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ARAŞTIRMA / RESEARCH

The relationship between aortic stiffness index and stroke severity in patients with acute ischemic stroke

Akut iskemik inmeli hastalarda aortik stiffnes indeksi ile inme şiddeti arasındaki ilişki

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Abstract

Purpose: Acute cerebrovascular diseases is an important reason of mortality and morbidity. Aortic stiffness is a important predictor of cerebrovascular, cardiovascular (CV) and all cause death, deadly and non-deadly coronary and neurologic situations, and severe strokes. In our study, we researched the association between aortic stiffness index (ASI) and stroke seriousness in acute ischemic stroke patients.

Materials and Methods: A total of 97 patients (females, 55; males, 42; 65 ± 16 years) with acute ischemic stroke were enrolled in this study. 17 patients were excluded. 80 patients were evaluated. Subjects were categorized into two groups according to the calculated NIHSS score (Group 1, NIHSS score < 16; Group 2, NIHSS score ≥ 16). Clinical characteristics, echocardiographic and laboratory parameters for all patients were evaluated. Cardiac parameters and aortic stiffness index were evaluated by two-dimensional echocardiography within 48 hours of hospitalization to the neurology clinic.

Results: There were no significant differences among the groups for age, gender, hypertension, diabetes mellitus, smoking, SBP, DBP, heart rate, dyslipidemia, infarct volume, troponin, HbA1c, glucose, creatinine, LDL cholesterol were significantly higher in Group 2 patients than in Group 1 patients. LV wall thickness, aortic stiffness index, E/e' were significantly higher in Group 2 patients than in Group 1 patients. LVEF was significantly lower in Group 2 patients than in Group 1 patients.

Conclusion: ASI was significantly higher in patients with severe acute ischemic stroke. Higher ASI is associated with higher NIHSS score in patients with acute ischemic stroke

Keywords:. Aortic stiffness index, echocardiography, stroke, cerebrovascular disease

Öz

Amaç: Akut serebrovasküler hastalıklar önemli bir mortalite ve morbidite nedenidir. Aortik Stiffnes İndeksi, serebrovasküler, kardiyovasküler ve tüm nedenlere bağlı ölüm, ölümcül ve ölümcül olmayan koroner ve nörolojik durumlar ve ciddi inmelerin önemli bir belirleyicidir. Çalışmamızda akut iskemik inmeli hastalarda Aortik Stiffnes İndeksi (ASI) ile inme ciddiyeti arasındaki ilişkiyi araştırdık.

Gereç ve Yöntem: Bu çalışmaya akut iskemik inmeli toplam 97 hasta (kadın, 55; erkek, 42; 65 ± 16 yıl) alındı. 17 hasta çalışma dışı bırakıldı. 80 hasta değerlendirildi. Hastalar, hesaplanan NIHSS skoruna göre iki gruba ayrıldı (Grup 1, NIHSS skoru < 16; Grup 2, NIHSS skoru ≥ 16). Tüm hastaların klinik özellikleri, ekokardiyografik ve laboratuvar parametreleri değerlendirildi. Kardiyak parametreler ve ASI, nöroloji kliniğine yatıştan sonraki 48 saat içinde iki boyutlu ekokardiyografi ile değerlendirildi.

Bulgular: Gruplar arasında yaş, cinsiyet, hipertansiyon, diabetes mellitus, sigara kullanımı açısından anlamlı fark yoktu. SBP, DBP, kalp hızı, dislipidemi, enfarktüs hacmi, troponin, HbA1c, glukoz, kreatinin, LDL kolesterol, Grup 2 hastalarında Grup 1 hastalarına göre anlamlı derecede yüksekti. LV duvar kalınlığı, aortik stiffness indeksi, E/e', Grup 2 hastalarında Grup 1 hastalarına göre anlamlı olarak daha yüksekti. LVEF, Grup 2 hastalarında Grup 1 hastalarına göre anlamlı derecede daha düşüktü.

Sonuç: ASI, şiddetli akut iskemik inmeli hastalarda anlamlı olarak daha yüksekti. Bu çalışmanın sonucunda, akut iskemik inmeli hastalarda daha yüksek ASI'nin, daha yüksek NIHSS skoru ile ilişkili olabileceği öne sürülebilir.

Anahtar kelimeler: Aortik Stiffnes İndeksi, ekokardiyografi, inme, serebrovasküler hastalık

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INTRODUCTION

Carotis arter and main branches atherosclerotic diseases are considered significant reason of acute cerebrovascular event. Therefore, early diagnosis of carotis artery atherosclerosis may important for early therapeutic interventions. Early treatment prevention of acute cerebrovascular event. Arterial stiffness is a significant characteristic of the arteries. Reduced arterial elasticity is a sensitive parameter of impaired arterial vessel wall function[1]. Some researchers have found that endothelial derived nitric oxide (NO) regulates arterial elasticity in vivo[2,3]. Cardiovascular risk factors such as hypercholesterolemia and diabetes mellitus, which are related with endothelial dysfunction. Endotelial dysfunction is lead to arterial stiffening.

Arterial stiffness is a significant determinant of cerebrovascular and cardiovascular risk, and it may be directly related with atherosclerosis. Pathogenesis of arterial stiffness are not well understood. Both structural and functional changes in the arterial vessel wall are significant. Diabetes mellitus and hypercholesterolemia, which are associated with endothelial dysfunction[4]. Cardiovasacular risk factors are responsible for the arterial stiffness. This risk factors causes increased stiffness and decreased elasticity[5]. Prior researchers have demonstrated that abnormal vascular tone plays an important act for ischemic stroke and cardiovascular disease[1,4]. Progression of aortic stiffness happens in the existence of diabetes mellitus (DM), hyperlipidemia, metabolic syndromes, and arterial hypertension. Aortic stiffness is an important predictor of cerebrovascular disease and coronary artery disease mortality, acute cardiovascular events, and severe strokes[5].

Previous researcher investigating the relation between arterial compliance and acute stroke have calculated arterial stiffness utilization pulse wave velocity (PWV)[6,7]. Nevertheless, PWV calculation might be difficult to apply in the situation of an acute cerebrovascular events. Indirect evaluation of arterial compliance based on echocardiographic calculation can offer a less invasive alternative in ensuring an approved method for evaluating arterial stiffness[8]. Saji et al demonstrated that arterial stiffness calculated by PWV is separately related with progressive neurological deficit after acute cerebrovascular events[9]. Nevertheless, there are no studies evaluating the aortic stiffness index (ASI) measured by echocardiography and stroke severity in an acute ischemic stroke patients.

The hypothesis of our study is that in acute phase of ischemic stroke values of markers of ASI could be increased in severe acute ischemic stroke patients. Because severe acute ischemic stroke patients have got severe immuno-inflammatory activation, endothelial dysfunction and other potentially toxic events characteristic of the acute phase of stroke. On this basis the aim of our study was to evaluate the association between ASI and the onset stroke severity measured by the National Institutes of Health Stroke Scale (NIHSS) in an acute ischemic stroke patients.

MATERIALS AND METHODS

Patient selection

This cross-sectional study screened 97 adult patients (males, 42; females, 55; mean age, 65±16 years; range 41–80 years) with acute ischemic stroke (≤24 hours of symptom beginning) hospitalized to the neurology care clinic, between October 2016 and December 2017. 17 patients were excluded. 80 patients were studied.

Clinical characteristics of patients, including neurological deficit severity assesment with NIHSS on admission to the neurology care unit were recorded. Patient clinical data, history of cardiovascular risk factors, and stroke onset were determined, and neurologic examination was conducted at the time of hospitalization.

The clinical definition of AIS was performed based on neurologic examination findings and diagnostic cranial imaging methods within 24 hours of acute neurologic symptom beginning. Patients with a well-defined time of beginning of ischemic stroke clinical findings were included in the study and those with any previous history of cerebrovascular disease or transient ischemic attack, cerebral hemorrhage, presence of atrial fibrillation, coronary heart disease, left ventricular systolic dysfunction, severe valvular heart disease, chronic pulmonary disease, chronic renal failure, congenital heart disease were excluded. In addition, patients in whom a proper position could not be obtained echocardiographic examination and those with improper echocardiographic image analysis were excluded. Seventeen patients were excluded because of previous history of cerebrovascular disease (n=2), documented atrial fibrillation (n=4), systolic heart failure (n=3),

ischemic heart disease (n=5), serious valvular heart disease (n= 2), a poor echocardiographic image quality (n=1). Initial stroke severity was assessed utilization the NIHSS score[10].

All patients underwent immediate computed tomography after being admitted to emergency care unit. Troponin parameters were calculated and electrocardiogram (ECG) was taken after hospitalization to the neurology care unit. Echocardiography was taken within the first 48 hours of hospitalization to the neurology clinic. The NIHSS evaluation and echocardiographic examination were conducted by blinded investigators. The study was approved by the SBU Diyarbakir Gazi Yasargil Education and Research Hospital Ethics Committee. (Date:09 September 2016, Ethics committee number:57), and informed consent was obtained. This study was performed in consistency with the the guideline of the Helsinki Declaration.

Two-dimensional echocardiography

Transthoracic echocardiographic analyses were performed with respect to the American Society of Echocardiography guidelines in all acute ischemic stroke patients. An echocardiography system (Philips EPIQ 7C, Philips Healthcare, Andover, MA, USA) was used with a tissue harmonic imaging feature and 3–8 MHz multifrequency transducer. Single-lead electrocardiogram was continuously recorded. Patients were kept in the left lateral position. Echocardiographic images were acquired from the parasternal short axes and long axes, apical two- and four-chamber, and long-axis views. All echocardiograms contained at least three cardiac cycles. For assessment offline analysis, echocardiographic images were digitally stored. Diastolic and systolic aortic diameters of ascending aorta (DD and SD, consecutively) were saved in M-mode echocardiographic images 3 cm above the aortic annulus from an echocardiographic images of parasternal long-axis window. Image depth, image gain, and sector width were individualized for the accurate calculation. SD and DD were calculated at the time of maximum anterior movement of the assendan aorta and at the beginning of the QRS complex, consecutively. Arterial elastic characteristics features were measured with respect to the priorly suggested and assessed formulas[11] aortic stiffness index (ASI) = Ln (Systolic BP/ Diastolic BP) × DD/(SD − DD). In addition to LVEF, end-systolic and end-diastolic volumes were calculated from the apical two- and four-chamber windows, using the standard 2D Simpson's technique. Interventricular septum, LV posterior wall thickness, left atrial antero-posterior diameter, and LV end-diastolic diameter were calculated from a parasternal long-axis window[12]. Echocardiographic parameters were calculated by qualified physician, and echocardiographic examination was conducted by an investigator who was blinded to the patients' clinical information.

Definition of stroke and assessment of stroke severity

Definition of acute ischemic stroke was made the combination of clinical characteristics of acute neurological dysfunction and cranial imaging evidence of acute ischemic stroke with respect to the American Heart Association/American Stroke Association guidelines. Acute ischemic stroke is described as a neurological dysfunction event caused by local retinal, spinal, cerebral infarction on cranial imaging[13].

NIHSS

NIHSS is a simple, valid, and realiable systematic assessment tool that measures acute stroke-related neurologic deficit[10]. The NIHSS score is very important scale for clinical assessment as it enables determination of appropriate treatment, prediction of lesion size, measurement of stroke severity, and estimation of patient consequence in acute ischemic stroke patients. The NIHSS comprises 11 different elements evaluating specific ability. Each ability is scored between 0 and 4, where 0 corresponds to normal functioning and 4 corresponds to complete impairment. A patient's NIHSS score is calculated by adding the score for each element of the scale; 42 is the highest score possible. A higher NIHSS score corresponds to greater impairment of cerebral function in a stroke patient.

The higher the NIHSS score, the higher the impairment of a stroke patient. According to NIHSS score, there are five stroke severity groups: NIHSS =0 (no stroke), NIHSS=1-4 (minor stroke), NIHSS=5-15 (moderate stroke), NIHSS=16-20 (moderate to severe stroke), NIHSS=21-42 (severe stroke). At admission NIHSS score higher than 16 shows a strong possibility of patient morbidity and mortality[10].

Stroke severity at hospitalization to the neurology clinic was evaluated by the NIHSS score by a

neurologist. Patients were categorized into two groups; Group 1 included of patients with non-severe stroke (NIHSS<16; n=58), whereas Group 2 included of patients with severe stroke (NIHSS≥16; n=22).

Cerebral infarct volume measurements

A neurolog calculated the "cerebral infarct volume" in every patient by using Analyze 12.0 software (Biomedical Imaging Resource, New York, NY, USA). The regions of interest were seperated using the Region Grow in the Volume Edit module. If artifacts exist, these are removed manually. The total cerebral infarct volume was described in mL.

Statistical analysis

The SPSS statistical package (Version 12.0; SPSS Inc., Chicago, IL, USA) was using for statistical analysis. All baseline parameters were analyzed. Categorical variables are defined as percentages, and continuous variables are defined as mean±SD. Intra-observer variability was computed as the absolute difference between the two parameters as a percentage of their mean. Mann–Whitney U test and Chi-square test were used for comparison of data as suitable. p values <0.05 were described statistically important. Pearson's correlation was used to defined the association between NIHSS score and other echocardiographic parameters. The Pearson's or Spearman's correlation was used for assessing correlations between variables. Multivariate logistic regression analysis used to examine the correlation between NIHSS score and clinical parameters (ASI, LVEF, age, heart rate) in patients with acute ischemic stroke.

RESULTS

Clinical parameters of patients are summarized in Table 1. Clinical characteristics of groups were similar with according to arterial hypertension, diabetes mellitus, age, gender, smoking (p>0.05). Heart rate, systolic blood pressure (BP), diastolic BP, dyslipidemia, and troponin levels in Group 2 patients were signficantly higher than Group 1 patients (p<0.05). Serum hemoglobin HbA1c and low density lipoprotein cholesterol values were significantly lower in Group 1 patients than Group 2 patients (p<0.05).

Table 1. Clinical characteristics of patients.

Variables	Group 1 (NIHSS score<16) n=58	Group 2 (NIHSS score≥l6) n=22	p Value
Age (years)	65.4±12.7	69.8±17.7	0.619
Gender (F/M), n	32 / 26	13 / 9	0.718
Hypertension, n %	28 (48%)	13 (59%)	0.062
SBP (mmHg)	143.5±15.2	159.8±18.5	0.043
DBP (mmHg)	76.4±8.6	84.3±12.7	0.048
Heart Rate (bpm)	92.3±14.7	115±16.5	0.027
Diabetes Mellitus, n %	14 (24%)	6 (29%)	0.091
Smoking, n %	7 (12%)	4 (16%)	0.076
Dyslipidemia, n %	9 (15%)	8 (36%)	0.043
Infarct volume (mL)	16 mL ± 2.3	44 mL ± 4.1	0.034
Troponin (ng/L)	6.143	14.705	0.037
HbA1c (%)	6.24±1.43	9.56±1.53	0.009
Glucose (mg/dl)	143.5±37.4	192.7±48.5	0.026
Creatinine (mg/dL)	1.3±0.4	1.8±0.6	0.023
LDL cholesterol (mg/dL)	103.3±27.1	128.4±39.5	0.008
HDL cholesterol (mg/dL)	42.1±12.3	39.4±10	0.384

*F:Female, † M:Male, ‡ SBP: Systolic Blood Pressure, § DBP: Diastolic Blood Pressure, || LDL: Low Density Lipoprotein, ¶ HDL: High Density Lipoprotein.

Echocardiographic parameters are summarized in Table 2. LV wall thickness, ASI and E/e' values were significantly lower in Group 1 patients than in Group 2 patients (p < 0.05) (Figure 1). LVEF were significantly higher in Group 1 patients having lower NIHSS scores than in Group 2 patients having higher NIHSS scores. Correlation analysis performed to investigate the relationship between NIHSS score and echocardiographic parameters, showed a negative correlation between the NIHSS score and

LVEF. In addition, there was a positive correlation between absolute value of the NIHSS score and ASI, age, heart rate and E/e' (Table 3) (Figure 2). Logistic regression analysis was performed to identify the potential predictors for stroke severity. Results of multivariate analysis revealed age, LV EF, and ASI powerful predictor of severe ischemic stroke (Table 4).

Table 2. Echocardiographic parameters of patients.

Variables	Group 1 (NIHSS score<16) n=58	Group 2 (NIHSS score≥16) n=22	p Value
LV septal thickness, mm	11.2±1.8	12.7±1.7	0.027
LVDd (mm)	51.2±6.3	54.6±6.8	0.348
LV posterior Wall thickness, mm	10.8±1.5	11.9±1.6	0.034
LVDs (mm)	40.5±4.2	43.2±5.8	0.241
LVEDV (mL)	86.0±17.7	95.4±24.3	0.192
LVESV (mL)	41.1±12.4	44.7±14.2	0.246
LAD (mm)	39.5±4.3	42.4±4.6	0.624
RAD (mm)	32.6±3.4	34.7±3.7	0.590
RVDd (mm)	28.1±2.5	30.7 ± 2.8	0.369
LVEF (%)	59.2±5.6	51.4±6.3	0.024
ASI	3.16±0.20	3.69±0.18	<0.001
E/e'	8.7±2.9	10.4 ±3.6	0.017

* NIHSS: National Institutes of Health Stroke Scale, † LV: Left Ventricle, ‡ LVDd: Left ventricular diastolic diameter, § LVDs: Left ventricular systolic diameter, || LVEDV: Left ventricular end-diastolic volume, ¶ LVESV: Left ventricular end-systolic volume, ** LAD: Left atrial diameter, †† RAD: Right atrial diameter, ‡‡ RVDd: Right ventricular diastolic diameter, §§ LVEF: Left ventricular ejection fraction, |||| ASI: Aortic stiffness index, ¶¶: E/e': Ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e').

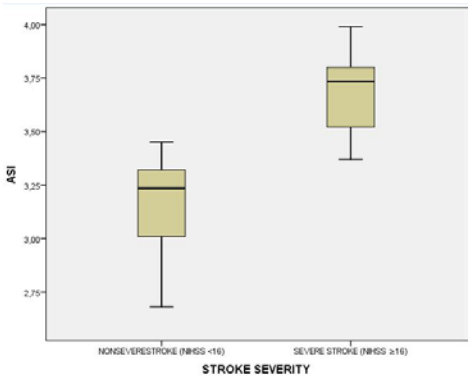

Figure 1. Relationship between NIHSS and ASI. (NIHSS: National Institutes of Health Stroke Scale, ASI: Aortic stiffness index.)

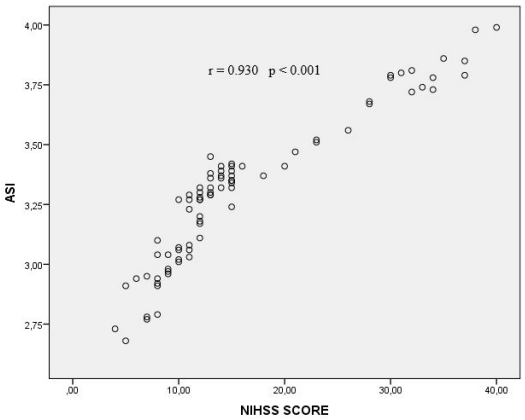

Figure 2. Correlations between NIHSS score and ASI. (NIHSS: National Institutes of Health Stroke Scale, ASI: Aortic stiffness index.)

Table 3. Correlation between NIHSS score and clinical parameters in patients with acute ischemic stroke.

Parameters	Pearson's correlation coefficient (r value)	p Value
ASI	0.930	<0.001
LVEF	-0.314	0.038
E/e'	0.217	0.026
Age	0.320	0.042
Heart rate	0.419	0.023

* NIHSS: National Institutes of Health Stroke Scale, † ASI: Aortic stiffness index, ‡ LVEF: Left ventricular ejection fraction, § E/e': Ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e').

Table 4. Multivariate logistic regression analysis between NIHSS score and clinical parameters in patients with acute ischemic stroke.

Parameters	OR	95 % CI	p Value
ASI	0.753	0.671-0.894	0.014
LVEF	0.835	0.770-0.920	0.025
Age	1.218	1.090-1.465	0.030
Heart rate	1.130	0.972-1.223	0.453

* NIHSS: National Institutes of Health Stroke Scale, † ASI: Aortic stiffness index, ‡ LVEF: Left ventricular ejection fraction.

DISCUSSION

Arterial stiffness is an significant reason of cerebrovascular and cardiovascular complications[14]. Increased aortic stiffness is the consequence of a damaging impact on the arterial wall over time by other atherosclerotic risk factors (especially arterial hypertension and advanced age). The detrimental consequence of aortic stiffness consist both in microvascular and macrovascular area. Therefore, arterial stiffness an important component in the pathway between vascular risk factors and cerebrovascular and cardiovascular diseases. Also, the aortic stiffness may show a likely important in the management of acute cerebrovascular disease and a marker of arterial vascular function to monitorize in the early phase and in the follow-up of acute stroke.

Assessment of aortic stiffness requires invasive methods. These techniques are inappropriate for application in clinical practice. In previous researchers, it has been showed that pulsatile alterations in proximal ascendan aortic diameter can be calculated during a 2D echocardiography[15]. Non-invasively assesment of ASI index as an important determinant of arterial stiffness is comparable with invasive technique with an important correctness[15]. Decreased arterial stiffness was related with advanced age, hypertension, and ethnicity. In addition, other atherosclerotic risk factors, such as dyslipidemia and smoking were related with arterial stiffness[15].

Previous studies have evaluated aortic stiffness in patients with acute cerebrovascular diseases[16,17]. Tuttolomondo et al. demonstrated that infarct subtype was related increased aortic stiffness in patients with acure cerebrovascular disease[4]. However, Manzano et al. suggested that infarct subtype was related with decreased aortic stiffness in acute cerebrovascular events[18]. They suggested that differences between stroke patients may be related with genetic, atherosclerotic risk factors and ethnicity[18].

We researched the ASI in acute ischemic stroke patients and the association between ASI and stroke severity. Aortic stiffness can be evaluated non-invasively by calculation of systemic arterial compliance and pulse wave velocity (PWV)[5]. In this study, aortic stiffness was calculated using the echocardiography. Our study demonstrated that ASI was lower in the lower NIHSS than in the higher NIHSS.

Hypertension, age, hyperlipidemia, Diabetes Mellitus, smoking are significant risk factors for atherosclerotic cerebrovascular disease[19]. Increased arterial stiffness are related with atherosclerotic risk factors[20]. Byun DS et al. found that, advanced age exerted the significant impact on arterial stiffness[5]. Fauchier L et al demonstrated that age is a significant risk factor for acute neurologic event[21]. Cigarette smoking is related with arterial stiffness[22]. Hypertension affects the mechanical features of the arterial wall and is associated with an increase of the ASI. Park JS et al. demonstrated that arterial stiffness associated with HT[23]. Byun DS et al. suggested that peripheric blood pressure were nearly related with aortic stiffness as well[5]. We found that, blood pressure at admission is importantly higher in patients who have higher NIHSS score. Li T et al. suggested that the NIHSS score on admission in the hypertension group was signifcantly higher than that in the control group[24]. However, Bonardo P et al. found that, young patients with acute cerebrovascular events, large cerebral infarct volume was not related with high blood pressure at admission[25]. Mandraffino G et al. demonstrated that arterial stiffness improved after statin therapy in patients with hyperlipidemia[26]. In our study, we found that LDL cholesterol was significantly higher in patients with higher NIHSS scores than in those with lower NIHSS scores.

Acute ischemic stroke is described by severe autonomic nervous system dysfunction. This autonomic dysregulation is containing changes in the autonomic reflex systems, and hormonal factors. Stroke-related sympathetic activation is high in

patients with higher NIHSS score. Regardless of previous cardiovascular history, an early phase of acute ischemic stroke significantly affects arterial BP, heart rate, LV function, and biochemical parameters (Glucose, troponin, creatinine)[27]. In our study, we found that troponin values were importantly higher in severe ischemic stroke patients. Chang et al observed that cardiac biomarkers, especially serum troponin values are related with acute major cerebral arterial occlusion in acute ischemic stroke patients[28]. Hendrix P et al. found that diabetes mellitus history is an important predictor of stroke severity[29]. Chirinos JA and et al. shown that diabetes mellitus is a significant risk factors for arterial stiffness[30]. Lindsberg *et al* suggested that increased blood glucose level is frequent in the acute period of stroke[31]. In our study HbA1c and blood glucose values were importantly higher in severe stroke patients on hospitalization. Even though up to one-third of severe acute ischemic stroke patients have diabetes mellitus. Presumably a significant percentage of patients have stress related hyperglycemia. Causes of hyperglisemia are increasing norepinephrine and cortisol values[31].

In our study we found that E/é value was significantly higher in severe stroke patients. Ryu WS et al. suggested that E/e' ratios were related with cerebral arterial occlusion in AF-associated stroke. They suggested that, E/e' ratios are important parameter for diagnosis of high risk severe ischemic stroke patients[32]. In our clinical study we found that creatinine values were importantly higher in severe stroke patients. Mostofsky E et al. suggesting that, cardiovascular risk factors including diabetes, arterial hypertension, advanced age may show a only vascular pathophysiology resulting from decreased renal function. Renal function predicts survival in acute ischemic stroke patients[33].

Our study has several limitations. The present study was limited by the limited sample size. Other a possible limitation of our study may have not been excluded patients with a history of vascular risk factors such as hypertension, diabetes, smoking and dyslipidemia that can influence arterial stiffness.

ASI was significantly higher in patients with severe acute ischemic stroke. The result of the present study suggested that higher ASI is associated with higher NIHSS score in patients with acute ischemic stroke. However, large prospective studies will be needed to establish the relationships between ASI and stroke severity.

Yazar Katkıları: Çalışma konsepti/Tasarımı: PAÖ, ÜÖ, ÖÖ; Veri toplama: ÜÖ, ÖÖ; Veri analizi ve yorumlama: PAÖ, ÖÖ; Yazı taslağı: PAÖ, ÜÖ, ÖÖ; İçeriğin eleştirel incelenmesi: PAÖ, ÜÖ, ÖÖ; Son onay ve sorumluluk: PAÖ, ÜÖ, ÖÖ; Teknik ve malzeme desteği: PAÖ, ÜÖ, ÖÖ; Süpervizyon: PAÖ, ÜÖ, ÖÖ; Fon sağlama (mevcut ise): yok.
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