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A correlation of the ratio of left atrial volume to left ventricular ejection fraction in predicting atrial fibrillation in ischemic stroke

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Ethics Committee Approval
This study was approved by the Non-Interventional Clinical Research Ethics Committee of Sancaktepe Şehit Professor Doctor İlhan Varank Training and Research Hospital before the initiation of the study (Decision No: 2021/197, Date: 29.09.2021).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The enlargement of left atrial volume index (LAVI) in diastolic dysfunction (DD) may predispose one to atrial fibrillation (AF) and is an important etiological reason for ischemic stroke (IS). The ratio of LAVI increase to left ventricular ejection fraction (LVEF) is a new parameter, and this work investigates the correlation between DD parameters, LAVI, LAVI/LVEF ratio, and AF in patients with sinus rhythm presenting with IS.
Methods: Here, 108 consecutive individuals who were diagnosed with IS were included in the case-control study. The patients were divided into two groups: Those with AF events on rhythm Holters (AF group, n=57) and those without (control group, n=51). LAVI was calculated from the apical four- and two-chamber views before the mitral valve was opened. LVEF was calculated by Simpson's method.
Results: The mean age of the AF group was 73.9 (6.3) years, and the control group was 72.1 (3.9) years. Hypertension, diabetes mellitus, glucose, HbA1c, CHA_2DS_2-VASc score, and previous stroke were higher in the AF group (P<0.05). LAVI (35.7 [25.3-38.2] vs 29.6 [27.7-30.9], P<0.001), the LAVI/LVEF ratio (0.7 [0.63-0.77] vs 0.5 [0.50-0.54], P<0.001), and the E/é ratio (14.6 [13.9-15.0] vs 10.7 [9.0-11.8], P<0.001) were higher in patients with AF. Multivariable analyses showed that LAVI (OR:7.985, 95%CI [2.586-4.767], P<0.001) and the LAVI/LVEF ratio (OR:0.010, 95% CI [0.000-0.007], P=0.015) were potential independent risk factors for AF events. A positive correlation was found between the CHA_2DS_2-VASc score and LAVI (P=0.032, r=0.407) and LAVI/LVEF ratio (P=0.041, r=0.253).
Conclusion: We concluded that the increase in LAVI and LAVI/LVEF ratio increases the risk of IS by increasing the tendency to AF. These parameters are useful in predicting IS.

Keywords: ischemic stroke, atrial fibrillation, left atrial volume, ejection fraction

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Introduction

Ischemic stroke (IS) is one of the leading causes of mortality and morbidity worldwide [1]. Cardiovascular diseases, diabetes mellitus (DM), hypertension (HT), and atrial fibrillation (AF) are the strongest risk factors for thromboembolism leading to acute ischemic stroke [2]. Having AF enhances the risk of IS five-fold [2, 3]. AF is the most common rhythm problem specifically in elderly patients, and many factors play a role in its etiology [2]. The enlargement of the left atrium as well as metabolic and hormonal factors pave the way for the formation of AF. In addition, one of the most important factors causing left atrial enlargement is left ventricular diastolic dysfunction (DD) [4, 5].

The dilatation of left atrial volume in DD may predispose one to AF which is one of the major etiological reasons for ischemic stroke. However, DD is not considered an etiological factor for ischemic stroke when making the current risk score calculation. However, the increased left atrial volume index (LAVI) is an important diagnostic indicator for the echocardiographic definition of DD [4]. The increasing ratio of LAVI to left ventricular ejection fraction (LVEF) is a new parameter and is being investigated in terms of efficacy in predicting AF. In this study, we investigated the correlation between DD parameters, LAVI, LAVI/LVEF ratio, and AF in patients with sinus rhythm presenting with IS.

Materials and methods

We included 108 consecutive individuals received to our hospital with IS. All subjects underwent 24-hour rhythm Holter recording and echocardiographic imaging within the first 72 hours after hospitalization. All patients were divided into two groups: those patients with newly diagnosed AF events on rhythm Holters (atrial fibrillation group) and those without (control group). The two groups were checked in terms of demographic, clinical, and echocardiographic characteristics.

Exclusion criteria: Patients with carotid artery disease, those diagnosed with heart failure and LVEF ≤40, patients with moderate or severe mitral/aortic stenosis or regurgitation, and patients who had previously diagnosed AF or received invasive or non-invasive treatment for AF were excluded.

Diagnosis of ischemic stroke: The diagnosis of IS was made based on the recommendations of the American Stroke Association after a detailed history, physical examination, and brain imaging [1]. Neurological examination was performed according to the National Institute Health Stroke Scale (NIHSS). [1]. Venous blood specimens were taken from all patients after at least 8 hours of fasting, and biochemical and hematological analyzes were performed using standard laboratory methods.

24-hour rhythm Holter and diagnosis of atrial fibrillation: A 24-hour rhythm Holter was performed on all patients diagnosed with ischemic stroke within the first 72 hours after hospitalization. Holter recordings were analyzed with Cardioscan 12.0 (DM Software Inc., Stateline, NV, US) software. All recordings were made in accordance with ISHNE-HRS expert opinions, and these results were interpreted by two different cardiologists [6]. The diagnosis of AF was made according to the recommendations of the current guidelines [7]. Standard 12-lead ECG registering or single-lead ECG trace ≥30 sec with an absence of recognizable repetitive P waves and non-uniform RR intervals (when the atrioventricular transmission is not impaired) were considered diagnostic for clinical AF.

Echocardiography: The Society of American Echocardiography recommendations were considered during echocardiography. All individuals visited a transthoracic echocardiographic consultation with an available trading device (Wisconsin, GE Vingmed, Milwaukee, Vivid 9 Pro, USA). Images were taken in the lateral left decubitus position [8]. All common measurements (LA end-systolic diameter, LV end-systolic/diastolic diameters, etc.) were taken from the apical four-chamber and parasternal long-axis views. Simpson's method was used for calculating LVEF. A single-lead electrocardiogram was continually registered.

Measurements were taken for LAVI from the apical two- and four-chamber view before the mitral valve was opened. According to DD guidelines, the LA volume was measured in custom views maximizing LA length and transverse diameters. When applying PW Doppler, the mitral peak E-wave (cm/s) velocity was acquired from color imaging of the apical four chambers for optimal alignment with blood flow (1-3 mm axial size) between the mitral leaflet tips. A PW Doppler velocity (cm/s) sample volume (mostly 5-10 mm axial size) in the mitral lateral and septal regions was measured in the apical four-chamber view; the mean and velocity were calculated. To attain the highest Doppler velocity aligned with the CW, the jet velocity (m/s) of tricuspid regurgitation (TR) was obtained using CW Doppler from apical four-chamber and parasternal view with color flow imaging. Echocardiographic data were reviewed by two diverse cardiologists blinded to the patients' characteristics [8].

Ethics committee approval

(Decision No: 2021/197, Date: 29.09.2021) was obtained from the Non-Interventional Clinical Research Ethics Committee of Sancaktepe Şehit Professor Doctor İlhan Varank Training and Research Hospital before the initiation of the study. Written and verbal consent was obtained from all participants. The Declaration of Helsinki was followed in the application of the ethical rules of the study.

Statistical analysis

The SPSS 20.0 (Armonk, IBM Corporation, USA) program was used for statistical analysis. Continuous factors are shown as the mean (standard deviation [SD]) or median (25-75 percentile), and categorical factors are presented as percentages (%) and n (number). Due to the number of cases in the groups, normality assumptions were examined with Kolmogorov-Smirnov tests. Student's t-test was used for continuous variables, and Pearson's x^2 test was used for categorical factors. The Mann-Whitney U test was used to compare two free groups (LVEF, LAVI, LAVI/LVEF, E/é, Mitral inflow E, E/a) when the variable was not normally distributed. Multivariable and univariable logistic regression analyses were used to study the relationship between AF and other risk factors. Pearson's correlation coefficient (r) analyses were used to investigate the strength of the association between LAVI, LAVI/LVEF ratio, and CHA_2DS_2-VASc score. A *P*-value below 0.05 was considered significant in all statistical results.

Results

The mean age of the patients in the AF group (n=57) was 73.9 (6.3) years, and the control group (n=51) was 72.1(3.9) years (*P*=0.265). There was no difference between the two groups in terms of gender, systolic and diastolic blood pressures, heart rates, current smoking, dyslipidemia, coronary artery disease, serum cholesterol levels, and renal functions.

HT (61.4% vs 41.1%, *P*=0.017), DM (50.8% vs 35.2%, *P*=0.008), serum glucose level (132.9 [31.7] vs 118.1 [28.6], *P*< 0.001), HbA1c level (7.2 [1.2] vs 6.6 [1.1], *P*=0.004), CHA_2DS_2-VASc score (5.6 [1.2] vs 4.2 [2.5], *P*<0.001), previous stroke episode (24.5% vs 7.8%, *P*=0.001) were higher in the AF group (Table 1).

Table 1: Clinical characteristics of patients with ischemic stroke with atrial fibrillation and control group

Variables	Atrial fibrillation group (n=57)	Control group (n=51)	*P*-value
Age (years)	73.9 (6.3)	72.1 (3.9)	0.265
Gender (male), n (%)	30 (52.6)	27 (52.9)	0.548
Systolic BP (mmHg)	132.6 (22.5)	128.7 (20.6)	0.158
Diastolic BP (mmHg)	82.9 (15.6)	77.8 (14.2)	0.458
Heart rate beats/min	74.4 (13.5)	75.7 (13.7)	0.450
Hypertension, n (%)	35 (61.4)	21 (41.1)	0.017
Diabetes mellitus, n (%)	29 (50.8)	18 (35.2)	0.008
Dyslipidemia, n (%)	16 (28.1)	14 (27.4)	0.578
Current smoking, n (%)	12 (21.1)	13 (22.8)	0.420
Coronary artery disease, n(%)	14 (24.5)	12 (23.5)	0.196
Previous stroke/TIA, n (%)	14 (24.5)	4 (7.8)	0.001
CHA_2DS_2-VASc score	5.6 (1.2)	4.2 (2.5)	0.000
Glucose (mg/dL)	132.9 (31.7)	118.1 (28.6)	0.014
HbA1c (%)	7.2 (1.2)	6.6 (1.1)	0.004
Creatinine (mg/dL)	0.9 (0.3)	0.9(0.5)	0.789
EGFR, ml/min/1.73 m^2	76.7 (38.7)	77.8 (40.4)	0.568
LDL cholesterol (mg/dL)	121.5 (34.5)	128.9 (36.7)	0.895
HDL cholesterol (mg/dL)	42.4 (19.5)	41.6 (15.5)	0.758
Triglyceride (mg/dL)	159.7 (45.6)	152.8 (42.8)	0.695

EGFR: Estimated glomerular filtration rate, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TIA: Transient ischemic attack.

Left ventricular wall thicknesses, systolic and diastolic diameters, and LVEF were not different between the two groups (*P*>0.05), LAVI (35.7 [25.3-38.2] vs 29.6 [27.7-30.9], *P*<0.001), the LAVI/LVEF ratio (0.7 [0.63-0.77] vs 0.5 [0.50-0.54], *P*<0.001). The E/é ratio (14.6 [13.9-15.0] vs 10.7 [9.0-11.8], *P*<0.001) was higher in patients with AF (Table 2).

Table 2: Echocardiographic features of patients ischemic stroke with atrial fibrillation and control group

Variables	Atrial fibrillation group (n=57)	Control group (n=51)	*P*-value
IVST, mm	1.1 (0.5)	1.1 (0.4)	0.752
LVPWT, mm	1.1 (1.7)	1.1 (1.7)	0.525
LVDD, mm	4.8 (0.3)	4.7 (0.3)	0.857
LVSD, mm	3.2 (0.5)	3.0 (0.4)	0.458
LAVi, ml/m^2	35.7 (25.3-38.2)	29.6 (27.7-30.9)	<0.001*
LVEF, %	55 (52.5-58.0)	57.0 (55.0-60.0)	0.067*
LAVI/LVEF ratio	0.7 (0.63-0.77)	0.5 (0.50-0.54)	<0.001*
Mitral inflow E, m/s	0.78 (0.62-0.85)	0.82 (0.71-0.93)	0.487*
E/A ratio	0.87 (0.75-1.18)	0.81 (0.71-0.98)	0.254*
E/é, mean	14.6 (13.9-15.0)	10.7 (9.0-11.8)	<0.001*
Peak TR velocity (m/s)	2.8 (0.9)	2.7 (0.7)	0.187

E/A: the ratio between mitral E- and A-wave flow velocity, IVST: Interventricular septal thickness, LVPWT: Left ventricular posterior wall thickness, LAVI: Left atrial volume index LVEDD: Left ventricle diastolic diameter, LVEF: Left ventricular ejection fraction, LVSD: Left ventricle systolic diameter, TR: Tricuspid regurgitation. *: Mann-Whitney U test

The relationship between AF events and other risk factors was examined by logistic regression analysis. Univariable regression analyses showed DM (OR: 2.754, 95% CI [1.737-6.122], *P*=0.014), serum glucose (OR: 1.017, 95% CI [1.003-1.032], *P*=0.018) , HbA1c (OR: 1.981, 95% CI [1.213-3.325], *P*=0.006), previous stroke episode (OR: 5.875, 95% CI [1.842-18.739], *P*=0.003), CHA_2DS_2-VASc score (OR: 1.474, 95% CI [1.154-1.882], *P*=0.002), the E/é ratio (OR: 2.495, 95% CI [1.818-3.422], *P*<0.001), LAVI (OR: 3.23, 95% CI [1.951-5.359], *P*<0.001), and the LAVI/LVEF ratio (OR: 8.1, 95% CI [1.052-6.351], *P*<0.001) were related to AF events. Multivariable analyses showed that only LAVI (OR: 7.985, 95% CI [2.586-4.767], *P*<0.001) and the LAVI/LVEF ratio (OR: 0.010, 95% CI [0.000-0.007], *P*=0.015) are potential independent risk factors for AF events with ischemic stroke patients (Table 3). A considerable positive correlation was found between the CHA_2DS_2-VASc score, LAVI, and the LAVI/LVEF ratio (Figure 1, 2).

Table 3: The association between AF and other risk factors with logistic regression analysis

Variables	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
HT	1.051 (0.439-2.513)	0.199		
DM	2.754 (1.737-6.122)	0.014		
Glucose	1.017 (1.003-1.032)	0.018		
HbA1c	1.981 (1.213-3.235)	0.006		
Previous stroke	5.875 (1.842-18.739)	0.003		
CHA_2DS_2-VASc	1.474 (1.154-1.882)	0.002		
E/é	2.495 (1.818-3.422)	<0.001		
LAVI	3.23 (1.951-5.359)	<0.001	7.985 (2.586-4.767)	<0.001
LAVI/LVEF	8.10 (1.052-6.351)	<0.001	0.010 (0.000-0.007)	0.015

DM: Diabetes Mellitus, LAVI: Left atrial volume index, LVEF: Left ventricle ejection fraction, HT: Hypertension.

Figure 1: The correlation between CHA_2DS_2-VASc score and left atrial volume index

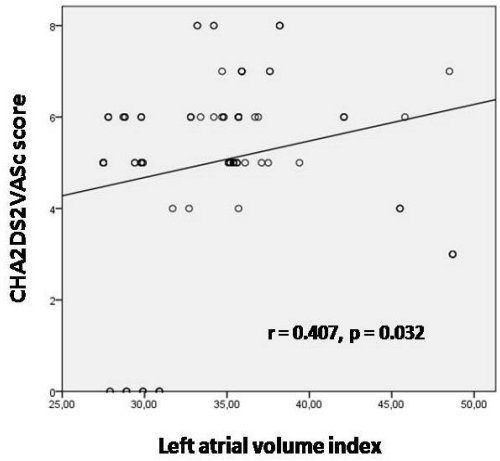
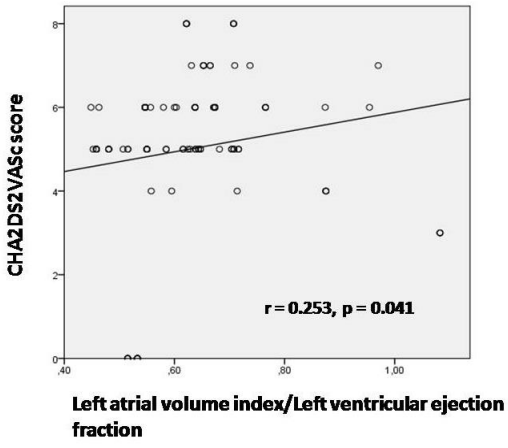


Figure 2: The correlation between CHA_2DS_2-VASc score and left atrial volume index/Left ventricular ejection fraction



Discussion

We found that an increase in LAVI and the LAVI/LVEF ratio was related to the AF events in patients with ischemic stroke with sinus rhythm. The LA/LVEF ratio was positively correlated with the CHA_2DS_2-VASc score and increased LAVI and the LAVI/LVEF ratios were independent risk factors for AF in patients with IS. To the best of our

knowledge, the LAVI/LVEF has not been evaluated previously in predicting AF with patients of IS.

AF incidence is the most common rhythm problem worldwide and increases with age. AF may be secondary to many underlying diseases or may occur alone. The most prominent anatomical feature in AF is left atrial or bi-atrial dilatation as defined by imaging. In DD, impaired left ventricular myocardial relaxation and increased LV chamber stiffness leads to high cardiac filling pressures [8, 9]. Increased pressure and volume in the left ventricle lead to atrial enlargement over time. Structural remodeling emerges when atrial pressure increases, which in turn leads to atrial fibrosis. This is moderated at the cellular plan by stimulation of various pro-fibrotic factors including transforming growth factor-beta, Ang II, and a platelet-derived growth factor that can act individually or synergistically to encourage fibrosis [5,10].

One of the important studies on the association between diastolic dysfunction and ischemic stroke outcomes was accomplished by Ryu et al. [11]; 503 patients with ischemic stroke and LVEF ≥ 50% were included in that study, and DD-related outcomes were investigated by measuring tissue Doppler values. They found an independent relation between DD, functional outcomes, and mortality after ischemic stroke. In particular, patients with an E/e' >14 had a four-fold higher mortality risk compared to patients with an E/é ≤8.8. In our study, the mitral E/é ratio was higher in the AF group [11]. In addition, we found that increased LAVI and LAVI/LVEF values were independent risk factors for the presence of AF versus the mitral E/é ratio.

Strahrenberg et al. [12] performed a 7-day Holter follow-up in patients with sinus rhythm and IS. Patients diagnosed with paroxysmal AF were evaluated by echocardiography, and the left atrial diameter, left atrial volume index, LAVI/A, and LAVI/a' were greater in these patients. A similar study was later performed by Walden et al. LAVI and the ventricular and atrial septum LAVI/a' ratio were higher in patients who had a stroke/TIA and developed AF during their follow-up [13]. Similarly, LAVI values were higher in the AF group in our study. Differently, the ratio of LAVI/LVEF, a new parameter, was found to be higher in the AF group. This parameter was also found to be correlated with the CHA_2DS_2-VASc score. The ratio of LAVI value to LVEF could be a useful new marker, like LAVI, in predicting DD and AF in patients with ischemic stroke.

The Framingham Offspring Study showed that left atrial functional index (LAFI) was associated with incidence AF and CVD [14]. The formula for LAFI is (LA emptying fraction x LVOT-VTI/ LA max index). These measurements need a quality image, and their measurement takes more time to collect. Compared to previous studies and complex formulas, the measurement of LAVI and LAVI/LVEF seems practical and time-saving for physicians.

The LA capacity volume index reflects the accumulative effects of increased LV filling pressure. Increased LAVI is an independent risk factor for heart failure, AF, death, and ischemic stroke. It is associated with an unfavorable prognosis [15]. A prior study evaluated LAVI values with three-dimensional echocardiography and found that the left ventricular volume (LVV)-to-LAV ratio decreased with age [16]. On the contrary, LAV increases more than left ventricular volume (LVV) with aging; the LAV/LVV ratio thus increases. Increased LAV values may increase both the frequency of AF and the incidence of ischemic stroke. Compared to a prior study, which showed that the LAV enlarges with aging using three-dimensional echo, our study evaluated the LAVI/LVEF ratio using a two-dimensional echocardiography. In this study, we tried to demonstrate the role of diastolic dysfunction parameters and a new parameter, the LAVI/LVEF ratio, in the etiology of ischemic stroke using two-dimensional echocardiography. In recent years, there have been new developments in imaging modalities, and measurements are made with more sophisticated devices. However, these devices are not readily available everywhere and using the device and interpreting images require experience. Two-dimensional echocardiography is easy to access and use, and many important parameters can be obtained quickly and reliably.

Limitation

One of the most main limitations of this study is the small number of patients. Another limitation is that the accurate diagnosis of DD was made by cardiac catheterization. However, our patients were newly diagnosed with acute IS, and catheterization could not be performed considering the current conditions. Another limitation is that left atrial volumes were evaluated with two-dimensional echo, and comparisons could not be made with methods such as three-dimensional echo or cardiac MRI. The retrospective nature of our study and the lack of long-term follow-up are controversial in terms of the usefulness of these parameters. It is known that a 72-hour rhythm Holter is more acceptable for the diagnosis of post-stroke AF. Our findings need to be validated prospectively and benchmarked against other means of risk stratification including two-week ambulatory ECG monitoring and cardiac MRI.

Conclusion

LAVI and the LAVI/LVEF ratios increased in subjects with AF events. LAVI and the LAVI/LVEF ratios were correlated with the CHA_2DS_2-VASc score. In the absence of significant structural heart and valvular disease, DD is the most likely cause of increased LAVI. Although DD does not directly cause IS events, it has important effects on left atrial dilatation and AF development. Although DD has not yet played a part in the risk factors involved in estimating ischemic stroke, larger studies will likely be conducted in the future to shed light on this issue.

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