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EVALUATION OF ATRIAL ELECTROMECHANICAL DELAY IN SILENT CEREBRAL ISCHEMIA PATIENTS

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ABSTRACT

Objective: Silent cerebral ischemia (SSI) is found on cranial imaging, with no signs of stroke and has similar risk factors as stroke. There are few studies evaluating the relationship between SSI and AF. In this study, we aimed to evaluate left atrial functions and atrial mechanical delay (AED) in SSI cases with noninvasive tissue doppler imaging (TDI). **Method:** 39 SSI and 29 healthy subjects as control group included in this study. Atrial conduction times calculated by Tissue Doppler Imaging (TDI), demographic features, laboratory findings, ECG, transthoracic ECO were recorded. AED was calculated by measuring the lateral mitral annulus (PA lateral), septal mitral annulus (PA septum) and right ventricular tricuspid annulus (PA tricuspid) by TDI. Left atrial volumes were measured in the apical fourchamber view with the disk method. Left atrial mechanical functions were evaluated. The heart rate variability parameters of the patient group were compared by the holter. **Results:** The mean age of 39 patients (32K/7E) was 51 ± 10 years and the mean age of 29 healthy controls (24K/5E) was 48.8±5.9 years. There was no difference between the two groups in demographic characteristics (p>0,05). Blood glucose was significantly higher in the SSI group (p=0.034). Parameters related to AED were not statistically significant in the SSI group but were found longer (p>0.05). The parameters of left atrial function such as LAPEF (0,3±0,1 versus 0,2±0,1, p=0,050), LAPEV (12,1± 6,8 versus 10,3±8, p=0,197) and LATEV (23,6±11,1 versus 21,6±9,4 p=0,496) were higher but were not statistically significant. Conduit volüm (26,8±12,7 versus 21,5±16,5, p=0,017), LVEDV (91,8±24,4 versus 74,8±25,3. P=0,002) and LVESV (41,4±13,4 versus 31,7,8±15,7. P=0,003) was found statistically significant. **Conclusion:** Regulation of blood glucose of SSI cases and follow-up the patienst for cardiac diastolic functions, and taking into consideration that these changes may lead to prolongation at the time of atrial conduction are important.

Keywords:
Silent cerebral ischemia, atrial electromechanical delay, tissue doppler, atrial fibrillation.

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INTRODUCTION

Silent cerebral ischemia (SCI); is well-defined, infarct-type cerebral lesions of a certain arterial area detected in radiological images in individuals with no history of stroke or related neurological symptoms and examination findings. The prevalence of SCI in the general population varied between 10-28% in different studies, while this rate increased to 38% in patients with stroke (1,2). Cardiac arrhythmias with a risk factor of 20% for ischemic stroke, especially AF, are also an important factor in the occurrence of SCI. Left atrial function disorders cannot be considered as adequate in routine examination methods, interventional methods have some difficulties in their application because they are invasive. As an alternative to long-term monitoring and interventional methods, nowadays the evaluation of atrial electromechanical delay time (AEMD) with tissue Doppler examination is an easy and noninvasive method has an important role for early diagnosis of cardiac rhythm disorders. The atrial electromechanical delay is measured from the onset of the P wave in the electrocardiogram (ECG) to the onset of atrial contraction in tissue Doppler examination. AEMD is associated with paroxysmal atrial fibrillation (PAF), which increases the risk of a thromboembolic event and can turn into permanent AF. In our literature review, we did not find any action evaluating the AEMD time, which was used in the evaluation of cardiac involvement of many diseases, in cases with SCI. We also thought that evaluating the AEMD time, which is considered to be the early marker of AF in SCI cases, would provide a significant benefit in the definition of SCI causes, in the modification of risk factors of ischemic stroke. In this study, we aimed to determine the relationship between left atrial functions and SCI with the atrial electromechanical delay in tissue Doppler examination and to determine whether there is an independent risk factor by comparing with healthy controls and to evaluate the importance of this simple non-invasive method.

MATERIALS AND METHODS

Patients between the ages of 30 and 65, with no history and examination findings for different reasons applied to the Neurology outpatient clinic of Istanbul Training and Research Hospital between August 2015 and February 2017, cerebral hemorrhage, subarachnoid hemorrhage, and intracranial mass lesion was not determined on cranial imaging, 39 patients with SCI lesions and 29 normal volunteers with cranial MRI were included in the study. The study was conducted in accordance with Helsinki Declaration Decisions, Patient Rights Regulation and ethical rules and approval were obtained from the local ethics committee on 29.06.2015.

Detailed anamnesis, autobiography and family history characteristics were investigated and neurological examinations on patients who included in the study were performed. Age, gender, body mass index (BMI), hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), cardiovascular disease, smoking history, chronic obstructive pulmonary disease (COPD) and drug use were investigated in all patients. Systolic blood pressure (SBP), diastolic blood pressure (BPD) and pulse values were recorded during outpatient referral of all patients.

Routine laboratory tests requested from outpatient clinic include hemoglobin (Hb), hematocrit (htc), fasting blood glucose (FBG), urea, creatinine, total cholesterol, triglyceride (TG), low density lipoprotein (LDL), high density lipoprotein (HDL), thyroid function tests and recorded carotid Doppler ultrasonography results were recorded. Holter ECG was performed for 24 hours.

History of AF and arrhythmia, hypertension, left bundle branch block on ECG, congestive heart failure, coronary artery disease and / or myocardial infarct history, DM, renal failure, chronic obstructive pulmonary disease, moderate-severe mitral and / or valvular disease, permanent pacemaker patients in need, patients using drugs affecting the atrial conduction were excluded.

SCI's were defined as MRI with 3-20 mm dimensions, T1 sections with hypointense, T2 and T2 with FLAIR sections as hyperintense lesions (1-2, 1-3). The lesions were graded using the Fazekas scoring in FLAIR examinations.

Evaluation of Left Atrial Mechanical Functions by Echocardiography

Left atrial volume measurements were performed using apical four spaces in accordance with the disc method. The left atrium maximum volume (Vmax) was recorded at the time of the complete opening of the mitral valve, and the left atrial minimum volume (Vmin) was recorded at the time of complete closure of the mitral valve, and the left atrial presystolic volume (Vp) was recorded at the onset of atrial systole (p-wave at ECG). All left atrial volumes were fixed to the body surface area (BSA). Left ventricular systole and end diastolic volume and BSA rates were also recorded.

Pulsed-wave Tissue Doppler measurements were performed to all patient after conventional echocardiography. Tissue Doppler measurements were performed by insertion of the volume of the interventricular septum and the mitral and tricuspid valve annuluses with the ventricular free wall. Systolic wave (Sm) amplitude, early diastolic wave amplitude, young diastolic wave (Am) amplitude was determined. The E wave peak velocities with Pulsed-wave Doppler and the Em wave velocities with tissue Doppler were compared to each other for the left and right ventricle.

RESULTS

Of the 39 patients included in the study, 7 (17.9%) were male and 32 (82.1%) were female and the mean age was 52.1±8.9. Of the 29 healthy volunteers included in the control group, 5 were male (17.2%), 24 were female (82.8%), and the mean age was 48.8±5.9. The patients were admitted with complaints of dizziness (41%), headache (28%), numbness (5%), and other patients with different complaints. The patients had a history of HT in 25.6%, DM in 15.4%, and hyperlipidemia in 23.1% were present. 33.3% of the patients were smoking.

24 (62%) patients had SCI, and 15 (38%) had multiple lesions. SCI's were found in 37 (94%) patients in the centrum semiovale, 35 (89%) in the corona radiate, 35 (89%) in the subcortical, 12 (30%) in the basal ganglion level, 3 (7%) in the brain stem, 2 (5%) were present in the cerebellum and 4 patients in the thalamus and the most common localization was the centrum semiovale, corona radiata, and subcortical areas. 34 (87%) of the patients were stage 1,8 (20%) were stage 2, and 3 (7%) were stage 3 according to the Fazekas scale.

Demographic and clinical features and laboratory results of the groups with and without SCI are summarized in Table 1. Control group and SSI group age, gender distribution, HT, DM, COPD, HL, smoking, BMI, BSA value, systolic pressure, diastolic pressure, pulse, pulse pressure, hemoglobin, ferritin, B12, folic acid, ST3, ST4, TSH, TG, LDL, LDL, T. cholesterol, HDL, uric acid, HbA1c values were not significant ($p > 0.05$) showed difference.

The mean glucose level (103.9 ± 23) was significantly higher in the SCI group than the control group (94.8±12) ($p<0.05$). The mean age of the SCI group ($p=0.088$), systolic ($p=0.126$) and diastolic blood pressures ($p=0.214$) and HbA1c ($p = 0.361$) were increased compared to the control group, but there was no statistically significant difference ($P>0.05$). The BMI of 30 (76%) patients with SCI was over 25.

When the echocardiographic findings of the patients were examined, the IVS value, Mitral A value, Mitral EDT value, Mitral ET value, Mitral ICT value were significantly higher in the SCI group than the control group ($p<0.05$). There was no statistically significant difference in the left atrial diameter and ejection fraction between the SCI group and the control group ($P>0.05$) (Table 2).

Table 1. Demographic and electrocardiographic data of groups

Variable	Control	SSİ	P value
Age	48.8±5.9	52.1±8.9	0.088
BMI	29.1±5.2	29.4±5.9	0.922
SBP, mmHg	117.8±14.7	125.4±17.0	0.176
DBP, mmHg	75.2±8.9	80.3±14.8	0.214
Heart rate	74.5±6.0	76.0±6.9	0.266
FBG	94.8±12.0	103.9±23.2	0.034
Total cholesterol, mg/dL	210.3±38.0	211.7±34.4	0.772
Triglyceride, mg/dL	118.5±55.2	118.0±60.0	0.658
LDL-C, mg/dL	133.3±30.6	137.9±30.9	0,688
HDL-C, mg/dL	55.1±20.9	53.7±14.0	0.638
Smoking, %	34,5	33,3	0,921

Values are presented as mean ± SD or number (%). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol

Table 2. Comparison of conventional, tissue Doppler parameters and diastolic functions of left ventricle

Variable	Control	SSİ	p
IVS mm	0.98±0.11	1.06±0.13	0.032
PW mm	0.95±0.12	1.41±2.73	0.282
AO mm	2.32±0.53	2.61±0.47	0.087
EF %	63,5±4,1	61,2±3,9	0,030
LA mm	3.40±0.35	3.52±0.55	0.790
AO VEL	1.24±0.21	1.22±0.20	0.529
Pul VEL	0.85±0.15	0.82±0.14	0.296
Mitral E	0.73±0.15	0.69±0.17	0.292
Mitral A	0.62±0.13	0.70±0.13	0.011
Mitral E/A	1.23±0.41	1.02±0.32	0.063
Mitral EDT	150.1±28.2	183.8±44.8	0.000
Mitral LVRT	74.3±21.8	72.2±17.2	0.833
Mitral ET	273.9±34.5	302.3±34.4	0.019
Mitral ICT	68.9±26.8	51.2±17.7	0.002
LVEDD	4.5±0.4	4.5 ±0.5	0.655
LVESD	2.7±0.6	2.8 ±0.6	0.330
TAPSE	2,8±0.7	2,6 ±0.5	0,225
MPI	0,4±0.2	0,3±0.2	0,001

LVEDD, left ventricle end diastolic diameter; LVESD, left ventricle end systolic diameter; IVS, interventricular septum; LA, left atrium; EF, ejection fraction; EDT, E wave deceleration time; IVRT, isovolumic relaxation time; ICT, isovolumic contraction time; ET, ejection time; TAPSE, tricuspid annular plane systolic excursion; MPI, myocardial performance index.

Table 3. Comparison of electromechanical coupling parameters of the groups

Variable	Control	SSİ	p
PA lateral	43.1±13.1	39.5±10.9	0.299
PA septal	35.0±9.9	27.4±8.6	0.004
PA tricuspit	31.9±12.8	26.4±12.4	0.062
İnterAED	11.6±12.2	15.4±7.9	0.444
İntraAED	3.2±9.8	6.6±5.3	0.169
LA AED	8.8±8.7	12.2±8.1	0.153

PA, the interval with tissue Doppler imaging, from the onset of P wave on the surface electrocardiogram to the beginning of the late diastolic wave (Am wave). AED atrial electromechanical delay.

Table 4. Left atrial volume measurements of the groups

Variable	Control	SSİ	p
V max	47.0 ±18.5	44.7±17.6	0.708
V min	25.4 ±13.9	21.1±10.1	0.286
V p	36.7±14.9	32.6±14.5	0.182
LAPEV	10.3±8.0	12.1±6.8	0.197
LAPEF	0.2±0.1	0.3±0.1	0.050
LAAEV	11.3±6.2	11.5±8.3	0.703
LAAEF	0.3±0.2	0.3±0.2	0.638
LATEV	21.6±9.4	23.6±11.1	0.496
CV	21.5±16.5	26.8±12.7	0.017
LVEDV	74.8±25.3	91.8±24.4	0.002
LVESV	31.7±15.7	41.4±13.4	0.003

Vmax, maximum left atrial volume; Vp, presystolic left atrial volume; Vmin, minimum left atrial volume; LAPEV, left atrial passive emptying volume; LAPEF, left atrial passive emptying fraction; CV, conduit volume; LAAEV, left atrial active emptying volume; LAAEF, left atrial active emptying fraction; LATEV, left atrial total emptying volume.

When left atrial mechanical functions were compared, conduit volume and LVEDD values were significantly higher in the SCI group. (Table 3, table 4).

When the atrial conduction delay parameters were evaluated, inter-AEMG, intra-AEMG and LAEMD values of the SCI group were higher than the control group (Table 3).

In tissue Doppler imaging, there was a statistically significant difference when compared to the control group in terms of other parameters examined except for Lateral, Septal and TC values of the two groups. The Lat Em / Am ratio (1.03 ± 0.61, p = 0.043, and 1.08 ± 0.61, p = 0.043) and the Septal Em / Am ratio were significantly lower in the SCI group than the control group (Table 5).

Table 5 Tissue doppler imaging parameters

Variable	Control	SSİ	p
S’ lateral	10,4±2,7	11,3±15,6	0,007
E’ lateral	11,6±3,6	9,1±3,1	0,002
A’ lateral	10±2,7	9,7±2,5	0,496
Lateral E/A	1,29±0,61	1,01±0,43	0,043
S’ septal	8,6±2,2	7,8±3,5	0,006
E’ septal	9,3±2,8	7± 2	0,000
A’ septal	8,8±2,2	8,8±1,8	0,746
E/m lateral	0,07±0,04	0,08±0,02	0,003
E/m septal	0,08±0,02	0,10±0,03	0,001
S’ TC	11,6±3,4	15,6±24,2	0,736
E’ TC	11,4±3,4	15,1±27	0,011
A’ TC	10,6±4,1	16,3±27,9	0,039

When compared with tissue Doppler imaging myocardial performance parameters A, B, EDT, RV-B were significantly lower than the control group (p<0.05). In the SCI group, MPI left, TC-E, MPI right values were significantly lower (p<0.05) (Table 2).

27 of 39 patients were holtered. In the SCI group, the heart rate variability parameters of the holter were determined to be within normal limits. In addition, 6 of the patients' holter APS, VPS, supraventricular tachycardia in 4, supraventricular extrasystoles in 6, 6 APS and VPS in 6, multiple APS in 1, tachycardia in VPS, bigemine in 1 revealed. AF was detected in 8 of 27 patients (29%).

DISCUSSION

With the widespread use of cranial imaging, more SCI has been identified. Although it may remain asymptomatic at times, it is associated with different clinical conditions ranging from an increased risk of stroke to walking and psychiatric disorders (3). SCI, which has been shown to be an independent risk factor for stroke, has become more important due to disability and increased mortality caused by possible stroke condition (2,4). There are many studies showing the association of SCIs with risk factors such as hypertension, age, and hyperlipidemia (1,3,5,6,7,8). In our study, age, systolic and diastolic blood pressure, fasting blood glucose and HbA1c levels of the SCI group increased compared to the control group, but only blood glucose levels were statistically significant.

This may be related to a large number of patients excluded who have a history of the systemic disease in patient group selection.

There are few studies evaluating the presence of AF in SCI. In some of these studies, there was an increased risk, while in some of them no relationship was found (3,9,10). As early detection of patients with atrial conduction disorders may be important in determining the risk of AF development of these patients and taking the necessary precautions, examination methods that can evaluate the intra and inter-atrial conduction are needed. In recent years, the electrophysiological evaluation of intra-atrial and atrial electromechanical delay used to determine the risk of AF has limited use due to being invasive and difficult to reach. P wave dispersion in ECG and left atrium (LA) dilatation with transthoracic ECO have low predictive value in determining AF risk. Tissue Doppler Imaging has become an alternative method. In contrast to the LA size, atrial conduction times may reflect both structural and electrical remodeling in atria, and previous studies have shown that AEMG times are significantly prolonged in patients with paroxysmal AF (11,12,13). This extension was suggested to be the predictor of AF (14, 15, 16). As early detection of patients with atrial conduction disorders may be important in determining the risk of AF development of these patients and taking the necessary precautions, examination methods that can evaluate the intra and inter-atrial conduction are needed (17,18,19,20,21).

In the literature, when we look at publications related to stroke and atrial electromechanical conduction time, Akıl and workmates showed an independent association between interatrial EMD and stroke. Also, passive SA discharge volumes (SAPBV) and total LA discharge volumes (SATBV) were increased in stroke patients. It was reported that the interatrial EMD was above 25 ms with a sensitivity of 83% and specificity of 75% (22). The inter-AEMG of 4 patients was over 25 msec. Although heart rate variability related parameters were in normal range, AF was detected in 8 (29%) of 27 patients who had holter in the SCI group. In our study, atrial conduction delay parameters were not evaluated. There was no significant difference in the lateral, PA tricuspid, intra-AEMG, and Inter-AEMG values in SCI and control groups. However, the values of inter-AEMG, intra-AEMG, S-AEMG and the values of atrial conduction time of the SCI group were found to be increased but not statistically significant when compared with the control group. Lack of statistical significance may be due to an insufficient number of patients. Increased number of patients may contribute to this issue. In addition, we did not find any study evaluating AEMG in patients with SCI, although many studies have highlighted the relationship between SCI and AF. We thought that our study could be valuable because it was the first study in which AEMG, atrial mechanical functions, and diastolic functions were evaluated in SCI cases.

Left atrial mechanical functions have an important role in the providing of cardiac output. Left ventricular pulse volume is composed of passive discharge volume of the left atrium, conduit volume and active discharge volume (23). In our study, although there were no significant ventricular deficits, the increase in left atrial discharge functions may be related to early diastolic insufficiency or early findings of atrial conduction disorder.

While many studies show the relationship between the increased volume of LA and paroxysmal and persistent AF, in the study of Akıl et al., there was no significant difference in LA volume between stroke patients and control group (22). In our study, no significant difference was found between the groups of LA in conventional ECO. Left atrial systolic volumes and left atrial maximal and minimal volumes were decreased compared to the control group when left atrial mechanical functions were compared, no statistically significant difference was found between them.

Atrial volumes may also be indicative of the healthy function of the atrium. Direct and indirect atrial tissue damage due to increased atrium burden, affects the atrial mechanical functions. The left atrial function is an important predictor of diastolic filling of the ventricle. In the study of Akıl et al., left ventricular isovolumetric relaxation time (LV IVRT), LA passive emptying volume (LAPEV) and LA total emptying volume (LATEV) were significantly higher in stroke patients (22). In our study, there was an increase in LAPEF, LAPEV and LATEV values in the SCI group, but not statistically significant. Among the left atrial discharge functions, the volume of the conduit volume obtained by subtracting the total discharge volume of the left atrium from the left ventricle's discharge volume was statistically significantly higher in the SCI group. This may be an early sign of atrial function and atrial conduction. Similarly, LVEDV and LVESV values were significantly higher in the SCI group compared to the control group. Considering all these findings, it can be suggested that the effects of left atrial mechanical functions may be related to AF development and SCI.

Tissue Doppler examinations, such as more sensitive and more easily applicable methods, can demonstrate diastolic dysfunction more accurately and independently of preload (79). Tissue Doppler methods allow the evaluation of both systolic and diastolic velocities of the myocardium locally. The E / Em ratio was the first choice in the evaluation of diastolic functions because of its low variability, practicality and relatively less pre-load dependent. Different results were found in studies related to diastolic dysfunction and left atrium dimensions. In our study, the left atrium diameters were similar between SCI and control group, but the E / A ratio measured on conventional echocardiography was less than 1 in 20 of 39 patients (51%), consistent with diastolic dysfunction. Mitral E and A/A ratios were not statistically significant when the left diastolic functions were compared with conventional Doppler parameters, whereas mitral A values were significantly higher in the SCI group compared to the control group. The duration of ICT was significantly lower in the SCI group than the control group. Diastolic functions were also assessed by DDG because they were dependent on conventional doppler load and affected by heart rate. Previous studies have shown that E/Em ratio measured from septal annuler level is significantly correlated with left ventricular end-diastolic pressure and diastolic dysfunction (24). In our study, E / Em (septal) and E/Em (lateral) values were significantly increased in the SCI group. These findings suggest that diastolic function is affected in patients with SSI and suggest that it may cause atrial conduction delay in patients.

The myocardial performance index is a parameter in which systolic and diastolic time intervals are evaluated together with doppler. This parameter is simple and independent from heart rate and blood pressure. It is important in the evaluation of global cardiac functions (25). In our study, ventricular myocardial performance indexes were significantly higher in SCI patients than in the control group. Increased MPI may be associated with early-onset diastolic dysfunction in cases where significant systolic dysfunction is not detected (26). The effect of diastolic dysfunction on SSI cases may be due to subclinical possible tension change or atrial conduction delay, as mentioned earlier.

An inadequate number of patients and lack of rhythm holter in the control group are among the limitations of our study.

In conclusion, atrial delay time parameters in our study were found to be prolonged in the SCI group although they were not statistically significant. High detection of myocardial perfusion index in the SCI group can be interpreted in favor of early diastolic dysfunction. Among the metabolic factors in SCI cases, attention to blood glucose regulation, simple follow-up of cases such as conventional echocardiography in terms of cardiac diastolic functions, and the fact that these changes may lead to prolongation of atrial delay in time may be important in the follow-up of cases. We thought that our findings might be important because there was no similar study before. The fact that these findings are supported by controlled studies in which the number of patients is increased will provide more benefit to the etiology of SCI and to determine the follow-up and treatment algorithms.

Conflict of interest

The authors declare that they have no conflict of interest.

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Informed consent:

Informed consent was obtained from all individual participants included in the study.

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