

The Role of Advanced Echocardiographic Parameters of the Left Atrial Function in the Incidence of Cryptogenic Ischemic Stroke: A Review

Mina Naghnaeian⁽¹⁾, Azam Soleimani⁽²⁾, Reihaneh Zavar⁽¹⁾, Masoumeh Sadeghi⁽³⁾

Review Article

Abstract

Stroke is one of the primary causes of morbidity and mortality worldwide, including a large proportion of cryptogenic strokes. Long-term electrocardiographic monitoring is beneficial in prospective studies for detecting atrial fibrillation in patients with cryptogenic stroke. This review aimed to evaluate the advanced echocardiographic parameters and their roles in assessing left atrial (LA) function in the incidence of cryptogenic and ischemic strokes. Main resources, including PubMed, Scopus, and ISI Web of Science databases, were evaluated for articles published in English from 2010 until May 2021. LA echocardiographic parameters such as LA strain and strain rate, isovolumetric relaxation time (IVRT), the mean left atrial volume index (LAVI), LA reservoir volume, systole strain rate (SSR) of left atrial appendage, and lack of LA function response to maximal exercise as measured by the LA ejection fraction during rest and exercise could be considered for assessing the risk of cryptogenic strokes and ischemic strokes. The results indicated that increased LA volumes and reduced LA strain rate were correlated with cryptogenic stroke. Advanced parameters of LA function, measured by speckle tracking echocardiography, such as strain and strain rate values in different parts of the cardiac cycle, in addition to standard measures of LA function such as LA ejection fraction and LAVI, will define an excellent understanding regarding LA myopathy and risk assessment of cryptogenic stroke, independent of considering conventional cardiovascular risk factors.

Keywords: Cryptogenic strokes, Ischemic strokes, Left atrium, Echocardiographic, Review

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Introduction

Atrial fibrillation (AF) is the most prevalent sustained heart rhythm abnormality worldwide¹. This disease's prevalence is rising and will be accompanied by an increase in mortality rate¹⁻³. In some high-income countries, the incidence of AF-related stroke has nearly tripled in the last three decades and is projected to triple again by 2050⁴. Studies report that AF-related strokes result in more disability and mortality than other types of strokes,

including cardiac embolic strokes caused by other sources^{5, 6}. Moreover, recent epidemiologic surveys confirmed that the global burden of AF is rising⁷.

While AF is most commonly associated with atrial diseases, the current examination and treatment of individuals with AF do not account for the amount of atrial myopathy that serves as the arrhythmia's substrate⁸. These patients have atrial cardiomyopathy, a risk factor for stroke and AF. AF is predicted by abnormalities of the atrial structure regardless of the presence

1- Echocardiography Department, Chamran Cardiovascular Medical and Research Hospital and Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran

2- Associate Professor, Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran

3- Professor, Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran

Address for correspondence: Azam Soleimani, Echocardiography Department, Chamran Cardiovascular Medical and Research Hospital, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail address: asoleimani@gmail.com

of known risk factors such as high blood pressure, heart failure, diabetes, and others⁸.

Although the source of this arrhythmia, the atria are seldom thoroughly evaluated except for atrial size and volume, which are usually assessed by echocardiography. Determining the exact risk of thromboembolic events leads to the accurate use of anticoagulants in patients at higher risk of thromboembolic events and also reduces the side effects of unnecessary anticoagulation in low-risk patients for stroke⁸. New evidence suggests that left atrial (LA) thromboembolism may occur even without AF. These findings cast doubt on the notion that the dysrhythmia characteristic of AF is both necessary and sufficient for thromboembolism to occur. It has been reported that the anatomic and physiological atrial derangements associated with AF may be a common substrate for thromboembolism⁹.

Thirty percent of the 690,000 ischemic strokes that occur each year in the United States are caused by an unknown or cryptogenic source (CS). CS can be caused by various factors, including occult paroxysmal AF. Antiplatelet medication remains the basis of the treatment in most patients with CS in the absence of AF, even though the scientific evidence for this therapeutic strategy is limited¹⁰⁻¹³. Several studies have evaluated the LA function with the help of different indicators to predict the occurrence of CS¹⁴. Atrial myopathy, especially atrial fibrosis, can initiate a vicious cycle of atrial fibrillation and atrial myopathy aggravation⁸. A larger left atrium volume associated with poorer active function is associated with embolic stroke, supporting the theory that poor left atrial function is associated with stroke¹⁵. LA function and structure are essential for stroke, yet it is frequently inadequately characterized. Due to the lack of review studies in this field, this research aimed to

determine the role of echocardiographic criteria of LA function in the incidence of ischemic and cryptogenic strokes by analyzing data from previous studies.

Materials and Methods

This study utilized several databases (PubMed, Cochrane Library, ISI, Google Scholar, and Scopus) to search for peer-reviewed articles through May 2021. The search was performed using the following keywords and combinations: [{"LA FUNCTION " OR "left atrial" OR "left atrial function" OR "LA mechanics" OR "LA strain" OR "LA speckle Echo") AND " ("stroke" OR "cryptogenic stroke" ischemic stroke"}].

Two researchers independently compiled a list of the titles and abstracts of all articles in databases during the initial search. Then, relevant articles were incorporated into the research process. Duplications and articles with unrelated titles and abstracts were excluded.

The inclusion criteria were:

1. The study population experienced an ischemic or cryptogenic stroke or will experience one in the future.
2. The study's findings utilized the evaluation of LA function by echocardiography.
3. The patient's sinus rhythm was normal during the LA function test.

The fact that the study was conducted on animals was used as a factor for exclusion.

Results

Figure 1 depicts the study selection flowchart for this study. After eliminating duplicates, abstracts, and reviews from the primary search of 246 articles, 85 papers were selected. After eliminating articles with unrelated topics and those with insufficient data, 25 articles were selected in the following step. After thoroughly evaluating the full text of the articles, 12 were selected for data extraction. Table 1 contains extracted characteristics and outcomes from included studies.

Table 1. Characteristics, outcomes, and details of included studies

Authors	Year	Country	Test groups	Control groups/other groups	Type of events	Outcomes related to left atrial (L/A)
Bhat et al. ¹⁶	2020	Australia	Young patients (less than 60 years old)/ low CVD risk	Healthy controls and patients with paroxysmal AF with a CHA2DS2-VA score of 0.	Cryptogenic stroke AF Acute embolism	Left atrial strain in stroke patients was significantly lower compared to the controls (median 33%; interquartile range (IQ) [32/39] vs 31 [27/34]; p = 0.008). LA strain was significantly lower in AF patients compared to stroke patients (median 21% [19/22] vs 31% [27/34]; p < 0.0001). Left atrial volume index remained an independent predictor of atrial fibrillation detected after stroke (OR 1.09 95% CI 1.02-1.16, p = 0.017).
Baturova et al. ¹⁷	2016	USA/ Sweden	Ischemic stroke patients without documented atrial fibrillation (n = 110, 67 ± 10 years)	age- and gender-matched patients with a history of paroxysmal atrial fibrillation before stroke (n = 55, 67 ± 10 years)	Ischemic stroke	Left atrial volume index remained an independent predictor of atrial fibrillation detected after stroke (OR 1.09 95% CI 1.02-1.16, p = 0.017).
Brecht et al. ¹⁸	2016	Germany	Women with early-stage DD (impaired relaxation [DD1]) & women with more advanced stage of DD (pseudonormal filling [DD2])	women with normal diastolic function (DD0)	Left ventricular (LV) diastolic dysfunction (DD)	LA reservoir and conduit function was markedly reduced before symptoms, LA enlargement, and elevations of noninvasively estimated LV filling pressures occurred. Analysis of LA function featured higher discriminative strength in diagnosing early-stage DD compared with the well-established parameter LA volume index.
Caşiorek et al. ¹⁹	2019	Germany	patients with confirmed ischemic stroke who were diagnosed with ESUS (age 54 (47-58) years (n=65))	patients without stroke but with a similar risk profile (age 53 (47-58) years (n=36))	Embolic Stroke of Undetermined Etiology	The isovolumetric relaxation time (IVRT) was longer and the mean left atrial volume index (LAVI) was higher in ESUS patients Parameters of arterial stiffness such as augmentation pressure, augmentation index, and augmentation index adjusted to a heart rate of 75 bpm (AIx75) were higher in ESUS patients compared to controls (p < 0.05). Increased arterial stiffness and indices of diastolic dysfunction is significantly associated with ESUS.
Gazagnes et al. ²⁰	2020	France	Patients aged 18 to 54 years, with their first Cryptogenic stroke		Cryptogenic stroke	Left atrial longitudinal strain in young subjects with cryptogenic stroke was impaired in the presence of overweight and hypertension, but not of patent foramen ovale (PFO) or PFO plus atrial septal aneurysm (ASA)
Kohsaka et al. ²¹	2005	USA	146 patients with first ischemic stroke	195 age-, gender-, and race/ethnicity-matched community control subjects	ischemic stroke	PTFV1 was independently associated with stroke in patients in the upper half of echocardiographically determined left ventricular mass (adjusted OR, 4.5; 95% CI, 2.20 to 9.15) but not in those in the lower half (OR, 0.58; 95% CI, 0.20 to 1.65; P=0.0008). ECG-LAA can supplement 2D echocardiography in assessing the risk of ischemic stroke, especially in subjects with increased left ventricular mass.

Authors	Year	Country	Test groups	Control groups/other groups	Type of events	Outcomes related to left atrial (LA)
Leong et al. ²²	2017	Netherlands	742 patients (mean age, 59 ± 13 years; 54% men; 371 with Cryptogenic stroke	371 control subjects	Cryptogenic stroke	Left atrial strain was significantly lower among patients with Cryptogenic stroke than control subjects (30 ± 7.3% vs 34 ± 6.7%, P < .001) lower LA reservoir strain (OR, 1.07 per 1% reduction; 95% CI, 1.05-1.10; P < .001) was associated with cryptogenic stroke A potential role for LA strain to risk-stratify patients in the prevention of stroke.
Meisel et al. ²³	2019	USA	18 ESUS patients (stroke subjects) age was 58 years old and 44% were female.	normal subjects matched by age, gender, and body surface area	ischemic strokes	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 ESUS subjects have LA dysfunction and remodeling at rest and exercise in comparison to healthy, controls.
Pirinen et al. ²⁴	2020	Finland	30 cryptogenic ischemic stroke patients aged 18 to 49 years	30 age and sex-matched stroke-free controls	Cryptogenic stroke	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) Stroke patients had significantly lower left atrial appendage orifice variation, lower LA cyclic volume change, and lower LA contraction peak strain rate left atrial dynamics has been changed in young patients with cryptogenic ischemic stroke, and thus that LA wall pathology might contribute to these strokes
Tan et al. ²⁵	2016	China	130 patients with paroxysmal AF & 50 patients with persistence AF (PerAF)	60 healthy individuals	AF	The ratio of total systole strain rate (SSR) of left atrial appendages (LAA) to that of left atrial (L/A) was not significant statistically different among the three groups
Tang et al. ²⁶	2015	China	79 cases with paroxysmal AF	32 cases with persistent AF or long-standing persistent AF (LS-AF)].	AF	The mouth diameters of LAA, CHADS2 score, and CHA2DS2-VASc score were statistically different between these two types of AF (p < 0.05). The mouth diameter of LAA, CHADS2 score, and CHA2DS2-VASc were not statistically correlated with paroxysmal AF or persistent AF (p > 0.05).
Obookata et al. ²⁷	2014	Japan	patients with paroxysmal or persistent AF with acute embolism	patients with paroxysmal or persistent AF without acute embolism	AF Acute embolism	LA strain analysis could improve the current risk stratification of embolism in patients with AF. LA strain can also predict post-stroke mortality.

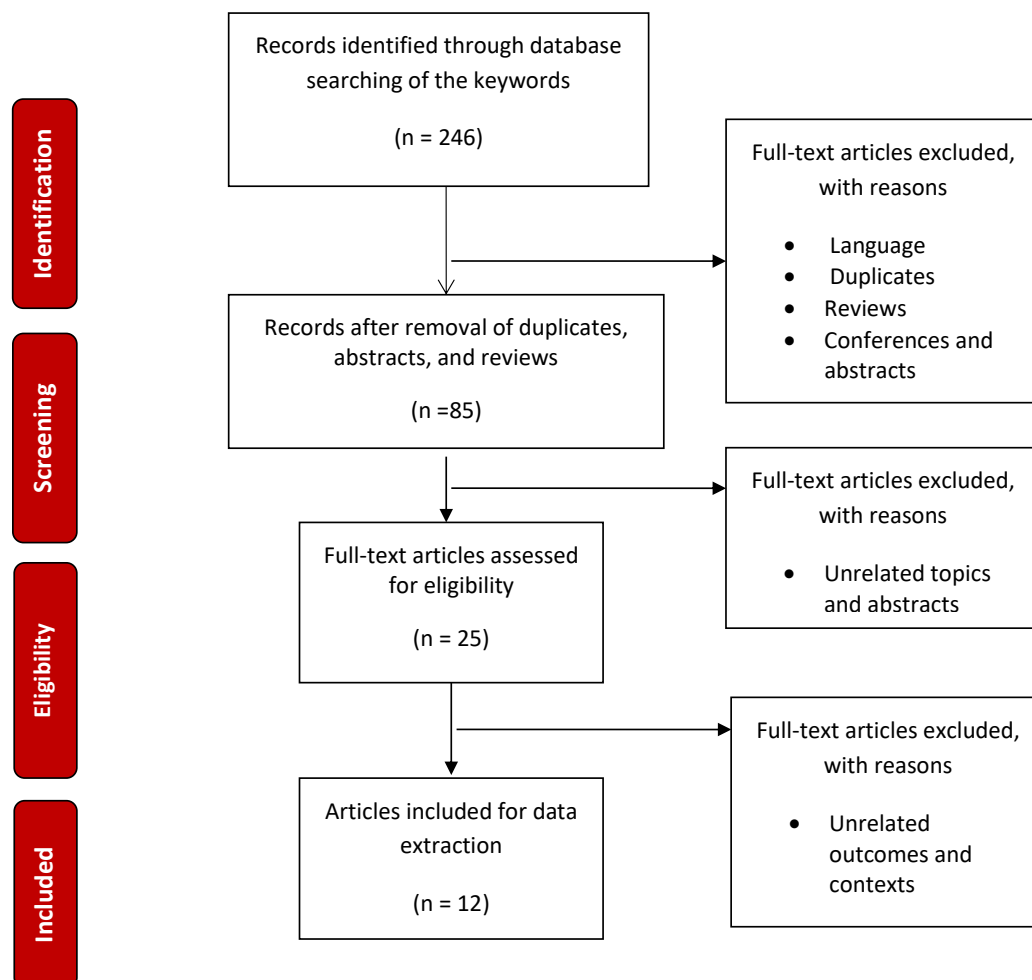


Figure 1. Flowchart of study selection

Discussion

Based on the current review, left atrial echocardiographic parameters, such as left atrial strain¹⁶⁻¹⁸, isovolumetric relaxation time (IVRT), the mean left atrial volume index (LAVI)¹⁹, LA reservoir volumes²⁰, lack of LA function response to maximal exercise as measured by the LA ejection fraction during rest and exercise in patients with embolic stroke of undetermined source (ESUS)²¹, and systole strain rate (SSR) of left atrial appendages²², could be reliable factors for assessing the risk of AF and strokes including CS and ischemic stroke (Table 1).

A study comparing young CS patients and healthy controls revealed that stroke patients

had smaller LA reservoir volumes, significantly less LA appendage orifice variation, and a lower LA contraction peak strain rate. The results indicated that young individuals with CS have abnormal LA dynamics, and LA wall pathology may play a role in cryptogenic stroke²⁰. Another study on young patients with first CS reported that LA longitudinal strain was impaired in patients with high blood pressure and overweight, which may indicate that LA strain can be used as a predictive marker for CS in these groups of patients¹⁷.

Several previous studies have used the measurement of LA strain in stroke patients. Most of the studies comprised elderly patients and focused on the relationship between LA dysfunction and cardiovascular diseases such

as AF or LA thrombus that increase the risk of cerebral emboli⁽²³⁻²⁵⁾. According to Habibi et al., regardless of known cerebrovascular risk factors and AF, lower total LA emptying fractions (LAEF) was associated with incident ischemic cerebrovascular events. Evaluating LA function may provide additional information for stratifying asymptomatic individuals at risk for ischemic stroke²⁴.

In the general population, the effects of hypertension and obesity on LA function are well-known, as they cause or contribute to atrial cardiomyopathy. In previous investigations, these parameters were linked to LA expansion²⁶. Xu et al. showed that LA deformation indexes are lower than normotensives in individuals with hypertension, including systolic strain, strain rate, early diastolic, and LA contractile function²⁷. In addition, it was hypothesized that total LA strain, positive peak strain, and early negative peak strain rate have an inverse correlation with body mass index²⁸. These studies corroborate the link between obesity and impaired reservoir and LA conduit function, as well as hypertension and reduced LA contractile function.

Bhat et al. also documented that in CS patients, LA strain is a predictor of atrial dysfunction, and it may further refine the risk for cardioembolic stroke. They observed a link between indicators of atrial pathology and ischemic stroke development in the absence of AF, implying that tissue substrate, rather than arrhythmia status, is the key driver of stroke risk; however, they found no significant change in LA volume in patients with cryptogenic ischaemic stroke¹⁶.

In the absence of AF, structural changes of the LA detected in the surface electrocardiogram as the P-wave terminal force, as a marker of LA pathology and fibrosis, have been linked to the increased risk of ischemic stroke²⁹. Similarly, even after controlling for the presence of AF, LA size, as measured by echocardiography, has been linked to ischemic stroke³⁰⁻³². In a cross-sectional study, Brecht et al. found that all three components of the left atrial (LA) strain, namely the LA reservoir, LA conduit, and LA contractile function, exhibited

specific alterations at various left ventricular (LV) diastolic dysfunction stages. Significant reduction in LA reservoir and conduit function was observed before symptom onset, LA enlargement, and elevated LV filling pressures (estimated non-invasively)³³.

AF is a known source of cardiac embolism in patients with a primary diagnosis of CS. Therefore, we evaluated three studies that assessed the risk of strokes and embolisms in AF patients^{22, 25, 34}. In a study on paroxysmal or persistent AF with acute embolism (as the test group) or without (as the control group), Obokata et al. observed that LA strain during ventricular systole (LAS) was lower in patients with acute embolism compared to the control group. According to their findings, LA strain analysis provided additional diagnostic information over the CHA2DS2-VASc score, implying that LA strain analysis could improve embolism risk classification in patients with AF. They stated that LA strain could also predict the rate of post-stroke mortality²⁵. Tang et al. evaluated echocardiographic and clinical parameters in 112 patients with AF (79 cases with paroxysmal AF and 32 cases with persistent AF or long-standing persistent AF (LS-AF)). They found that the left atrial appendage (LAA) mouth diameter, CHADS2 score, and CHA2DS2-VASc score were significantly lower in patients with paroxysmal AF than those with persistent AF or LS-AF³⁴. Tan et al. reported that the left atrial appendages (LAA) systolic strain rate (SSR) of AF patients was lower than that of healthy individuals, and the degree was associated with disease progression²².

Conclusion

Subclinical atrial myopathy is hypothesized to cause silent AF and subsequent embolic stroke. Early detection of atrial myopathy by different imaging modalities is a valuable method to risk-stratify patients for stroke incidence. Advanced parameters of LA function, measured by speckle tracking echocardiography, such as strain and strain rate values in different parts of the cardiac

cycle, in addition to standard measures of LA function such as LA ejection fraction and LAVI, will define an excellent understanding of LA myopathy using a readily available, non-invasive, cost-benefit imaging modality. Reduced LA strain and strain rate measurements in stages preceding obvious atrial dilation and dysfunction (measured by LAEF) can identify the subset of patients prone to microthrombus formation and embolic stroke. This strategy will provide high-risk groups with cost-effective preventive measures. Future research will declare the best imaging modalities in this area.

Conflict of interest

No conflicts of interest to disclose.

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