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ARAŞTIRMA / RESEARCH

Evaluation of aortic stiffness parameters in premenopausal migraine patients

Premenapozal migren hastalarında aort sertliği parametrelerinin değerlendirilmesi

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Abstract

Purpose: Migraine is an episodic primary headache disorder, which affects approximately 10% of the adult population, predominantly females. Based on the changes detected in migraine and previous findings, arterial stiffness can be considered to be an important contributor to vascular events in patients with migraine. The aim of this study was to investigate the associations between atherosclerosis and migraine through the evaluation of aortic stiffness in premenopausal migraine patients.
Materials and Methods: The study included 68 female patients with migraine, and a control group of 39 healthy females. To reveal the association between migraine and arterial stiffness, echocardiography was applied and aortic stiffness was evaluated. Blood pressure measurements, basic biochemical tests and the 12 derivation-ECG recordings of each patient were taken simultaneously.
Results: Basic echocardiographic findings were similar in patients and the control group. Systolic and diastolic diameters of the aorta, and the change in aortic diameter were also similar in both groups. Aortic distensibility, aortic strain and beta indices were also similar in both groups. No significant differences were determined between patients with and without aura migraine and the control group in respect of systolic blood pressure, diastolic blood pressure and pulse pressure.
Conclusion: As a marker of atherosclerosis, the aortic stiffness parameters didn't differ between migraine and control group.
Keywords: Migraine, arterial stiffness, atherosclerosis

Öz

Amaç: Migren, ağırlıklı olarak kadınlar olmak üzere yetişkin nüfusun yaklaşık %10'unu etkileyen epizodik birincil baş ağrısı bozukluğudur. Migrende tespit edilen değişikliklere ve önceki bulgulara dayanarak, arteriyel sertliğin migren hastalarında vasküler olaylara önemli bir katkıda bulunduğu düşünülebilir. Bu çalışmanın amacı, premenapozal migren hastalarında aort sertliğinin değerlendirilmesi ile ateroskleroz ve migren arasındaki ilişkiyi araştırmaktır.
Gereç ve Yöntem: Çalışmaya migreni olan 68 premenapozal kadın hasta ve 39 sağlıklı kadın kontrol grubu olarak dahil edildi. Migren ve arteriyel sertlik arasındaki ilişkiyi ortaya çıkarmak için tüm katılımcılara ekokardiyografi uygulandı ve aort sertlikleri değerlendirildi. Katılımcıların kan basıncı ölçümleri, temel biyokimyasal testleri ve 12 derivasyon EKG kayıtları eşzamanlı alındı.
Bulgular: Temel ekokardiyografik bulgular hasta ve kontrol grubunda benzerdi. Aortun sistolik ve diastolik çapları, aort çapındaki değişim oranları her iki grupta benzerdi. Auralı ve aurasız migrenli hastalar ve kontrol grupları arasında sistolik, diastolik ve nabız basınçları açısından anlamlı farklılık tespit edilmedi.
Sonuç: Aterosklerozun bir belirteci olarak aort sertliği parametreleri Migren hastaları ile kontrol grubu arasında farklı değildir.

Anahtar kelimeler: Migren, arteriyel sertlik, ateroskleroz

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INTRODUCTION

Headache is one of the most common reasons patients seek help from family physicians, and treatment is often suboptimal. Thus, acute headache is a common and important clinical condition, the nature of which has to be determined as benign or secondary to other systemic abnormalities. Migraine is an episodic primary headache disorder, which affects approximately 10% of the adult population, predominantly females[1,2]. According to World Health Organization (WHO) data, migraine is known to be the 19th leading cause of years lived as disabled, independent of age[3].

As a neurovascular disorder, migraine may be defined as a paroxysmal disorder of vascular control in respect of cranial vasculature[4]. Several hypotheses indicating the pathophysiology of migraine have been proposed, such as contractile dysfunction of cranial blood vessels, neurogenic inflammation, and cortical spreading depression. Moreover, several studies have also shown that some cytokines and neuropeptides could be associated with the development of migraine[5,6]. On the whole, the neurovascular hypothesis has combined both neurogenic and vascular mechanisms. However, the pathophysiology of migraine has not yet been clearly understood.

Increased blood pressure, endothelial dysfunction and increased sympathetic tone may cause arterial stiffness, and increased arterial stiffness is known to be a risk factor for the development of cardiovascular disorders[7-10]. Endothelial dysfunction has also been postulated to be found in patients with migraine[11]. Beyond vascular changes in the cranium, generalized peripheral vasoconstriction may be observed during migraine attacks[12]. Some studies have shown associations between increased peripheral arterial stiffness and decreased arterial compliance, and migraine[13,14]. Several studies have indicated that the risks of vascular events such as myocardial infarction and ischemic stroke were increased in migraine patients[15-17]. Cardiovascular mortality has also been found to be higher in migraine patients[15]. Based on the changes detected in migraine and previous findings, arterial stiffness can be considered to be an important contributor to vascular events in patients with migraine. The aim of this study was to evaluate the aortic stiffness parameters, which are among the early findings of the atherosclerotic process in women with premenopausal migraine. In this respect, our study is first one in current literature

MATERIALS AND METHODS

Eighty-five premenopausal women with migraine who applied to the neurology outpatient clinic were evaluated. Total of 7 patients had diabetes, 8 patients had hypertension and 2 patients had thyroid disease, and these were excluded from the study. Finally 68 patients were included in the study. In all cases, the diagnosis of migraine was made by the same neurologist, according to the criteria of the International Classification of Headache Disorders. The neurologist also defined the type of migraine as with aura or without aura. The migraine types were not differentiated as chronic or episodic. Each patient was informed of the content of the study and informed consent was obtained from each participant. To reveal the association between migraine and arterial stiffness, echocardiography (ECHO) was applied and aortic stiffness was evaluated by an experienced cardiologist, unaware of the clinical and laboratory data of the participants. Blood pressure measurements and the 12 derivation-electrocardiography (ECG) recordings of each patient were taken simultaneously. Basic biochemical tests of the patients were recorded. A control group was formed of 39 age-matched, healthy non-smoker females who had no comorbidities associated with atherosclerosis. Written informed consent was obtained from each participant in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The study protocol was approved by the Institutional Human Research Ethics Committee (Kayseri Training and Research Hospital EPK 2012/014).

Patients were excluded if they had diabetes mellitus, hypertension, chronic renal failure, epilepsy, thyroid dysfunction, coronary artery disease, smoking history, moderate or severe degree valvular stenosis, cardiomyopathy, atrial fibrillation, atrial flutter, tachyarrhythmia, bradyarrhythmia, bundle branch block on ECG, congenital heart disease, symptomatic heart failure, systemic diseases involving the aorta (Marfan or Ehler-Danlos syndrome), or aortic aneurysms.

Procedure

Body mass index (BMI) was calculated with the formula of body weight (kg)/ square of height (m). Complete blood count was measured with an automated counter. Biochemistry laboratory tests were applied for the measurement of LDL, HDL,

triglyceride, total cholesterol, creatinine, fasting blood glucose, and uric acid. Biochemical parameters were studied with routine autoanalyzer (Roche Diagnostics, Basel, Switzerland) in the central laboratory of Kayseri Training and Research Hospital. In our study, parameter evaluation requiring a special kit was not performed.

Blood pressure was measured with a mercury sphygmomanometer from each patient in a supine position simultaneously with ECG. Korotkoff sounds were used to determine phase 1 (systolic) and phase 5 (diastolic).

All participants were evaluated with a GE Vingmed Vivid 7 system ECHO device using a 2.5-3.5 MHz transducer. M-mode and 2-D images, and spectral and color-flow Doppler images were recorded. After routine ECG evaluation, ascending aortic recordings were taken with M-mode guided by 2-D images in a slightly supine position. These recordings were taken 3 cm above the aortic valve. Aortic diameter was measured as the distance between the inner borders of the anterior and posterior walls of the aorta, in systole and diastole. The systolic diameter of the aorta was measured with the aortic valve in a fully open position and the diastolic diameter of the aorta was measured at the peak point of QRS in simultaneous ECG. The average values were calculated from 5 consecutive measurements (Figure 1). In addition, in all patients, the left ventricle ejection fraction (EF), left ventricle end systolic diameter (LVSD), left ventricle end diastolic diameter (LVDD), left ventricle posterior wall diameter (LVPW), and interventricular septum thickness (IVS) were measured.

Aorta systolic (AoS) and aorta diastolic (AoD) indices were calculated as the systolic and diastolic diameters of the aorta divided by BMI, respectively. The elastic parameters of the aorta were calculated using these indices:

Pulse pressure: systolic blood pressure-diastolic blood pressure
Aortic strain (%)=100 x (AoS - AoD) / AoD
Distensibility (cm^2.dyn–1.10-3) = 2x (AoS - AoD) / pulse pressure x AoD
Beta Index= ln (systolic pressure/diastolic pressure) / aortic strain.

Statistical analysis

We used SPSS 24.0 software program. Conformity of the data to normal distribution was evaluated with the Shapiro-Wilk test, and homogeneity of variance was evaluated with the Levene test. When comparing the quantitative data of two independent groups, the Independent-Samples T test was used. In the comparison of the quantitative data of more than two groups, One-Way Anova was used. Quantitative variables were shown as mean±standard deviation (SD), and categorical variables as number (n) and percentage (%). Variables were analyzed at a 95% confidence level and a value of $p<0.05$ was accepted as statistically significant.

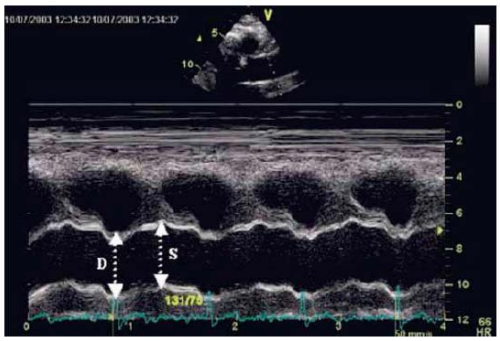

Figure 1. An example of echocardiographic measurement.

RESULTS

Patients were divided into two groups according to aura; Group 1 (migraine with aura, n=37) and Group 2 (migraine without aura, n=31). There was no significant difference between the patient and control groups in respect of mean age (37.93 ± 7.741 years, 35.22 ± 6.370 years, respectively). The mean age was 35.36 ± 10.116 years in Group 1 and 39.97 ± 12.912 years in Group 2. Mean age, height, body weight, BMI, LDL, HDL, glucose, creatinine, uric acid, hemoglobin, platelet, and white blood cell (WBC) counts were determined to be similar in patients and the control group. Triglyceride and total cholesterol levels were significantly higher in patients than in the control group (Table 1).

Basic echocardiographic findings were similar in patients and the control group. Systolic and diastolic diameters of the aorta, and the change in aortic diameter were also similar in both groups (2.810 ± 0.285 vs 2.820 ± 0.288 p=0.852, 2.539 ± 0.354 vs 2.462 ± 0.318 p=0.253, 0.310 ± 0.193 vs 0.358 ± 0.190 p=0.122, respectively) (Table 2).

Table 1. Demographic and laboratory features of the participants.

	Patient (n=68)	Control (n=39)	p value
	Mean±SD.	Mean±SD.	
Age(years)	37.93 ± 11.71	35.22 ± 6.370	0.219
Height (cm)	159.58 ± 9.82	162.54 ± 10.44	0.171
Body weight (cm)	70.08 ± 13.04	66.49 ± 13.44	0.166
BMI (kg/m²)	25.500 ± 4.885	25.211 ± 5.254	0.222
Fasting blood glucose (mg/dl)	90.72 ± 11.022	86.22 ± 7.826	0.114
Total cholesterol (mg/dl)	203.48 ± 53.11	171.61 ± 45.097	0.027
LDL (mg/dl)	116.57 ± 38.872	104.28 ± 32.516	0.231
HDL (mg/dl)	55.85 ± 14.961	53.72 ± 9.348	0.573
Triglyceride (mg/dl)	187.11 ± 115.068	95.44 ± 37.660	0.001
Creatinine (mg/dl)	833 ± 0.522	583 ± 0.092	0.499
Uric acid(mg/dl)	3.943 ± 1.319	3.867 ± .734	0.817
Hemoglobin (g/dl)	13.906 ± 4.387	13.139 ± 1.030	0.467
Platelet (10^3/uL)	302.74 ± 74.851	310.56 ± 68.412	0.697
WBC	6.585 ± 1.533	6.266 ± 1.725	0.779

BMI: Body Mass Index, LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein, WBC: White Blood Cell SD.: Standard deviation. Groups were compared with the Independent t-test and $p<0.05$ was accepted as statistically significant.

Table 2. Comparison of echocardiographic parameters of the patients and the control group.

	Patient (n=68)	Control (n=39)	p value
	Mean ±SD.	Mean ± SD.	
EF (%)	67.05 ± 3.671	67.12 ± 6.124	0.961
LVSD (cm)	4.840 ± 0.454	4.321 ± .422	0.124
LVDD (cm)	3.275 ± .824	2.753 ± .389	0.133
IVS (cm)	1.04 ± 0.19	0.99 ± 0.16	0.152
LVPW (cm)	1.01 ± 0.12	0.96 ± 0.15	0.148
Systolic diameter of aorta (cm)	2.810 ± 0.285	2.820 ± 0.288	0.852
Diastolic diameter of aorta (cm)	2.539 ± 0.354	2.462 ± 0.318	0.253
Change in aortic diameter (cm)	0.310 ± 0.193	0.358 ± 0.190	0.122

EF: Ejection Fraction, LVSD: Left Ventricle Systolic Diameter, LVDD: Left Ventricle Diastolic Diameter, IVS: Interventricular Septum, LVPW: Left Ventricular posterior wall, SD.: Standard deviation; Groups were compared using the Independent t-test and $p<0.05$ was accepted as statistically significant.

Table 3. Comparison of arterial stiffness parameters of the participants.

	Patient (n=68)	Control (n=39)	p value
	Mean ±SD.	Mean ±SD.	
Systolic blood pressure (mmHg)	118.43 ± 14.392	113.22 ± 14.343	0.067
Diastolic blood pressure (mmHg)	76.14 ± 10.579	70.76 ± 11.798	0.140
Pulse pressure (mmHg)	42.29 ± 9.998	42.46 ± 9.206	0.928
Aortic distensibility (cm2.dyn–1.10-3)	0.588 ± 0.349	0.700 ± 0.408	0.127
Aortic strain (%)	11.953 ± 6.993	14.060 ± 6.901	0.125
Beta index	0.054 ± 0.038	0.043 ± 0.031	0.157

SD: Standard deviation. Groups were compared using the Independent t-test and $p<0.05$ was accepted as statistically significant.

No significant differences were determined between patients and the control group in respect of systolic blood pressure, diastolic blood pressure and pulse pressure. Aortic distensibility, aortic strain and beta indices were also similar in both groups (0.588 ± 0.349 vs 0.700 ± 0.408 p=0.127, 11.953 ± 6.993 vs 14.060 ± 6.901p=0.125, 0.054 ± 0.038 vs 0.043 ± 0.031 p=0.157; respectively (Table 3).No significant differences were determined between Group 1, Group 2 and the control group in respect of systolic blood pressure, diastolic blood pressure and pulse pressure. Aortic distensibility, aortic strain and beta indices were also similar in all groups (Table 4).

Table 4. Comparison of arterial stiffness parameters of the patients and the control group.

	Patient (n=68)		Control (n=39)	p
	Group 1 (n=37)	Group 2 (n=31)		
	Mean ± SD.	Mean ± SD.	Mean ± SD.	
Systolic diameter of aorta (cm)	2.779 ± 0.279	2.845 ± 0.293	2.820 ± 0.288	0.614
Diastolic diameter of aorta (cm)	2.528 ± 0.369	2.552 ± 0.341	2.462 ± 0.318	0.501
Change in aortic diameter (cm)	0.251 ± 0.207	0.293 ± 0.174	0.358 ± 0.190	0.057
Systolic blood pressure (mmHg)	117.49 ± 12.87	119.55 ± 16.136	113.22 ± 14.34	0.156
Diastolic blood pressure (mmHg)	76.33 ± 10.91	75.91 ± 10.339	70.76 ± 11.79	0.059
Pulse pressure (mmHg)	41.15 ± 9.27	43.64 ± 10.779	42.46 ± 9.20	0.557
Aortic distensibility (cm2.dyn–1.10-3)	0.567 ± 0.343	0.613 ± 0.360	0.700 ± 0.408	0.274
Aortic strain (%)	11.491 ± 6.868	12.499 ± 7.205	14.060 ± 6.901	0.257
Beta index	0.053 ± 0.033	0.055 ± 0.044	0.043 ± 0.031	0.359

SD: Standard deviation. Groups were compared using the Independent t-test and $p<0.05$ was accepted as statistically significant.

DISCUSSION

The results of this study demonstrated that blood pressure, pulse pressure, aortic strain, beta index, and aortic distensibility were not significantly different between patients with migraine and without migraine. To the best of our knowledge, there are few studies that have investigated the association between aortic elasticity and migraine using aortic strain, distensibility and the beta index.

Migraine is an important disorder not only for the neurologist but also for all primary care physicians, as it is known to be an independent risk factor for myocardial and cerebral ischemia[15-17]. Many studies have reported the associations of elasticity indices with several disorders such as hypothyroidism, aortic disorders, and coronary artery disease etc[18-22]. Akturk et al compared migraine patients with a low cardiovascular risk with a healthy control group and found no differences between the groups according to the beta index and aortic distensibility[23]. Although the basic pathophysiology underlying this situation is not yet clearly understood, it has been shown that vascular changes are not only limited to the cranial vasculature during migraine attacks, but also involve peripheral vessels. Peripheral vasoconstriction has been reported to have been observed in migraine patients during attacks. Increased coronary and radial artery vasoconstriction has also been observed in some studies and decreased distensibility of cranial and peripheral vessels during stable periods between attacks[13]. These findings of systemic vascular dysfunction may explain the underlying mechanistic link between migraine and ischemic vascular disorders. Yetkin et al. showed that endothelial dysfunction was an important factor in migraine[24,25]. The associations of endothelial dysfunction with migraine or other disorders suggest that the mechanism of vascular dysfunction could cause all these disorders[26]. Arterial stiffness is a valuable marker predicting vascular disorders[9]. In some studies, increased aortic stiffness or augmentation index (AI) has been shown in patients with migraine. In brief, both microvascular dysfunction and large artery stiffness have a significant role in the mechanisms causing increased risk of cardiovascular disease in patients with migraine.

Carotid-femoral pulse wave velocity (CFPWV) is the gold standard non-invasive test to measure aortic stiffness[27]. In one study, 93 middle-aged/elderly obese adult subjects with at least one additional cardiovascular risk factor were grouped according to no headache, tension-type headache (TTH) or migraine and AI and carotid-femoral pulse wave velocity were measured as an indicator of aortic stiffness[28]. It was found that elevated AI was independently associated with the presence of either migraine or TTH, but could not discriminate between

migraine and TTH. Due to the sample selection, it could be said that this study suggested the possible association of AI with cardiovascular risks. However, the patients were not grouped according to the presence or absence of aura, and no correlation analysis was applied. In the current study, AI was not measured and no differences were determined between the migraine patients and the control group in respect of aortic stiffness. In addition, patients with cardiovascular disorders or cardiovascular risk factors were excluded, thus only patients with pure migraine were evaluated. In contrast, analysis of the study data of the obese patients with at least one additional cardiovascular risk factor showed that higher AI may be linked to these factors. Moreover, the participants in the current study had a lower mean age compared to those of the above-mentioned study. It is known that with increasing age, the cardiovascular risk increases due to age-related changes and the increased frequency of comorbidities in elderly patients. In the current study, the patients selected were premenopausal, aged < 49 years and with migraine only, so that analysis could be made of the association between aortic stiffness and migraine independent of other factors.

Schillaci et al compared CFPWV and AI measurements in 60 migraine patients and age-, gender-, and blood pressure-matched healthy control subjects. The migraine patients were seen to have higher CFPWV and AI values than the control group, and migraine patients with aura had higher CFPWV than those without aura[29]. According to that study it can be said that migraine patients with aura have a higher cardiovascular risk. Dogan et al compared migraine patients without cardiovascular risk factors with a control group and found higher CFPWV in the migraine patients[30]. In the current study, no difference was determined between patients with and without aura.

Ikeda et al compared 22 migraine patients with aura, 89 patients without aura, and 110 healthy subjects in terms of arterial stiffness parameters[31]. PWV was found to be higher in migraine patients compared to the control group. There were no differences between the subtypes of migraine in terms of PWV, and ABI did not differ between the groups. Only middle-aged subjects and patients with a low risk of cardiovascular diseases were included in that study. In this context, the finding that increased PWV was found in the patients with migraine was especially important. Furthermore, brachial-ankle PWV was measured in this study, and the results were similar to those of previous studies evaluating CFPWV. Nagai et al showed that elderly migraine patients had increased AI and stiffness independent of other factors[14]. In several studies, a weaker association has been determined between stiffness and ischemic stroke in elderly migraine patients compared to younger patients. However, an important finding of the current study was that increased stiffness parameters were found in younger migraine patients by excluding the other confounding factors.

A previous study demonstrated the possible positive effect of prophylactic treatment of migraine on stiffness parameters.30. Generally, the finding of increased CFPWV both in migraine patients and in patients with vascular disorders supports the link between migraine and vascular disorders. There is a need for further extensive studies to clarify the effects of migraine treatment on cardiovascular events in migraine patients. In addition, not only CFPWV but also other stiffness parameters such as aortic strain and distensibility could be evaluated as important predictors of cardiovascular diseases in migraine patients.The most important limitation of our study is the low number of patients. In addition, we could use an objective method to evaluate endothelial function such as brachial artery flow mediated dilatation.

In this study, stiffness was evaluated through aortic distensibility and strain measurements. There are few studies in literature which have investigated aortic stiffness in migraine using these parameters. Although no differences were determined between patients with and without migraine there is a need for large sample size studies on this subject.

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