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Transthoracic echocardiography indices as a biomarker in patients with embolic stroke of undetermined source

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Abstract

Background: Embolic stroke of undetermined source (ESUS) refers to a nonlacunar, nonatherosclerotic infarct in the absence of cardioembolic source or other specific causes of stroke. The presence of ESUS strokes indicates that the conventional risk factors cannot fully account for the pathogenesis of stroke. It is very important to detect useful biomarkers of the risk of ESUS for appropriate 2ry prevention.

Results: The present study showed significant increase in left ventricular hypertrophy (LVH) measured by left ventricular mass index and increased left atrial volume index, measuring left atrial dilatation, among ESUS patients.

Conclusions: Patients with ESUS tended to have Echocardiographic features of heart failure with a preserved ejection fraction (HFpEF) as LVH and left atrial dilatation. Therefore, they should be considered as biomarkers for cardioembolic cerebrovascular accidents with the consideration of anticoagulation with new oral anticoagulants as a primary preventive measure.

Keywords: Embolic stroke of undetermined source (ESUS), Echocardiography, Biomarkers

Background

Stroke is a major health problem in Egypt. The number of new strokes in Egypt per year may be around 150,000 to 210,000, and ischemic stroke accounts for approximately 80% of them. In addition, stroke accounts for 6.4% of all deaths in Egypt and thus ranks 3rd after heart disease and gastrointestinal diseases [1].

Identification of the etiology of stroke is necessary to prepare an adequate preventive strategy [2]. According to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification system, 25% of all ischemic strokes are of undetermined etiology (cryptogenic stroke) [3]. The term cryptogenic stroke is replaced by embolic stroke of undetermined etiology (ESUS) by The International Working Group in 2014 [4].

ESUS refers to a nonlacunar, nonatherosclerotic infarct in the absence of cardioembolic source or other specific causes of stroke [4]. The presence of ESUS strokes indicates that the conventional risk factors cannot fully account for the pathogenesis of stroke. It is very important to detect useful biomarkers of the risk of ESUS for appropriate 2ry prevention [5].

Objectives

To identify echocardiographic indices of embolic stroke of undetermined source.

Methods

A case–control observational analytical study conducted in Ain Shams University Specialized Hospital Stroke unit after obtaining approval from Ain Shams University Faculty of Medicine local research ethics committee. All participants provided informed written consent to participate in the study. One hundred and twenty patients were recreuited; 60 patients as a case group with

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diagnosis of ESUS and 60 patients with ischemic stroke other than ESUS as control group matched to case group in age and sex. All included patients were submitted to detailed medical history, thorough general and neurological examination, full metabolic profile, 72 h Electrocardiogram monitoring, carotid and vertebral duplex, and computed tomography (CT) brain. All patients were submitted to transthoracic echocardiogram examination using Doppler Echocardiography unit (GE vingmed ultrasound, Horton Nerway model vivid expert) with emphasizing on: (1) the left ventricular (LV) ejection fraction (EF%) using biplane Simpson's method and M-mode, (2) the segmental LV wall motion abnormalities (SWMAs), and the LV mass was calculated using the Devereux formula, and (3) the left atrial volume index (LAVI) was measured using the biplane method [6]. All recruited patients were submitted to Magnetic Resonance Imaging (MRI) brain, including T1- and T2-weighted images, diffusion-weighted images (DWI), fluid-attenuated inversion recovery (FLAIR), magnetic resonance angiography (MRA), and gradient recalled echo (GRE) T2*-weighted images, using a machine 1.5T General Electric machine. All case patients had the diagnosis of ESUS that is defined as nonlacunar infarct, which means a subcortical infarct ≤ 1.5 cm on CT or ≤ 2.0 cm on MRI in the absence of the following: cardioembolic sources, such as permanent or paroxysmal atrial fibrillation (AF) or atrial flutter, intracardiac thrombus or tumors, prosthetic cardiac valve, mitral stenosis, myocardial infarction within the past 4 weeks, left ventricular ejection fraction < 30%, valvular vegetations, or infective endocarditis as well as extracranial or intracranial atherosclerosis causing > 50% luminal stenosis in the artery supplying the ischemic region and other specific causes of stroke (e.g., dissection, arteritis, migraine/vasospasm, hematological diseases and coagulopathies, and drug misuse) [4, 5]. All control patients had the diagnosis of ischemic stroke other than ESUS verified by MRI and MRA brain, echocardiographic, and carotid duplex indicies. The exclusion criteria were as follows: various types of intracerebral haemorrhge, unstable hypertension, renal dialysis, cancer, autoimmunologic disease, reception of cytostatic, immunosuppression drugs, glucocorticosteroids, alcoholism, and addiction to medicines.

Statistical analysis of data
Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Probability (*p* value): *p* value < 0.05 was considered significant, *p*-value < 0.001 was considered as highly significant, *p*-value > 0.05 was considered insignificant.

Results
One hundred and twenty patients (60 patients as a case group with diagnosis of ESUS and 60 patients with ischemic stroke other than ESUS) were recruited in the time period between July 2016 and October 2017.

There were no significant differences between both groups in the age, sex, or additional diseases, such as coronary artery disease, hypertension, diabetes, and dyslipidemia, as shown in Table 1.

The LV mass index indicating left ventricular hypertrophy (LVH) was higher in the ESUS group than in controls (*p* = 0.006), as shown in Table 2, Fig. 1.

The mean left atrial volume index indicating left atrial diameter (LAD) was higher in the ESUS group than in controls (*p* < 0.001), as shown in Table 3, Fig. 2.

Discussion
On one hand the characteristics and predictors of ESUS are still unknown [7]. On the other hand, a growing number of studies have demonstrated the association between left ventricular hypertrophy (LVH) and left atrial dilatation, that reflect the aggravation of stroke of different origins as well as cryptogenic stroke [8].

Echocardiographic findings of normal ejection fraction (exceeding 50%), LVH and left atrial dilatation are strong predictors for heart failure with a preserved ejection fraction (HFpEF) [9]. Patients with heart failure are at risk from thromboembolic events which is a result of Virchow's triad of risk factors for thrombus formation. In addition, undetected (paroxysmal) AF may be common in patients with HFpEF and not detecting this may lead to associated cerebral infarcts [10].

Interestingly, nearly half of all patients with heart failure have a preserved ejection fraction and its prevalence is rising, with morbidity and mortality, equal to that of reduced ejection fraction [11]. Little is known about the incidence of stroke in HFpEF yet, Cogswell et al., hypothesized that stroke risk in patients with HFpEF without atrial fibrillation (AF) and AF only was similar [12].

The results of the present study showed significant increase in LVH measured by left ventricular mass index and increased left atrial volume index, measuring left atrial dilatation, among ESUS patients, which is in agreement with many studies.

In the study by Lee et al., the authors compared the LAVI values between ESUS patients with patent foramen ovale (PFO) and healthy subjects with PFO and found that the ESUS patients had larger left atrial (LA) volumes than controls regardless of the presence of PFO. What is interesting is that LA enlargement, but not the amount

Table 1 Basic characteristics of patients in both groups:

	Controls		Patients		Total		Chi-square	
	N	%	N	%	N	%	X^2	*p*-value
Age group								
<60	26	43.3%	36	60.0%	62	51.7%	3.353	0.067
>60	34	56.7%	24	40.0%	58	48.3%		
Sex								
Male	26	43.3%	35	58.3%	61	50.8%	2.134	0.144
Female	34	56.7%	25	41.7%	59	49.2%		
Smoker								
Yes	20	33.3%	27	45.0%	47	39.2%	2.213	0.331
No	33	55.0%	25	41.7%	58	48.3%		
Ex-smoker	7	11.7%	8	13.3%	15	12.5%		
Alcohol								
Yes	2	3.3%	0	0.0%	2	1.7%	2.806	0.094
No	58	96.7%	60	100.0%	118	98.3%		
Handedness								
Right	60	100.0%	60	100.0%	120	100.0%	–	–
Type2 diabetes mellutis								
Yes	40	66.7%	36	60.0%	76	63.3%	0.323	0.570
No	20	33.3%	24	40.0%	44	36.7%		
Hypertension								
Yes	43	71.7%	39	65.0%	82	68.3%	0.347	0.556
No	17	28.3%	21	35.0%	38	31.7%		
Heart disease								
No	38	63.3%	38	63.3%	76	63.3%	2.868	0.238
Atrial fibrillation	0	0.0%	2	3.3%	2	1.7%		
Ischemic heart disease	22	36.7%	20	33.3%	42	35.0%		
Dyslipidemia								
No	46	76.7%	50	83.3%	96	80.0%	0.469	0.493
Yes	14	23.3%	10	16.7%	24	20.0%		
Transient ischemic attacks								
No	47	78.3%	52	86.7%	99	82.5%	0.924	0.336
Yes	13	21.7%	8	13.3%	21	17.5%		
Antiplatelet								
No	32	53.3%	40	66.7%	72	60.0%	1.701	0.192
Yes	28	46.7%	20	33.3%	48	40.0%		
Anticoagulant								
No	60	100.0%	60	100.0%	120	100.0%	–	–
Lipid lowering								
No	43	71.7%	49	81.7%	92	76.7%	1.165	0.281
Yes	17	28.3%	11	18.3%	28	23.3%		

of shunting, was associated with cortical infarcts, which could imply recurrent embolic strokes. In addition, Lee et al. suggested that left atrial dysfunction could be a marker of incident AF, atrial thrombi, and thromboembolic risks of AF [13].

Baturova et al. reported that left atrial dilatation assessed by LAVI independently predicted AF after stroke in patients without prior AF history, while the other clinical or electrocardiography (ECG) markers were not predictive for AF detection early after ischemic stroke. The authors suggest that initially, there is development of subtle structural changes predictive for future AF seen in echocardiography (for example, increased LAVI) [14].

Table 2 Evaluation of LVH in both groups

| | Echo-LVH | | | | | | Chi-square | |
| | Controls | | Patients | | Total | | | |
	N	%	N	%	N	%	X^2	*p*-value
No	47	78.3%	32	53.4%	79	65.8%	10.309	0.006*
Yes	13	21.7%	28	46.7%	41	34.2%		
Total	60	100.0%	60	100.0%	120	100.0%		

*Significant

Fig. 1 Comparison between both groups in LVH
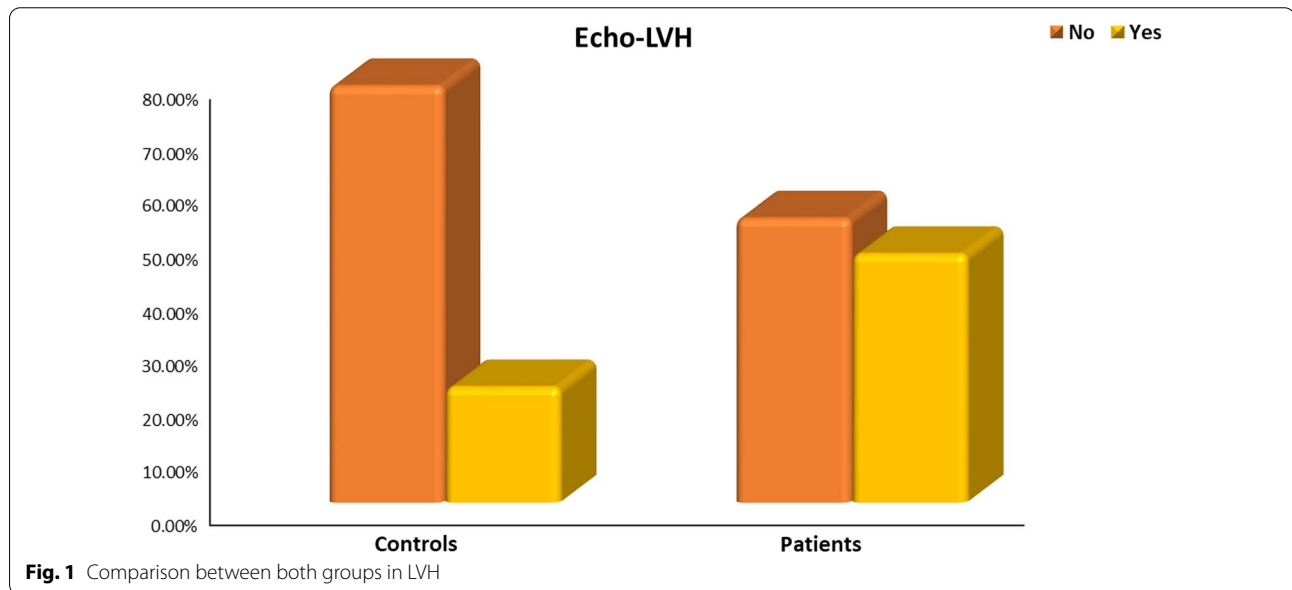
Table 3 Evaluation of LAD in both groups

| Echo-LAD | Controls | Patients | T-test | |
			t	*p*-value
Range	25–42	29–51	10.152	< 0.001*
Mean ± SD	33.433 ± 4.064	42.10 ± 5.216		

*Significant

The increased LAVI in the aspect of ESUS stroke may also be important as a predictor of paroxysmal AF as a true cause of stroke. Detecting AF after ischemic stroke is challenging because of its paroxysmal nature and often silent, asymptomatic course, as was confirmed in studies with implantable devices [14].

Accordingly, patients with Echocardiographic features of HFpEF should be considered at risk of cardioembolic cerebrovascular accidents with consequently, anticoagulation with new oral anticoagulants should be considered as a primary preventive measure for cardioembolic stroke.

It is clear that the design of this study was observational, which can only demonstrate associations and is susceptible to giving confounding results. Therefore, there is a need for larger scale multicenter randomized control trials to confirm the association between LVH measured by left ventricular mass index and increased LAVI, measuring left atrial dilatation, and ESUS.

Limitations
The sample size was small. Verification of results on a larger sample size is required. Echocardiographic indices are not the only markers to detect ESUS. Biomarkers of other modalities need to be explored to detect pathogenesis of ESUS events.

Conclusions
Patients with ESUS tended to have echocardiographic features of HFpEF as LVH and left atrial dilatation. Consequently, these parameters can be used as

Fig. 2 ROC chart for LAD in both groups
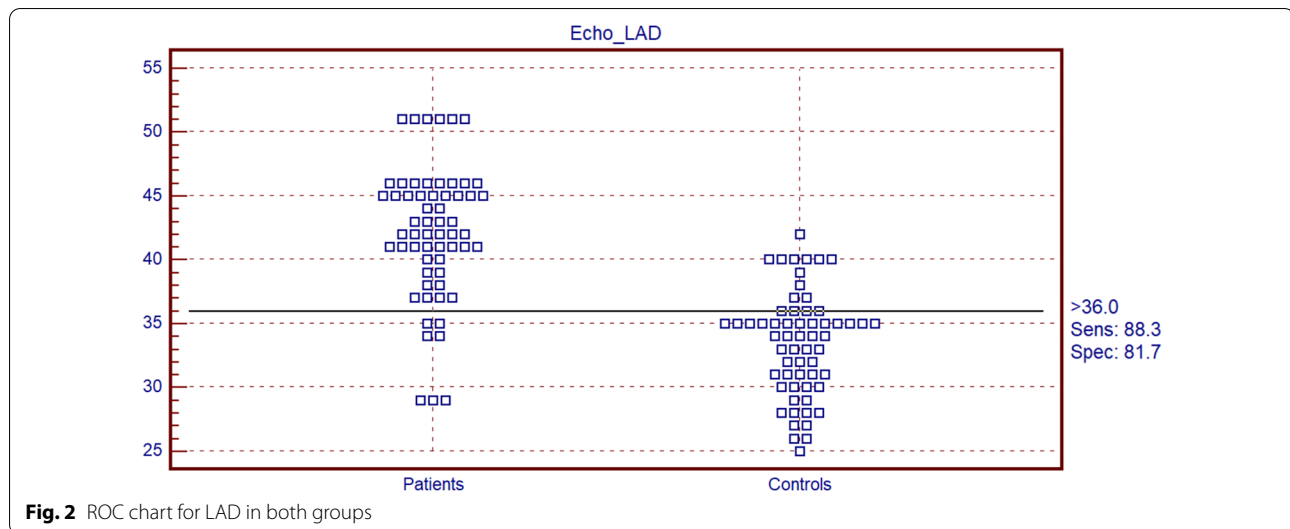
biomarkers for the liability of cardioembolic cerebrovascular accidents which could be primarily prevented using new oral anticoagulants, thus reducing morbidity and mortality. These biomarkers are easy to perform as it is done using a cheap, non-invasive modality, such as transthoracic echocardiographic, negating the need for more sophisticated investigations, such as transoesophageal echocardiography.

Abbreviations
AF: Atrial fibrillation; CT: Computed tomography; DWI: Diffusion weighted imaging; ECG: Electrocardiography; EF: Ejection fraction; ESUS: Embolic stroke of undetermined source; FLAIR: Fluid attenuated inversion recovery; GRE: Gradient recalled echo; HFpEF: Heart failure with preserved ejection fraction; LA: Left atrial; LAD: Left atrial diameter; LAVI: Left atrial volume index; LV: Left ventricle; LVH: Left ventricular hypertrophy; MRA: Magnetic resonance angiography; MRI: Magnetic resonance imaging; PFO: Patent foramen ovale; SWMA: Segmental wall motion abnormality; TOAST: Trial of Org 10172 in acute stroke treatment.

Declarations

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