Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.276588.3247 Volume 31, Issue 7 July. 2025
Manuscript ID ZUMJ-2403-3247
DOI:/10.21608**zumj.2024.276588.3247**

ORIGINAL ARTICLE

Left atrial Functions in Patients with Cryptogenic Stroke: Echocardiographic Speckle Tracking Study

Alaa El-Sayed Salama, Salwa Mohammed Elsayed Ghoneim, Marwa Mohamed Gad, Amgad Rabea Soliman Mohammed, Abdelrahman A. Adel
Cardiology Department, Faculty of Medicine, Zagazig University

Correspondence and requests for reprints to: Amgad Rabea Soliman Mohammed
E-mail:
rabea.amgad@gmail.com

Submit Date 13-03-2024
Revise Date 18-03-2024
Accept Date 23-03-2024

ABSTRACT

Background: The evaluation of left atrial (LA) function through myocardial strain analysis using speckle-tracking echocardiography could uncover subtle abnormalities offering unique insights into LA pathophysiology among individuals with cryptogenic stroke (CS) who have no history of atrial fibrillation. So, the aim of this study was to discover the predictors of stroke in patients who presented with structurally normal heart with sinus rhythm (SR) and uncover the role of left atrial (LA) imaging and to Identify patients who will benefit from antithrombotic therapy. **Patients and Methods:** This case control study including 155 patients, from them 83 was control (Group I) and 72 was diagnosed with cryptogenic stroke Patients were collected from Neurology Critical Care Unit and Neurology department. The median age of included patients was 63 years. The majority of included patients were females. The studied patients presented with a clinical diagnosis of acute ischemic stroke and probable start of symptoms during the 24 to 48 hours before. **Results:** there were a statistically significant decrease in LA reservoir strain and contraction strain in group II compared with group I. ($p<0.001$). Contraction strain ≤13.95% predicted cryptogenic stroke with sensitivity 79.17% and specificity 87.95%. LA volume index more than 36 ml/m^2 predicted cryptogenic stroke with sensitivity 69.44% and specificity 100.00%. Reservoir strain ≤23.49 %predicted cryptogenic stroke with sensitivity 83.33% and specificity 89.16%. **Conclusion:** The discovery of impaired LA functions using LA strain analysis may provide insight into the mechanisms underlying cryptogenic stroke. **Keywords:** Stroke**,** Left atrial, Echocardiographic

INTRODUCTION

Stroke is a serious health issue that ranks among the top causes of death and disability. If the cause is known, it is also avoidable **[1].** The diagnosis of an ischemic stroke might be difficult. A third of ischemic strokes still have unclear causes after thorough diagnostic testing **[2].** The measurement of left atrial strain (LAS), recent developments in two-dimensional echocardiography (2DE) have made it possible to assess atrial deformation, which has been demonstrated to be predictive of cardiovascular events and atrial fibrillation (AF) in stable outpatients. This comprises strain based on speckles **[3].**

The left atrium is crucial to the pathophysiology of embolic stroke; aberrant contractility or undiagnosed atrial arrhythmias can cause LA thrombi, which in turn can cause embolic stroke **[4].** Left atrial (LA) strain (LAS) analysis is a non-Doppler echocardiographic method based on LA myocardial deformation that reflects LA contractility, and assesses LA function, stiffness and fibrous remodeling **[5,6].** This technique allows analyzing precisely the 3 different phases (reservoir, conduit and contraction) of LA function. The main advantages of LAS compared to Doppler are its angle-independence, the lower reverberations effects, its feasibility and its reproducibility **[5]**. Bi-dimensional speckle tracking echocardiographic (2DSTE) parameters of LA dysfunction have been associated with AF occurrence in several clinical settings, as ischemic stroke or heart failure **[7, 8].**

AIM OF WORK

The aim of this work was to discover the predictors of stroke in patients who presented with structurally normal heart with sinus rhythm (SR) and uncover the role of left atrial (LA) imaging and to Identify patients who will benefit from antithrombotic therapy.

PATIENTS AND METHODS

This case control study was conducted in Cardiology department, Faculty of Medicine, Zagazig University hospital during the period between august 2023 and February 2024. We recruited 72 patients diagnosed as cryptogenic stroke Patients were collected from Neurology Critical Care Unit and Neurology Stroke Unit and 83 was control group recruited during preoperative evaluation for non-cardiac surgery. Written informed consent and the study was authorized by the Zagazig University Faculty of Medicine's Research Ethical Committee (ZU-IRB:10829-31-5-2023). The study was carried out according to the Ethical code of the World Medical Association (Declaration of Helsinki) for Studies including humans.

Inclusion criteria: Patients that were admitted to the hospital with a diagnosis of cryptogenic stroke attack confirmed using computer tomography or magnetic resonance imaging.

Exclusion criteria: Patients with cardiac muscle disease and LV ejection fraction <40%. Patients Known AF. Patients with subpar picture quality when analyzing LA strain. Individuals with Congenital Heart illness, a recognized organic cardiac illness, Rheumatic heart disease and ischemic heart disease. Patients with prothrombotic syndromes, antiphospholipid syndrome and vasculitis. Patients with known stroke etiology.

Every patient underwent a thorough history taking, general and local examination, with a focus on measuring blood pressure in those whose systolic and/or diastolic blood pressure were found to be higher than 140 mmHg on two separate occasions **[7]**

Wight and height for calculating body mass index (BMI) and body surface area (BSA).

The study population was categorized based on BMI, which was computed as body weight in kilograms (kg) divided by the square of body height in meters (m) **[9].**

Based on the patient's medical history, neurological examination, and computer tomography or magnetic resonance imaging, a neurologist verified the diagnosis of ischemic stroke. The neurologist used the TOAST classification to diagnose the cause. The etiology of stroke was classified into five categories: unknown (cryptogenic stroke), big artery atherosclerosis, small vessel occlusion, and cardioembolic. Patients with cryptogenic stroke were included in the study, other stroke subtypes were excluded **[7]**

Routine Laboratory investigations with special attention to Complete blood count (CBC). Liver function tests (ALT, AST, S.Albumin, Total Bilirubin). Kidney function tests (S.Creatine, S.Urea). Random plasma glucose level on admission followed by fasting and 2 hours post-prandial plasma glucose assessment in diabetic patients. Total cholesterol (TC), triglycerides (TGS), high density lipoprotein (HDL), low density lipoprotein (LDL). Total cholesterol level > 200 mg/dL. Low density lipoprotein (LDL) “Bad cholesterol” ≥ 100 mg/dL. High density lipoprotein (HDL) “Good cholesterol” <40 mg/dL. Triglyceride’s level > 150 mg/dL **[10].**

Coagulation profile: Prothrombin time (PT), prothrombin concentration (PC), international normalized ratio (INR). Protein S, Protein C, anticardiolipin igG & igM, Lupus anticoagulant. Factor V leiden mutation, homocysteine for prothrombotic diseases and, in case of suspicion, to rule out vasculitis and antiphospholipid syndrome [11].

Electrocardiography (12 leads ECG) to assess patient rhythm, presence of Q waves and evidence of chamber enlargement. Either ambulatory Holter monitoring or inpatient telemetry (for hospitalized patients only) within 72 hours following the incident. Echocardiographic assessment was done to all patients using vivid E95, GE healthcare ultrasound Horten, Norway with MSc-D probe. This was done by two independent expert cardiologists blinded to patient data. **[7]**

Assessment of left atrial volume index (LAVI); the transthoracic apical four- and two-chamber images are used to quantify the left atrial volume in two dimensions. The left atrial endocardial margins are delineated in each of these views at the conclusion of ventricular systole, right before the mitral valve opens, at the left atrium's maximum size. It is thus possible to compute a modified Simpson's (method of disks) biplane volume [12].

An alternative method is to measure the lengths (cm) and area (cm2) of the left atrium in each view, and make use of the main axis's reduced length in the two- or four-chamber view to determine the volume, which is equal to (0.85 × Area4c × Area2c)/length. It is recommended to use either the area-length approach or the biplane Simpson's technique to index left atrial volume to body surface area in order to account for gender differences. Less than 34 mL/m2 is the top limit of normal for both men and women. If volumetric evaluation from the apical views is not feasible, the left atrium can be quantified using the 2D linear anterior-posterior length from the parasternal long-axis image. This is the distance measured from the posterior wall of the left atrium to the posterior edge of the aortic root at the end of the cardiac cycle's ventricular systole [12].

Assessment of left atrial appendage:

LA appendage assessed by aortic valve in parasternal short-axis picture and in apical 2-chamber views. Pulsed Doppler echocardiography was used to evaluate the flow velocity at the left atrial appendage orifice using a sampling volume positioned there [13].

Left atrial (LA) strain analysis:

Using an automated speckle tracking program with a LAS-specific mode, LAS analysis was produced. Reservoir strain in systole (LASr) and contraction strain in late diastole (LAScd) are the two stages of strain values that make up the LAS. While LACcd is a negative value, LASr is a positive value. An automated method was used to extract the LAS values for each phase from an optimal apical four-chamber image. When necessary, the manual adjustment of the LA endocardial border was made in addition to the automatically created regions of interests (ROI). The original zero-baseline strain ECG reference point was the QRS complex. An expert cardiologist who was blind to clinical data conducted all of the LAS measures (Figure 1) **[7]**

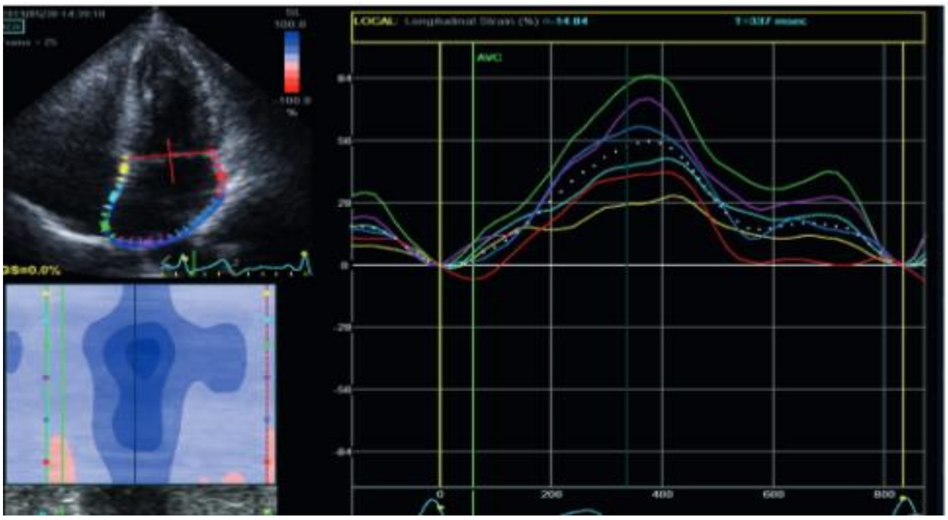

Figure 1: LA strain analysis by Speckle tracking echocardiography in patient diagnosed with cryptogenic stroke

LA cycle:

Based on the longitudinal strain curve of the LA, the software automatically determined the LAS values. When the QRS complex is utilized as the zero-reference point, the first peak positive deflection represents the value of the LA reservoir function. The value of the LA contraction function was ascertained at the beginning of the P wave contraction. The American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) recommendations were followed for the defining of LA phases and LAS assessment **[12]**

Radiological investigations:

Initial plain CT scan of the brain; all patients was subjected to plain CT scan of the brain to confirm the diagnosis of acute ischemic stroke and exclude intracranial hemorrhage. If CT came free, it was repeated after 48 hours **(Figure 2).**

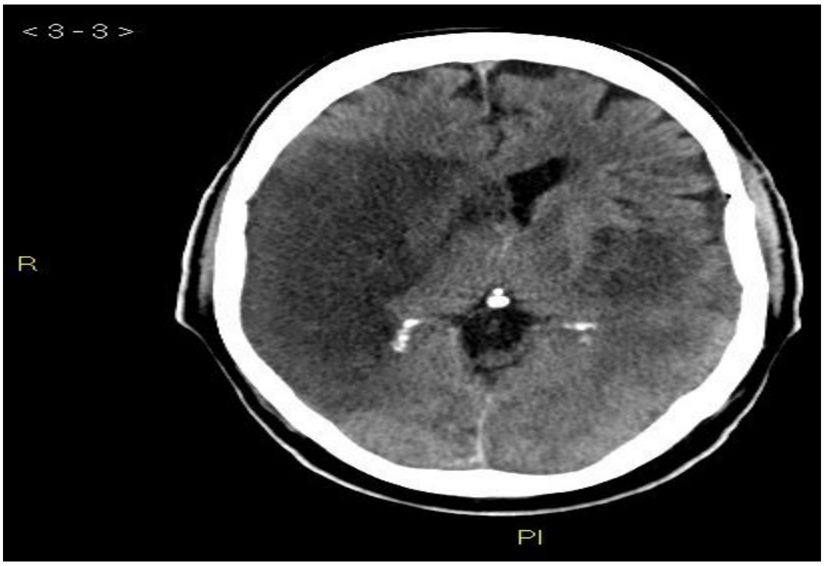

Figure 2: CT brain showing ischemic stroke

When a follow-up CT scan shows no brain lesion and there is a possibility of brain stem lesions, magnetic resonance imaging (MRI) of the brain is performed **[7]**

STATISTICAL ANALYSIS

The data was analyzed using SPSS (Statistical Program for Social Science) version 24. Quantitative data was expressed using the mean ±SD. The qualitative data were expressed using percentages and frequencies. The central value, or mean, of a discrete set of integers is calculated by dividing the sum of the values by the total number of values in the set. Multivariate logistic regression analysis was used to look at the parameters that were indicative of a cryptogenic stroke. A P-value of less than 0.05 was deemed significant.

RESULTS

Regarding parameters of echocardiography; **table 1**; showed that there was a statistically significant increase in LA diameter and LA volume index in group II compared with group I. There was a statistically significant decrease in left atrial appendage (LAA) velocity in group II compared with group I.

Table (1): Parameters of echocardiography in both groups

	Total	**Group I**	**Group II**	**Mann-Whitney U**	**P value**
	Median [IQR]	Median [IQR]	Median [IQR]		
LA diameter (mL)	40 [36, 43]	39 [35, 42]	41.0 [38, 45]	2064.5	**0.001**
LA volume index (mL/m^2)	35 [32, 38]	35[26, 35]	38 [36, 41]	839.5	**0.00**
LAA velocity (cm/s)	31 [27, 38]	36[29, 41]	28.5 [26, 32]	1562	**0.00**

LA: left atriam

LAA: left atrial appendage

Table 2; showed that there was a statistically significant decrease in LA reservoir strain and contraction strain in group II compared with group I.

Table (2): Left atrial reservoir and contraction in both groups

	Total	**Group I**	**Group II**	**Mann-Whitney U**	**P value**
	Median [IQR]	**Median [IQR]**	**Median [IQR]**		
Reservoir strain (%)	24.05 [18.60, 30.04]	29.6 [25.39, 31.78]	18.11[15.58, 22.75]	456.5	**0.00**
Contraction strain (%)	15.243 [11.75,18.936]	17.49 [15.48, 20.0]	11.71[9.80, 13.61]	831	**0.00**

Table 3; showed that the decrease one degree in LA reservoir and contraction increase the incidence of cryptogenic stroke by 0.80 and 0.66, respectively. The increase one degree in LA volume index increases the incidence of cryptogenic stroke by 1.3.

Table (3): Prediction of cryptogenic stroke

	Odds ratio	95% confidence interval		P value
		Lower	Upper	
LA diameter	0.94	0.76	1.15	0.52
Reservoir	0.80	0.68	0.94	**0.01**
Contraction	0.66	0.51	0.86	**0.00**
BSA	0.02	0.00	3.92	0.15
Platelets	1.00	0.99	1.01	0.67
S.cholesterol	0.98	0.95	1.02	0.41
TG	1.01	0.97	1.05	0.56
LA volume index	1.31	1.07	1.60	**0.01**
LAA velocity	0.92	0.83	1.02	0.11
Dyslipidemia(1)	4.67	0.25	86.30	0.30
BMI	0.98	0.75	1.27	0.87
Sex (1)	0.42	0.08	2.10	0.29
HTN (1)	0.14	0.03	0.76	**0.02**
DM (1)	1.00	0.22	4.55	1.00
Smoking (1)	0.71	0.12	4.16	0.70

Multiple logistic regression

LA: left atriam

BSA: Body Surface Area **TG:** triglycerides

LAA: left atrial appendage

BMI: Body Mass Index **HTN:** Hypertension **DM:** Diabetes Mellitus

Contraction strain ≤13.95 predicted cryptogenic stroke with sensitivity 79.17% and specificity 87.95%. LA volume index more than 36 predicted cryptogenic stroke with sensitivity 69.44% and specificity 100.00%. Reservoir ≤ 23.49 predicted cryptogenic stroke with sensitivity 83.33% and specificity 89.16%. table 4

Table (4): Accuracy of left atrial strain in prediction of cryptogenic stroke

	AUC	95%	Cut-off	Sensitivity	Specificity	Youden index J	P value
Contraction Strain	0.861	0.796 to 0.911	≤13.95	79.17%	87.95%	0.6712	<0.0001
LA volume index	0.860	0.795 to 0.910	>36	69.44%	100.00%	0.6944	<0.0001
Reservoir strain	0.924	0.870 to 0.960	≤23.49	83.33%	89.16%	0.7249	<0.0001

Kappa test

LA: left atriam

AUC: Area Under the Curve

DISCUSSION

The primary discovery of this research is the notable negative correlation identified between left atrial (LA) function, evaluated through speckle-tracking reservoir strain, contraction strain and the incidence of cryptogenic stroke (CS) in individuals without documented atrial fibrillation (AF). This association demonstrates additional value beyond conventional clinical and echocardiographic cardiovascular risk factors.

In our study we found that there was a statistically significant decrease in LA reservoir strain and contraction in group II compared with group I **(pvalue < 0.001).**

CS and ESUS were predicted by LA reservoir strain apart from CHA2DS2-VASc score. In an earlier case-control research that was retrospective **[14].** Noted that LA dysfunction, as measured by LA reservoir strain, was linked to CS irrespective of other cardiovascular risk factors; however, because the study was retrospective in nature, normal procedures for detecting AF were not possible, and definitive conclusions about individuals requiring ESUS could not be drawn. According to a recent study, in patients with sinus rhythm, LA reservoir strain is a reliable indicator of LA appendage thrombus **[15].**

The decrease one degree in LA reservoir strain and contraction increases the incidence of cryptogenic stroke by 0.80 and 0.66, respectively. The increase one degree in LA volume index increases the incidence of cryptogenic stroke by 1.3.

Contraction strain ≤13.95% predicted cryptogenic stroke with sensitivity 79.17% and specificity 87.95%. LA volume index more than 36 predicted cryptogenic stroke with sensitivity 69.44% and specificity 100.00%. Reservoir ≤23.49 predicted cryptogenic stroke with sensitivity 83.33% and specificity 89.16%.

Using multivariate logistic regression analysis, we found that the following factors were predictive for cryptogenic stroke:

LA reservoir strain (odds ratio 0.80 p< 0.001 95% CL = 0.68—0.94)

LA contraction strain (odds ratio 0.66 p< 0.001 95% CL = 0.51—0.86)

LAVI (odds ratio 1.31 p< 0.01 95% CL = 1.07—1.60)

HTN (odds ratio 0.14 P <0.02 95% CL =0.03--0.76)

Therefore, impaired LA function and increased LAVI are more likely a risk factors of ischemic stroke.

A considerable subset of cryptogenic stroke patients represents a pertinent cohort for examining the relevance of left atrial (LA) dysfunction in guiding clinical decisions regarding the use of anticoagulant therapy **[16].**

The evidence from earlier research is based on observational studies that were conducted retrospectively, without the use of targeted echocardiographic image acquisition, and with poorly characterized AF episodes of unknown length. Furthermore, because the primary objective of CS was still to anticipate AF, prior data are insufficient to suggest a paradigm shift in patient care **[17].**

In our study we provided a tool using LA imaging for risk stratification and stroke prevention.

Our results suggest that echocardiographic LA measures could be used to guide the management of patients with ESUS since they show a substantial correlation between CS and LA remodelling, independent of the development of AF, and they offer novel ideas for secondary prevention from ESUS.

Transthoracic echocardiography provides quantitative imaging of LA that is easily accessible, precise, and repeatable thanks to modern, reliable instruments. By assisting in the identification of the target group for anticoagulation, Quantitative

LA imaging may improve recurrent CS prevention when added to clinical findings **[18].**

While large randomized clinical trials have demonstrated the efficacy of anticoagulants in patients with AF, the idea of focusing on a targeted patient population where imaging can make a difference is further supported by the lack of benefit of new anticoagulants over aspirin to prevent recurrent embolic stroke after an initial ESUS in unselected patient populations **[19].**

Our research demonstrates that, in the course of LA remodeling, cryptogenic stroke can transpire even prior to overt AF episodes, and that, regardless of detectable AF, LA remodelling is linked to CS. The management of patients with cryptogenic stroke may benefit from the use of LA imaging biomarkers in conjunction with other thromboembolic risk factors, provided that they are validated in further series **[19].**

Pathogenesis of CS

The exact cause of CS remains elusive by definition. Nevertheless, numerous conventional risk factors for cardiovascular issues are prevalent among affected individuals, such as hypertension, high cholesterol levels, and smoking. Additionally, there's growing interest in the potential contribution of undetected paroxysmal AF to CS. **[20].**

Evidence from studies like the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial strongly suggests a link between subclinical atrial tachyarrhythmia and ischemic stroke development. Studies observing individuals with noncardioembolic strokes or TIAs, particularly those using extended telemetry or telephonic electrocardiography, have reported incidences of paroxysmal AF ranging from 10% to 23%. However, these methods for detecting infrequent AF have limited sensitivity. **[21].**

Possible Mechanisms of Reduced LA Deformation in CS

The strain of the LA reservoir serves as an indicator of LA compliance, offering insights into the structural and functional condition of the LA myocardium. **[22].**

Previous studies have delved into the factors contributing to diminished LA strain, linking it to atrial fibrillation (AF). However, whether AF directly causes this mechanical impairment or if other factors are involved remains uncertain. Motoki et al **[23].** revealed a connection between decreased LA deformation and increased risk of AF recurrence post-catheter ablation, while Obokata et al. **[24].** observed higher odds of thromboembolism among AF patients with reduced LA deformation. These findings imply that reduced LA function in AF patients may play a significant role in stroke risk.

Our research expands on these findings by establishing a link between decreased LA function and cerebrovascular events (CS) in patients without confirmed AF.

Factors like age, hypertension, and diabetes mellitus have also been associated with compromised LA deformation, possibly leading to an LA substrate that predisposes individuals to AF. Reduced LA reservoir strain and heightened LA fibrosis are more evident in persistent AF compared to paroxysmal AF. Collectively, these findings suggest an intricate relationship between diminished LA deformation, cardiovascular risk factors, LA fibrosis, and AF. **[24]**

LA dilatation is another characteristic of AF and cardiovascular risk factors. Evidence from Mondillo et al. **[25]** who found a significant association between hypertension, diabetes mellitus, or both, and reduced LA deformation, even among patients with normal LA volume.

Clinical Implications of Reduced LA Deformation in CS

This study suggests that diminished LA reservoir strain and contraction strain could potentially serve as a screening tool for detecting patients with CS who would benefit greatly from extensive cardiac rhythm monitoring to uncover asymptomatic AF. Currently, detecting AF in CS patients involves a challenging balance between enhancing detection through intensive or invasive monitoring methods and considering patient discomfort and inconvenience, which remains unresolved.

CONCLUSION

The discovery of impaired LA functions using LA strain analysis may provide insight into the mechanisms underlying cryptogenic stroke. For the purpose of primary or secondary prevention of CS, transthoracic echocardiography, and specifically the estimation of LA reservoir strain and LA contraction strain, may be useful in risk stratification.

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Citation

Salama, A., Ghoniem, S., Gad, M., Soliman Mohammed, A., Adel, A. Left atrial Functions In Patients with Cryptogenic Stroke: Echocardiographic Speckle Tracking Study. Zagazig University Medical Journal, 2024; (3986-3995): -. doi: 10.21608/zumj.2024.276588.3247