ASIAN JOURNAL OF MEDICAL SCIENCES

Role of echocardiography in acute stroke patients admitted to ICU

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Submission: 24-11-2024

Revision: 09-12-2024

Publication: 01-01-2025

ABSTRACT

Background: Stroke is gaining worldwide importance as the focus now shifts to non-communicable diseases. The etiological investigation of the potential cardiac source of acute ischemic stroke (AIS) is important for the secondary prevention of recurrent and future embolization and also helps in finding other etiology. Aims and Objectives: Our aim was to evaluate echocardiographic findings in patients with AIS admitted to a tertiary care hospital in ESICMC PGIMSR Rajajinagar. Materials and Methods: The prospective study was conducted on patients admitted in medical college hospitals affiliated to ESICMC PGIMSR Rajajinagar. All patients aged more than 18 years presenting with acute onset ischemic stroke were taken into the study. After demographic data transthoracic echocardiography was done and various finding was noted. Results: In our study, mean age was 56.07 years. Male was 55 (82.1%) and female were 12 (17.9%). In our study stroke in young i.e. <45 years is 10 patients (14.9%). Out of 67 patients, 31 had degenerative mital and aortic valvular, 7 had left atrial thrombus, 7 had left ventricular thrombus, mitral valve prolapse in 3 patients, regional wall motion abnormalities in 17 patients, heart failure with reduced ejection fraction in 21 patients, 4 patients had atrial septal defect, 2 patients had ventricular septal defect. Conclusion: This study reinforces the importance of transthoracic echocardiography in stroke. Transthoracic echocardiography is not only an effective tool in picking up the clots inside the cardiac chambers but also it was found to be significantly effective in detecting valvular lesions and small septal defects, such as patent foramen ovale.

Key words: Ischemic stroke; TIA; Echocardiography; Stroke unit; Guidelines

INTRODUCTION

Stroke causes significant mortality and morbidity worldwide and is the third-largest cause of mortality in the developed world. Ischemic stroke represents 85% of all forms of stroke. Therapy of an acute phase of cerebrovascular accident (CVA) is focused on immediate actions to limit further brain damage with the earliest possible initiation of reperfusion strategy. The next immediate step is to initiate secondary prevention. The essential prerequisite for adequate and effective secondary prevention is recognition of the cause of the ischemic CVA because the highest risk of repetition of the cerebral ischemic event is during the first few weeks after the primary CVA. Searching for possible origins of thromboembolism is an integral part of the management of ischemic stroke.^{3,4} Cardiovascular abnormalities are common in patients with acute ischemic stroke (AIS), and they are one of the main causes of stroke mortality. Cardiac abnormalities can cause an AIS through an embolic event and more than 1.5 million people die of post-stroke cardiovascular complications worldwide annually, such as myocardial infarction, unstable angina, congestive, heart failure, coronary artery diseases, and recurrent strokes. Various cardiac disorders including atrial fibrillation (AF), ventricular thrombus, valvular heart disease, cardiac tumors, and structural heart defects can cause cardioembolic stroke and recurrent strokes.¹ Current published data suggest the need for basic categorization

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Access this article online			
Website:			
https://ajmsjournal.info/index.php/AJMS/index			
DOI: 10.71152/ajms.v16i1.4364			
E-ISSN: 2091-0576			
P-ISSN: 2467-9100			

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Table 1: Cardic lesion and their risk ofthromboembolism						
S. No.	Medium-high risk	Low risk				
1	Atrial flutter/ fibrillation	Thrombi in the left ventricle and on left-sided heart valves spontaneous echo contrast Prosthetic mechanical valves				
2	Patent foramen ovale, septal defects	Persistent left superior vena cava intracardiac tumors Infective endocarditis pulmonary arteriovenous malformations				

of possible origins of thromboembolism according to the presumed risk of a thromboembolic event. There are high-risk origins as well as medium and low-risk origins (Table 1).^{5,6}

The use of echocardiography has largely replaced the electrocardiogram (ECG) in knowing the cardiac structural abnormalities. The early focus of echocardiographic predictors of vascular outcome was on LV morphology.² however the use of echocardiogram (ECHO) is changed. Now ECHO is used for early recognition and treatment of cardiovascular abnormalities after AIS. Since Transthoracic echocardiogram (TTE) is non-invasive and gives detailed information on the structures and functioning of the heart. Hence our study's goal is to analyze the echocardiographic results of AIS patients who were admitted to the intensive care unit of our hospital to ascertain how frequently potential pathologic cardiac findings were seen on TTE for secondary stroke prevention as well as to pinpoint circumstances in which echocardiography may be highly or minimally useful.

Aims and objectives

- 1. To identify echocardiography finding in acute stroke
- 2. To assess the relation of echocardiographic findings in patients with anterior circulation and posterior circulation stroke.

MATERIALS AND METHODS

The prospective study was conducted in patients admitted to medical college hospitals affiliated to ESICMC PGIMSR Model Hospital Rajajinagar, Bangalore, Karnataka, from September 2022 to March 2024. The subjects meeting the study criteria explained the nature and purpose of this study and included them after obtaining the informed consent. A detailed history was taken and examination findings were noted. The severity of the stroke was measured by using the National Institute of Health Stroke Scale (NIHSS) and the Glasgow Coma Scale. All the routine investigations including the complete blood counts and biochemical metabolic parameters were done. The chest X-ray and ECG, 24 h Holter monitoring, and Non-contrast computed tomography/magnetic resonance imaging (MRI) brain were done to confirm ischemic stroke followed by TTE have been done. The data collected were analyzed using a statistical package for social sciences version 21.

Inclusion criteria

- 1. Patient willing to give informed consent to participate in the study
- 2. Patients of either gender aged between 18 years
- 3. Patients with either anterior and posterior circulation stroke or also hemorrhagic stroke.

Exclusion criteria

- 1. Patients with venous stroke secondary to Dural Sinus Thrombosis as these strokes do not follow an arterial territory
- 2. Patients with metabolic derangement, such as hypoglycemia, electrolyte imbalance, and hepatic encephalopathy.

Study tools

Detailed pro forma to record the serial number, age, sex, presenting complaints, time in the presentation to the health facility, Presence of co-existent co-morbidities, Family history of stroke, Family history of Diabetes, personal history of Smoking, Alcohol consumption, vitals and detail clinical examination for each patient.

Investigations done-Gamma-ray bursts, computed tomography (CT) scan brain (plain or contrast), MRI scan if required, renal function test, liver function tests and serum electrolytes. CT scan brain and all patients received treatment according to national stroke protocol. All patients were transthoracic echocardiograph was done and details were noted.

Statistical analysis

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean±standard deviation (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. Results were also recorded as frequencies and P-values. P<0.05 was taken as the criteria of significance for all purposes. The Chi-square/Fisher Exact test has been used to find the significance of study parameters on a categorical scale between two or more groups. Student t-test (two-tailed, independent has been used to find the significance of study parameters on a continuous scale between two groups Intergroup analysis) on metric parameters.

RESULTS

In our study during the study period, 67 patients were admitted had AIS. The mean age was 56.07 years. Male was 55 (82.1%) and female were 12 (17.9%). In our study stroke in young i.e. <45 years is 10 patients (14.9%). Table 2 depicts the demographic of the patients admitted during the study period. Table 3 indicates the ECG findings and Table 4 indicates the ECHO cardiographic findings.

The most common ECG finding was sinus rhythm (n=42) followed by AF (n=13), Left ventricular hypertrophy (LVH) (n=8), sinus bradycardia with poor R wave progression (n=1) and sinus tachycardia (n=2) and right bundle branch block (RBBB) (n=1). In our study, the most common ECHO cardiographic finding was concentric LVH (n=22) followed by degenerative mitral valve and aortic (n=31) and Regional wall motion abnormalities (RWMA) (n=17), heart failure with reduced ejection fraction (n=21), followed by dilated cardiomyopathy (DCM) (n=10), LV apical clot (n=7) and left atrial clot (n=7), 4 patients had atrial septal defect (ASD) 2 had a ventricular septal defect (VSD), 2 had Mitral valve prolapse

(MVP) and 1 patient had endocarditis and 1 patient had left atrial myxoma.

DISCUSSION

In our study, patients belong to the age in years for anterior circulation stroke 55.88 ± 12.5 and posterior circulation stroke 56.27 ± 12.22 . Males (n=55) were more than females (n=12) and the majority of them were hypertensive (n=34) and diabetes (n=20). According to Basu et al.,⁷ (Median age 60 years, mean age= 60 ± 13 years, range 25–88 years).

The mean NIHS score at the time of admission was 8.5 ± 4.15 in anterior circulation stroke and 7.94 ± 5.2 in posterior circulation stroke. In Katsanos et al.,⁸ the mean being 5.5 and the study by Mansour et al.,⁹ reported a median NIHSS score of 20.

In the current study, the most common ECG finding was sinus rhythm (n=42) followed by AF (n=13), LVH (n=8), sinus bradycardia with poor R wave progression (n=1), and sinus tachycardia (n=2) and RBBB (n=1).

Table 2: Demographic distribution among anterior and posterior stroke						
Anterior stroke (n=34)	Posterior stroke (n=33)	P-value				
55.88±12.5	56.27±12.22	0.89 on unpaired T-test (Not significant)				
28	27	0.95 on Chi-square				
6	6	(Not significant)				
11	10	0.85 on Chi-square (not significant)				
16	18	0.54 on Chi-square (Not significant)				
8	12	0.25 on Chi-square (not significant)				
1	1	1 on Chi-square (Not significant)				
2	2	1 on Chi-square (Not significant)				
163.79±8.91	160.88±6.98	0.14 on unpaired T-test (Not significant)				
64.88±8.65	63.73±6.25	0.53 on unpaired T-test (Not significant)				
24.24±2.9	24.68±2.6	0.51 on unpaired T-test				
	Anterior stroke (n=34) 55.88±12.5 28 6 11 16 8 1 2 163.79±8.91 64.88±8.65	Anterior stroke (n=34) Posterior stroke (n=33) 55.88±12.5 56.27±12.22 28 27 6 6 11 10 16 18 8 12 1 1 2 2 163.79±8.91 160.88±6.98 64.88±8.65 63.73±6.25				

Table 3: ECG findings in the study participants

Anterior stroke (r	Posterior stroke (n=33)			
ECH fidings	Frequency	Percentage	Frequency	Percentage
Sinus rhythm	19	55.88	23	69.6
Left ventricular hypertrophy	4	11.70588	4	12.12121
Sinus bradycardia with poor R-wave progression	1	2.941176	0	0
Sinus tachycardia	1	2.941176	1	3.030303
Right Bundle Branch block	1	2.941176	0	0
Atrial fibrillation	8	23.5	5	15.1

Anterior stroke	e (n=34)		Posterior stroke (n=33)			
Findings	Frequency	Percentage	Findings	Frequency	Percentag	
Concentric LVH	10	29.4	Concentric LVH	12	36.3	
DCM	5	14.7	DCM	5	15.1	
LV apical clot	5	14.7	LV apical clot	2	6	
Left Atrial clot	5	14.7	Left atrial clot	2	6	
RWMA	7	20.5	RWMA	10	30.3	
Degenerative mitral valve and aortic	17	50	Degenerative mitral valve and aortic	14	42.4	
Patent foramen ovale	2	5.9	Patent foramen ovale	0	0	
ADS	2	5.9	ADS	2	6	
VSD	2	5.9	VSD	0	0	
Heart failure with reduced ejection fraction	7	20.5	Heart failure with reduced ejection fraction	14	42.4	
Cardiac tumor-left atrial myxoma	1	2.9	Cardiac tumor-left atrial myxoma	0	0	
Endocarditis	1	2.9	endocarditis	1	3	
MVP	2	5.9	MVP	1	3	

Table 4: ECHO findings in acute ischemic stroke patients

prolapse, RWMA: Regional wall motion abnormalities

According to Hutyra et al.,¹⁰ AF is the most frequent arrhythmia with exponentially increasing prevalence with age and in individuals with a structurally damaged heart. The prevalence of AF in non-selected populations is estimated in the rather broad estimated range of 1-6%. In the seventh decennium-aged patients, the AF prevalence reaches 5%. The octogenarians' population carries a 10% AF prevalence. More than two-thirds of all atrial cases represent patients between 65 and 85 years of age and the median of age of a patient with AF is set at the age of 75. Atrial flutter is the second most common supraventricular arrhythmia and also has age-dependent incidence which oscillates from 0.005% in patients aged 50 years or younger to 0.59% in patients above the age of 80. Atrial flutter is 2.5 times more frequent in men than in women and again occurs more frequently in patients with structural heart disease or in patients suffering from chronic obstructive pulmonary disease. Of importance, there is no difference in risk of thromboembolic event in between permanent and paroxysmal forms of both AF and atrial flutter. The risk of formation of thrombi in the left atrium (LA) or left atrial appendage is virtually identical. There is well-established relation between AF and ischemic CVA, which represent about 85% of all thromboembolic events in patients with AF. Vice versa, AF is considered to be a cause of 16% of all ischemic CVA. Ten percent of ischemic CVA sufferers have LA thrombi found in the LA. It represents two-thirds of all patients suffering an ischemic stroke due to AF. AF is a cause of almost 80% of all thromboembolic CVA. AF is associated with 5 times higher risk of CVA, 2 times higher risk of death (due to CVA or heart failure) and finally it is associated with higher risk of vascular cognitive deficit in comparison to healthy controls.

In our study most common ECHO cardiographic findings were concentric LVH (n=22) followed by degenerative

mitral valve and aortic (n=31) and RWMA (n=17), heart failure with reduced ejection fraction (n=21), followed by DCM (n=10), LV apical clot (n=7) and left atrial clot (n=7), 4 patients had ASD 2 had VSD, 2 had MVP and 1 patient had endocarditis and 1 patients had left atrial myxoma.

According to Hutyra et al.,¹⁰ Chronic congestive heart failure delivers a 2–3-fold increase in relative risk of CVA. Clinically silent brain embolizations are detectable up to 40% of heart failure patients. Retrospective study of Fuster et al.,¹⁸ showed an 18% incidence of thromboembolic CVA in patients suffering from DCM without anticoagulation therapy in comparison to no case of CVA in patients treated with anticoagulation. Another prospective study demonstrated only a 3% incidence of arterial thromboembolism in 264 heart transplant candidates with LV ejection fraction of <20% in an average 1-year follow-up period.

The incidence of prior ischemic CVA in patients with left ventricle thrombus is estimated to be 12%. Noncompaction cardiomyopathy, restrictive cardiomyopathy, and Löffler's endocarditis represent specific entities with increased risk of intraventricular thrombi formation.

Cryptogenic etiology of ischemic CVA is found in nearly 50% of patients below the age of 55 years and approximately in 25% of individuals with ischemic CVA in all age groups. Cryptogenic etiology means that there is no evidence of intracardiac thrombi, the arterial origin of embolization and there is no evidence of atherosclerosis of intracardial brain vessels. There is relatively substantial evidence in literature proving an association in between cryptogenic CVA and Patent foramen ovale (PFO) (odds ratio [OR] 3.1) or an association in between aneurysms of LA and cryptogenic CVA (OR 6.1) in all age groups. Though the results of

published observational studies are not unequivocal, there are well-known associations that suggest the causal relations in between the cryptogenic recurrent CVA and the presence of PFO, partial gut obstruction morphology, the amount of right to left shunt in particular in younger aged group of patients under the age of 55.

Atrial septum defect is the most common inherited heart defect detected in adulthood. The clinical manifestation may be associated with paradoxical embolization into the cerebral vessels. The most frequent variant of atrial septum defect is the septum secundum atrial defect localized in the central part of the atrial septum. It represents approximately ³/₄ of all atrial septum defect cases. The other variants (sinus venosus superior and inferior defect) are less frequent. Nevertheless, it is important to consider them and to use contrast TEE to visualize them in hard to visualize cases. The rapid passing of contrast material into the left-sided heart chambers is a typical finding.

In the study conducted by Pedipina¹¹ TTE of 80.6% of subjects was normal and the remaining 19.4% had LVH, clot, EF <50%, and mitral valve lesion. The study by Uma et al.,¹² and Caplan et al.,¹³ also had similar findings, such as LVH, mitral valve lesions, and calcifications. LVH was the most common which was a similar finding in the study by Di Tullio et al.,¹⁴ In our study, there were 2 patients with infective endocarditis (IE). In the study conducted by Thuny et al.¹⁵ Embolic events represent one of the most common complications of IE. And according to a study conducted by Mylonakis and Calderwood et al.¹⁶ the incidence of ischemic stroke associated with IE is 15–20%, with the highest risk in the first 7–10 days after presentation. The incidence of ischemic stroke associated with IE is 15–20%, with the highest risk in the first 7–10 days after presentation.

In our study left atrial myxoma is present in 1 patient according to Reynen.¹⁷ Primary cardiac tumors are rare (a prevalence of 0.002–0.3%), accounting for a small number of cerebrovascular events. Two common primary cardiac tumors in adults are myxoma and papillary fibroelastoma, both of which often cause stroke and/or other embolisms. Echocardiography with color and Doppler should be considered in all patients with suspected cardiac tumors. Two-dimensional echocardiographic and RT3DE imaging can reliably identify mass location, attachment, shape, size, and mobility, while defining the presence and extent of any consequent hemodynamic derangement. Cardiac myxoma is the most common benign primary tumor of the heart, accounting for more than 50% of all primary cardiac tumors.¹⁷ Approximately 75% of myxomas are found in the LA, with 20% in the right atrium and the remaining 5% equally distributed between the LV and right ventricle.¹⁷ Valvular origin of these tumors is uncommon. In over 50% of patients, LA myxomas cause symptoms of mitral valve stenosis due to obstruction of flow from LA to LV. Embolic events occur in 30–40% of patients with LA myxoma.¹⁷ TTE imaging is usually sufficient, although small tumors or those that involve the right heart may require TEE for diagnosis.

Limitations of the study

- Only a small number of the population is taken for the study
- As it is a hospital-based study, it may not be representative of the general population.

CONCLUSION

This study reinforces the importance of transthoracic echocardiography in stroke in young patients. Transthoracic echocardiography is not only an effective tool in picking up the clots inside the cardiac chambers but also it was found to be significantly effective in detecting valvular lesions and small septal defects, such as PFO. It is recommended that all stroke patients need to undergo transthoracic echocardiography to find the source and etiology of cardioembolic stroke. More detailed recommendations regarding echocardiography should be included in future guidelines. Moreover, evaluating the impact of echocardiographic examinations on long-term prognosis in stroke patients should be a focus of further evaluation. Moreover echocardiography not only gives details regarding etiological factors but also regarding risk factors that contributed to the stroke per say.

ACKNOWLEDGMENT

I sincerely thank all staff in the Department of Anesthesiology and Department of General Medicine, ESICMC PGIMSR Model Hospital Rajajinagar, Bangalore, Karnataka, India.

REFERENCES

- Nakanishi K and Homma S. Role of echocardiography in patients with stroke. J Cardiol. 2016;68(2):91-99. https://doi.org/10.1016/j.jjcc.2016.05.001
- Savage DD, Garrison RJ, Kannel WB, Levy D, Anderson SJ, Stokes J 3rd, et al. The spectrum of left ventricular hypertrophy in a general population sample: The Framingham Study. Circulation. 1987;75(1 Pt 2):126-133.
- Kral M, Herzig R, Sanak D, Skoloudik D, Bartkova A, Veverka T, et al. Prevention of cardioemboligenic stroke in the Olomouc region of the Czech Republic. J Neurol Sci. 2009;285(Suppl 1):S160. https://doi.org/10.1016/S0022-510X(09)70612-4
- Král M, Šaňák D, Veverka T, Hutyra M, Vindiš D, Kunčarová A, et al. Troponin T in acute ischemic stroke. Am J Cardiol. 2013;112(1):117-121.

https://doi.org/10.1016/j.amjcard.2013.02.067

- Doufekias E, Segal AZ and Kizer JR. Cardiogenic and aortogenic 5. brain embolism. J Am Coll Cardiol. 2008;51(11):1049-1059. https://doi.org/10.1016/j.jacc.2007.11.053
- Pepi M, Evangelista A, Nihoyannopoulos P, Flachskampf FA, 6. Athanassopoulos G, Colonna P, et al. Recommendations for echocardiography use in the diagnosis and management of cardiac sources of embolism: European Association of Echocardiography (EAE) (a registered branch of the ESC). Eur J Echocardiogr. 2010;11(6):461-464.

https://doi.org/10.1093/ejechocard/jeg045

- Basu S, Sanyal D, Roy K and Bhattacharya K. Is post-stroke 7 hyperglycemia a marker of stroke severity and prognosis: A pilot study: Neurol Asia. 2007;12:13-19.
- 8 Katsanos AH, Bhole R, Frogoudaki A, Giannopoulos S, Goyal N, Vrettou AR, et al. The value of transesophageal echocardiography for embolic strokes of undetermined source. Am Acad Neurol. 2016;87(10):988-995.

https://doi.org/10.1212/WNL.000000000003063

- Mansour OY, Megahed MM and Abd Elghany WH. Acute 9 ischemic stroke prognostication, comparison between glasgow coma score, NIHS scale and full outline of unresponsiveness score in intensive care unit. Alex J Med. 2015;51(3):247-253. https://doi.org/10.1016/j.ajme.2014.10.002
- 10. Hutyra M, Pavlů L, Šaňák D, Přeček J, Köcher M, Tüdös Z, et al. The role of echocardiography in patients after ischemic stroke. Cor Vasa. 2016;58(2):e261-e272. https://doi.org/10.1016/j.crvasa.2016.02.003
- 11. Pedipina S, Singhal S, Guleria V and Sarvani B. Correlation

of ischemic stroke with echocardiographic findings in young patients. Med Res Arch. 2022;10(9):1-6. https://doi.org/10.18103/mra.v10i9.3074

- 12. Uma N, Chugh SK, Harshwardhan, Goel A and Gopal D. Echocardiography in patients with cerebral infarction. J Assoc Physicians India. 1999;47(3):291-293.
- 13. Caplan LR, Hier DB and D'Cruz I. Cerebral embolism in the michael reese stroke registry. Stroke. 1983;14(4):530-536. https://doi.org/10.1161/01.str.14.4.530
- 14. Di Tullio MR, Zwas DR, Sacco RL, Sciacca RR and HommaS. Left ventricular mass and geometry and the risk of ischemic stroke. Stroke. 2003;34(10):2380-2384.

https://doi.org/10.1161/01.STR.0000089680.77236.60

15. Thuny F, Avierinos JF, Tribouilloy C, Giorgi R, Casalta JP, Milandre L, et al. Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: A prospective multicentre study. Eur Heart J. 2007;28(9): 1155-1161.

https://doi.org/10.1093/eurheartj/ehm005

- 16. Mylonakis E and Calderwood SB. Infective endocarditis in adults. N Engl J Med. 2001;345(18):1318-1330. https://doi.org/10.1056/NEJMra010082
- 17. Reynen K. Cardiac myxomas. N Engl J Med. 1995;333(24): 1610-1617.

https://doi.org/10.1056/NEJM199512143332407

18. Fuster V, Gersh BJ, Giuliani ER, Tajik AJ, Brandenburg RO and Frye RL. The natural history of idiopathic dilated cardiomyopathy. Am J Cardiol. 1981;47(3):525-531.

https://doi.org/10.1016/0002-9149(81)90534-8

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LSB- Concept, design, sample collection, analysis, manuscript preparation, preparation of 1st draft of the manuscript, review of result analysis and interpretation, review of manuscript, intensive care unit (ICU) case management; LV- Protocol, sample collection, edition, manuscript revision, statistical analysis, ICU case management and literature survey.

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Source of Support: Nil, Conflicts of Interest: None declared.