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Left atrial function index in embolic stroke of undetermined source: A case-control study

[1]Marzieh Tajmirriahi, [2]Parisa Salari, [3]Mohammad Saadatnia

[1]Hypertension Research Center, Isfahan Cardiovascular Research Institute; [2]Department of Cardiology; [3]Isfahan Neurosciences Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.

Abstract

Background & Objectives: Previous studies showed left atrial volume index (LAVi) is a precise surrogate of atrial cardiopathy and associated with new-onset atrial fibrillation and embolic stroke undetermined source (ESUS). Recent data suggest that the left atrial functional index (LAFi) is associated with the risk of developing AF recurrence. However, there was no study to show LAFi in ESUS. We aim to compare the performance of different surrogates of atrial cardiopathy (LAVi and LAFi) in a cohort of ESUS patients and healthy adults. *Methods:* Between Dec 2018 to Feb 2020, consecutive patients diagnosed with ESUS and normal healthy controls (>18 years) were included. Left atrial diameter (LAD), left atrial diameter index (LADi), LAVi and LAFi were measured by transthoracic echocardiogram under American Society of Echocardiography guidelines. Results: A total of 125 patients (43 controls and 82 ESUS patients) were compared. Significant differences of LADi, LAVi, and LAFi were detected between ESUS and control (p=0.04, p=0.002, and p=0.001, respectively). On adjustment for age, sex, hypertension, and diabetes mellitus, LADi and LAVi the association with ESUS and LAFi (aOR decrease, 0.928; 95% CI 0.882–0.976; p = 0.004) remained significant and LAD, LADi, and LAVi were not associated with ESUS in this analysis.
Conclusions: LAFi may be a more comprehensive predictor of atrial cardiopathy as compared to LADi and LAVi in risk stratification of ESUS or cryptogenic stroke.

Keyword: embolic stroke undetermined source, Left atrial function index, left atrial volume index, left atrial diameter index

INTRODUCTION

Determining the Ischemic stroke mechanism helps clinicians to recognize patients with preventable causes and create an appropriate approach for secondary and tertiary prevention.[1] Embolic stroke of undetermined source (ESUS) accounts for 9 to 30% of all ischemic strokes, where the exact etiology, pathophysiology, and preventable treatment of the stroke remain unknown.[1,2] Two large randomized trials, the NAVIGATE ESUS and RE-SPECT ESUS which studied rivaroxaban and dabigatran respectively, could not confirm a preventive role for direct oral anticoagulation in ESUS patients.[3,4]

The ASSERT study showed an association between subclinical atrial fibrillation (AF) and an increased risk of embolic stroke and ESUS. However, there was a lack of a clear temporal relationship between arrhythmia and stroke development.[5] This suggests that there may be other etiologic factors that may play a role in the pathogenesis of AF and ESUS. Evolving evidence suggests that left atrial (LA) remodeling in the absence of captured AF may be associated with the pathophysiology of incident AF, adverse cardiovascular outcomes, and ischemic stroke development.[6-13]

Indeed, left atrial remodeling mainly refers to structural and functional factors. The marker of LA structural factors consist of left atrial diameter (LAD), left atrial diameter index (LADi), and left atrial volume index, and functional factors mainly consist of the left atrial functional index (LAFi) and LA strain.[8-13]

Many studies showed LAD, LADi, LAVi as structural changes markers in the left atrium have been linked to the pathophysiology of incident AF, ischemic stroke, and adverse cardiovascular

Address correspondence to: Mohammad Saadatnia, Isfahan Neurosciences Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. Alzahra Hospital, Sofeh Street, Isfahan, 81744 Iran. Tel: 00989131147179; Email: mosaadatnia@yahoo.com

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outcomes, however, they showed LAVi may be a superior predictor of atrial cardiopathy to LADi in aiding risk stratification of ESUS.[9,13]

Additionally, there is evidence supporting LA strain as a measure of subclinical LA dysfunction with incremental value in prediction of AF in stroke cohort over traditional clinical and echocardiographic parameters and may further refine the risk for cardioembolic stroke.[10-12]

In addition to these markers, LAFi has been advocated as a composite standard 2-dimensional echocardiographic measure of both LA structure and function that also adjusts for LV systolic function in comparison to LA strain.[14] And maybe better able to account for both structural and functional LA remodeling than other echocardiographic measures when they are considered in isolation.[14] Recent data suggest that LAFi is strongly associated with risk for developing AF recurrence, heart failure, and stroke in select CVD-based samples.[14]

However, there was no study to show LAFi in ESUS, hence the purpose of the current study is to compare the performance of different surrogates of atrial cardiopathy (LAVi, LAD, LADi, and LAFi) in a cohort of ESUS patients and healthy adult.

METHODS

Study population

The study was conducted from Dec 2018 to Feb 2020 in the department of neurology and cardiology of Khorshid and Alzahra Hospital of Isfahan University of Medical Sciences. In the study period, consecutive patients (aged >18) diagnosed with ESUS were included. ESUS was diagnosed in accordance with the consensus criteria defined by the Cryptogenic Stroke/ESUS International Working Group as the presence of non-lacunar ischemic stroke, absence of atherosclerosis causing ≥50% luminal stenosis, left ventricular ejection fraction (LVEF) ≥30%, and no identifiable cardioembolic source of embolism such as prior AF.[1] All patients had neuroimaging (computed tomography [CT] or magnetic resonance imaging [MRI]) and vascular studies (CT angiography, magnetic resonance angiography, or transcranial and extracranial Doppler sonography), 24-h inpatient cardiac telemetry or Holter monitoring, and transthoracic 2D-echocardiography (TTE). These patients were compared to age (>18 years) and sex-matched (simple matching) normal healthy without any history of coronary artery disease, stroke, AF, and congestive heart failure as control group identified from referrals to our echocardiography laboratory. Demographic data such as age, sex, comorbidities, history of cardiovascular disease, hypertension, diabetes mellitus, smoking, and hyperlipidemia were recorded in both groups. All participants (or their parents or guardians) have given their written informed consent. The study obtained the approval of the University Ethics Committee (Number: IR.MUI.MED.REC.1398. 324)

Echocardiography

TTE was performed using available tools according to recommendations of the American Society of Echocardiography (ASE).[15] All subjects were in sinus rhythm at the time the measurements were obtained with analysis performed using a mean of three cardiac cycles.

Echocardiographic measurements

Echocardiographic image acquisition was performed by one cardiologist (MT) with settings optimal for LV assessment. Routine M- mode and 2- dimensional echocardiography were performed using a standard protocol as described previously. In the apical- 2 and apical 4 chamber views, LV end- diastolic and end- systolic volumes and LV ejection fraction were measured using Simpson's biplane method. LV outflow tract (LVOT) diameter was measured in the parasternal long- axis view.[15] Left ventricular outflow tract velocity time integral (LVOT- VTI) was calculated by placing the pulsed Doppler sample volume in the outflow tract below the aortic valve and recording the velocity (cm/s).[16]

LAD was measured using the anteroposterior diameter of LA in the parasternal long-axis view perpendicular to the aortic root long axis and at the level of aortic sinuses by the leading-edge to leading-edge convention and LADi was equal to LAD divided by the body surface area. For LA volume measurement, we used LAVi with the area-length method that divided by the body surface area. A "high" LAVi was >34 mL/m2, "high" LADi was >23 mm/ m2, and "high" LAD was >40 mm, defined in accordance with guidelines from the American Society of Echocardiography.[15] LAFi was calculated using a previously derived formula: LAFI= (LA emptying fraction×LVOT-VTI) - (LAmax index). LA emptying fraction was derived as ([LAmax – LAmin]/LAmax)×100.[14]

Continuous variables were presented as mean ± standard deviation and compared using the t-test. Categorical variables were presented as

Table 1: Baseline characteristic of ESUS and control groups

Variable	Control groups (n=43)	ESUS patients (n=82)	P value
Age	55.58 ± 10.5	59.57 ± 13.6	0.97
Sex (female %)	23 (53.5%)	37 (45.1%)	0.24
Body surface area	1.79 ± 0.19 m^2	1.77 ± 0.17 m^2	0.62
Hypertension	39 (47.6%)	18 (41.9%)	0.33
Diabetes	4 (9.3%)	5 (6.1%)	0.37
Smoking	2 (4.7%)	6 (7.3%)	0.43
Hyperlipidemia	4 (9.3%)	5 (6.1%)	0.36

percentages and analyzed using the $\chi 2$ test or Fisher's exact test as appropriate. A multivariable logistic regression model adjusting for age, sex, hypertension, and diabetes mellitus, LADi, LAVi, and LAFi was performed to identify independently associated with ESUS. All statistical tests were performed using SPSS (version 24; IBM SPSS, Chicago, IL), where a p-value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

A total of 125 patients (43 controls and 82 ESUS patients) were compared. Table 1 showed the baseline characteristic of both groups. There were no significant differences in age, sex, vascular risk factors (hypertension, diabetes, smoking, and hyperlipidemia), or body surface area (BSA) between the two groups.

Echocardiographic parameters

Table 2 showed significant differences in left ventricular ejection fraction (LVEF) and LVOT-VTI between the two groups. Though there were no significant differences in the measurement of left atrial empty fraction (LAEF), a reduction in LAFi was appreciated in ESUS patients in comparison to the healthy controls (P=0.001) (Table 2). When stratified by LAVi, 38 (46.9%) patients and 11 (25.6 %) healthy control had a "high" LAVi (>34 mL/m2) (p=0.016). On adjustment for age, sex, hypertension, and diabetes mellitus, LADi and LAVi the association with ESUS and LAFi (aOR decrease, 0.928; 95% CI 0.882–0.976; p = 0.004) remained significant and LAD, LADi, and LAVi were not associated with ESUS in this analysis.

DISCUSSION

Our study findings showed a significant reduction in LAFi and a significant increase in LAVi in ESUS patients in comparison to the control group despite similar age and comorbidities. In addition reduction of LAFi remained significant after regression analysis with age, sex, and LAVi.

Table 2: Comparison of echocardiographic parameters between healthy controls and ESUS patients

Variable	Control group (n=43)	ESUS patients (n=82)	P value
LVEF (%)	57.44 ± 2.52	55.85 ± 4.56	0.03
LVOT-VTI*	20.39 ± 2.63	19.01 ± 2.96	0.01
LA max volume (ml)	55.03 ± 13.42	63.93 ± 17.12	0.004
LA min volume (ml)	29.84 ± 8.23	35.04 ± 11.44	0.009
LAD	32.62 ± 4.37	34.64± 4.80	0.056
LADi	18.21± 2.94	19.70±3.51	0.04
LA volume index (LAVi) (ml/m^2)	30.71 ± 6.99	36.00 ± 9.45	0.002
LA EF (%)	45.46 ± 10.34	45.33 ± 8.24	0.93
LA functional index (LAFi)	31.68 ± 11.00	25.49 ± 8.24	0.001

The most commonly used measurement of LA size in ESUS trials was LAD in NAVIGATE ESUS[17,18] and LADi in ARCADIA trial.[19] NAVIGATE ESUS showed anticoagulant therapy in ESUS patients with LAD >4.6 cm reduced risk of ischemic stroke and the ARCADIA trial investigates the use of anticoagulation in ESUS patients at high risk of atrial cardiopathy, adopting a LADi cutoff of ≥3 cm/m2 as a marker of left atrial enlargement.[17-19] In recent study showed, LAVi is associated with new-onset AF and stroke recurrence in ESUS patients and may be a better surrogate of atrial cardiopathy than LAD and LADi.[13] LA volume takes into account all directions of enlargement and is a more precise marker of cardiovascular events than LAD and LADi in patients with sinus rhythm.[13] Consistent with the past literature, we also observed significant differences of LADi and LAVi in ESUS patients in comparison to the control group.

However, a recent study showed that LAFi was associated with incident cardiovascular disease (CVD) and AF, overall and among those with normal LA volume, even after adjustment for clinical and echocardiographic CVD risk factors.[14] Indeed, two recent studies[20,21] using cardiac magnetic resonance (CMR) showed that reduced total LAEF was associated with incident stroke independent of known cerebrovascular and risk factors, and incident AF and impaired LA function and LA enlargement were associated with more PACs/hour on extended ambulatory electrocardiographic monitoring. In this study, we showed LAFi can be associated with ESUS even after regression with LAVi. It seems LAFi can be a more comprehensive index for the prediction of LA cardiopathy than LADi and LAVi in ESUS patients. On the other hand, LAFi might be a good indicator of LA cardiopathy in the presence of normal LA volume in assisting risk stratification of ESUS and LAFi may add further information in stratifying asymptomatic individuals at risk for ischemic stroke.

The limitations of this study were: First, we utilized 2-dimensional echocardiography to measure LA volumes, which have a lower correlation with magnetic resonance imaging–measured volumes than those measured by 3-dimensional echocardiography.[22] Second, non-volumetric measures of atrial function, such as atrial strain, were not available for our analyses. Therefore, we were unable to directly compare the predictive ability of LAFi with atrial strain. The sample size in our study was small and thus some of the negative findings may be due to a lack of power, on the other hand, because of bubble injection in echography, many controls refused to participate in the study. Therefore control group was smaller than case group. Third, there was only one person doing the echo with the associated tendency for bias.

In conclusion, we propose that LAFi may be a more comprehensive predictor of atrial cardiopathy to LADi and LAVi in assisting risk stratification of ESUS. Consideration should be given to the measurement of atrial function over atrial volume alone in case selection for randomized controlled trials investigating anticoagulation strategies for ESUS. Our findings are consistent with other studies, which have shown an association between indicators of atrial pathology and ischemic stroke in the absence of captured AF, suggesting that tissue substrate rather than arrhythmia status can be the primary driver of stroke risk.

DISCLOSURE

Ethics approval: The study obtained the approval of the University Ethics Committee (Number: IR.MUI.MED.REC.1398. 324).

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