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# Transesophageal echocardiogram in the evaluation of acute ischemic stroke of young adults

Muhammad K. Ahmed<sup>1,2</sup>, Haris Kamal,<sup>3</sup> Jessica L. Weiss<sup>4</sup>, Annemarie Crumlish<sup>2</sup>, Peyman Shirani,<sup>5</sup> Robert N. Sawyer,<sup>2</sup> Ashkan Mowla<sup>6</sup>

## Abstract:

**INTRODUCTION:** Acute ischemic stroke (AIS) in the young age ( $\leq 50$  years) is a major cause of disability. The underlying mechanism of AIS in this age group is usually different from elderly. Transthoracic echocardiography (TTE) is used to detect the potential cardiac sources of embolism in AIS patients. Transthoracic echocardiogram (TEE) is superior to detect specific underlying cardio-aortic source of embolism when compared to TTE. We aim to evaluate the diagnostic yield and therapeutic impact of TEE in AIS of young adults.

**METHODS:** We retrospectively reviewed the consecutive patients with AIS in our comprehensive center in a 5-year period from our prospectively collected registry. We selected patients with age  $\leq 50$  years who had acute infarcts on brain magnetic resonance imaging or head computed tomography and underwent TEE as part of their diagnostic workup. Demographic details including, age, gender, body mass index, cardiovascular risk factors profile, and TEE findings were collected.

**RESULTS:** Among a total 7,930 patients, 876 (11.04%) were found to be  $\leq 50$  years old. Among those, TEE was done in 113 patients (12.8%) in addition to TTE. Those who underwent TEE had a mean age of  $40.4 \pm 7.9$  years, 60 were male (53%), 7 (6.2%) had a history of coronary artery disease, 38 (33%) had a history of diabetes, and 45 (40%) had a history of smoking. TEE showed new abnormal findings in a total of 15 patients (13.2%) that were not reported in their TTEs. Out of these, left atrial appendage thrombus was found in 5, infective endocarditis in 4, atrial septal aneurysms associated with patent foramen ovale (PFO) in 3, and spontaneous mobile echo density in three patients. Overall, new findings from TEE resulted in change in the secondary stroke prevention strategy in 14 patients of those who underwent TEE (12.3%). TEE also confirmed the presence of PFO, which was present on TTE with bubble study in 20 (17.6%) patients.

**CONCLUSION:** TEE may provide additional information in the evaluation of the AIS in young adults, which could lead to change of the secondary stroke prevention strategy.

## Keywords:

Evaluation, stroke, transthoracic echocardiogram, young

## Introduction

Acute ischemic stroke (AIS) in young adults with age  $\leq 50$  years is a major cause of disability and the rate of AIS in this age group is increasing.<sup>[1-17]</sup> Risk factors and underlying mechanisms for AIS in young

adults differ from elderly.<sup>[1,12,14,18,19]</sup> Cardiac sources of embolism contribute to 17%–47% of AIS in young adults, while cryptogenic or undetermined etiology accounts for 19%–40% of AIS in young adults in most population-based studies.<sup>[2,19-22]</sup> There is no consensus on the optimal diagnostic workup and how to approach AIS with undetermined etiology in young adults. Determination of the underlying mechanism

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<sup>1</sup>Department of Neurology, Georgia School of Medicine, HCA Education Consortium, Rome, GA, <sup>2</sup>Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, State University of New York at Buffalo, Buffalo, <sup>3</sup>Department of Neurology, New York Medical College, Valhalla, NY, <sup>4</sup>Department of Medicine, Division of Cardiology, Keck School of Medicine, University of Southern California, <sup>5</sup>Department of Neurological Surgery, Division of Endovascular Neurosurgery, Keck School of Medicine, University of Southern California, Los Angeles, CA, <sup>6</sup>Departments of Neurology and Neurosurgery, University of Cincinnati, Cincinnati, OH, USA

## Address for correspondence:

Dr. Ashkan Mowla, Department of Neurological Surgery, Division of Endovascular Neurosurgery, Keck School of Medicine, University of Southern California, 1200 North State St, Suite 3300, Los Angeles, CA 90033, USA. E-mail: mowla.ashkan@gmail.com

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for AIS is pivotal in planning the secondary prevention strategy.<sup>[23,24]</sup> Since 2014, the concept of embolic stroke of undetermined source (ESUS) has been introduced, which subclassifies the AIS with undetermined etiology into ESUS based on the presence of nonlacunar type brain infarct on brain imaging, absence of extracranial or intracranial atherosclerosis causing  $\geq 50\%$  luminal stenosis in arteries supplying the area of infarct, absence of cardiac source on transthoracic echocardiogram (TTE), or any other potential underlying mechanisms such as arteritis, arterial dissection, vasospasm, and drug misuse.<sup>[25]</sup>

Transthoracic echocardiogram (TTE) is generally a part of the diagnostic workup to determine the underlying mechanism for AIS and has a good sensitivity in detecting certain pathologies such as left ventricular thrombi, ventricular aneurysms, certain valvular abnormalities, intracardiac device-associated thrombi, and cardiac tumors.<sup>[26]</sup> With advancements in imaging modalities, cardiac magnetic resonance imaging (MRI) is also being utilized to detect cardiac source of embolism in AIS.<sup>[6]</sup> Despite all, transesophageal echocardiogram (TEE) remains a pivotal modality and has been shown to be superior to TTE in detecting certain cardiac and aortic arch pathologies including the left atrial appendage (LAA) pathologies, atrial septal abnormalities such patent foramen ovale (PFO), atrial septal aneurysm (ASA), valve vegetations, intracardiac device-associated thrombi (central venous catheters, pacemaker/implantable cardioverter-defibrillator leads, and prosthetic valves), cardiac tumors, and aortic arch atheroma as potential sources of embolism.<sup>[27]</sup>

There are limited comparative data available regarding the role of TEE in comparison with TTE to detect the underlying mechanism of AIS in young adult population.

We aimed to study the diagnostic yield of TEE for the detection of underlying mechanism of AIS in young adult patients where our routine diagnostic work (RDW) including TTE was not diagnostic.

## Methods

This is a single-center retrospective study of all consecutive patients who were admitted to our comprehensive stroke center at Buffalo General Medical Center, Buffalo, NY, with the diagnosis of AIS in a 5-year period. Patients who were  $\leq 50$  years and had AIS confirmed on their brain MRI/diffusion-weighted imaging or head CT were selected. In our center, these patients generally undergo a RDW for the detection of the underlying mechanism of AIS. RDW in this age group in our center includes laboratory workup including lipid profile and hemoglobin A1c, head computed

tomography (CT) without contrast, CT angiogram head and neck, electrocardiogram (EKG) and continuous cardiac rhythm monitoring with automated rhythm detection during the hospital course, MRI of the brain without contrast, and TTE with bubble study. If the patient cannot get CT angiogram of the head and neck for any reason, MR angiogram of the head and neck without contrast or carotid doppler ultrasonography plus transcranial doppler was obtained.

Based on the judgment of the treating of vascular neurologist and particularly when RDW did not reveal any specific underlying mechanism for AIS and the pattern of the acute infarct was thought to be embolic based on the brain imaging, TEE was obtained. In some of these patients and depending on their family history or medical history and if TEE was unremarkable, testing for central nervous system vasculitis and inherited thrombophilia were also obtained, including erythrocyte sedimentation rate and C-reactive protein, antinuclear antibody, rheumatoid factor, complements level, hepatitis B and C serology, lupus anticoagulant, anticardiolipin antibodies, beta-2 glycoprotein antibodies, factor V Leiden mutation, prothrombin gene mutation, protein C, protein S, antithrombin 3, and homocysteine level.

TEE was generally performed by an experienced cardiologist, who was independently performing TEE without active involvement in the stroke care. TEE reports were reviewed carefully by our team member and all the potential cardiac or aortic arch sources for AIS were collected for each patient. For each patient with a potential cardiac or aortic arch source reported on TEE, we reviewed the chart to see whether this new finding has changed the secondary stroke prevention strategy.

In addition to the TEE findings, the demographics and baseline characteristics, i.e., age, gender, race, history of tobacco use, history of recreational drug use, cardiovascular risk factors (hypertension, diabetes mellitus, coronary artery disease, dyslipidemia, prior use of antiplatelets or anticoagulants, personal or family history of thrombophilia, and presenting stroke severity based on the National Institute of Health Stroke Scale), were collected.

## Results

The study population included 7,930 patients with AIS, and out of these, 876 (11.04%) patients were found to be  $\leq 50$  years old as shown in Figure 1. The baseline characteristics of these patients are summarized in Table 1.

TTE results were available in all these 876 patients. TEE was performed in 113 patients (12.8%) based on the

vascular neurologist discretion or suggestion made by a cardiologist performing the TTE. All the patients who underwent TEE already had a TTE obtained during the same hospital course. The baseline characteristics for patients who underwent TEE in addition to TTE are summarized and compared in Table 1.

TEE resulted in new abnormal findings of potential cardiac or aortic arch sources for AIS in a total of 15 (13.2%) patients when compared to TTE findings. TEE revealed the presence of LAA thrombus in 5 (4.4%),

infective endocarditis (IE) in 4 (3.5%), ASA in 3 (2.7%), and a mobile echo density in 3 (2.7%) patients. All patients with abnormal finding of LAA thrombus had sinus rhythm on their EKG and telemetry. TEE also confirmed the presence of PFO, which was present on TTE with bubble study in 20 (17.6%) patients. Overall, new findings from TEE resulted in change in the secondary stroke prevention strategy in 14 (12.3%) patients. These findings led to starting of oral anticoagulation for patients with LAA thrombus or spontaneous mobile echo density in eight patients (7%). New findings of ASA along with PFO resulted in referral for PFO closure in two patients (1.7%). Detection of vegetation resulted in initiation of antibiotic therapy in four patients (3.5%). The new abnormal findings shown on TEE in 15 (13.2%) patients are summarized in Table 2. Changes to secondary stroke prevention strategy based on new abnormal findings are summarized in Table 3.

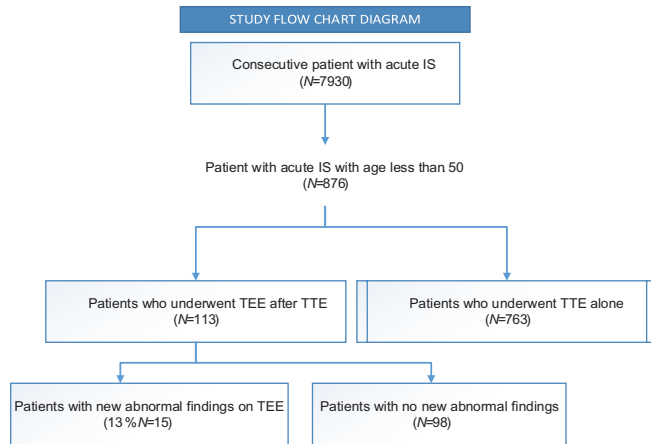


Figure 1: The study flowchart diagram

### Discussion

The findings of the current study, which included consecutive AIS patients <50 years old from a high-volume comprehensive stroke center, indicated that TEE detected new pathologies in 12.3% of the patients who underwent TEE which changed their secondary stroke prevention strategy. These findings highlight the importance of

**Table 1: Baseline characteristics of patients with acute ischemic stroke aged ≤50 who had transthoracic echocardiography alone compared to transthoracic echocardiography+transthoracic echocardiogram**

Characteristics	AIS<50	TTE alone	TEE+TTE	P
Patients (n)	876	763	113	
Age, mean±SD	42.24±7.28	42.28±7.43	40.4±7.9	0.592
Gender, n (%)				
Male	391 (44.70)	346 (45.4)	60 (53)	0.322
Female	484 (55.30)	417 (54.6)	53 (47.80)	
Race, n (%)				
Caucasian	648 (74.10)	571 (74.9)	92 (81.50)	0.165
African American	206 (23.50)	172 (22.5)	20 (17.40)	
Other	21 (2.40)	17 (2.6)	1 (1.10)	
Social history, n (%)				
Tobacco use	386 (44.10)	327 (42.8)	45 (40.10)	0.05
Drug and alcohol abuse	111 (12.78)	20 (11.6)	21 (19)	0.007
Past medical history, n (%)				
Hypertension	426 (48.60)	385 (50.10)	51 (41.50)	0.002
Diabetes mellitus	179 (20.50)	144 (19)	38 (33.30)	0.875
Dyslipidemia	224 (20.56)	190 (25)	26 (23.10)	0.42
Coronary artery disease	68 (7.80)	58 (7.60)	7 (6.20)	0.809
Migraine	47 (5.40)	41 (5.40)	6 (5.60)	0.685
Sleep apnea	10 (1.30)	10 (1.30)	1 (1.10)	-
Prior antiplatelet or anticoagulant use, n (%)				
Aspirin	105 (11.90)	78 (10.7)	13 (11.50)	0.43
Initial blood pressure, mean±SD				
Systolic	145.09±29.18	144.92±27.2	146.58±31.39	0.592
Diastolic	89.27±18.85	89.31±18.57	88.93±19.21	0.85
BMI, mean±SD	30.65±8.21	30.68±8.32	30.36±8.1	0.735

TTE: Transthoracic echocardiography, TEE: Transthoracic echocardiogram, AIS: Acute ischemic stroke, SD: Standard deviation, BMI: Body mass index

utility of TEE in AIS patients when RDW is not able to detect the underlying mechanism. Several recent studies have reported that TEE is essential in determining the underlying mechanism in ESUS patients.<sup>[28-31]</sup> There are limited data comparing the utility and therapeutic impact of TEE along with TTE compared to TTE alone when RDW does not reveal the underlying mechanism for AIS. Gaudron *et al.*<sup>[26]</sup> and Rettig *et al.*<sup>[31]</sup> reported that the diagnostic yield of TEE is up to 24%–30% and the therapeutic impact is 10%–12% in patients where initial TTE was unremarkable.

Etiological and diagnostic workup in young adults with AIS includes wide array of tests and differs from elderly due to different risk factors and underlying mechanisms. There is no universally accepted diagnostic work protocol due to limitation of data on cost-effectiveness and diagnostic yield of different tests.<sup>[22,32,33]</sup> There is also heterogeneity in the results of the previously published data with the diagnostic tests used for the detection of cardiac sources of embolism rating 20%–47%. The underlying mechanism of AIS in young adults remains unknown after the RDW in at least 35% of the patients in our center. Bang *et al.*<sup>[34]</sup> reported that the undetected underlying mechanism for AIS is associated with increased risk of recurrence when compared to AIS with defined underlying mechanisms.

There are different strategies or protocols being utilized at different institutions to improve detection of the cardiac or aortic arch sources for AIS with a different range of cost-effectiveness. However, most of these studies have compared the diagnostic yield of these modalities including TTE, TEE, or cardiac MRI to detect cardiac or aortic arch sources of emboli in AIS patients in all age groups.<sup>[6,35]</sup> Only few studies particularly reported the diagnostic yield and therapeutic impact of TEE in young adults with AIS.<sup>[3,36]</sup> Two previous studies by de

Bruijn *et al.*<sup>[3]</sup> and Rettig *et al.*<sup>[31]</sup> reported the detection rate of cardiac or aortic arch sources for embolism by TEE in young adults with AIS to be in range of 26%–30%, which is line with the findings of our study.

TEE provides more detailed information about certain structural abnormalities such as PFO, size of PFO, presence of ASA, and also complex aortic arch atheroma compared to TTE. These findings have been associated with increased recurrence of AIS.<sup>[37-39]</sup> The most common location for thrombus formation in the heart is LAA.<sup>[35,40]</sup> TEE provides better understanding of LAA morphology, emptying velocities, and presence or absence of thrombus.<sup>[27,41-43]</sup> Our study reported newly detected LAA thrombus on TEE in 4.4% of the patients who had unremarkable TTE. These findings further changed the secondary stroke prevention strategy in those patients from antiplatelet therapy to anticoagulation. With further studies reporting that the size and structural characteristics of LAA are independent predictors of AIS recurrence, the utility of TEE or multimodal imaging looks even more helpful in the guidance of optimal secondary stroke prevention strategies.<sup>[6,44]</sup>

Previous studies have reported interobserver and intraobserver variability in the detection of abnormalities on TEE (i.e., detection of ASA, morphology of LAA, or spontaneous echo contrast). There are very few studies which defined these echocardiographic findings clearly.<sup>[45]</sup> These limitations have led to reporting of different rates of findings such as spontaneous mobile echo density, defined as an area of mixed echo density different from the background. This finding is contraindication to mechanical cardioversion and is an indication for oral anticoagulation; however, there is no clear consensus. In our study, TEE detected spontaneous mobile echo density in three patients (2.7%) of those undergoing TEE and all were started on oral anticoagulation.

The prevalence of PFO in young adults with AIS ranged from 24% to 47%, which is reported in a meta-analysis by McGrath *et al.*<sup>[27]</sup> Association of PFO with cryptogenic AIS particularly in young adults is a long-standing evolving controversy. Imaging modalities such as TEE with contrast are considered as gold standard for the detection of PFO along with ASA, with one study reporting 100% sensitivity.<sup>[46]</sup> Currently, TTE with

**Table 2: New abnormal findings on transthoracic echocardiogram**

Findings	n (%)
No new abnormal findings	98 (86.7)
LAA thrombus	5 (4.40)
PFO+atrial septal aneurysm	3 (2.70)
Infectious endocarditis	4 (3.50)
Spontaneous mobile echo density	3 (2.7)

LAA: Left atrial appendage, PFO: Patent foramen ovale

**Table 3: Secondary stroke prevention strategy changes in patients with new abnormal findings on transthoracic echocardiogram**

New abnormal findings	n	Secondary prevention strategies	n (%)
LAA thrombus	5	Initiation of anticoagulation	5 (100)
PFO+atrial septal aneurysm	3	PFO closure	2 (66)
Infectious endocarditis	4	Initiation of antibiotic therapy	4 (100)
Spontaneous mobile echo density	3	Initiation of anticoagulation	3 (100)

LAA: Left atrial appendage, PFO: Patent foramen ovale

bubble study is being used as the initial diagnostic modality to detect PFO in AIS patients  $\leq 50$  years old in our center as it is a noninvasive procedure. TEE is advantageous when compared to TTE as it provides detailed description of the morphology of PFO (i.e., size and shape) and its associated atrial abnormalities such as presence of ASA and intra-aneurysmal thrombus. These associated findings are crucial in risk stratification of PFO in cryptogenic AIS and help in further secondary stroke prevention strategies.<sup>[38,47,48]</sup> Recent clinical trials reported that cryptogenic AIS patients with PFO along with structural abnormalities such as ASA are at higher risk of paradoxical emboli and might benefit from PFO closure resulting in lower recurrence rate.<sup>[39]</sup> Our study confirms that TEE was able to detect ASA associated with PFO in 2.3% of cases. These findings resulted in referral for PFO closure in 2 out of three patients as part of the secondary stroke prevention despite no clear guideline recommendations at the time of patients' management.

IE could be fatal as it has high in-hospital mortality rate with increased risk of cerebral and systemic embolism and could be an underlying mechanism of AIS in young adults. The diagnosis of IE may require TEE, as IE can be missed with TTE.<sup>[49,50]</sup> Furthermore, TEE may help assess the risk for septic embolization, which guides further management, i.e., emergent surgical intervention or antibiotic therapy.<sup>[51]</sup> For example, TEE may provide detailed information about the vegetation size with the size  $>10$  mm being associated with higher risk of embolism. In our study, vegetations were detected in 3.5% of patients who underwent TEE. These findings provoked initiation of antibiotic therapy in four patients.

Nonbacterial endocarditis is associated with an increased risk of thromboembolism, with a rate of approximately 13% in a 4-year follow-up study.<sup>[49]</sup> TEE is crucial in the detection of nonbacterial endocarditis, particularly in patients with systemic lupus erythematosus.<sup>[52]</sup> There are also other underlying mechanisms for AIS such as aortic atheroma and atrial myxoma, which are commonly detected on TEE. However, none of these findings was detected in our patients. Studies have reported high sensitivity of TEE in detecting aortic arch atheroma; however, aortic atherosclerosis is generally not common in young adults, consistent with the results of our study.

Our study has a number of limitations. As it is a retrospective study, there is lack of consistent prespecified definitions for abnormal diagnostic findings detected during the study. This study also does not specifically report the particular order of different diagnostic tests performed during the RDW. In addition, the TEE and TTE interpreter experience and number of interpreters involved in reporting these results was not available for reporting.

## Conclusion

TEE carries significant diagnostic yield to determine the underlying mechanism for AIS in young adults and should be considered as part of the workup when no clear mechanism is found with RDW.

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## Declaration of ethical approval and patient consent

The study was approved by the institutional ethics committee (Kaleida Health) in 2013. Patient informed consent was waived since this was a retrospective study and the data were collected anonymously.

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## Conflicts of interest

There are no conflicts of interest.

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