients had severe strokes precluding safe transportation to the echo lab, and 50 patients were discharged within 24 h post-EVT prior to TTE. The final analysis included 180 who received TTE examinations with speckle tracking analysis. Forty-five patients who met the exclusion criteria and four patients with strokes due to causes other than large artery atherosclerosis, non-valvular AF-related cardioembolic strokes, or ESUS were excluded. Considering the potential impact of AF on LA dysfunction, we did not include five AF patients with AIS due to large artery atherosclerosis. Additionally, we selected a control group consisting of individuals without prior strokes (referred to as "controls"), who were sex- and age-matched with ESUS patients in a 1:1 ratio (Figure 2). Overall, 126 patients were finally analyzed, with a cross-sectional analysis conducted. The mean age of the patients was 67.7 ± 12.3 years, and 39.7% of them were women. The patient cohort consisted of 49 individuals with large artery atherosclerosis, 49 with non-valvular AF-related cardioembolic strokes, and 28 with ESUS. Vascular risk factors were highly prevalent in the patient cohort, with 66.7% having hypertension, 16.7% having diabetes mellitus, and 4.0% having hypercholesterolemia. According to the FRS categorization, 26.2% of the patients were classified as being at high risk of cardiovascular disease. Most of the patients experienced severe strokes, with a median NHISS score of 13 (IQR: 7–17) upon admission. Of these patients, 66.1% had a NIHSS score ≥ 10.

Table 1 presents the baseline characteristics and echocardiographic data of patients with ESUS in comparison to patients with large artery atherosclerosis and the control group. There were no statistically significant differences in clinical characteristics except BMI between patients with ESUS and large artery atherosclerosis. Patients with large artery atherosclerosis had greater weight. As compared with the control group, ESUS patients were more likely to have hypertension (60.7% vs. 21.4%, $p = 0.003$) and had higher levels of total cholesterol (4.4 ± 1.0 mmol/L vs. 3.7 ± 0.8 mmol/L, $p = 0.007$).

3.2 | Comparison of LA Function Between Patients With ESUS and Large Artery Atherosclerosis

Patients with ESUS had lower LASr (27.8 ± 7.1% vs. 32.0 ± 5.3%, $p = 0.004$) and LAScd (14.3 ± 3.8% vs. 17.3 ± 4.6%, $p = 0.005$) compared to large artery atherosclerosis patients (Table 1).

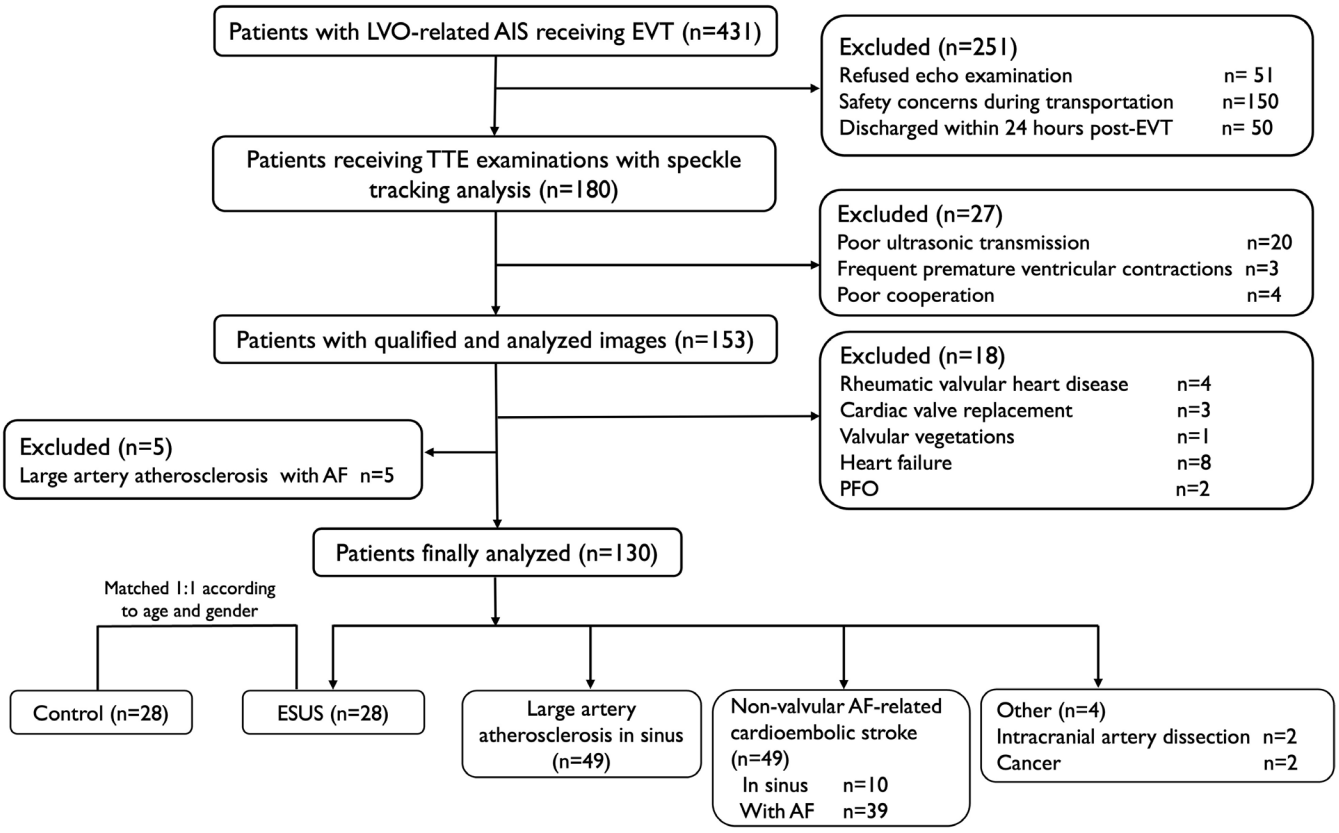

FIGURE 2 | Flowchart of patients included in this study. AIS, acute ischemic stroke; ESUS, embolic stroke of undetermined source; EVT, endovascular thrombectomy; LVO, large-vessel occlusion; TTE, transthoracic echocardiography.

TABLE 1 | Comparison of the baseline characteristics and echocardiographic parameters among patients with embolic stroke of undetermined source (ESUS), patients with large artery atherosclerosis, and the control group.

	ESUS	Large artery atherosclerosis	P_1[a]	Control	P_2[b]
N	28	49		28	
Age (years)	64.2 ± 13.5	62.4 ± 11.3	0.475	64.1 ± 13.5	0.969
Height	167.3 ± 7.0	169.9 ± 5.5	0.102	167.5 ± 7.0	0.94
Weight	61.8 ± 10.6	69.0 ± 11.3	0.004	64.3 ± 11.7	0.405
Male sex, *n* (%)	18 (64.3)	39 (79.6)	0.141	18 (64.3)	
BMI (kg/m^2)	22.0 ± 3.1	23.8 ± 3.1	0.008	22.8 ± 3.1	0.338
Systolic blood pressure (mmHg)	147.4 ± 24.5	153.2 ± 23.0	0.300	128.0 ± 5.8	< 0.001
Diastolic blood pressure (mmHg)	82.7 ± 17.2	85.4 ± 13.3	0.446	75.1 ± 8.4	0.039
Hypertension, *n* (%)	17 (60.7)	37 (75.5)	0.172	6 (21.4)	0.003
Diabetes mellitus, *n* (%)	3 (10.7)	12 (24.5)	0.142	3 (10.7)	1.000
Smoker, *n* (%)	7 (38.9)	26 (60.5)	0.070	12 (42.9)	0.584
Total cholesterol (mmol/L)	4.4 ± 1.0	4.4 ± 1.1	0.907	3.7 ± 0.8	0.007
HDL (mmol/L)	1.0 ± 0.2	1.0 ± 0.2	0.576	1.2 ± 0.4	0.146
Framingham risk score, *n* (%)					
Risk (low)	3 (10.7)	2 (4.1)	0.509	11 (39.3)	0.001
Risk (moderate)	4 (14.3)	6 (12.2)		7 (25)	
Risk (high)	21 (75)	41 (83.7)		10 (35.7)	
LAD (mm)	37.3 ± 4.8	36.2 ± 3.6	0.317	33.8 ± 4.0	0.005
LAVImax (mL/m^2)	34.9 ± 7.8	32.9 ± 5.8	0.351	31.3 ± 3.5	0.032
LVDd (mm)	48.0 ± 2.7	47.0 ± 3.7	0.247	45.4 ± 4.2	0.008
LVDs (mm)	31.6 ± 2.2	31.2 ± 2.9	0.597	29.2 ± 3.2	0.002
LVEF (%)	62.5 ± 1.9	62.6 ± 2.0	0.911	65.1 ± 3.6	0.002
RAD (mm)	34.5 ± 3.8	32.8 ± 2.5	0.102	33.6 ± 2.6	0.293
RVD (mm)	33.8 ± 3.2	33.4 ± 3.0	0.611	33.2 ± 2.3	0.448
E	77.7 ± 23.0	73.2 ± 18.1	0.345	69.3 ± 13.4	0.101
E/e′	10.4 ± 4.9	9.2 ± 2.6	0.132	9.4 ± 3.4	0.387
Grade ≥ 2, *n* (%)	7 (25.0)	8 (16.3)	0.355	5 (17.9)	0.737
TAPSE (mm)	20.3 ± 1.8	20.3 ± 1.4	0.770	20.1 ± 1.8	0.152
LASr (%)	27.8 ± 7.1	32.0 ± 5.3	0.004	37.6 ± 7.2	< 0.001
LASct (%)	13.9 ± 5.4	14.9 ± 4.1	0.355	16.1 ± 5.1	0.123
LAScd (%)	14.3 ± 3.8	17.3 ± 4.6	0.005	21.5 ± 7.9	< 0.001
LVGLS (%)	19.0 ± 2.6	19.5 ± 2.0	0.504	21.2 ± 2.4	0.001

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FRS, Framingham risk score; HDL-C, high-density lipoprotein cholesterol; LAD, left atrial anteroposterior diameter; LAScd, left atrial conduit strain; LASct, left atrial contractile strain; LASr, left atrial reservoir strain; LV, left ventricular; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; RAD, right atrial diameter; RVD, right ventricular diameter; SBP, systolic blood pressure; TC, total cholesterol; TRV, tricuspid regurgitation velocity.
[a]ESUS group versus large artery atherosclerosis group.
[b]ESUS group versus Control group.

The fully adjusted model (Model 3) in Table 2 reveals that a 5% reduction of LASr (OR, 1.919, 95% CI, 1.071–3.360) and LAScd (OR, 2.451, 95% CI, 1.171–5.128) was associated with a significantly increased likelihood of having an ESUS subtype.

Figure 3A presents ROC curves illustrating the accuracy of these parameters in distinguishing ESUS and large artery atherosclerosis. Only LASr ($p = 0.013$) and LASd ($p = 0.004$) had statistically significant differences, with cut-off values

TABLE 2 | Multivariable logistic regression of atrial characteristics with embolic stroke of undetermined source (ESUS) versus large artery atherosclerosis group.

Cardiac variables	Univariate	95% CI	*p*	Model 1 OR	95% CI	*p*	Model 2 OR	95% CI	*p*	Model 3 OR	95% CI	*p*
LAVImax (mL/m^2)	1.046	0.974–1.124	0.212	1.015	0.935–1.102	0.721	1.001	0.916–1.095	0.975	1.004	0.916–1.100	0.938
E/e′	1.100	0.951–1.271	0.199	1.081	0.906–1.290	0.387	1.080	0.896–1.302	0.418	1.079	0.886–1.314	0.449
LASr (per 5% reduction)	1.802	1.173–2.770	0.007	1.934	1.149–3.257	0.013	2.012	1.142–3.546	0.016	1.919	1.071–3.360	0.029
LAScd (per 5% reduction)	2.457	1.272–4.739	0.007	2.544	1.25–5.181	0.010	2.558	1.263–5.291	0.011	2.451	1.171–5.128	0.017
LASct (per 5% reduction)	1.287	0.762–2.174	0.347	1.165	0.647–2.101	0.609	1.143	0.624–2.092	0.665	1.110	0.606–2.037	0.735
LVGLS (%)	1.120	0.907–1.383	0.291	1.170	0.928–1.473	0.186	1.165	0.925–1.471	0.194	/	/	/

Note: Adjustment models: Model 1: Age (years), sex, BMI; Model 2: Model 1+ LAVImax, E/e′; Model 3: Model 2+ LVGLS.
Abbreviation: Please refer to the footnote of Table 1.

of 23.5% and 16.8%, respectively. The sensitivity and specificity were 35.7% and 98.0% for LASr and 55.1% and 85.7% for LAScd. Additionally, Figure 3B,C illustrated the comparison of ESUS and large artery atherosclerosis based on the cutoff value of LASr and LAScd derived from ROC analysis. Among ESUS patients, 35.7% had LASr below 23.5%, and 85.7% had LAScd below 16.8%. While among patients with large artery atherosclerosis, 2% had LASr below 23.5%, and 42.9% had LAScd below 16.8%.

3.3 | Comparison of LA Function Between Patients With ESUS and Controls

Patients with ESUS had decreased LASr (27.8 ± 7.1% vs. 37.6 ± 7.2%, $p < 0.001$), LAScd (14.3 ± 3.8% vs. 21.5 ± 7.9%, $p < 0.001$), and LVGLS (19.0 ± 2.6% vs. 21.2 ± 2.4%, $p = 0.001$) compared with their sex- and age-matched controls (Table 1). Table 3 shows that a 5% reduction of LASr was significantly associated with a greater likelihood of having an ESUS subtype in the fully adjusted model (OR, 18.519, 95% CI, 1.481–250.000; Model 3).

3.4 | Distribution of all Enrolled Patients and the Control Group According to LASr

Figure 4 illustrated the distribution of all enrolled patients and the control group according to their LASr value. The LASr values in 98.0% ($n = 48$) of the large artery atherosclerosis patients and all in the control group were all above 23.5%. In addition, 35.7% ($n = 10$) patients with ESUS and 93.9% ($n = 46$) patients with non-valvular AF-related cardiogenic stroke had impaired LASr (< 23.5%).

3.5 | Follow-Up of ESUS Patients

During the 2 years of follow-up for the 28 ESUS patients, three patients developed AF and three patients had ischemic stroke, with one having both AF and stroke. Notably, all five patients with cardiovascular events had impaired LASr (< 23.5%) and LAScd (< 16.8%).

4 | Discussion

In our study, patients with ESUS had lower LASr and LAScd compared to those with large artery atherosclerosis or the control group. A 5% reduction in LASr and LAScd was associated with a 1.92- and 2.45-fold increased risk of having ESUS versus large artery atherosclerosis. Impaired LA function, as indicated by lower LASr and LAScd, may be suggested as a key differentiator for stroke etiology in patients with ESUS related to LVO.

In this study, ESUS patients accounted for 22.2% of the total enrolled patients with ischemic stroke. All the patients we enrolled in our study had AIS with LVO, allowing us to gather valuable cardiac strain data in individuals with severe stroke.

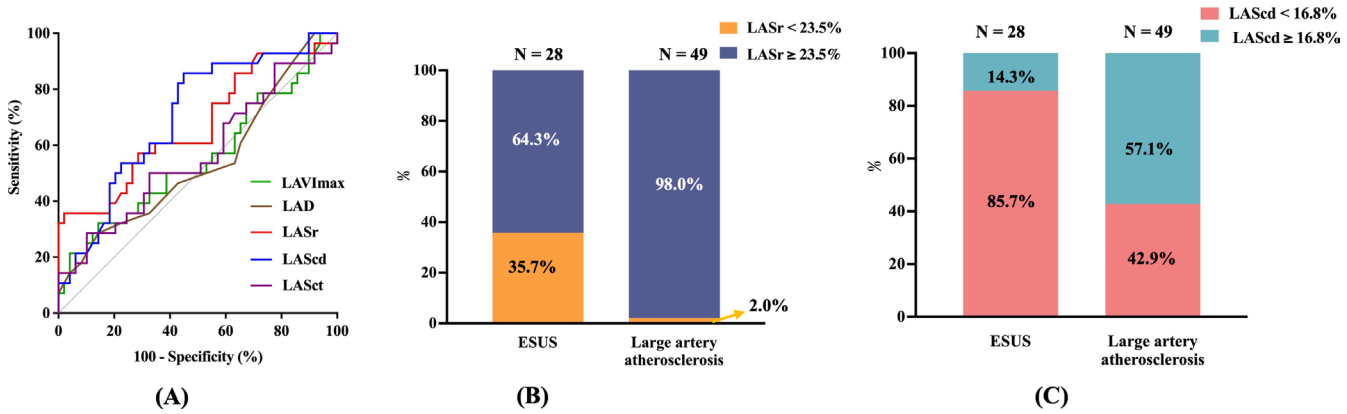

FIGURE 3 | Left atrial strain function in ESUS and large artery atherosclerosis. (A) ROC curves for accuracy of left atrial parameters in distinguishing ESUS and large artery atherosclerosis. (B) Comparison of ESUS and large artery atherosclerosis stratified by the cutoff value of LASr. (C) Comparison of ESUS and large artery atherosclerosis stratified by the cutoff value of LAScd. ESUS, Embolic stroke of undetermined source; LAD, left atrial dimension; LAScd, left atrial conduit strain; LASct, left atrial contractile strain; LASr, left atrial reservoir strain; LAVImax, left atrial maximum volume index.

Potential cardiogenic embolic sources overlapped highly with ESUS. Covert paroxysmal AF was once widely accepted as a leading cause of stroke in ESUS (Ntaios et al. 2019). However, it is worth noting that even after 3 years of monitoring, approximately 70% of patients with cryptogenic stroke did not show evidence of AF (Sanna et al. 2014). This suggests that AF may not be the primary cause of ESUS. In recent years, there has been a growing consensus that thromboembolism in AF may not solely result from the chaotic, disorganized contraction of the atrium but rather from underlying atrial cardiomyopathy, which refers to structural and pathologic changes in the left atrium (Jalini et al. 2019). This concept is supported by studies demonstrating that structural, functional, and electrophysiological abnormalities of the atrium—such as atrial fibrosis, impaired atrial strain, and reduced atrial ejection fraction—can contribute to blood stasis and thrombus formation, even in the absence of AF episodes (Shen et al. 2019). However, this does not mean that the disorganized contraction of AF is unrelated to thromboembolism. Instead, it suggests that atrial cardiomyopathy may predispose patients to thromboembolism independently of AF, and when AF develops, it further exacerbates the risk by worsening atrial dysfunction and promoting stasis (Kamel et al. 2016). Regarding LA appendage (LAA) velocity, it remains an important predictor of thromboembolic risk, as reduced LAA emptying velocity has been consistently associated with increased stroke risk (Tabak et al. 2024). However, the growing recognition of atrial cardiomyopathy suggests that additional markers—such as impaired LA strain, reduced LA ejection fraction, and atrial fibrosis—may provide complementary risk stratification beyond LAA velocity alone (Delgado et al. 2017). Some studies have indicated that LA dysfunction, even in patients without AF, can contribute to stroke risk, reinforcing the idea that atrial cardiomyopathy plays a crucial role (Bhat et al. 2022).

TTE has been recommended to assess LA structure, including LA maximal and minimal volume, as well as LA function, including LA reservoir strain, conduit strain, and contraction strain, after an AIS (Warner et al. 2019). Previous studies have shown that patients with non-valvular AF-related cardioembolic stroke had increased LA volumes (Jordan et al. 2019), which is consistent with the findings of our current study. However, no significant differences in LA size and volume were found when comparing patients with ESUS versus those with large artery atherosclerosis, while patients with ESUS were compared to their controls without stroke in our study. LA strain, which can sensitively reflect atrial mechanical function, has received significant attention in patients with ischemic stroke. It has been reported that reduced LA reservoir function was independently associated with ischemic cerebrovascular events (Mohammadali Habibi et al. 2019) and left atrial appendage thrombosis (Kurzawski et al. 2020) in patients at sinus rhythm.

Our study revealed that ESUS patients exhibited decreased LASr and LAScd compared to large artery atherosclerosis patients or their controls, while LAD, LAVImax, and LASct had no significant difference between ESUS and large artery atherosclerosis. These findings suggested that impaired atrial mechanical function occurred earlier than the changes in atrial structure, which is in line with the findings of a previous study (Bhat et al. 2022). Therefore, it is crucial to closely monitor LA function in ESUS patients, even when LA structure appears normal. In our study, 5 in 10 ESUS patients with impaired LASr and LAScd had cardiovascular events (AF or recurrent stroke). As a result, impaired LA strain in ESUS patients is likely to indicate a high risk for cardiovascular events. Regarding LA function monitoring in ESUS patients, our study demonstrates that patients with ESUS of LVO exhibit impaired LA strain despite normal LA structure, suggesting a possible role of subclinical atrial dysfunction in stroke mechanisms. While this does not imply an immediate need for targeted interventions, it does indicate that future prospective studies should be performed to investigate whether LA function metrics such as LASr or LAScd could refine risk stratification or influence secondary prevention strategies.

Our results also provided quantitative evidence that only a subset of ESUS patients had mild to moderate LA dysfunction, suggesting that not all ESUS cases may have a cardiogenic origin. This finding may help explain the negative results of the ARCADIA trial, in which ACM was defined based on ECG parameter, BNP level, or LA diameter (Kamel et al. 2024). While

TABLE 3 | Multivariable logistic regression of atrial characteristics with embolic stroke of undetermined source (ESUS) group versus the control group.

Cardiac variables	Univariate	95% CI	*p*	Model 1 OR	95% CI	*p*	Model 2 OR	95% CI	*p*	Model 3 OR	95% CI	*p*
LAVImax (mL/m^2)	1.112	1.004–1.232	0.043	1.058	0.918–1.219	0.438	1.002	0.837–1.200	0.978	1.032	0.831–1.283	0.775
E/e′	1.063	0.924–1.222	0.393	1.182	0.898–1.557	0.233	1.18	0.855–1.628	0.315	1.356	0.876–2.098	0.172
LASr (per 5% reduction)	2.519	1.533–4.149	<0.001	4.484	1.706–11.765	0.002	5.128	1.739–15.152	0.003	18.519	1.481–250.000	0.024
LAScd (per 5% reduction)	3.268	1.613–6.623	<0.001	10.638	1.767–66.667	0.003	8.547	1.406–52.632	0.02	7.246	0.900–58.824	0.063
LASct (per 5% reduction)	1.524	0.886–2.618	0.128	1.304	0.649–2.618	0.455	1.304	0.631–2.695	0.473	1.202	0.367–3.937	0.761
LVGLS (%)	1.481	1.126–1.946	0.005	1.887	1.249–2.849	0.003	2.058	1.282–3.311	0.003	/	/	/

Note: Adjustment models: Model 1: sex, age, BMI, hypertension, HDL; Model 2: Model 1 + LAVImax, E/e′; Model 3: Model 2 + LVGLS.
Abbreviation: Please refer to the footnote of Table 1.

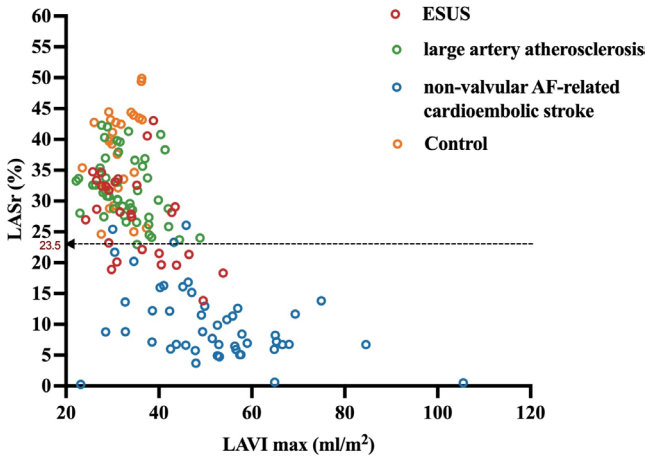

FIGURE 4 | Distribution of all enrolled patients and the control group according to LASr and LAVImax. ESUS, embolic stroke of undetermined source; LASr, left atrial reservoir strain; LAVImax, left atrial maximum volume index.

previous studies (e.g., RE-SPECT ESUS, NAVIGATE ESUS, and ARCADIA) did not demonstrate a significant benefit of novel oral anticoagulants over aspirin in reducing recurrent stroke in ESUS patients (Hart et al. 2018; Diener et al. 2019; Kamel et al. 2024), our study raises the hypothesis that a subset of ESUS patients with LA dysfunction may warrant further investigation in anticoagulation trials. However, we do not propose that LASr or LAScd should currently guide treatment decisions outside of a trial setting.

5 | Limitation

Our study has some limitations that need to be acknowledged. Firstly, the sample size in our study was relatively small. It would be beneficial to validate our findings through larger-scale studies. Secondly, our study was a cross-sectional research, with only ESUS patients being followed up, limiting our ability to assess long-term outcomes. Therefore, conducting longitudinal studies with extended follow-up periods is necessary. Thirdly, as per our inclusion criteria, all patients were required to have TTE with speckle tracking analysis performed within 1 week of the index stroke. Therefore, the echo examination was contingent on the clinical stability of the patients. Indeed, some patients with severe stroke were not eligible for inclusion, as they could not be safely transported to the echocardiography lab for evaluation. This selection bias may limit the generalizability of our findings, particularly in patients with severe stroke who were unable to undergo TTE. Lastly, our study primarily focused on changes in atrial function in stroke cases related to LVO, while the alterations in LA function in strokes associated with small vessel occlusion should also be considered and investigated in future research.

6 | Conclusion

LA strain is associated with ESUS in stroke patients with LVO. Further studies are needed to explore its utility in identifying specific stroke etiologies. The addition of LA strain analysis to

assess cardiac function may have the potential to aid in the identification of stroke etiology in ESUS patients related to LVO.

Author Contributions

Mingfang Li, Yanjuan Zhang, Jincheng Jiao and Minglong Chen: conceived the idea and designed the research. **Yanjuan Zhang, Jincheng Jiao, Yingying Wang, Sheng Liu, Yuezhou Cao and Haibing Shi:** collected the data. **Yanjuan Zhang and Jincheng Jiao:** analyzed the data. **Yanjuan Zhang, Jincheng Jiao and Mingfang Li:** did the statistical analysis . **Yanjuan Zhang and Jincheng Jiao:** draft the manuscript. **Mingfang Li and Yanjuan Zhang:** revised the manuscript. All authors read and approved the final draft.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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