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Original Article

Does left atrial appendage morphology and dimension differ amongst etiological stroke subtypes in patients without known atrial fibrillation? Results from the left atrial appendage morphology and dimension assessment by TEE in patients with stroke without known atrial fibrillation (LAMDA-STROKE) study

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A B S T R A C T

Context: Complex left atrial appendage (LAA) morphology is increasingly associated with cryptogenic ischemic stroke as compared to cardioembolic stroke due to atrial fibrillation (AF). However, data on such an association in patients with other etiological stroke subtypes in the absence of AF is limited.
Aim: The study aimed to assess the LAA morphology, dimension and other echocardiographic parameters by transesophageal echocardiography (TEE) in patients with embolic stroke of undetermined source (ESUS) and compare it with other etiological stroke subtypes without known AF.
Methods: This was a single-Centre, observational study involving comparison of echocardiographic parameters including LAA morphology and dimension in ESUS patients (group A; n = 30) with other etiological stroke subtypes i.e., TOAST (Trial of Org 10172 in Acute Stroke Treatment) class I-IV without AF (group B; n = 30).
Results: Complex LAA morphology was predominant in group A (18 patients in group A versus 5 patients in group B, p-Value = 0.001). Mean LAA orifice diameter (15.3 + 3.5 mm in group A versus 17 + 2.0 mm in group B, p-Value = 0.027) and LAA depth were significantly lower in group A (28.4 + 6.6 mm in group A versus 31.7 + 4.3 mm in group B, p-Value = 0.026). Out of these three parameters only complex LAA morphology was found to be independently associated with ESUS [OR = 6.003, 95% CI {1.225–29.417}, p = 0.027].
Conclusion: Complex LAA morphology is a predominant feature in ischemic stroke patients with ESUS and may contribute to an increased risk of stroke in these patients.

1. Introduction

Ischemic stroke is a major health burden throughout the world accounting for 83–86% of strokes.[1,2] The disability resulting from stroke warrants thorough evaluation for the possible etiology of the stroke to streamline the management and more importantly prevent the recurrence.[1–3] Despite the advancement in various

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imaging modalities including brain imaging and cardiac evaluation, 15–40% of ischemic strokes are labeled as cryptogenic as the etiology in such cases cannot be attributable to the definite cardio-embolism, large artery atherosclerosis or small vessel disease after extensive work up.[4] In an attempt to precisely define cryptogenic stroke, a particular subset of patients with ischemic stroke having non-lacunar infarct in brain imaging, in the absence of intracranial or extracranial atherosclerotic arterial disease causing significant (>50%) lumen narrowing in the arteries supplying the area of ischemia and in which no major cardioembolic source or other specific cause of stroke identified has been termed as "embolic stroke of undetermined source (ESUS)".[5] ESUS is considered a subtype of cryptogenic stroke in which the presumed mechanism of stroke is embolic.[6] ESUS is a more accurately defined entity as compared to cryptogenic stroke due to the presence of clearly defined criteria.[4–6] Although, both terms are being used interchangeably to denote a stroke population subset in which the cause of stroke remained undetermined despite extensive evaluation, however, cryptogenic stroke also includes patients with multiple stroke etiologies or incomplete diagnostic workups.

ESUS with a stroke recurrence rate of 4–5% per year, has been an area of extensive research with an ultimate aim to find the cause or a risk factor which leads to increased stroke risk in these patients. Most of the studies have been engaged in finding occult atrial fibrillation (AF) in these patients.[7] The results of the studies detecting AF using various modalities suggest that in more than two-thirds of the cases, AF could not be detected.[8] Thus, paving the way for searching for the cause of stroke "other than AF". LAA is considered a harbinger of the source of thrombo-embolism in such cases and has been studied through various imaging modalities including computed tomography (CT) and transesophageal echocardiography (TEE).[8,9] However, in most of the studies,the patient population consisted of associated AF or the comparison has been done with the patient having AF in association with stroke.[10] Therefore, the data on the comparison of patients with cryptogenic stroke (or ESUS) with other stroke subtypes in the absence of AF for the role of LAA morphology is still limited. Thus, the *Left Atrial Appendage **m**orphology* and ***d**imension **a**ssessment* by TEE in patients with ischemic *stroke* without known Atrial Fibrillation (LAMDA-Stroke study) was done to identify the possible contributing factor for ischemic stroke in patients with ESUS by imaging LAA using TEE and comparing it with other etiological stroke subsets i.e., TOAST (Trial of Org 10172 in Acute Stroke Treatment) class I-IV without AF.

2. Methods

2.1. Study design and settings

This prospective analytical study was carried out from May 2019 to April 2020 in a tertiary care teaching hospital in north India after approval from the Institutional Ethics committee.

2.2. Participants

Subjects were recruited after fulfilling the inclusion and exclusion criteria (Fig. 1). A total of 60 patients consisting of 30 patients in each group A and group B were included in the study after obtaining written informed consent. Patients referred to the cardiology unit for cardiac workup of recurrent stroke were evaluated for the presence or history of AF. This has been done by excluding the past history of AF using clinical documents and previous electrocardiogram (ECG), and ECG at the time of initial evaluation, and using inpatient telemetry/24-h Holter monitoring records. Patients with known or detected AF at the time of initial evaluation were excluded from the study. The remaining patients were divided into two groups based on the etiology of stroke. Group A (ESUS group) consisted of patients fulfilling the criteria of ESUS namely i) non-lacunar stroke in brain imaging ii) Absence of significant (>50%) luminal atherosclerotic narrowing of arteries supplying the area of ischemia iii) Absence of major cardiac-embolism iv) Absence of other specific cause of stroke identified.[11] Group B (Other stroke subsets (TOAST I-IV) without known AF) consisted of patients with other etiological stroke subtypes and without known AF.

Patients in both groups were observed for their baseline characteristics, available blood investigations, echocardiography report, TEE images and other relevant investigations done within 7 days of the index event (stroke). TEE images were assessed in the Q-lab image analyzer for various echocardiographic parameters including LAA orifice diameter (the distance from the lateral ridge of the left superior pulmonary vein to the left coronary artery), LAA depth (midpoint of the orifice diameter to the farthest point from the center of the main lobe), inflow velocities (pulsed wave Doppler aimed at the proximal third of the LAA cavity) and LAA morphology (simple i.e., Chicken wing versus complex i.e., non-chicken-wing morphologies namely cactus, cauliflower, windsock, and multi-lobed).[12] LAA morphology was classified into simple/chicken-wing (CW) and complex/non-chicken-wing (NCW) by two independent observers. Any discrepancy in them was evaluated and finalized by a third observer. TEE images were also evaluated for the other potential sources of thromboembolism including thrombus, spontaneous echogenic contrast, PFO (including agitated saline contrast study), atrial septal defect, mitral valve prolapse and other possible sources.

2.3. Variables

The primary variable was the detection of complex LAA morphology in stroke patients in both groups. The secondary variable was the assessment of other parameters of LAA including its diameter, depth, filling velocity and emptying velocity.

2.4. Data sources

Data was collected and recorded in a patient information document proforma designed at the time of initiation of the study. In-hospital data records including laboratory investigations, neuroimaging and TEE images were analyzed for the evaluation of the patient and classification of these patients into stroke subtypes. Further analysis of TEE images and analysis was done in a Q-lab image analyzer to obtain the results.

2.5. Statistical methods

The characteristics of the patients at baseline and the observations including TEE parameters were summarized as mean with standard deviation (SD) and as percentages for different variables and their comparison was done using chi-square tests or fisher's test (for categorical variables) and student t-tests (for continuous variables). Multivariate logistic regression analysis was used for assessing the independent predictors of outcomes while Cohen's Kappa was utilized for inter-rater reliability of two independent observers for analyzing LAA morphology. A two-sided p-value of <0.05 was considered statistically significant. All analyses were performed using SPSS 25 (IBM Corp, Armonk, NY, USA).

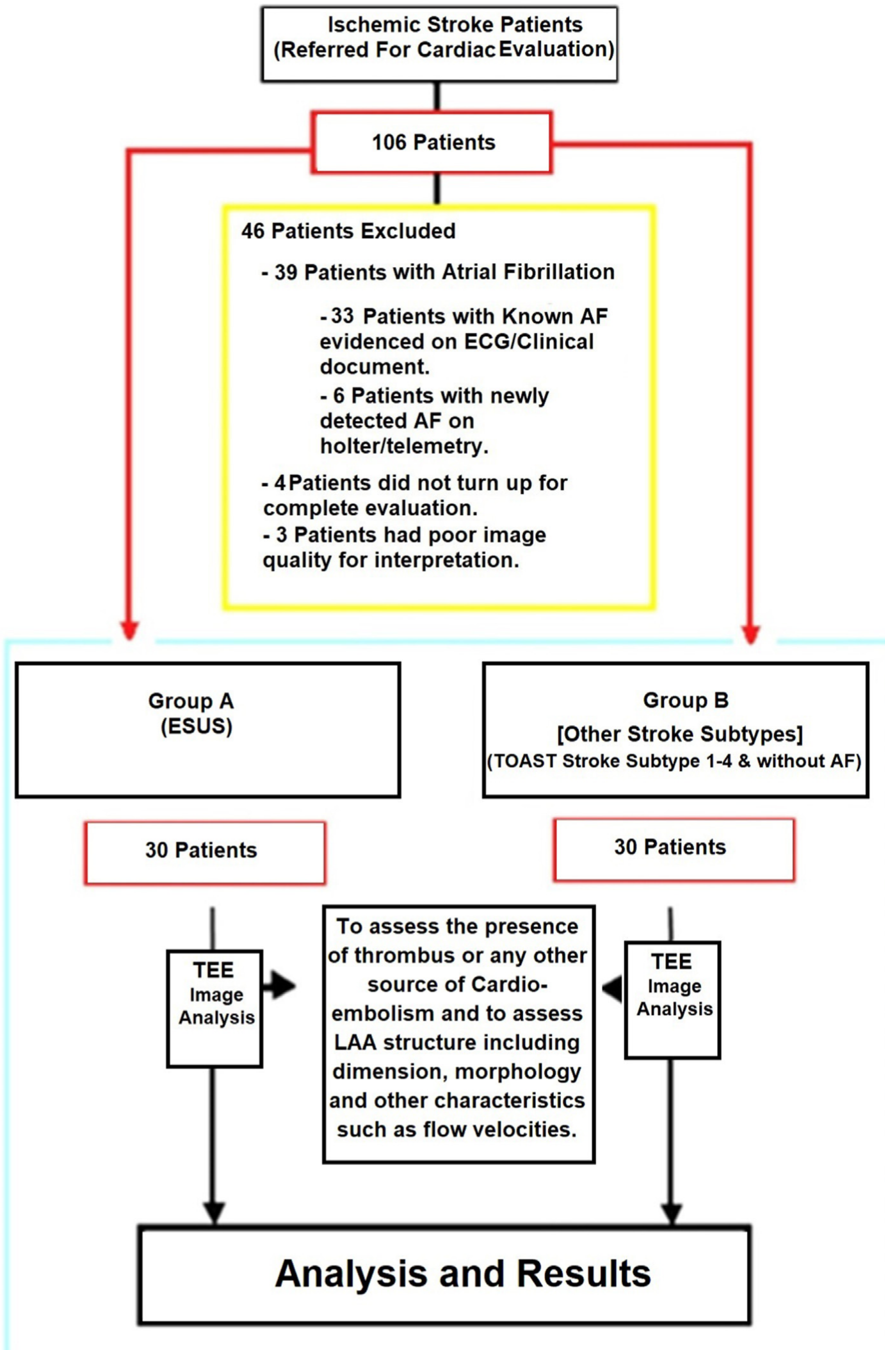

Fig. 1. Study design and flow chart.

3. Results

3.1. Baseline characteristics

In this study, 30 patients with ESUS (Group A) were compared with 30 patients with other stroke subtypes i.e., TOAST Class I - IV and without known AF (Group B) based on baseline characteristics, TEE findings, and other features. In group B consisting of patients without AF and with etiology other than ESUS/Cryptogenic, 14 patients had evidence of large artery atherosclerosis, 12 had high/medium risk source of Cardio-embolism while 4 had lacunar infarct on CT/MRI brain study. Comparing both the groups, baseline characteristics including age, sex, weight, and BMI had non-significant differences (Table 1).

3.2. Findings on TEE

On TEE, three findings had significant ($p < 0.05$) differences between the two groups (Table 2). Complex LAA morphology was found in 18 (60%) patients in group A as compared to only 5 (16.7%) patients in group B. Patients in group A had narrow orifice diameter (mean orifice diameter = 15.3 ± 3.5 mm) and shallow depth (mean depth = 28.4 ± 6.6 mm) of LAA as compared to group B (mean orifice diameter = 17.0 ± 2.0 mm and mean depth = 31.7 ± 4.3).

Table 1
Comparison of the baseline Characteristics of two groups.

Parameters	Group 1 (ESUS, n = 30)	Group 2 (Other stroke etiology[a], n = 30)	p-Value
Age (Years)	48.3 ± 11.4	49.2 ± 10.8	0.752
Weight (Kg)	60.7 ± 4.4	62.10 ± 6.2	0.313
Height(cm)	166.9 ± 6.2	165.9 ± 6.6	0.550
BMI (kg/m^2)	21.8 ± 1.4	22.5 ± 1.8	0.109
Females	7(23.3%)	11(36.7%)	0.260
Hypertension	8	10	0.573
Diabetes	2(6.7%)	5(16.7%)	0.424
Coronary artery disease	0	4(13.4%)	0.112
Smoking	4(13.4%)	6(20%)	0.488

[a] Other stroke etiology: Large artery atherosclerosis (n = 14), Cardio-embolic (n = 12), Lacunar Infarct (n = 4).

Table 2
Comparison of the echocardiographic findings of two groups.

Parameters (TEE/TTE**)	Group 1 (ESUS, n = 30)	Group 2 (Other stroke etiology, n = 30)	p-Value
Complex LAA morphology (non-chicken wing)	18 (60%)	5(16.7%)	0.001[a]
LAA orifice diameter in mm	15.3 ± 3.5	17.0 ± 2.0	0.027[a]
LAA depth in mm	28.4 ± 6.6	31.7 ± 4.3	0.026[a]
LAA filling velocity in cm/sec	44.5 ± 4.2	44.6 ± 5.3	0.915
LAA emptying velocity in cm/sec	48.2 ± 4.5	49.2 ± 5.5	0.480
LA size** in mm	30.0 ± 1.9	29.6 ± 3.3	0.578
LA volume** (mL)	33.1 ± 2.0	33.0 ± 2.8	0.875
LV IDD** (mm)	44.9 ± 2.8	44.8 ± 3.2	0.836
LAA thrombus (n)	0	2	0.492
Chiari malformation(n)	1	0	1.000
SEC(n)	2	4	0.671

LAA: Left atrial appendage, LA: Left atrium, LVIDD; Left ventricle internal diameter, SEC: Spontaneous Echogenic Contrast, TEE: Transesophageal echocardiography, TTE: Transthoracic echocardiography.
[a] Significant p-value.

Out of three parameters that were found significant on univariate analysis, only complex LAA morphology was found to be independently associated with the ESUS stroke subtype (Table 3). Complex LAA morphology had the odds ratio of 6.003 for ESUS etiology of stroke with a 95% confidence interval of 1.225–29.417.

LAA morphology was assessed by two observers independently and the third observer assessed and finalized only those observations which were discrepant between the first two observers. Cohen's kappa analysis for inter-rater variability between two observers showed a kappa value of 0.964 which indicates almost perfect agreement between two observers for the assessment of LAA morphology.

3.3. Complex versus simple LAA morphology

The analysis was done to find the differentiating features between patients belonging to two different LAA morphology i.e., simple versus complex LAA morphology. Out of 60 patients, 37 patients had simple LAA morphology while 23 patients had complex LAA morphology. On comparing both the morphology (simple versus complex), baseline characteristics had non-significant differences. Out of various parameters assessed on TEE and TTE, only two parameters were found to have a significant association with complex LAA morphology namely orifice diameter and depth of LAA (Table 4).

Other parameters including LAA flow velocity, LA size, LA volume, and LV dimension were comparable between these two morphology groups.

4. Discussion

This study shows that complex LAA morphology is independently associated with the ESUS-Stroke subtype when compared with other stroke subtypes in the absence of AF. Furthermore, shallow depth and narrow orifice diameter are the predominant features of the ESUS-subtype of stroke in this study.

Previous studies have shown an association between complex morphology of LAA with cryptogenic stroke when compared with cardioembolic stroke patients, however, the majority of patients in the comparison group had AF.[8,9,12,13] Moreover, the presumed mechanism for patients with cryptogenic stroke or ESUS was postulated to be cardioembolic.[14] Thus, AF has been the major confounding factor while evaluating such comparisons and the results. Therefore, knowing the LAA morphology in patients without AF with ischemic stroke can be useful. Such patients with ischemic stroke and without AF can be divided into two types i) those with undetermined etiology such as ESUS and ii) Stroke

Table 3
Multivariable logistic regression analysis for association between cryptogenic stroke and complex left atrial appendage (LAA) morphology adjusted for LAA orifice diameter and depth.

Variable	Odds Ratio	Std. Error	p-Value	[95% Confidence interval]
Complex LAA morphology	6.003	0.811	0.027[a]	1.225-29.417
LAA Orifice Diameter	1.140	0.112	0.243	0.915-1.422
LAA depth	1.001	0.070	0.986	0.872-1.149

[a] Significant p-value.

Table 4
Comparison of the echocardiographic findings of simple and Complex LAA morphology.

Parameters	Simple (Chicken-wing) LAA morphology	Complex (non-chicken wing) LAA morphology	p-Value
LAA orifice diameter (mm)	17.0 ± 1.8	14.7 ± 3.9	0.017[a]
LAA depth (mm)	32.9 ± 3.8	25.5 ± 5.6	0.000[a]
LAA filling velocity (cm/sec)	44.9 ± 5.2	44.0 ± 4.0	0.518
LAA emptying velocity (cm/sec)	49.2 ± 5.3	47.9 ± 4.4	0.327
LA size (mm)	29.6 ± 2.9	30.0 ± 2.4	0.661
LA volume (ml)	32.7 ± 2.5	33.7 ± 2.1	0.094
LV IDD (mm)	44.3 ± 3.3	45.7 ± 2.4	0.056
LVEF (%)	59.0 ± 1.9	58.9 ± 1.9	0.824

[a] Significant p-value.

subtypes (TOAST I-IV) with determined etiology excluding AF. This study has mainly compared these two groups. Another challenge while evaluating patients with cryptogenic stroke is the absence of clear differentiating criteria which has been solved to some extent after the introduction of the term "ESUS" which is a type of cryptogenic stroke with clearly defined criteria.[15,16]

A recent study found an association of the ESUS-stroke subtype with the high-risk morphology of LAA(LAA-H) which is structurally similar to the complex LAA morphology/NCW LAA morphology.[17] In another study, the prevalence of NCW LAA morphology was higher in patients with ESUS and cardioembolic stroke than in non-cardioembolic stroke.[18] In a similar study by Gwak et al evaluating recurrent stroke in ESUS patients with atrial cardiomyopathy, a higher prevalence of NCW LAA morphology was observed in these patients.[10,19] A meta-analysis by Anan AR et al assessing LAA morphology as a determinant for stroke risk in AF patients found a higher incidence of cerebrovascular accidents in patients with NCW LAA morphology.[20] However, these studies used CT images to evaluate the LAA morphology and had a patient population with AF.[17,21]

LAA morphology has been part of research evaluating cryptogenic stroke or ESUS, however, it has two major drawbacks. One is the different classification systems used in different studies. Another drawback was different imaging modalities such as TEE, CT etc. used for evaluating LAA morphology.[17,18,21]

Initial studies have classified LAA morphology into various subtypes including CW, cauliflower, cactus and windsock.[14–18,21] Although recent studies have classified them into two types namely CW and NCW, some have proposed new classifications with alternative names for NCW variety of LAA morphology such as "complex", and "LAA-H" with slight modifications in defining criteria.[22] For LAA morphology, the result of the present study is similar to the previous studies stating that complex/NCW LAA morphology is associated with patients with ESUS and may pose a risk of recurrence of stroke in these patients.

Apart from analyzing the LAA morphology for providing any possible clue for the cause of stroke in ESUS patients, there are several studies which have evaluated other factors such as LAA dimensions/depth, LAA orifice diameter, LAA inflow velocities etc.[23,24] The ASSAM study group found that the distance of LAA ostium to the first bend of LAA in patients with AF was associated with stroke risk.[25] This distance is different (being shorter) from the depth of LAA used in the present study as well as in other recent studies.[9,22,25] Nevertheless, shallow depth of LAA was associated with ESUS patients, moreover, our study population excluded patients with AF. Thus, it can be concluded that the shallow depth of LAA is associated with ESUS in contrast to the other stroke subtypes. These results are similar to the other previous studies evaluating patients with cryptogenic stroke or ESUS.

Another parameter which was found to be increasingly associated with ESUS patients in this study was narrow orifice diameter which was similar to the study by Khurram et al in which narrow orifice diameter was prevalent in such patients.[26] However, various other studies consider broad orifice diameter to be associated with increased stroke risk in patients with AF.[27–29] The possible reason seems to be the higher prevalence of distinct complex morphology i.e. cactus and cauliflower type LAA morphology which has broader orifice but shallow depth while windsock type LAA morphology which is also a complex morphology with narrow orifice and deeper LAA length and is known to be associated with increased stroke risk in previous studies. Another contributory factor might be the presence of AF which also affects the dimensions of LAA and LA. Moreover, the study on patients with stroke without AF is limited.

In the present study, patients with ESUS had a mean LAA orifice diameter of 15.3 ± 3.5 mm and LAA depth of 28.4 ± 6.6 mm, which is lower compared to other stroke subtypes without AF.

Other parameters such as LAA inflow velocities were not significantly different in the two groups, and in previous other studies evaluating the role of LAA inflow velocity in stroke, no convincing evidence was seen except in a few studies in which lower inflow velocities were associated with increased risk of thrombus or spontaneous echogenic contrast.[30]

All these findings may help in the risk stratification of patients with ESUS into the high-risk and low-risk groups based on LAA morphology and dimension. Whether this evidence will bring any change in guidelines is just a possibility as current guidelines do not recommend anticoagulation in patients with ESUS.[31] A larger, well-designed study may help in providing future directions for patients with ESUS to prevent the risk of recurrent stroke.

5. Limitations

Single-Centre and small sample size were the major limitations of this study. Patients with AF were excluded from the study, however, some of these patients might have occult AF which requires long-term rhythm monitoring. The presence of complex LAA morphology alone does not establish LAA as the source of stroke, thus a well-designed multi-Centre study with a larger sample size of ESUS can better unmask the role of LAA appendage morphology and dimensions in the etiopathogenesis of ischemic stroke.

6. Conclusion

Complex LAA morphology was found to have an independent association with ESUS when compared with ischemic stroke with other etiology (TOAST Class I-IV) in the absence of AF.

7. Key questions of the study

I) **What is already known on this subject?**

Complex LAA morphology is increasingly associated with patients with ESUS when compared to stroke patients with AF (Cardioembolic stroke).

ii) **What does this study add?**

LAA morphology in patients with ESUS is predominantly of complex variety as compared to the patients with recurrent stroke even without AF.

III) **How might this impact on clinical practice?**

The findings of this study suggest the need for a larger study to further establish the role of complex LAA morphology in increasing the risk of stroke.

Declaration of competing interest

The Authors have no conflict of interest.

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