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Utilization of Left Atrial Size as An Independent Predictor of Cerebrovascular Stroke in Patients with Sinus Rhythm and Preserved Left Ventricular Systolic Function

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ABSTRACT

Background: The enlargement of the left atrium (LA) is thought to be a reflection of the long-term influence of left ventricular (LV) filling pressure against the LA. There is a correlation between increased LA volume and the risk of stroke and mortality.

Objective: The aim of the current work was to determine the significance of LA size in stroke prognosis in patients of all ages who first presented with preserved left ventricular systolic function (LVSF) and sinus rhythm (SR).

Patients and methods: This cross-sectional study included a total of 156 patients with acute ischemic stroke (AIS) with suspected symptom onset within the preceding 24 - 48 hours. Patients were divided into 2 groups, **group I** included 120 patients (76.9%) of cardio-embolic + large artery disease + small vessel disease patients and **group II** included 36 patients (23.1%) of cryptogenic and undetermined patients. Echocardiography was performed for all subjects.

Results: Highly statistically significant (p-value < 0.001) increased LA volume index in group II patients (37.4 ± 3.9) when compared with group I patients (33.3 ± 6.2). Using Roc curve, it was shown that LA volume index can be used to discriminate between group I and group II at a cutoff value of > 37.5, with 52.8% sensitivity, 80.8% specificity, 73.3% PPV and 63.1% NPV (AUC = 0.69 & p-value = 0.0005).

Conclusion: As a clinical tool, left atrial enlargement (LAE) may help determine the likelihood of a stroke and guide decisions about how to treat those who suffer from ischemic stroke.

Keywords: Left Atrial Size, Cerebrovascular Stroke, Sinus Rhythm, Left Ventricular Systolic Function.

INTRODUCTION

Even if sinus rhythm is present, the elderly are at increased risk for heart failure, atrial fibrillation (AF), and stroke if their left atrium (LA) is enlarged [(1)].

There is substantial evidence linking AF to ischemic stroke; most of these strokes have been observed in patients who initially appeared to be in sinus rhythm. Therefore, it has been hypothesized that greater LA size is linked to stroke in sinus rhythm older adults [(2)].

Having a larger LA increases the chances of having a stroke or dying. There is an elevated risk of stroke in those with an indexed LA volume of 32 ml/m2, and this higher risk persists after adjusting for age and other clinical risk factors for cerebrovascular illness. Even in senior people with no prior history of ischemic neurological episodes, atrial fibrillation (AF), or valvular heart disease, an enlarged LA is an independent predictor of a first stroke [(3)].

Size of the LA is thought to indicate the average effect of left ventricular (LV) filling pressure over time. There is talk of using it as a diastolic pressure indicator as well [(4)].

Insufficient myocardial contractility or impaired myocardial relaxation leads to a rise in left ventricular (LV) filling pressure, which is the primary pathophysiological component of heart failure. The size of the patient's left atrium will rise as a result (LA)[(5)].

The purpose of this study was to investigate the impact of LA size as a predictor of stroke in participants f varying ages who initially presented with preserved left ventricular systolic function (LVSF) and sinus rhythm (SR).

PATIENTS AND METHODS

This cross-sectional study included a total of 156 patients with acute ischemic stroke (AIS) with suspected symptom onset within the preceding 24 - 48 hours, attending at Neurology Critical Care Unit and Neurology Stroke Unit and studied at Department of Cardiology, Faculty of Medicine, Zagazig university hospital and Al-Ahrar teaching hospital, Zagazig.

Patients were divided into 2 groups, **group I** included 120 patients (76.9%) of cardio-embolic + large artery disease + small vessel disease patients and **group II** included 36 patients (23.1%) of cryptogenic and undetermined patients. Echocardiography was performed for all subjects.

Inclusion criteria:

- Patients who met the diagnostic criteria for acute ischemic stroke (AIS) established by the World Health Organization [(6)].

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- Patient's age: Above 18 years.
- Clinical symptoms and signs (focal or global) of alterations in brain function that develop suddenly and last more than 24 hours (unless halted by surgery or death) are diagnostic of a stroke.
- Patients were included if they showed signs of a cerebral infarction on CT or MRI, either at an early stage or within the past few days.
- Patients whose 12-lead electrocardiograms show sinus rhythm.
- Patients whose echocardiograms demonstrate normal systolic function.

Exclusion criteria:

- Patients with diagnosis other than AIS, CT scan findings of intracerebral hemorrhage, subarachnoid hemorrhage and venous infarctions, head injury or surgery, with brain tumors or other systemic malignancies, with CNS infections or systemic sepsis, with metabolic disorders or systems failure, with LV ejection fraction <50%, Known AF, History of previous MI or CABG or PCI or coronary artery disease or Q wave on ECG were not included in the study.

All Patients were subjected to:

- **Complete history taking:** Factors such as age, history of heart attack, high blood pressure, diabetes, and other cardiac diseases.
- **Clinical evaluation:** Measurements of BP, HR, basal rales, and body mass index. They were used to divide participants into research groups [(7)].

Laboratory investigations: cardiac enzymes (troponin, CK-MB), serum creatinine, hemoglobin, platelets count, and lipid profile were taken at admission.

Twelve lead surface ECG.

Echocardiography was done for all patients. Assessment of left atrial volume index (LAVI): Left atrial volume is measured in two dimensions using apical four- and two-chamber transthoracic images. At the conclusion of ventricular systole, just prior to mitral valve opening, the left atrium is at its largest, hence the endocardial margins of the left atrium are traced in each of these perspectives. The result is a biplane volume estimated using a variant of Simpson's (the disc approach).

Assessment of left atrial appendage:

The LA appendage was evaluated in parasternal short-axis images of the aortic valve and in apical 2-chamber views. A sampling volume was positioned near the orifice of the left atrial appendage, and flow velocities were obtained using pulsed Doppler echocardiography.

Radiological investigations:

Plain CT scan of the brain:

Initial plain CT scan of the brain

Every patient had a plain CT scan of the brain performed to rule out intracranial bleeding and confirm the diagnosis of acute ischemic stroke. CT was repeated if it was negative after 48 hours.

Magnetic Resonance Imaging (MRI) of the brain:

Follow-up CT scans reveal no lesions on the brain's surface in cases where they were performed for suspected brain stem lesions or early ischemic stroke.

Stroke subtypes:

According to the Trial of Org 10171 in Acute Stroke Treatment (TOAST) and the National Institute of Neurological Disorders and Stroke's classification standards, strokes were divided into five groups:

1) Large artery atherosclerosis individuals who had atherosclerotic stenosis or blockage of a major brain artery or cortical arterial branch as determined by clinical and brain imaging results were included.

2) Cardio-embolism Patients with a diagnosis of cerebral infarction who had a heart-borne embolus as the likely cause were considered to have this classification. It's important to rule out thromboembolism or embolism caused by atherosclerosis in the major arteries.

3) Small artery occlusion (lacuna) incorporated cases with characteristic lacunar symptoms, severe big artery stenosis, and no signs of cardiac embolism. Patients should also have a subcortical lesion of less than 1.5 cm in diameter, either at the level of the posterior fossa or in one hemisphere.

4) Patients who experienced a stroke for reasons other than atherosclerotic vasculopathy, hypercoagulable condition, or hematologic disease were placed in the "other cause" category.

5) Unknown cause is the diagnosis given to patients whose strokes cannot be pinned down to a specific cause. Extensive diagnostic testing was performed, including a battery of laboratory tests, magnetic resonance imaging (MRI), echocardiogram (ECHO).

***Ethical Consideration*:**

This study was ethically approved by Zagazig University's Research Ethics Committee. and submitted them to Zagazig University (ZU-IRB #9215/19-1-2022). Written informed consent of all the participants was obtained. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical analysis

Data was analyzed using SPSS 20 (Statistical Package for the Social Services) (SPSS). The findings were displayed using both tabular and graphical formats. Results were displayed using standard statistical measures such as means, medians, standard deviations, and confidence intervals. The accuracy of the data was demonstrated with the help of statistics. When assessing data involving quantitative independent variables, the student's t test (T) is utilized. Pearson Chi-Square and Chi-Square for Linear Trend were used to analyze the quantitatively diverse data (X2). In this example, a P value of 0.05 or less was judged statistically significant.

RESULTS

Table (1) shows that the average age was (62.8 ± 8.5) years ranged from 49 to 89 years. 60 (38.5%) were females and 96 (61.5%) were males.

Regarding risk factors, there were 104 HTN patients (66.7%), 72 DM patients (46.2%), 69 smokers (44.2%) and 77 dyslipidemia patients (49.4%). **Regarding BMI,** it was 26.9 ± 4.3 kg/m^2, ranged from 19.5 to 40 kg/m^2.

Table (1): Demographics

		Studied patients (N = 156)	
Age (years)	**Mean ±SD**	62.8 ± 8.5	
	Min - Max	49 – 89	
Gender	**Female**	60	38.5%
	Male	96	61.5%
Risk factors	**HTN**	104	66.7%
	DM	72	46.2%
	Smoking	69	44.2%
	Dyslipidemia	77	49.4%
BMI (kg/m²)	**Mean ±SD**	26.9 ± 4.3	
	Min - Max	19.5 – 40	
	Min - Max	1.49 – 2.4	

Table (2) shows that LA diameter was 39.8 ± 4.7 mm., ranged from 27 to 55 mm. As regard LA **volume index,** it was 34.2 ± 6.01 mL/m^2, ranged from 18 to 46 mL/m^2. **As regard LAA velocity,** it was 32.8 ± 7.6 cm/s, ranged from 14 to 62 cm/s.

Table (2): Description of studied Echocardiography data in all studied patients.

		Studied patients (N = 156)
LA diameter	**Mean ±SD**	39.8 ± 4.7 mm
	Min - Max	27 – 55 mm
LA volume index	**Mean ±SD**	34.2 ± 6.01 mL/m^2
	Min - Max	18 – 46 mL/m^2
LAA velocity	**Mean ±SD**	32.8 ± 7.6 cm/s
	Min - Max	14 – 62 cm/s

Table (3) shows the description of stroke sub-types in all studied patients. There were 39 patients (25%) of CE stroke, 36 patients (23.1%) of LAD stroke, 45 patients (28.8%) of SAD stroke, 34 patients (21.8%) of cryptogenic stroke and 2 patients (1.3%) of other stroke types in the studied patients. Patients were classified into 2 groups, group I include 120 patients (76.9%) of CE + LAD + SAD patients while group II include 36 patients (23.1%) of cryptogenic and undetermined patients.

Table (3): Description of stroke sub-types in all studied patients.

		Studied patients (N = 156)	
Stroke sub-types	**CE (cardio-embolic)**	39	25%
	LAD (large artery disease)	36	23.1%
	SVD (small vessel disease)	45	28.8%
	Cryptogenic	34	21.8%
	Other	2	1.3%
Stroke sub-types	**Group I (CE + LAD + SAD)**	120	76.9%
	Group II (Cryptogenic + Undetermined)	36	23.1%

Table (4) shows a statistically significant **(p-value < 0.05)** increased percentage of HTN in group I patients (87 patients, 72.5%) when compared with group II patients (17 patients, 47.2%). Regarding to age, BMI, Sex, DM, smoking, and dyslipidemia, patients in either group I or group II did not differ from one another statistically.

Table (4): Comparison of demographic data between both groups.

		Stroke sub-types		Test	p-value
		Group I (n = 120)	Group II (n = 36)		
Age (years)	**Mean**	62.6	63.4	MW = 2090	> 0.05 NS
	±SD	8.3	9.5		
BMI (kg/m²)	**Mean**	27.0	26.7	MW = 1803.5	> 0.05 NS
	±SD	4.0	5.4		
Gender	**Male**	45 37.5%	15 41.7%	$X^2 = 0.2$	> 0.05 NS
	Female	75 62.5%	21 58.3%		
HTN		87 72.5%	17 47.2%	**$X^2 = 7.9$**	**< 0.05 S**
DM		57 47.5%	15 41.7%	$X^2 = 0.37$	> 0.05 NS
Smoking		54 45%	15 41.7%	$X^2 = 0.12$	> 0.05 NS
Dyslipidemia		63 52.5%	14 38.9%	$X^2 = 2.05$	> 0.05 NS

Table (5) shows that: Significantly higher LA volume index in group II patients (37.4 ± 3.9) when compared with group I patients (33.3 ± 6.2). When comparing LA diameter between groups I and II, there was no discernible change. Group I patients had a mean age of 39.7 ± 4.9, while group II patients had a mean age of 40.3 ± 4.5. Patients in groups I and II showed no discernible variation in LAA velocity. Group I patients had a mean SD of 33.2 ± 8.1, while group II patients had a mean SD of 31.3 ± 5.6.

Table (5): comparison of echocardiographic data between both groups.

		Stroke sub-types		MW	p-value
		Group I (n = 120)	Group II (n = 36)		
LA diameter mm	**Mean**	39.7 mm	40.3 mm	2089.5	> 0.05 NS
	±SD	4.9	4.5		
LA volume index mL/m²	**Mean**	33.3 mL/m²	37.4 mL/m²	**1326.5**	**< 0.001 HS**
	±SD	6.2	3.9		
LAA velocity cm/s	**Mean**	33.2 cm/s	31.3 cm/s	1862.5	> 0.05 NS
	±SD	8.1	5.6		

Using Roc curve, **LA volume index** can be used to discriminate between group I and group II at a cutoff level of > 37.5, with 52.8% sensitivity, 80.8% specificity, 73.3% PPV and 63.1% NPV **(AUC = 0.69 & p-value = 0.0005)** Table (6).

Table (6): Diagnostic performance of LA volume index in discrimination of group I & group II.

	Cut off	AUC	Sensitivity	Specificity	PPV	NPV	p-value
LA volume index	**> 37.5**	**0.69**	**52.8%**	**80.8%**	**73.3%**	**63.1%**	**0.0005**

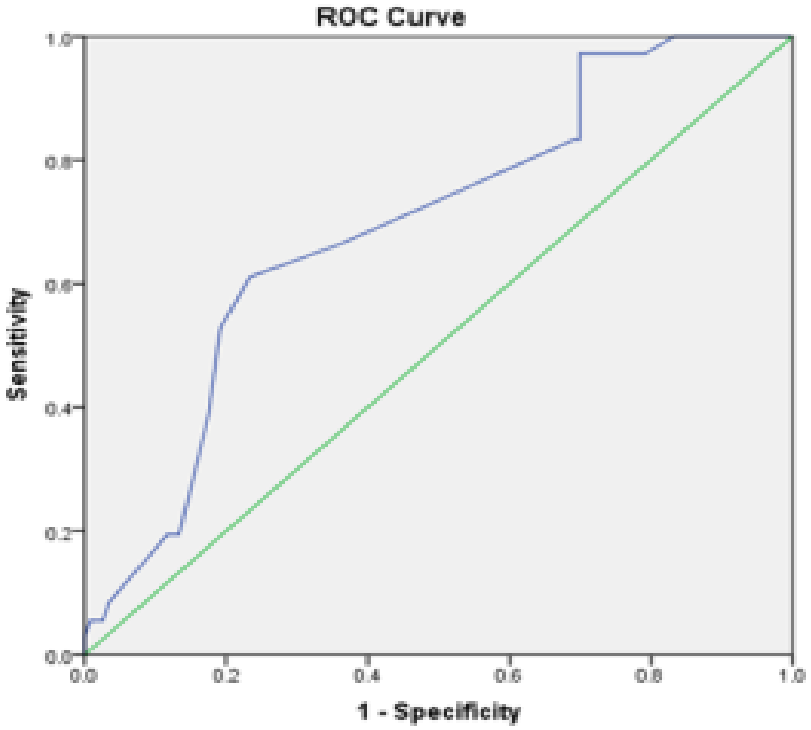
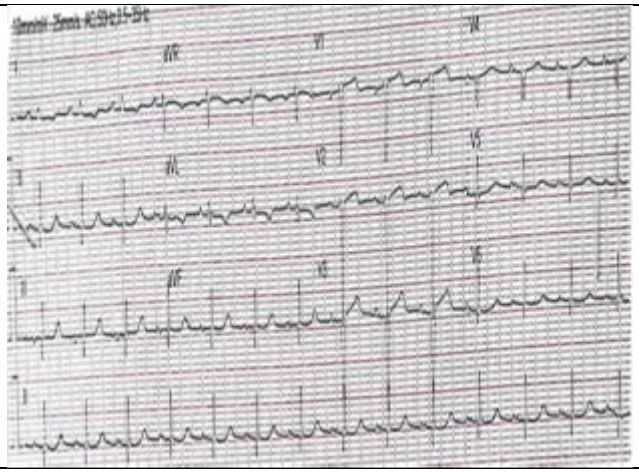


Figure (1): ROC curve between group I & group II as regard LA volume index

Using multivariate logistic regression analysis, this table demonstrates that the following factors were predictive for cryptogenic stroke: HTN (B = - 1.08, SE = 0.39, p < 0.05, Odds = 0.33 & 95% CL = 0.15 – 0.73). LA volume index (B = 0.14, SE = 0.045, p < 0.001, Odds = 1.16 & 95% CL = 1.06 – 1.26) Table (7).

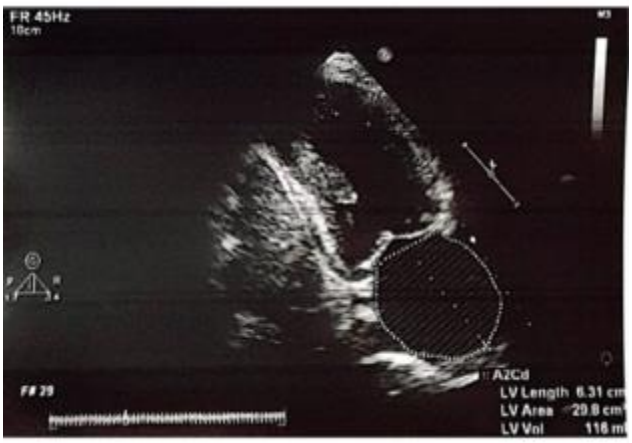
Table (7): Multivariate logistic regression analysis for factors predictive of cryptogenic stroke.

	B	**SE**	**p-value**	**Odds**	**95% CL**	
Age	0.01	0.022	> 0.05	1.01	0.96	1.05
Sex	- 0.17	0.38	> 0.05	0.84	0.39	1.7
HTN	**-1.08**	**0.39**	**< 0.05**	**0.33**	**0.15**	**0.73**
DM	- 0.23	0.38	> 0.05	0.78	0.37	1.6
Smoking	- 0.13	0.38	> 0.05	0.87	0.41	1.85
Dyslipidemia	- 0.55	0.38	> 0.05	0.57	0.26	1.23
BMI	- 0.013	0.045	> 0.05	0.98	0.9	1.07
BSA	- 1.02	1.03	> 0.05	0.36	0.04	2.7
PLTs	- 0.003	0.003	> 0.05	0.99	0.99	1.002
CHOL	- 0.009	0.006	> 0.05	0.99	0.97	1.0
TG	0.002	0.006	> 0.05	1.0	0.9	1.0
LA diameter	0.028	0.04	> 0.05	1.02	0.95	1.11
LA volume index	**0.14**	**0.045**	**< 0.001**	**1.16**	**1.06**	**1.26**
LAA velocity	- 0.03	0.027	> 0.05	0.96	0.91	1.01

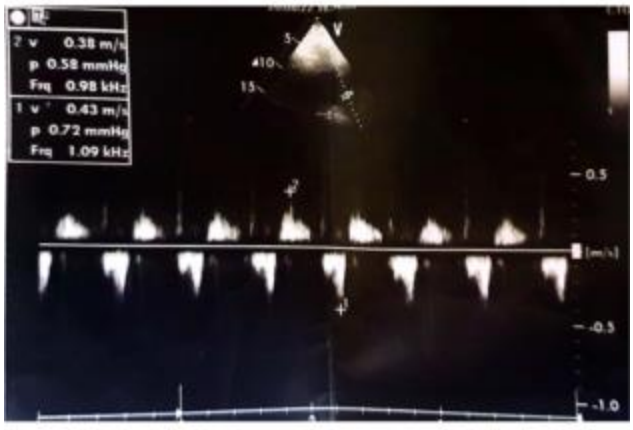


(A) 12-lead surface ECG of case

(B) Assessment of LA volume in A4C view



(C) Assessment of LA volume in A2C view



(D) Assessment of LAA Flow velocity in A2C view

Figure (2): 58 years male with type 2 DM, hypertensive, smoker weighing 110 kg, Heght 180 cm, BMI: 34kh/m2, BSA: 2.3 m2, The patient admitted to stroke unit complaining of left sided weakness with no other symptoms of cardiac or other systems affection. His past and family history was irrelevant apart from regular treatment with oral hypoglycemic drugs and not regularly antihypertensive drugs. ECG of the patient showed normal sinus rhythm. By Echo: LAV index: 50 ml/m2, LA appendage velocity: 38 cm/sec.

DISCUSSION

In the absence of atrial fibrillation or flutter, new data suggests that left atrial thromboembolism may be the underlying cause of certain occurrences of cryptogenic stroke (AF) **[8].**

Ischemic stroke has been linked to several indications of aberrant atrial structure and function outside of AF. Although increased left atrial volume is a hallmark of atrial cardiopathy, the association between left atrial volume and ESUS is still up for debate due to contradictory results from previous research **[9].**

So, the purpose of this cross-sectional study was to examine the relationship between left atrial (LA) size and stroke risk in patients of varying ages who otherwise presented with maintained left ventricular systolic function (LVSF) and sinus rhythm (SR). The aim of this study was to determine the relationship between LA size and the risk of having an ischemic stroke, and 156 individuals with ischemic stroke were surveyed and examined.

Patients were classified into two groups, according to MRI picture of stroke into ***Group I*** which includes ***cardio-embolic, large artery disease and small vessels diseases stroke patients***, And ***Group II*** which includes ***cryptogenic, and others stroke patients***.

In our study we found that there was highly statistically significant **(p-value < 0.001)** increased LA volume index "LAVI" in group II patients ($37.4\pm3.9ml/m^2$) compared with group I patients ($33.3\pm6.2ml/m^2$). No statistically significant difference between both groups as regard LA diameter.

The result was nearly agreed with **Walter *et al.* [10],** who stated that when comparing LA size, LAV is preferable to LA diameter and should be used routinely in clinical assessment.

According to our study and by using Roc curve, it was shown that **LAVI** can be used to discriminate between group I and group II at a cutoff level of >37.5, with 52.8% sensitivity, 80.8% specificity, 73.3% PPV and 63.1% NPV **(AUC = 0.69 & p-value = 0.0005)**.

Most patients in all ischemic stroke subtypes were found to have increased LAVI, with the prevalence being highest in Group II, which included cardioembolic and cryptogenic stroke subtypes, when compared to Group I, which included large artery and small vessel disease subtypes. Because of this, abnormally high LAVI is a more significant risk factor for ischemic stroke, and for the cryptogenic stroke subtype, than is normal LAVI. It has been hypothesized that LAE raises stroke risk **(11).**

When comparing patients with acute ischemic stroke to a control group, those with significantly larger-than-average left atrial anteroposterior diameters and LAVIs had an elevated risk of cerebral infarction due to LAE **(12).**

75% of individuals with an ischemic stroke for the first time have elevated LAVI levels, according to another study **(13).** Patients with an elevated LAVI after an ischemic stroke tended to be older and to have higher cardiovascular risk factors than those with a normal LAVI. After accounting for other potential causes of death, LAVI was still linked to mortality.

In contrast, though. Other researchers have put out a vascular theory of cryptogenic stroke as opposed to an embolic one. It appeared that the Ambulatory Arterial Stiffness Index ("AASI"), a measure of the dynamic relation between diastolic and systolic blood pressure over the entire day, was a good predictor of the occurrence of real cryptogenic stroke **(14).**

When comparing cryptogenic and non-cardioembolic stroke cases, the difference in LAVI between cardioembolic and cryptogenic instances was substantially higher. This may in part reflect an upper limit to LAVI in the cryptogenic group, as LAVI values over this point are commonly accompanied by the onset of atrial fibrillation and a diagnosis of cardioembolic stroke. Nonetheless, the fact that many cryptogenic instances are likely not brought on by cardiac embolism is supported by the fact that there is a high degree of overlap between these groups and individuals with recognized non-cardioembolic etiologies **(15)**.

Furthermore, in older people without a history of ischemic neurologic episodes, AF, or valvular heart disease, a larger LA volume has been demonstrated to predict the commencement of a first stroke in a clinical setting **(16).** Increased risk of stroke (hazard ratio [HR] 1.67, 95% confidence interval [CI] 1.08 to 2.58) was associated with an indexed LA volume of 32 ml/m2 over 4.3 ± 2.7 years, regardless of age or other clinical risk factors for cerebrovascular disease.

The other explanation for a larger LA is that it is an adaptive reaction to endothelial dysfunction affecting the systemic vascular bed. Endothelial dysfunction can be caused by Nitric oxide, angiotensin II, its receptor, plasminogen inhibitor I, thrombomodulin, and endothelin are only some of the cytokines and paracrine hormones that exhibit aberrant regulation and responsiveness **(17).**

It is widely recognized that both angiotensin II and its receptor have a role in promoting thrombogenicity as well as fibrosis; they can also cause atrial dilatation and thromboembolism by interfering with the electrical coupling of the atria **(18).**

These findings might help explain why LAE is linked to stroke. Since patients who have had many cerebrovascular strokes without apparent cause and who initially presented with sinus rhythm may develop repeated bouts of sub-clinical atrial fibrillation, Holter monitoring is indicated for such patients.

In the present study and regarding echocardiographic parameters we found that there was no statistically significant difference **(p-value > 0.05)** between group I and group II patients as regard LAA velocity. It was 33.2 ± 8.1 in group I patients and 31.3 ± 5.6 in group II patients. This finding may be debatable as we used transthoracic not transesophageal echocardiogram.

CONCLUSION

Patients suffering from ischemic stroke often have LAE. The results of this study indicate that LAE is a major risk factor for ischemic stroke, especially in the case of cardioembolic and cryptogenic stroke subtypes. Clinically, a thorough evaluation of LAVI could be helpful in estimating the risk of stroke and managing ischemic stroke. Patients with cryptogenic stroke had larger left atriums than those with non-cardioembolic stroke. Many cases of cryptogenic stroke are not caused by a cardioembolic event, yet there was a substantial overlap in left atrial size between cryptogenic and non-cardioembolic stroke patients.

Prognostic significance of left atrial volume index for identifying subset of individuals at high risk for stroke.

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Competing interests: Nil.

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