ORIGINAL ARTICLE

AL-ANBAR MEDICAL JOURNAL
Anb. Med. J. 20(2): 224–229, 2024

Transesophageal Echocardiography in the Detection of Potential Cardiac Source of Embolism in Embolic Stroke of Undetermined Source: A Preliminary Study

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(Received : 6 August 2024; Accepted : 31 October 2024; First published online: 22 November 2024)

ABSTRACT

Background: Embolic stroke of undetermined source (ESUS) occurs when the recommended diagnostic workup fails to identify a convincing underlying cause. ESUS is more common among male patients of younger age. One of the most common underlying findings among ESUS patients is a patent foramen ovale (PFO). Transesophageal echocardiography (TEE) offers enhanced diagnostic information for certain patients due to its proximity to the heart and major vessels, making it superior to transthoracic echocardiography in various conditions.
Objectives: To assess the diagnostic yield of the TEE in young patients with ischemic stroke who fulfil the diagnostic criteria of ESUS.
Materials and methods: This was a descriptive-observational cross-sectional study. It was conducted at Shaheed Al-Mehrab Center for Cardiac Catheterization from January 2, 2024, to June 1, 2024. The study included young patients with ischemic stroke, referred by their treating neurologist, who fulfilled ESUS diagnostic criteria and underwent TEE. We designed a specific questionnaire to document relevant information.
Results: A total of 13 patients were enrolled in the current study. The mean age was 36.77 ± 4.88 years, with the majority of cases (n = 8) being males. Among patients with ESUS, TEE detected PFO in 23.1% and atrial septal aneurysm in 15.4%. All patients had normal left atrial appendage (LAA) parameters and ejection fraction. The mean body mass index was significantly lower in patients with PFO. The mean of early and late LAA emptying velocities were significantly lower in patients with PFO.
Conclusion: TEE was effective in identifying underlying cardiac abnormalities in ESUS patients, with a significant detection rate for PFO and atrial septal defects. We recommend further studies with larger sample sizes to confirm the study's results.
Keywords: Transesophageal Echocardiography; Embolic Stroke of Undetermined Source; Patent foramen ovale; Stroke.

DOI: 10.33091/amj.2024.152605.1856

INTRODUCTION

Stroke, also known as a cerebrovascular accident (CVA), is a clinical syndrome characterized by an acute, focal neurological deficit that results from vascular injury to the central nervous system, either through infarction or hemorrhage [1]. Globally, stroke is the second-leading cause of death and disability [2].

Strokes are classified into three main types: Ischemic strokes, hemorrhagic strokes, and transient ischemic attacks (TIA). Conditions such as small vessel arteriolosclerosis, cardio-embolism, and large-artery athero-thromboembolism block blood vessels, causing ischemic strokes, which make up 85% of all stroke case [3]. Hemorrhagic strokes, responsible for about 15% of stroke cases, result from bleeding in or around the brain, leading to intracerebral or subarachnoid hemorrhages [3, 4]. TIAs are defined as brief episodes of focal neurological dysfunction that last less than 24 hours without resulting in permanent cerebral infarction [5].

Clinically, acute ischemic stroke presents as a sudden focal-neurological deficit lasting more than 24 hours, with symptoms varying based on the affected brain region. Vision issues like amaurosis fugax and hemianopia, motor issues like

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http://doi.org/10.33091/amj.2024.152605.1856

hemiparesis and ataxia, sensory deficits like hemisensory loss and hemineglect, speech and language issues like aphasia and dysarthria, and cognitive impairments are some of the most common signs [1].

While traditionally seen as a condition affecting older adults, stroke incidence among individuals under 50 years old is rising, now comprising 10-14% of all strokes. In the United States, the incidence among adults aged 20-44 reached 28 per 100,000 population in 2015, with even higher rates in low-middle-income countries like India. Young stroke survivors often face significant psychosocial challenges, including epilepsy, permanent cognitive deficits, and chronic fatigue [6, 7].

A new term, "embolic stroke of undetermined source" (ESUS), was created in 2014 to describe non-lacunar cryptogenic ischemic strokes that are most likely caused by an embolism [8]. ESUS is diagnosed when no convincing underlying cause is found despite comprehensive diagnostic workups [9]. Potential etiologies include covert atrial fibrillation, atrial cardiopathy, atherosclerotic plaques, patent foramen ovale (PFO), left ventricular disease, cardiac valvular disease, and cancer [10].

The diagnostic evaluation of ESUS involves head imaging, cardiac evaluation, arterial imaging, and exclusion of differential diagnoses [11, 12]. Transesophageal echocardiography (TEE) plays a crucial role in identifying potential cardiac embolism sources in individuals with ESUS, as it effectively detects intracardiac thrombi, atrial septal defects, and complex aortic atheroma, which transthoracic echocardiography may miss. By finding these high-risk sources, TEE helps to explain what causes strokes, guide the right antithrombotic treatment, and make secondary prevention strategies better [10, 13].

The rationale for conducting this study is the clinical need for precise identification of embolic sources among the young population. Despite advances in stroke diagnostics, a significant proportion of ESUS cases remain unexplained, leading to suboptimal prevention strategies. TEE holds the potential to identify cardiac irregularities that could trigger embolism. Given the lack of a local, relevant study in Iraq, this preliminary study is crucial in assessing the feasibility of using TEE as a diagnostic tool. This involves identifying procedural challenges, refining imaging protocols, evaluating initial detection rates of embolic sources, and determining the appropriate patient population. The results will guide the design and methodology of a larger-scale study to optimize the use of TEE in diagnosing cardiac-related embolism in ESUS patients.

MATERIALS AND METHODS

This is a preliminary descriptive observational cross-sectional study that evaluates the role of TEE among patients with ESUS. The study was conducted at the Shaheed Al-Mehrab Center for Cardiac Catheterization, Hilla, Iraq. It included young patients with ischemic stroke, recruited from January 2, 2024, to June 1, 2024. Due to the small number of young patients diagnosed with ESUS and undergoing TEE testing during the study period, the sample size was determined by including all ESUS patients in the census study. The study excluded patients with significant valvular heart disease, prosthetic mitral or aortic valve, left ventricle (LV) systolic dysfunction, paroxysmal persistent or permanent atrial fibrillation (AF), and those with contraindications for TEE.

A specialist radiologist's report confirmed the stroke diagnosis in all the studied patients who underwent brain magnetic resonance imaging (MRI). We performed TEE procedures using the Philips Affiniti 70 device, located in Bothell, Washington, USA. The TEE technique involves inserting an ultrasound probe into the esophagus, which is positioned directly behind the heart, allowing for clearer and more precise images. The procedure requires the patient to fast for 6-8 hours beforehand. Upon arrival, an intravenous line was placed for sedation, and a local anesthetic spray was applied to the throat to reduce discomfort. During the procedure, the patient was usually sedated to minimize anxiety and gag reflex. The flexible probe, equipped with an ultrasound transducer, is then gently inserted through the mouth and advanced into the esophagus. This positioning provides high-quality images of the heart and surrounding structures, aiding in accurate diagnosis and treatment planning.

The study documented variables such as age, sex, and body-mass-index (BMI) categories (Underweight: BMI $<$ 18.5, normal weight: BMI 18.5–24.9, overweight: BMI 25.0–29.9, and obese if the BMI $\geq$ 30). In addition to smoking status, heart rate, blood pressure, and specific TEE findings including, peak left atrial appendages (LAA) filling velocity, LAA emptying velocities, ejection fraction (EF), LAA dimensions, and the presence of LA thrombus or PFO. Normal LAA orifice diameter is 10–20 mm, LAA depth 20–30 mm, and EF 55%–70%. The Committee on Publication Ethics at the College of Medicine, University of Babylon approved the study (Reference number 3355/js on 12-8-2024). We informed the enrolled patients about the research subject and obtained their informed consent before their participation. We conducted the study in accordance with the ethical principles rooted in the Declaration of Helsinki.

Data were entered and analyzed using the statistical package for the social sciences (SPSS) version 26. Quantitative data were presented as mean ± standard deviation, in addition to median (interquartile range) with minimum and maximum values. Qualitative data were presented as frequencies and percentages. The Fisher's Exact test was used to estimate the association between categorical variables. Shapiro–Wilk test was used as a test of normality. An independent Two-sample t-test was used to compare the means of the two groups. In all statistical analyses, the level of significance (P-value) was set at less than 0.05.

RESULTS

The total number of patients was 13. The mean age of the patients was 36.77 ± 4.88 years, ranging from 22-40 years. Male patients represented 61.5% of the sample. The majority were non-smokers. The mean BMI was 28.41 ± 3.17 kg/m^2, ranging from 22 to 33 kg/m^2. 53.8% and 38.5% of the patients were in the overweight and obese categories, respectively (Table 1).

The mean peak LAA filling velocity was 56.42 cm/s ± 14.62. The LAA early emptying velocity mean was 25.38 cm/s, while the LAA late emptying velocity mean was 73.58 cm/s. The mean orifice diameter of the LAA was 11.69 ± 0.89 mm, and the LAA depth mean was 20.15 ± 3.67 mm. while the mean of EF was 62.08 ± 3.23% (Table 2).

Figure 1 summarizes the distribution of PFO, atrial septal aneurysm (ASA), LA thrombus, vegetation, and aortic arch atheroma within the study population. Among the participants, 23.1% were found to have a PFO, while 76.9% did not

Table 1. Demographic and clinical characteristics of the 13 studied patients*.

Variable	Mean ± SD	Median (IQR)	Minimum	Maximum
Age (years)				
Age range (22–40 years)	36.77 ± 4.88	38.00 (4)	22.00	40.00
Gender	Male: Number (%)		Female: Number (%)	
	8 (61.5%)		5 (38.5%)	
Smoking	Smoker: Number (%)		Non-smoker: Number (%)	
	4 (30.8%)		9 (69.2%)	
HR (beat/min.)	81.44 ± 7.66	83.50 (13)	69.00	91.00
BP systole (mmHg)	123.06 ± 8.77	122.50 (13)	110.00	135.00
BP Diastole (mmHg)	77.22 ± 7.32	80.00 (10)	60.00	90.00
Weight (kg.)	79.92 ± 8.14	79.00 (8)	66.00	90.00
BMI categories		Frequency	Percentage (%)	
	Normal	1	7.7	
	Overweight	7	53.8	
	Obese	5	38.5	
BSA (m^2.)	1.73 ± 0.18	1.70 (0.30)	1.50	2.00

* HR: Heart Rate, BP: Blood Pressure, BMI: Body Mass Index, BSA: Body Surface Area.

Table 2. Left atrial appendage (LAA) and ejection fraction (EF) related parameters of the 13 patients. IQR = Interquartile range.

Variable	Mean ± SD	Median (IQR)	Minimum	Maximum
Peak LAA filling velocity (cm/s)	56.42 ± 14.62	58.00 (17)	42.2	65
LAA early emptying velocity (cm/s)	25.38 ± 4.88	25.00 (8)	20	34
LAA late emptying velocity (cm/s)	73.58 ± 15.45	76.00 (22)	58	80
LAA orifice diameter (mm)	11.69 ± 0.89	12.00 (2)	10	13
LAA depth (mm)	20.15 ± 3.67	21.00 (3)	12	25
EF (%)	62.08 ± 3.23	62.00 (6)	58	68

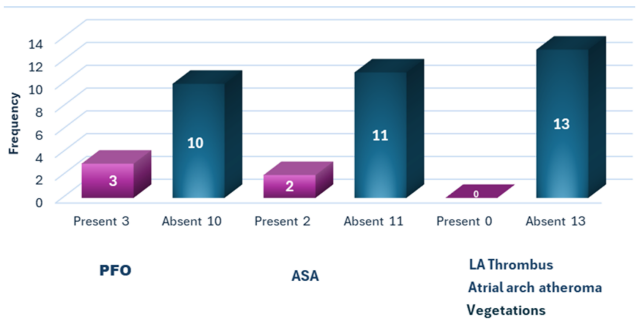

Figure 1. Clustered bar chart showing the distribution of patent foramen ovale (PFO), atrial septal aneurysm (ASA), vegetations, aortic arch atheroma, and left atrial (LA) thrombus in the study population. PFO: Patent Foramen Ovale, ASA: Atrial Septal Aneurysm, LA: Left Atrium.

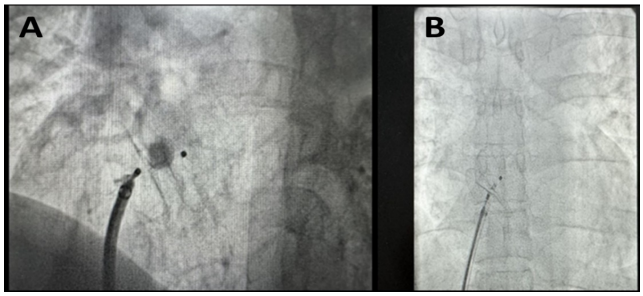

Figure 2. Patent foramen ovale (PFO) closure procedure during cardiac catheterization using an occluder performed on young patients with embolic stroke of undetermined source who was diagnosed with PFO by transesophageal echocardiography, (A) Lateral view, (B) Antero-posterior view.

have this condition.

A smaller proportion, 15.4%, presented with ASA, while the majority, 84.6%, did not. No cases of LA thrombus, vegetation, or aortic arch atheroma were identified among all patients. All three patients with PFO were advised to undergo PFO-closure. One of these patients had PFO closure performed successfully by an interventional cardiologist without complications as demonstrated in Figure 2. For the second patient, an attempt for PFO closure was made at another cardiology center, but the procedure was aborted due to the inability to cross the PFO. The third patient declined the procedure.

There were no statistically significant differences (P-value > 0.05) in the mean age, sex, and smoking status between the two groups, presence or absence PFO. Furthermore, the mean BMI was significantly lower in patients with PFO compared to patients without PFO (P-value = 0.048). Additionally,

http://doi.org/10.33091/amj.2024.152605.1856

Table 3. Comparison of left atrial appendage (LAA) parameters and ejection fraction (EF) by presence of patent foramen ovale (PFO).

Variable	PFO	Mean ± SD		P-value
Age (years)	Present	34.00 ± 10.392		0.281*
	Absent	37.60 ± 2.119		
Gender	Present 3 (23%)	Male: 2 (66.6%)	Female: 1 (33.4%)	0.685†
	Absent 10 (77%)	Male: 6 (60%)	Female: 4 (40%)	
Smoking	Present 3 (23%)	Yes: 1 (33.4%)	No: 2 (66.6%)	0.706†
	Absent 10 (77%)	Yes: 3 (30%)	No: 7 (70%)	
Body mass index	Present	26.21 ± 0.16		0.048*
	Absent	29.06 ± 3.37		
Peak LAA filling velocity (cm/s)	Present	54.00 ± 10.81		0.760*
	Absent	57.14 ± 16.01		
LAA early emptying velocity (cm/s)	Present	24.60 ± 4.57		0.043*
	Absent	28.00 ± 2.64		
LAA late emptying velocity (cm/s)	Present	68.33 ± 9.29		0.038*
	Absent	75.15 ± 16.95		
LAA orifice diameter (mm)	Present	12.00 ± 0.82		0.545*
	Absent	11.60 ± 0.96		
LAA depth (mm)	Present	22.00 ± 2.00		0.342*
	Absent	19.60 ± 3.95		
EF (%)	Present	62.67 ± 3.51		0.735*
	Absent	61.90 ± 3.31		

* Independent samples t-test was used.
† Fisher's Exact test was used.

no significant difference was found (P-value > 0.05) in the mean EF, mean peak LAA filling velocity, mean orifice diameter, and mean depth of the LAA between the PFO-present and PFO-absent groups. The means of early and late LAA emptying velocities were significantly lower in the PFO group compared to the absence group with a P-value of 0.043 and 0.038, respectively, as shown in Table 3.

DISCUSSION

The TTE is a standard diagnostic tool with good sensitivity for detecting certain cardiac pathologies linked to acute ischemic stroke, however, for more detailed assessment in certain conditions including the evaluation of the LAA, atrial septal abnormalities like PFO, atrial septal aneurysm, valvular vegetations, intracardiac device-associated thrombi, cardiac tumors, and aortic arch atheroma, TEE offers superior imaging capabilities [14]. This study's findings could highlight the value of TEE in guiding treatment decisions, particularly the use of anticoagulation therapy to prevent recurrent strokes; however, for more precise diagnostic approach for managing ESUS patients.

In the present study, young male patients constituted 61.5% of the study population. Similarly, a study by K. Feil, et al, found that nearly two-thirds of the patients with ESUS were males [15]. This is under previous studies referring to the higher prevalence of ESUS among males, the higher prevalence of ESUS in men is likely due to more cardiovascular risk factors, lifestyle habits like smoking, and the lack of estrogen's protective effects [16].

In this study, patients had a mean BMI of 28.41 ± 3.17 kg/m^2, with nearly 92% falling into the overweight or obese categories, this could be a part of the overall high prevalence of overweight and obesity in Iraq [17]. A number of mechanisms increase the risk of stroke in patients with high BMI. These include its association with hypertension, dyslipidemia, insulin resistance, and a pro-inflammatory state. It may also increase the likelihood of cardiac embolic sources such as atrial fibrillation or thromboembolism [18].

PFO, is a congenital condition where an opening in the interatrial septum, allows for the passage of oxygenated blood from the right atrium to the left atrium. It causes thrombus formation or facilitates paradoxical embolism, leading to ischemic strokes. Studies have consistently shown a higher prevalence of PFO among patients with cryptogenic stroke compared to the general population [19, 20]. In the current study, the TEE was able to diagnose PFO abnormalities in 5 out of 13 patients (38.46%). Specifically, 23.1% of patients had PFO and 15.4% of them had AAA. This was slightly higher than the diagnostic rates of TEE among ESUS patients reported by Gaudron et al. [21] and Rettig et al. [22] who found that the diagnostic rate of TEE ranges from 24%–30%.

A study by Strambo, et al. demonstrated that TEE was able to diagnose 184 (40%) of ESUS patients with PFO, which is comparable to our findings (38.46%). Their study also found that PFO was associated with younger age and being non-smoker [23]. However, no statistically significant association with smoking or age was demonstrated in the present study. These variations are likely to be attributed to the variation in sample size, study design, and methodology between the two studies.

The present study also found an association between BMI and PFO-related stroke. ESUS patients with PFO had a significantly lower BMI compared to those without PFO. Contrarily, a study by Roy et al. found an association between higher BMI and increased risk of ischemic stroke among patients who had PFO with pulmonary embolism [24]. The data

regarding the association of BMI among stroke patients with PFO are limited. The lower BMI in the current study could refer to the lower probability of having conventional vascular risk factors (such as obesity) in ESUS-ischemic stroke patients [25]. It also can be an incidental finding due to the small sample size in the current study.

This study also showed a significant difference in the mean early and late LAA emptying velocity between the PFO group and the non-PFO group. This could indicate altered hemodynamics in PFO patients. Failure to close the foramen ovale results in a persistent right-to-left shunt through a one-way flap mechanism when the right atrial pressure becomes higher than the left atrial pressure. PFO may facilitate the passage of vaso-active substances, thrombi, fat, and air from the venous to the arterial circulation, leading to a paradoxical embolism in cryptogenic stroke [26, 27].

In the present study, none of the patients enrolled had aortic arch atheroma (ASA) on TEE. While a study by Ntaios, et al. found that among 1382 ESUS patients, 29% had aortic arch atheroma [28]. This can be explained by the small sample size and the patient selection criteria in this study, which included young patients with no identified risk factor, making detecting atheroma less likely. The detection of aortic arch atheroma among patients with ESUS is usually associated with an overall increased risk of recurrent ischemic stroke or death [29].

None of the patients in this study sample showed any signs of vegetation. TEE is a highly sensitive tool for detecting vegetation [30]. However, the small sample size, the exclusion of patients with prosthetic valves, and the fact that all included patients had normal transthoracic echocardiography likely account for the variation from other studies.

Despite its small sample size, the present study provides valuable insights into the use of TEE in detecting potential cardiac sources of embolism in patients with ESUS. By examining all eligible cases at a single center, the study highlights the role of TEE in identifying hidden cardiac abnormalities that may contribute to stroke, laying the groundwork for future larger-scale studies to further explore its diagnostic potential in ESUS patients.

The limitations to this study include a small sample size, single-center experience, and selection bias that might be present as the treating neurologist referred the patients included in this study.

CONCLUSION

TEE was able to identify significant cardiac abnormalities, such as PFO and ASA. These findings suggest that TEE should be considered a component of the diagnostic workup for ESUS, particularly in young patients, as it may influence secondary prevention strategies. Further research with larger sample size is recommended to confirm these results and better understand the implications of these findings on clinical practice. To draw more definitive conclusions, future studies should aim to include a larger and more diverse group of participants, which would enhance the validity and robustness of the findings.

ETHICAL DECLARATIONS

Acknowledgments

None.

Ethics Approval and Consent to Participate

The study was approved by the Committee on Publication Ethics at the College of Medicine, University of Babylon (Reference number 3355/js on 12-8-2024). Informed consent was obtained from every participant in the current study.

Consent for Publication

Not applicable (no individual personal data included).

Availability of Data and Material

Data generated during this study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that there is no conflict of interest.

Funding

No funding.

Authors' Contributions

All of the listed authors were significantly, directly, and intellectually contributed to the work. The authors read and approved the final version of the manuscript.

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