Left Atrial Strain, Embolic Stroke of Undetermined Source, and Atrial Fibrillation Detection

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Abstract

Background: Atrial cardiopathy is a proposed mechanism of embolic stroke of undetermined source (ESUS). Left atrial (LA) strain may identify early atrial cardiopathy prior to structural changes. We aim to study the associations between LA strain, ESUS, and atrial fibrillation (AF) detection in ESUS. **Methods:** The study population included patients with ESUS and non-cardioembolic (NCE) stroke presenting to statewide stroke center between January 2016 and June 2017 who underwent transthoracic echocardiography. Speckle tracking echocardiography (STE) was used to measure the 3 phases of LA strain (reservoir, conduit, and contractile). Binary logistic regression analysis was performed to determine the associations between LA strain and stroke subtype (ESUS vs. NCE) as well as follow-up detection of AF in ESUS patients. **Results:** We identified 656 patients, 307 with ESUS and 349 with NCE. In binary logistic regression, the lowest tertiles of LA reservoir (adjusted OR 1.944, 95% CI 1.266-2.986, p = 0.002), contractile (aOR 1.568, 95% CI 1.035-2.374, p = 0.034), and conduit strain (aOR 2.288, 95% CI 1.448-3.613, p = 0.001) were more likely to be significantly associated with ESUS compared to NCE stroke. Among all ESUS patients, the lowest tertiles of LA reservoir strain (OR 2.534, 95% CI 1.029-6.236, p = 0.043), contractile strain (OR 2.828, 95% CI 1.158-6.903, p = 0.022), and conduit strain (OR 2.614, 95% CI 1.003-6.815, p = 0.049) were significantly associated with subsequent detection of AF. **Conclusion:** Reduced LA strain is associated with ESUS occurrence and AF detection in ESUS patients. Therefore, quantification of LA strain in ESUS patients may improve risk stratification and guide secondary prevention strategies.

Full title: Left Atrial Strain, Embolic Stroke of Undetermined Source, and Atrial Fibrillation Detection

Short title: Reduced Left Atrial Strain and ESUS

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Tweet: Reduced Left Atrial Strain is associated with ESUS and AF detection on cardiac monitoring. #Left Atrial Strain, #ESUS, #Atrial Fibrillation

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Abstract

Background: Atrial cardiopathy is a proposed mechanism of embolic stroke of undetermined source (ESUS). Left atrial (LA) strain may identify early atrial cardiopathy prior to structural changes. We aim to study the associations between LA strain, ESUS, and atrial fibrillation (AF) detection in ESUS.

Methods: The study population included patients with ESUS and non-cardioembolic (NCE) stroke presenting to statewide stroke center between January 2016 and June 2017 who underwent transthoracic echocardiography. Speckle tracking echocardiography (STE) was used to measure the 3 phases of LA strain (reservoir, conduit, and contractile). Binary logistic regression analysis was performed to determine the associations between LA strain and stroke subtype (ESUS vs. NCE) as well as follow-up detection of AF in ESUS patients.

Results: We identified 656 patients, 307 with ESUS and 349 with NCE. In binary logistic regression, the lowest tertiles of LA reservoir (adjusted OR 1.944, 95% CI 1.266-2.986, p = 0.002), contractile (aOR 1.568, 95% CI 1.035-2.374, p = 0.034), and conduit strain (aOR 2.288, 95% CI 1.448-3.613, p = 0.001) were more likely to be significantly associated with ESUS compared to NCE stroke. Among all ESUS patients, the lowest tertiles of LA reservoir strain (OR 2.534, 95% CI 1.029-6.236, p = 0.043), contractile strain (OR

2.828, 95% CI 1.158-6.903, p = 0.022), and conduit strain (OR 2.614, 95% CI 1.003-6.815, p = 0.049) were significantly associated with subsequent detection of AF.

Conclusion: Reduced LA strain is associated with ESUS occurrence and AF detection in ESUS patients. Therefore, quantification of LA strain in ESUS patients may improve risk stratification and guide secondary prevention strategies.

Key words: Left Atrial Strain; Atrial Cardiopathy; ESUS; Atrial Fibrillation;

Clinical Perspectives:

What is known:

Speckle tracking echocardiography is a sensitive and reproducible technique that identifies subtle changes in the atrial biomechanics prior to any significant volumetric changes.

LA dysfunction is associated with ESUS stroke subtype

What this study adds:

This study adds to the growing body of evidence suggesting early recognition of atrial cardiopathy in ESUS stroke subtype using speckle tracking echocardiography.

It also provides evidence that routine quantification of LA strain in ESUS patients may identify a subset of ESUS patients that may benefit from intensive cardiac arrhythmia surveillance and potential anticoagulation therapy.

Introduction:

Ischemic stroke accounts for 87% of all strokes[1], and cryptogenic stroke constitutes approximately 30-40% of all ischemic strokes[2, 3]{Perera, 2022 #584}. Embolic Stroke of Undetermined Source (ESUS) is a subtype of cryptogenic stroke in which there is embolic-appearing infarction on CT and/or MRI without an identifiable etiology despite standard diagnostic evaluation[4]. It is associated with a high recurrence[5, 6]; thus, in addition to risk factor modification, identifying and targeting the primary causal mechanisms may improve secondary prevention strategies[7]. Better characterization of left atrial (LA) structure and function may elucidate a mechanistic pathway in the development of cryptogenic stroke. Previous studies have shown an association of left atrial enlargement (LAE)[8, 9] and left atrial volume index (LAVI)[10] with ESUS stroke subtype as compared to non-cardioembolic (NCE) stroke subtype. However, LA chamber remodeling and biomechanical dysfunction precede volumetric changes in LA chamber[11]. Speckle tracking echocardiography (STE) and strain analysis have been shown to detect these early signals prior to structural changes found on traditional imaging methods[12-14]. Atrial cardiopathy has been characterized as a time-dependent adaptive structural remodeling with electrical and mechanical dysfunction causing stasis of blood. It may provide a potential substrate for the development of thrombus even in the absence of atrial enlargement or fibrillation[13, 15]. Atrial fibrosis, an early sign of atrial remodeling, correlates inversely with LA strain[16, 17] and is reported more frequently in ESUS compared NCE subtype[18]. A recent single-center study showed the association of LA strain and stroke subtypes including cryptogenic stroke[19].

The goal of our study is to investigate the relationship between LA strain and stroke, specifically ESUS and NCE stroke subtypes, in a geographically distinct population using a comprehensive stroke database. Additionally, we aim to examine the relationship between LA strain and future atrial fibrillation (AF) events in ESUS patients.

Methods:

This study was approved by Lifespan Institutional Review Board. Informed consent was waived as this is a retrospective study.

The study population included all patients presenting to a comprehensive regional stroke center with a primary diagnosis of ischemic stroke between January 2016 and June 2017. All patients enrolled in the

stroke database underwent standard ischemic stroke evaluation including laboratory testing, neuroimaging, 12-lead EKG, transthoracic echocardiography (TTE), and cardiac telemetry monitoring for at least 24 hours. The stroke subtype was assigned by a vascular neurologist, who was following the patients over the course of index hospitalization, based on the TOAST criteria[20] and ESUS subtype was defined based on the ESUS consensus criteria[21]. This data was extracted by chart review. Stroke subtype was divided into two categories: ESUS and NCE. Demographic variables, vascular risk factors, and laboratory covariates (age, sex, history of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, renal disease, systolic blood pressure, smoking status, National Institutes of Health Stroke Scale (NIHSS) score) were also extracted and collected on the Research Electronic Data Capture database (REDCap; Vanderbilt University, Nashville, TN). All ESUS patients were given a prescription of cardiac event monitor (CEM) as per guidelines regardless of symptoms. Those with negative CEM results were given implantable loop recorders (ILR). The presence of AF was defined as identification of AF for more than 30 seconds on monitoring.

Patients with a history of atrial fibrillation or any of the following conditions were excluded: moderate to severe valve disease (as determined by clinical echocardiography reports), a left ventricular ejection fraction (LVEF) of less than 40%, pericardial effusion causing tamponade, any type of congenital heart disease, a prosthetic heart valve, left ventricular assist device, or poor image quality (LA chamber foreshortening, or unclear atrial walls etc.) to perform STE analysis (Figure 1).

Echocardiographic Parameters

2D TTE was performed either during the index hospitalization or within three months of the indexed ischemic stroke. Studies were performed according to the guidelines from the American Society of Echocardiography (ASE)[22], and reports were generated by cardiologists board-certified in echocardiography. Phasic LA function was quantified off-line using TOMTEC (Chicago, IL)[23]according to guidelines from the European Association of Cardiovascular Imaging (EACVI)/ASE Task Force[24]. The procedure entailed a careful selection of TTE images capturing optimal views of the left atrium (LA). Specifically, the LA-focused apical 4-chamber (A4-C) and 2-chamber (A2-C) views providing the clearest visualization were obtained. In cases where the A4-C view did not provide sufficient clarity, the A2-C view was used independently. After thorough assessment of multiple cardiac cycles, a single cardiac cycle presenting the best image quality was chosen. The LA endocardial border was manually traced from mitral annulus at one side, extrapolating across the pulmonary veins and atrial appendage orifices to the opposite side in the end-diastolic and end-systolic phases of a cardiac cycle (Figure 2). This generated average atrial strain curve with two peaks. LA reservoir strain was calculated by measuring the peak atrial longitudinal strain (PALS) at the end of ventricular systole, corresponding with the first peak. LA contractile strain was calculated by measuring the peak atrial contraction strain (PACS) at the onset of atrial contraction, corresponding with the second peak. Conduit (passive emptying) strain was calculated by the difference between the PALS and PACS[12, 24] (Figure 2). The quality of wall tracking was recorded according to the number of walls appropriately tracked. Echocardiography analysis was blinded to stroke subtype and outcomes.

Statistical Analysis

We compared demographic, clinical, and laboratory data between the two groups using t-tests for continuous variables and Fisher's exact tests for categorical variables. LA strain was divided into three components—LA reservoir, conduit, and contractile—to determine the association of each phase of atrial function with stroke subtypes. Multivariable logistic regression analysis adjusting for covariates was performed. The first model was adjusted for age and sex. The second model was adjusted for covariates in model 1 plus systolic blood pressure, history of congestive heart failure defined as heart failure with mid-range and preserved ejection fraction according to the guidelines from the Heart Failure Society of America[25], and NIHSS. LA strain components (reservoir, conduit, and contractile) were assessed both as linear and tertile categorical variables to simplify the analysis for easier interpretation and to study the trend within the LA strain dataset. All ESUS patients were give a prescription of cardiac event monitor (CEM). Those with negative CEM were given implantable loop recorders (ILR). The presence of AF was defined as identification of AF for more

than 30 seconds on monitoring.

We compared three phases of LA strain between all ESUS patients with and without AF detection using t-tests. The association between LA strain and detection of AF was assessed using logistic regression analysis. Sensitivity analyses were performed adjusting for age, focusing only on ESUS patients who received cardiac monitoring, and focusing only on ESUS patients found to have AF on cardiac monitoring to compare differences in LA strain between those with an AF burden of less than 24 hours versus greater than or equal to 24 hours. Analysis was performed using STATA SE v17 with a p-value < 0.05 as statistically significant.

Results:

Baseline Characteristics

In total, 1313 eligible patients were screened for inclusion based on the criteria mentioned above. Among the excluded subjects, those with uninterpretable echocardiograms stood out as the most notable group. Due to the inherent limitations of clinical research and the challenges associated with speckled tracking strain analysis on clinical echocardiograms, meticulous care was taken to ensure accurate tracking of the LA chamber walls. Consequently, approximately 22% of the echocardiograms were deemed uninterpretable and subsequently excluded from the final cohort of the analytic sample (Figure 1). The criteria for defining echocardiograms as uninterpretable included foreshortening of the LA chamber view, inadequate visibility of one or more walls of the LA chamber for endocardial tracing, and echocardiograms with a wall tracking score of 1 where more than one endocardial wall did not show appropriate tracking despite its adequate gross visibility.

Among the 656 total stroke patients utilized in the study sample, 349 patients were classified as NCE and 307 as ESUS. Among the NCE patients, 208 had large artery atherosclerosis, 87 had small vessel disease, and 54 had other determined or undetermined etiology. The clinical characteristics of the NCE cohort and ESUS cohort were largely similar, except for a few notable differences. The NCE cohort had a higher percentage of males (61.3% vs. 48.5%, $p = 0.001$) and a higher mean systolic blood pressure in mm Hg ($152.2 + 29.5$ vs. $144.6 + 26.5$, $p = 0.001$). Conversely, the NCE cohort had a lower percentage of individuals with a history of congestive heart failure (0.6% vs. 4.2%, $p = 0.003$) and a lower median NIHSS (National Institutes of Health Stroke Scale) score (7 vs. 10, $p < 0.001$) compared to the ESUS cohort (Table 1).

On echocardiography analysis, compared to NCE, patients with ESUS had a significantly lower LA reservoir strain (32.0 ± 16.1 vs. 36.7 ± 17.9, $p < 0.001$), LA contractile strain (15.5 ± 9.6 vs. 17.4 ± 10.7, $p = 0.018$), and LA conduit strain (16.5 ± 10.7 vs. 19.3 ± 11.5, $p = 0.001$) (Table 1).

Multivariable Analysis of Associations between LA Reservoir, Contractile, and Conduit Strain and ESUS

On binary logistic regression analysis utilizing LA strain as tertiles, the lowest tertiles (Tertile 1) of LA reservoir (OR 1.860, 95% CI 1.272-2.721, $p = 0.001$), contractile (OR 1.845, 95% CI 1.261-2.699, $p = 0.002$), and conduit (OR 1.930, 95% CI 1.319-2.825, $p = 0.001$) strain were associated with ESUS compared to NCE (Table 2). After adjustment, low LA reservoir (OR 1.944, 95% CI 1.266-2.986, $p = 0.002$), contractile (OR 1.568, 95% CI 1.035-2.374, $p = 0.034$), and conduit (OR 2.288, 95% CI 1.448-3.613, $p = 0.001$) strain continued to be significantly associated with ESUS compared to NCE.

On binary logistic regression analyses utilizing LA strain as continuous variables, there was an inverse relationship of higher LA reservoir (OR 0.983, 95% CI 0.974-0.993, $p = 0.001$) and conduit (OR 0.977, 95% CI 0.962-0.991, $p = 0.001$) strain and ESUS compared to NCE in the unadjusted model, and these findings persisted after adjustment (reservoir strain OR 0.985, 95% CI 0.974-0.995, $p = 0.005$; conduit strain OR 0.971, 95% CI 0.955-0.988, $p = 0.001$) (Table 2). There was also an inverse association of higher LA contractile strain and ESUS compared to NCE in the unadjusted model (OR 0.982, 95% CI 0.966-0.997, $p = 0.019$); though the effect size remained the same, the association was no longer significant after adjustment for confounding variables (OR 0.990, 95% CI 0.973-1.007, $p = 0.239$).

Atrial Fibrillation Detection in ESUS patients

All 307 patients with ESUS were given a prescription for CEM. Out of the 307 patients, 155 completed the monitoring process successfully. The rest either declined or were unable to complete the process. Of the 155 patients who completed monitoring, 88 only had a 30-day CEM and 67 also had successful ILR in addition to the CEM, while the rest either declined or were lost to follow-up. Among all 307 ESUS patients, AF was detected in 32 patients who received scheduled cardiac monitoring. Additionally, 7 patients who did not receive scheduled cardiac monitoring were incidentally found to have AF in subsequent outpatient or hospital visits. Patients with AF detected had significantly decreased mean LA reservoir strain (25.15±13.57 vs. 32.95±16.20, p = 0.005), LA contractile strain (12.24±10.00 vs. 15.95±9.41, p = 0.023), and LA conduit strain (12.91±6.45 vs. 17.00±11.09, p = 0.025) compared to patients without AF detected (Table 3). In the sensitivity analysis using the 32 ESUS patients found to have AF on cardiac monitoring, there was no significant difference in LA reservoir strain (26.15+ 15.25 vs. 26.50+ 12.17, p = 0.953), LA contractile strain (12.79+ 11.90 vs. 11.56+ 6.74, p = 0.785), and LA conduit strain (13.36 + 6.31 vs. 14.94+ 7.12, p = 0.557) between those with an AF burden of less than 24 hours compared to those with an AF burden of greater than or equal to 24 hours likely due to small sample size (Table 4). In the sensitivity analysis using only the 155 ESUS patients who received cardiac monitoring, the effect size of LA strain remained stable, but significance was also lost likely due to small sample size (Supplementary Table 1).

Multivariable Analysis of Associations between LA strain and Atrial Fibrillation Detection in ESUS patients

Among all ESUS patients, in binary logistic analysis using LA strain as tertiles, the lowest tertile of strain values (Tertile 1) showed significant association of LA reservoir strain (unadjusted OR 2.534, 95% CI 1.029-6.236, p = 0.043), LA contractile strain (unadjusted OR 2.828, 95% CI 1.158-6.903, p = 0.022) and LA conduit strain (unadjusted OR 2.614, 95% CI 1.003-6.815, p = 0.049) with AF detection (Table 5). When utilizing LA strain as a continuous variable, decreased LA reservoir strain (unadjusted OR 0.957, 95% CI 0.929-0.987, p = 0.005), LA contractile strain (unadjusted OR 0.949, 95% CI 0.907-0.993, p = 0.025), and LA conduit strain (unadjusted OR 0.952, 95% CI 0.912-0.994, p = 0.025) were significantly associated with detection of AF (Table 5). Findings remain unchanged in the sensitivity analyses adjusting for age. In the sensitivity analysis using only the 155 ESUS patients who received cardiac monitoring, the effect size of LA strain remained stable but significance was lost likely due to small sample size (Supplementary Table 2).

Discussion:

In this large single-center retrospective observational study of atrial cardiopathy and stroke, we found that atrial dysfunction as evidenced by reduced left atrial strain was associated with ESUS stroke when compared to NCE strokes. In addition, reduced LA strain was predictive of future detection of AF in these ESUS patients.

Clinical Implications

LA remodeling is a time-dependent adaptive change in the atrial cardiomyocyte that is followed by biomechanical changes[17] affecting all the three phases of LA function [26]. Thus, LA strain is a surrogate of atrial fibrosis and remodeling[16]. Previous studies have shown a correlation between enlarged LA chamber size with adverse cardiovascular outcomes including the risk of strokes and arrhythmias[27, 28]. Our study shows the association of reduced LA strain with ESUS compared to NCE, further potentiating previously reported LA strain's association with cryptogenic stroke[13, 19]. In addition, it also demonstrates that reduced LA conduit and contractile strains are more commonly associated with ESUS compared to NCE stroke. This may be explained by underlying atrial fibrosis, remodeling, and biomechanical dysfunction causing stiffening of the atrial chamber, which impairs the compliance and booster-pump function of the atrium leading to atrial reservoir and contractile dysfunction. LA reservoir strain has been shown to be a predictor of thrombus formation in LA appendage in patients with sinus rhythm[29]. Our study adds to the existing literature showing significant association of all phases of reduced LA strain with ESUS subtype in patients in sinus rhythm with midrange and normal LVEF and in the absence of acute heart failure[30].

Furthermore, the extent of atrial fibrosis inversely correlates with LA reservoir strain in AF irrespective of chamber size[31]and independently predicts progression from paroxysmal AF to persistent AF[32]. Our study

demonstrates the association of all phases of reduced LA strain with AF in ESUS patients. This adds to the previously reported association of AF with reduced LA strain in cryptogenic stroke patients[33] . However, our study demonstrates the association of AF with ESUS subtype, which is a more enriched population with a high recurrence rate of stroke within the spectrum of cryptogenic stroke subtype. Our findings also confirm recently published studies showing contractile strain as an emerging echocardiographic parameter for predicting AF in cryptogenic stroke patients[34, 35]. This provides a mechanistic pathway for the occurrence of ESUS, where atrial cardiomyopathy and biomechanical dysfunction provide a potential substrate for embolic source and also increases the likelihood of AF detection.

Recent trials, NAVIGATE ESUS[5] and RE-SPECT ESUS[6], did not show any benefit of oral anticoagulants over antiplatelet therapy for secondary prevention in ESUS patients overall. This is likely explained by significant heterogeneity in the underlying mechanisms of the ESUS subtype. However, anticoagulation may not work for all ESUS patients but may benefit those with atrial cardiopathy[36] and those with ESUS and moderate to severe LV dysfunction[37].

Our study demonstrates the utility of LA strain as a measure of early atrial cardiopathy in identifying the subset of ESUS patients that can benefit from a more rigorous cardiovascular risk factor modification, intensive cardiac arrhythmia surveillance with prolong atrial fibrillation monitoring, and potentially anticoagulation therapy.

Mechanism of Association

A number of potential mechanisms for ESUS have been identified which include substenotic or aortic arch atherosclerosis, patent foramen ovale, occult paroxysmal AF, LA cardiopathy and LV dysfunction[7, 38].

Notably, atrial cardiopathy involves a complex interplay of electrical and biomechanical changes at cellular and molecular levels causing atrial remodeling and electro-mechanical dysfunction[39-41]. These changes lead to stasis of blood promoting thrombus formation in the LA chamber and at sites of adversely remodeled endocardial borders, thereby predisposing to thrombo-embolic events. To assess atrial dysfunction, different techniques have been utilized, including echocardiography, electrocardiography (EKG), and biomarker analysis. Enlarged left atrial chamber, prolongation of the peak P wave terminal force and PR interval on EKG[42, 43], and elevated biomarkers like cardiac troponin and N-Terminal pro-Brain Natriuretic Peptide have been associated with myocardial injury, atrial remodeling, fibrosis, and dysfunction[44]. These factors have been identified as potential risk factors for thrombus formation and can independently predict future embolic events in patients with non-valvular atrial fibrillation[44, 45]. However, STE can detect atrial dysfunction at an earlier stage, even before the changes identified by these other techniques become apparent. In addition, cardiac magnetic resonance (CMR) imaging has shown comparable amounts of fibrosis in patients with ESUS and those with AF, regardless of prior stroke history in AF group. Interestingly, both these groups were also found to have higher LA fibrosis than those with lacunar strokes [46]. Therefore, LA strain analysis using STE may be a useful tool to further risk stratify ESUS patients for recurrence and future AF detection.

Limitations:

Our study sample was extracted from a single medical center, which may limit the generalizability of our results. Out of 307 ESUS patients, only 155 patients completed cardiac monitoring, and AF was detected in 32 of these patients. This small sample size may limit the significance of our associations. For strain analysis, approximately 22% of the total eligible patients had suboptimal images, which may lead to potential bias in our results. This is due to the nature of our clinical-based research, which utilized clinical echocardiographic images instead of dedicated research echocardiograms. In addition, several different software options are available for STE including TomTec, which may contribute to potential variability in echocardiographic measurements. However, our study reported comparative measurements instead of absolute values, thus attenuating possible variability. Finally, we did not use absolute values for abnormal LA strain because these do not currently exist for the stroke population to predict neurovascular clinical outcomes and is an ongoing area of research.

Conclusion:

In conclusion, our study adds to the existing body of evidence by reaffirming the established associations between atrial cardiopathy, stroke subtypes, and atrial fibrillation (AF) in a geographically distinct population. Our findings highlight the association between lower LA strain and ESUS stroke subtype, as well as the higher prevalence of AF in ESUS patients, which supports the hypothesis that atrial cardiopathy plays an important role in the mechanistic pathway of ESUS. Consequently, we propose that incorporating routine quantification of LA strain may be a valuable tool for clinicians in risk stratification and selecting appropriate secondary prevention strategies for ESUS patients identified at high risk of recurrence.

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Table 1. Baseline Characteristics based on Stroke Subtype

Variable	NCE (n = 349)	ESUS (n = 307)	p-value
Age (mean + SD)	64.6 ± 13.9	65.8 ± 14.8	0.298
Sex (% men)	214 (61.3%)	149 (48.5%)	0.001
Hypertension (%)	234 (67.0%)	211 (68.7%)	0.723
Diabetes (%)	85 (24.4%)	85 (27.7%)	0.376
Hyperlipidemia (%)	152 (43.6%)	146 (47.6%)	0.371
Coronary Artery Disease (%)	52 (14.9%)	43 (14.0%)	0.723
Congestive Heart Failure (%)*	2 (0.6%)	13 (4.2%)	0.003
Renal Disease (%)	18 (5.16%)	21 (6.8%)	0.383
Current Smoker (%)	94 (26.9%)	69 (22.5%)	0.158
Systolic blood pressure	152.2 ± 29.5	144.6 ± 26.5	0.001
NIHSS (median, IQR)	7 (3-15)	10 (4-19)	<0.001
Left Atrial Reservoir Strain (mean + SD)	36.7 ± 17.9	32.0 ± 16.1	<0.001
Left Atrial Contractile Strain (mean + SD)	17.4 ± 10.7	15.5 ± 9.6	0.018
Left Atrial Conduit Strain (mean + SD)	19.3 ± 11.5	16.5 ± 10.7	0.001

NCE: Non Cardioembolic. ESUS: Embolic Stroke of Undetermined Source. NIHSS: National Institute of Health Stroke Scale.

*Fisher's exact test used

Table 2. Multivariate Model Showing Associations between LA Reservoir, Contractile, and Conduit Strain in ESUS compared to NCE

	Overall LA Reservoir Strain	Tertile 1 LA Reservoir Strain	Tertile 2 LA Reservoir Strain	Tertile 3 LA Reservoir Strain
LA Reservoir Strain Range	7.20 – 105.23	7.20 – 25.48	25.55 – 36.64	36.66 – 105.23
Unadjusted **OR (95% CI)**	0.983 (0.974-0.993) p = 0.001	1.860 (1.272-2.721) p = 0.001	1.314 (0.898-1.921) p = 0.159	Reference
Model 1 **OR (95% CI)**	0.986 (0.976-0.996) p = 0.004	1.741 (1.178-2.572) p = 0.005	1.273 (0.868-1.867) p = 0.216	Reference
Model 2 **OR (95% CI)**	0.985 (0.974-0.995) p = 0.005	1.944 (1.266-2.986) p = 0.002	1.240 (0.818-1.881) p = 0.311	Reference
LA Contractile Strain Range	**LA Contractile Strain** 0.58 – 68.90	**LA Contractile Strain** 0.58 – 11.18	**LA Contractile Strain** 11.23 – 18.16	**LA Contractile Strain** 18.18 – 68.90
Unadjusted **OR (95% CI)**	0.982 (0.966-0.997) p = 0.019	1.845 (1.261-2.699) p = 0.002	1.223 (0.836-1.787) p = 0.300	Reference
Model 1 **OR (95% CI)**	0.985 (0.969-1.001) p = 0.061	1.735 (1.180-2.551) p = 0.005	1.200 (0.816-1.766) p = 0.354	Reference
Model 2 **OR (95% CI)**	0.990 (0.973-1.007) p = 0.239	1.568 (1.035-2.374) p = 0.034	1.191 (0.785-1.807) p = 0.410	Reference
LA Conduit Strain Range	**LA Conduit Strain** 0.00 – 79.94	**LA Conduit Strain** 0.00 – 11.76	**LA Conduit Strain** 11.79 – 20.31	**LA Conduit Strain** 20.33 – 79.94

Unadjusted **OR (95% CI)**	0.977 (0.962-0.991) p = 0.001	1.930 (1.319-2.825) p = 0.001	1.266 (0.866-1.852) p = 0.224	Reference
Model 1 **OR (95% CI)**	0.979 (0.964-0.994) p = 0.006	1.873 (1.244-2.820) p = 0.003	1.250 (0.849-1.841) p = 0.259	Reference
Model 2 **OR (95% CI)**	0.971 (0.955-0.988) p = 0.001	2.288 (1.448-3.613) p = 0.001	1.532 (1.007-2.333) p = 0.047	Reference

Model 1: Adjusted for age and sex

Model 2: Adjusted for model 1 plus variables differing between the two groups (SBP, NIHSS, and CHF)

Table 3. LA Strain and AF detection in 307 ESUS patients

	AF detected (n = 39)	**No AF detected** (n = 268)	**p-value**
Left Atrial Reservoir Strain (mean + SD)	25.15 ± 13.57	32.95 ± 16.20	0.005
Left Atrial Contractile Strain (mean + SD)	12.24 ± 10.00	15.95 ± 9.41	0.023
Left Atrial Conduit Strain (mean + SD)	12.91 ± 6.45	17.00 ± 11.09	0.025

AF: Atrial Fibrillation

Table 4. LA Strain in 32 ESUS patients found to have AF on Cardiac Event Monitoring: Comparing AF Burden < 24 hours versus AF Burden > 24 hours

	AF Burden < 24hr (n = 24)	**AF Burden > 24hr** (n = 8)	**p-value**
Left Atrial Reservoir Strain (mean + SD)	26.15 ± 15.25	26.50 ± 12.17	0.953
Left Atrial Contractile Strain (mean + SD)	12.79 ± 11.90	11.56 ± 6.74	0.785
Left Atrial Conduit Strain (mean + SD)	13.36 ± 6.31	14.94 ± 7.12	0.557

AF: Atrial Fibrillation

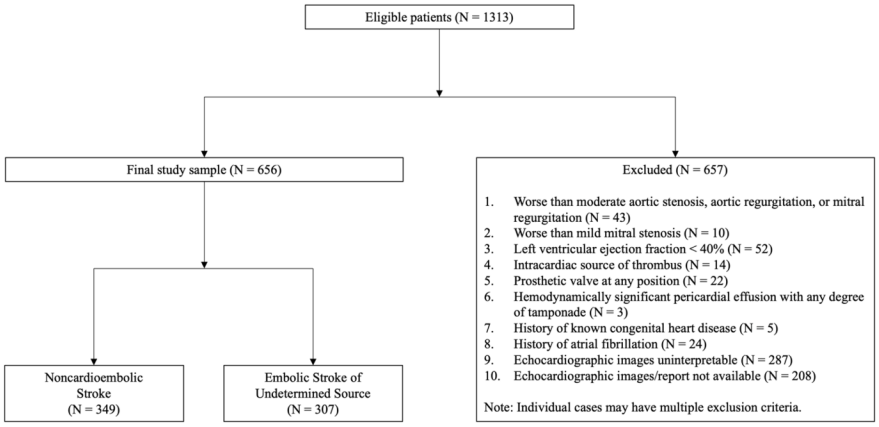
Table 5. Multivariable Analysis Showing Associations between LA Reservoir, Contractile, and Conduit Strain and Atrial Fibrillation Detection in 307 ESUS Patients

	Overall LA Reservoir Strain	**Tertile 1 LA Reservoir Strain**	**Tertile 2 LA Reservoir Strain**	**Tertile 3 LA Reservoir Strain**
LA Reservoir Strain Range	7.20 – 103.78	7.20 – 25.48	25.60 – 36.57	36.97 – 103.78
Unadjusted **OR (95% CI)**	0.957 (0.929-0.987) p = 0.005	2.534 (1.029-6.236) p = 0.043	1.240 (0.451-3.411) p = 0.677	Reference
Model 1 **OR (95% CI)**	0.966 (0.938-0.995) p = 0.023	2.092 (0.836-5.237) p = 0.115	1.255 (0.451-3.495) p = 0.663	Reference
LA Contractile Strain	**LA Contractile Strain**	**LA Contractile Strain**	**LA Contractile Strain**	**LA Contractile Strain**

Range	0.58 – 56.44	0.58 – 11.18	11.23 – 18.08	18.27 – 56.44
Unadjusted **OR (95% CI)**	0.949 (0.907-0.993) p = 0.025	2.828 (1.158-6.903) p = 0.022	1.005 (0.349-2.894) p = 0.993	Reference
Model 1 **OR (95% CI)**	0.954 (0.913-0.996) p = 0.033	2.797 (1.133-6.905) p = 0.026	1.245 (0.423-3.662) p = 0.691	Reference
LA Conduit Strain Range	**LA Conduit Strain** 0.00 – 79.94	**LA Conduit Strain** 0.00 – 11.76	**LA Conduit Strain** 11.82 – 19.70	**LA Conduit Strain** 20.54 – 79.94
Unadjusted **OR (95% CI)**	0.952 (0.912-0.994) p = 0.025	2.614 (1.003-6.815) p = 0.049	2.016 (0.731-5.557) p = 0.176	Reference
Model 1 **OR (95% CI)**	0.969 (0.928-1.011) p = 0.148	1.776 (0.657-4.806) p = 0.258	1.786 (0.639-4.995) p = 0.269	Reference

Model 1: Adjusted for age

Figure 1



Flowchart of study population

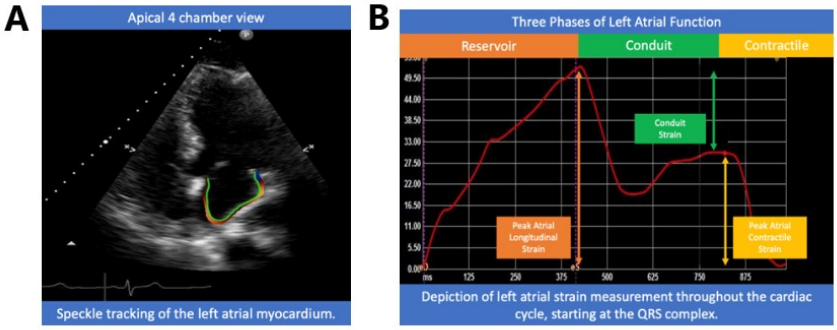
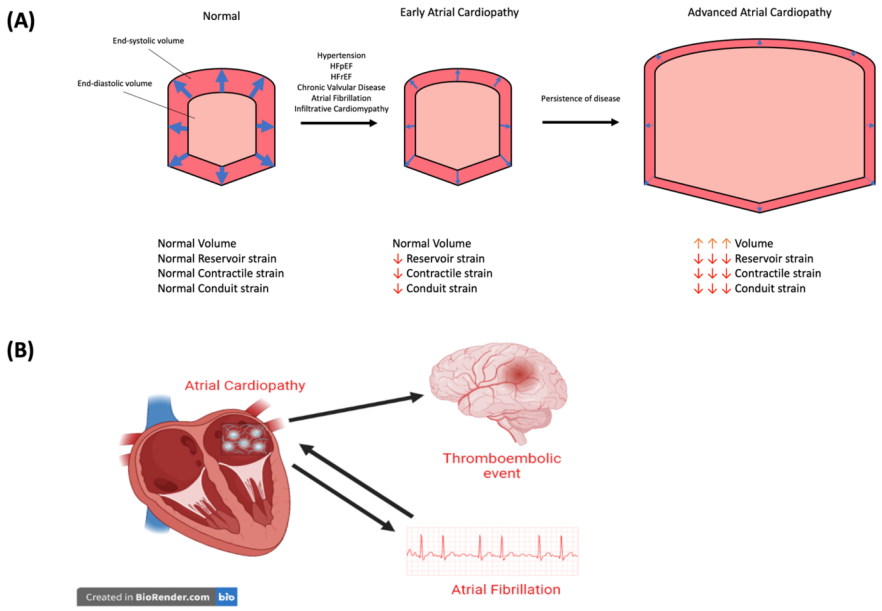


Figure 2

Panel (A): Left atrial tracking. **Panel (B)** Left atrial strain curve

Figure 3: Central Illustration



Panel (A) illustrates the progression of left atrial cardiopathy. Subtle changes in all three phases of left atrial strain in the early stages of atrial cardiopathy precede more drastic changes in left atrial volume and strain in advanced stages of atrial cardiopathy.**Panel (B)** illustrates the pathophysiologic consequences of atrial cardiopathy, including atrial fibrillation and thromboembolism. Note that atrial fibrillation can be both a cause and a result of atrial cardiopathy.