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Left atrial and ventricular longitudinal strain in embolic stroke of undetermined source

Kaynağı belirlenemeyen embolik inmede sol atriyal ve ventriküler longitudinal strain

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Abstract

Purpose: Left atrial (LA) and left ventricular (LV) remodelling may lead to stroke. The aim of this study was to analyze LA function and LV strain in patients with embolic stroke of undetermined source (ESUS).

Material and methods: This prospective study included 35 ESUS patients and 37 age and sex-matched controls. All participants underwent brain computed tomography (CT), conventional and diffusion-weighted magnetic resonance imaging (MRI), CT or MR angiography, 12 lead ECG, transthoracic echocardiography, and 48 hour Holter ECG monitoring. LA volume and function were determined by echocardiography. LA reservoir and LV strains were measured longitudinally by speckle-tracking method. CHA2DS2-VASc, The National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS) scores were calculated.

Results: Major cardiovascular risk factors were similar between the two groups. The mean CHA2DS2-VASc score was 2.6±1.2. NIHSS was 3.9±3.0 and mRS was 1.3±0.8. Atrial electromechanical coupling intervals and delays, LA emptying fraction and volumes were similar between the two groups. LA reservoir strain was lower than controls (25.2±7.2% vs. 29.7±8.8%, *p*=0,019). LV global longitudinal strain was lower than controls (-14.7±4.2% vs -16.4±3.9%, *p*=0,031). There was no correlation between LA, LV strains and the scores (CHA2DS2-VASc, NIHSS, mRS).

Conclusions: ESUS patients had lower LA reservoir and LV longitudinal global strains than controls. Left atrial volume index, LA emptying fraction did not differ between the two groups. Echocardiographic quantification of LA and LV remodelling has great potential for secondary prevention from ESUS. Further studies are needed to confirm our findings.

Key words: Embolic stroke, left atrial function, left ventricular function, left atrial strain, left ventricular strain.

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Öz

Amaç: Sol atriyal ve sol ventriküler yeniden şekillenme inmeye neden olabilir. Bu çalışmanın amacı, kaynağı belirsiz embolik inme (ESUS) hastalarında sol atriyum fonksiyonlarını ve sol ventrikül strain değerlerini analiz etmektir.

Gereç ve yöntem: Bu prospektif çalışma cinsiyet ve yaş açısından benzer olan 35 adet ESUS'lu hasta (61±10 yaşında) ve 37 adet kontrol grubunu (60±10 yaşında) içeriyordu. Tüm hastalara beyin bilgisayarlı tomografisi (BT), konvansiyonel ve difüzyon manyetik rezonans görüntüleme (MRG), BT veya MR anjiyografi, 12 derivasyonlu EKG, transtorasik ekokardiyografi ve 48 saat Holter EKG monitörizasyonu yapıldı. Sol atriyum hacimleri ve fonksiyonları ekokardiyografi ile belirlendi. Sol atriyum rezervuar ve ventrikül strain değerleri speckle-tracking metoduyla longitudinal olarak ölçüldü. CHA2DS2-VASc, Amerikan Ulusal Sağlık Enstitüsü İnme Skalası (NIHSS), Modifiye Rankin Skalası (mRS) skorları hesaplandı.

Bulgular: Major kardiyovasküler risk faktörleri iki grup arasında da benzerdi. ESUS'lu hastaların ortalama CHA2DS2-VASc skoru 2,6±1,2, NIHSS 3,9±3,0 ve mRS 1,3±0,8 saptandı. Atrial elektromekanik süreler ve gecikme zamanları, sol atriyum boşalma fraksiyonu ve hacim indeksleri 2 grup arasında benzer bulundu. Sol atriyal rezervuar strain, kontrol grubuna göre düşük saptandı (25,2±%7,2 vs. 29,7±%8,8, *p*=0.019). Sol ventrikül global longitudinal strain kontrol grubuna göre düşük saptandı (-14,7±%4,2 vs -16,4±%3,9, *p*=0.031). Sol atriyum rezervuar ve sol ventrikül strain değerleri ile skorlar arasında korelasyon saptanmadı (CHA2DS2-VASc, NIHSS, mRS).

Sonuç: ESUS'lu hastalar, kontrol grubuna göre daha düşük sol atriyal rezervuar ve sol ventriküler global longitudinal straine sahipti. Sol atriyal hacim indeksleri, sol atriyum boşalma fraksiyonu ve elektromekanik süreler 2 grup arasında farklılık göstermemektedir. Sol atriyal ve ventriküler yeniden şekillenmesinin ekokardiyografik ölçümü, ESUS'tan ikincil koruma için büyük bir potansiyele sahiptir. Bulgularımızın doğrulanması için daha fazla çalışmaya ihtiyaç vardır.

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Anahtar kelimeler: Embolik inme, sol atriyal fonksiyon, sol ventriküler fonksiyon, sol atriyal strain, sol ventriküler strain.

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Introduction

Stroke is a clinical syndrome of vascular origin, characterized by signs of focal cerebral function loss and rapid localization of symptoms (within seconds or hours) without any apparent causes other than vascular causes. Approximately 85% of strokes are ischemic, while 15% are hemorrhagic. Stroke is the third most common life-threatening cause of mortality after heart disease and cancer, not only in developed countries but worldwide [1]. Cryptogenic mechanisms constitute 10-40% of all ischemic strokes [2]. Investigation of cryptogenic stroke patients includes evaluation of atherosclerotic and non-atherosclerotic diseases, cardiac embolism, and coagulopathies [3]. Embolic stroke of undetermined source (ESUS) is a new concept used as a functional definition of non-lacunar stroke of presumed embolic or thromboembolic origin, unlike cryptogenic stroke [4]. Myocardial strain analysis may offer insights into left atrial (LA) and left ventricular (LV) pathophysiology. This study aimed to determine whether or not ESUS patients might have atrial or ventricular dysfunction. We also examined atrial volumes of ESUS patients using echocardiography.

Materials and methods

The study protocol was approved by the Medical Ethics Committee of the Pamukkale University, written informed consent was obtained from the participants and was conducted in accordance with the Helsinki Declaration.

The study design was prospective. This study included 35 patients and 37 controls between September 2016 and March 2018. The patient group consisted of patients over age 45, diagnosed with embolic stroke of undetermined source, with cardioembolic risk ruled out. Demographic data, nicotine and alcohol use, history of cerebrovascular disease, medication use, comorbid coronary artery disease, and the presence of diabetes mellitus or hypertension were questioned and documented. The CHA_2DS_2-VASc, National Institutes of Health Stroke Scale (NIHSS), and modified Rankin Scale (mRS) scores were calculated on admission. In this study, electrocardiography (ECG), 48 hour Holter ECG and transthoracic echocardiography, computerized tomography (CT) of the brain, conventional and diffusion cerebral magnetic resonance imaging (MRI), cervical CT angiography of the carotid and vertebral arteries or cervical MRI angiography, and Doppler ultrasound were performed on ESUS patients. Also we did perform transesophageal echocardiography (TEE) to rule out patent foramen ovale, aortic arch atheroma, and LA appendage thrombus on all our patients. ECG, 48 hour Holter ECG and transthoracic echocardiography were performed on controls. Exclusion criteria for both groups were: 1) ischemic or valvular heart disease, 2) left ventricle ejection fraction (LVEF) <50%, 3) acute or chronic kidney failure (serum creatinine >1.5 mg/dl), 4) liver disease (bilirubin >2 mg/dl, AST two times higher than normal upper limit), 5) age younger than 45 years, 6) the presence of cardioembolic conditions that could cause cerebrovascular disease (for instance LA dilatation), 7) the presence of lacuna on CT or MRI imaging, 8) intra- or extra-cranial atherosclerosis (more than 50% stenosis on angiography) compatible with ischemic site, 9) active smoker or history of smoking, 10) obesity (BMI>30 kg/m^2), 11) use of statins or other anti-inflammatory drugs, 12) moderate or severe valvular disease, 13) ventricular hypertrophy, 14) history of acute coronary syndrome, cardiac operation, slow coronary flow, pacemaker implantation, left bundle branch block, and variant angina.

Echocardiography of all patients were performed using a 1-5 MHz transducer with a Phillips CX50 xMATRIX device. 2-D, M-mode, pulsed and color flow Doppler and tissue Doppler echocardiography were performed on all participants. During the examination, a continuous 1-lead ECG was recorded. Apical 2-chamber (A2C), apical 4-chamber (A4C), and apical 3-chamber (A3C) imaging were obtained on all participants. Left atrium volumes (maximum, minimum, presystolic, and emptying) were measured with A4C and A2C windows using the biplane method and indexed to body surface

area. Maximum LA volume was measured at LV end-systole, while minimal LA volume was measured at LV end-diastole. Left atrium emptying fraction was calculated as percentage with the formula {[(LA maximum volume - LA minimum volume)/LA maximum volume] × 100%} using biplane volumes measured from A4C and A2C imaging. Emptying volume was calculated using the formula (LA maximum volume - LA minimum volume) acquired from biplane volume. Pre-atrial contraction volume was measured at the start of P wave in ECG. Volume indices were calculated by dividing the calculated volumes by body surface area. Atrial electromechanical coupling (PA) was defined as the time interval from the onset of the P wave on surface ECG to the beginning of the late diastolic wave (Am wave) on tissue Doppler imaging. PA was obtained from the lateral mitral annulus (PA lateral), septal mitral annulus (PA septum), and right ventricular tricuspid annulus (PA tricuspid). Values were averaged over three consecutive beats. The difference between PA lateral and PA tricuspid was defined as inter-atrial electromechanical delay (EMD), the difference between PA lateral and PA septum was defined as left intra-atrial EMD, and the difference between PA septum and PA tricuspid was defined as right intra-atrial EMD.

In order to measure optimal strain, myocardial walls were clearly determined and myocardium and neighboring structures were distinguished from one another. When myocardial velocity and deformation curves varied between different speeds, it was ensured that transducer axis was parallel to the myocardium wall to obtain better results. All routine echocardiographic studies were performed according to current recommendations [5, 6]. Images for strain analysis were obtained with 60-90 frames/sec [7]. These values were accessed by narrowing the viewing window to only include the wall segment to be measured. At least three consecutive strokes were recorded and digitally processed data were analyzed with the software program incorporated in the equipment. Longitudinal strain values of LV and LA reservoir were calculated using the speckle-tracking method from A4C, A2C, and A3C imaging. LV global longitudinal strain values were also calculated. Holter ECG monitoring was performed for 48 hours in all patients. There was no arrhythmia detected.

Statistical analysis

When parametric test hypotheses were established, Independent Samples t test was used to compare differences between independent groups; when parametric test hypotheses could not be established, Mann-Whitney U test was used for comparing differences between independent groups. In addition, relationships between continuous variables were assessed with Spearman correlation analysis while Chi-square was used to assess differences between categorical variables. Data were analyzed with SPSS 25.0 (SPSS, Chicago, IL, USA). The value of $p<0.05$ was considered statistically significant.

Results

35 patients with ESUS and 37 controls participated in the study (Table 1). There was no significant age or gender difference between the two groups. Both groups had the same cardiovascular risk factors. PA septal, PA lateral, PA tricuspid, right intra-atrial (EMD; PA septum - PA tricuspid) and inter-atrial (EMD; PA lateral - PA tricuspid) intervals were compared and no significant difference was found. PA and EMD of the patient group tended to be longer than the control group (Table 2). LA maximum volume index (maxVI), minimum volume index (minVI), pre-atrial contraction volume index (pVI), systolic volume index (sVI), and emptying fractions of the patient and control groups were compared. There was no significant difference between the groups. LA emptying fraction of the patient group tended to be lower compared to the control group (Table 3). LA reservoir strain, LV apical 4-chamber longitudinal strain (4CLS), apical 3-chamber longitudinal strain (3CLS), apical 2-chamber longitudinal strain (2CLS), and LV global longitudinal strain (GLS) measurements were compared between the patient and control groups. There was a significant difference in terms of LV 4CLS, LV global longitudinal strain, LA reservoir 4CLS and LA reservoir 3CLS values; these values were lower in the patient group (Table 4). In the patient group, mean CHA_2DS_2-VASc score was 2.6±1.2, mean NIHSS score was 3.9±3.0, and mean mRS score was 1.3±0.8. There was no correlation between LA, LV strain values and the scores (CHA_2DS_2-VASc, NIHSS, mRS) (Table 5).

Table 1. Demographic data of the study population

	Gender			Age			
	Female	**Male**	***p***	**Mean±S.D.**	**min**	**max**	***p***
Patients n=35	11 (31%)	24 (69%)	0,568	61±10	45	82	0,964
Controls n=37	14 (37%)	23 (63%)		60±10	46	79	

max: maximum, min: minimum; S.D.: standard deviation

Table 2. Atrial electromechanical coupling findings measured by tissue Doppler imaging

	Patients n=35	**Controls n=37**	
	Mean ± S.D.	**Mean ± S.D.**	***p***
PA Lateral (ms)	43.94±14.33	38.57±14.81	0.178
PA Septum (ms)	33.03±12.99	28.08±11.85	0.096
PA Tricuspid (ms)	24±11.4	21.11±8.38	0.222
EMD Right Intra-atrial (ms)	8.8±7.27	6.97±5.59	0.344
EMD Inter-atrial (ms)	19.94±9.07	17.46±10.54	0.351

EMD: electromechanical delay, PA: the time interval from the onset of the P wave on surface ECG to the beginning of the late diastolic wawe (Am wawe) on tissue Doppler imaging
S.D.: standard deviation

Table 3. Left and right atrial volume measurements

	Patients (n=35)		**Controls (n=37)**		
	Mean±S.D.	**Median [min-max]**	**Mean±S.D.**	**Median [min-max]**	***p***
LA maxVI A4C (ml/m²)	24.34±7.42	22.79 [12.12-41.49]	24.83±7.13	23.72 [12.41-40.99]	0,640
LA minVI A4C (ml/m²)	10.41±5.04	8.41 [3.82-25.51]	9.42±4.34	8.52 [2.28-20.22]	0,488
LA pVI A4C (ml/m²)	16.34±5.85	14.62 [5.75-32.6]	14.7±5.7	13.46 [5.36-27.53]	0,234
LA maxVI A2C (ml/m²)	23.23±6.7	22.66 [13.88-47.21]	23.68±5.42	23.17 [12.2-34.75]	0,569
LA minVI A2C (ml/m²)	10.49±4.59	9.54 [4.65-23.18]	9.45±3.56	8.74 [2.74-17.54]	0,450
LA pVI A2C (ml/m²)	16.02±5.42	15.54 [7.65-31.84]	14.52±4.25	14.22 [6.24-24.34]	0,195
RA maxVI A4C (ml/m²)	19.33±5.44	19.8 [9.44-31.45]	19.33±5.39	18.93 [8.65-29.73]	0,997
RA minVI A4C (ml/m²)	8.46±3.26	8.12 [3.39-15.99]	8.25±3.01	8.19 [3.18-15.51]	0,773
RA pVI A4C (ml/m²)	13.23±4.58	12.99 [6.63-22.14]	12.33±4	11.95 [5.64-21.43]	0,550
LA Emptying Fraction Biplane(%)	56.7±9.8	58.7 [34.5-68.9]	61.2±8.6	61 [39.8-78.6]	0,137
LA maxVI Biplane (ml/m²)	24.17±6.5	23.29 [14.15-42.96]	25.18±5.8	24.03 [13.8-39.5]	0,489
LA sVI Biplane (ml/m²)	13.61±3.67	13.37 [7.68-23.07]	15.43±3.48	15.05 [8.69-24.19]	0,013*
LA minVI Biplane (ml/m²)	10.73±4.38	9.28 [4.75-20.41]	9.75±3.74	9.03 [2.95-18.57]	0,414

A2C: apical two-chamber, A4C: apical four-chamber, EF: emptying fraction, LA: left atrial
max: maximum, maxVi: maximal volume index, min: minumum, minVi: minimum volume index
pVi: pre-atrial contraction volume index, RA: right atrial, S.D.: standard deviation
sVi: stroke volume index

Table 4. Left atrial and left ventricular strain values

	Patients (n=35)		Controls (n=37)		
	Mean±S.D.	**Median (min-max)**	**Mean±S.D.**	**Median (min-max)**	***p***
LV 4CLS (%)	-14.94±3.96	-14 [-27--10]	-17.11±4.25	-17 [-25--9]	0,015*
LV 2CLS (%)	-14.34±5.02	-14 [-26--6]	-16.38±4.41	-16 [-24--9]	0,072
LV 3CLS (%)	-14.66±4.77	-14 [-27--8]	-16.05±4.14	-15 [-25--8]	0,188
LV GLS (%)	-14.66±4.16	-14 [-26--9]	-16.41±3.86	-16 [-24--8]	0,031*
LA reservoir strain A4C (%)	24.11±7.16	24 [13-44]	32.35±13.06	29 [6-61]	0,003*
LA reservoir strain A2C (%)	25.69±9.61	26 [5-50]	26.84±7.72	27 [14-50]	0,576
LA reservoir strain A3C (%)	26.66±9.06	27 [3-48]	30.43±8.64	30 [5-45]	0,050*

2CLS: Apical two-chamber longitudinal strain, 3CLS: Apical three-chamber longitudinal strain 4CLS: Apical four-chamber longitudinal strain A4C: Apical four-chamber
A2C: Apical two-chamber, A3C: Apical 3-chamber, GLS: Global longitudinal strain
LA: Left atrial, LV: Left ventricular, max: maximum, min: minumum, S.D.: Standard deviation

Table 5. Correlation of LA, LV strain values with CHA2DS2-VASc, NIHSS, mRS

		CHA2DS2-VASc	**NIHSS**	**mRS**
LV 4CLS	r	,237	,151	,128
	p	,171	,387	,463
LV 2CLS	r	,232	-,053	,110
	p	,179	,763	,530
LV 3CLS	r	,066	,224	,309
	p	,705	,195	,071
LV GLS	r	,213	,166	,277
	p	,219	,341	,107
LA reservoir strain A4C	r	,098	-,139	-,277
	p	,576	,427	,107
LA reservoir strain A2C	r	-,209	,026	-,142
	p	,229	,882	,417
LA reservoir strain A3C	r	-,233	,034	-,004
	p	,178	,848	,981

2CLS: Apical two-chamber longitudinal strain, 3CLS: Apical three-chamber longitudinal strain 4CLS: Apical four-chamber longitudinal strain, A4C: Apical four-chamber
A2C: Apical two-chamber, A3C: Apical 3-chamber, GLS: Global longitudinal strain
LA: Left atrial, LV: Left ventricular, mRS: modified Rankin Scale
NIHSS: The National Institutes of Health Stroke Scale

Discussion

The main findings of this study are: 1) LA reservoir and LV global longitudinal strains were lower in ESUS; 2) Left atrial volume index (LAVI) and EMD did not differ between ESUS and controls; and patients did not show any episode of AF on 48-hour Holter ECG monitoring. These results suggest that atrial and ventricular remodelling may themselves play a role in ESUS patients.

One out of four patients who have had stroke fall in the category of stroke of undetermined source. Asymptomatic AF episodes might be the cause. Therefore, various tools have been used to identify silent AF episodes to clarify the etiology of this patient group. In this study, we did not observe any AF episode on 48-hour Holter ECG monitoring. In contrast, EMBRACE and CRYSTAL studies found that patients had more frequent AF episodes on long-term rhythm monitoring than 24-hour Holter ECG monitoring [8, 9]. Both studies enrolled patients with cryptogenic stroke. EMBRACE study used 30-day event recorder and CRYSTAL study used implantable cardiac monitor.

In this study, EMD did not differ between ESUS patients and controls. No significant correlation was found between ESUS and EMD. In contrast, Bayar et al. [10] demonstrated that longer EMD was associated with stroke/TIA in

patients with paroxysmal AF. They suggested that longer EMD predicts atrial conduction heterogeneity which is associated with stroke; therefore, evaluation of EMD could be helpful in determining patients at high-risk of stroke/ TIA in PAF patients. We excluded patients with paroxysmal AF.

In this study, LAVI and LA emptying fraction did not differ between ESUS patients and controls. Skaarup et al. [11] investigated whether or not left atrial parameters were predictive in paroxysmal AF diagnosis in patients with stroke or TIA. They demonstrated that LA function measurements (minimum LA volume and LA emptying fraction) were independently correlated with paroxysmal AF and that the presence of PAF after ischemic stroke or TIA increased risk. Recently, Jordan et al. [12] sought to determine the association between LAVI and cardioembolic stroke and ESUS subtypes. They demonstrated that LAVI was associated with cardioembolic stroke as well as AF detection in ESUS. In line with their findings, LAVI was similar in both our patients and controls. We did not observe any AF episode on Holter ECG monitoring either. LA emptying fraction did not differ between our patients and controls either. Recent work demonstrated that risk of cardioembolism or PAF increased as LA emptying fraction decreased [13-15].

In this study, LA reservoir strain was significantly decreased in ESUS patients compared to controls. Similarly, Leong et al. [16] demonstrated that LA strain was significantly decreased in cryptogenic stroke patients compared to controls. LV global longitudinal strain (LVGLS) was also decreased in our patients compared to controls. Russo et al. [17] recently demonstrated that decreased LVGLS was associated with AF risk. However, we did not observe any AF episodes on 48-hour Holter ECG monitoring. Sade et al. [18] demonstrated ESUS patients had significantly worse LA strain than control patients. Echocardiographic quantification of LA remodelling has great potential for secondary prevention from ESUS.

Our findings highlight the important interplay between LA/LV remodelling and ESUS. The exact mechanism remains unclear. LAVI, EMD, and LA emptying fraction were similar between patients and controls. Atrial remodelling may start with fibrotic changes in LA. Atrial remodelling may itself be an independent risk factor [19]. AF may not be the only prerequisite for atrial thromboembolism.

As a result, our study demonstrates LA and LV remodelling in ESUS as well as similar LAVI, EMD, and LA emptying fraction between patients and controls. LA and LV remodelling may play a role in ESUS. Echocardiographic quantification of LA and LV remodelling has great potential for secondary prevention from ESUS. More studies are needed to confirm our findings.

Study limitations

This study is single-centered also we were not able to do more than 48-hour Holter ECG monitoring.

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

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Author contributions

Conception and design of the research, analysis and interpretation of the data and critical revision of the manuscript for intellectual content: E.K., Y.T.Y., E.T., H.S., G.N.; Acquisition of data: E.K., Y.T.Y., E.T.; Statistical analysis: H.S.; Writing of the manuscript: E.K., Y.T.Y.