Decreased aortic root elasticity-as a novel systemic manifestation of the pseudoexfoliation syndrome: an observational study

Psödoeksfoliyasyon sendromunun yeni bir sistemik göstergesi olarak azalmış aorta kökü esnekliği: Gözlemsel bir çalışma

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ABSTRACT

Objective: To assess the aortic root function in patients with pseudoexfoliation syndrome (PEXS).
Methods: In this case- controlled observational study, aortic root function in 31 PEXS patients (mean age 71±9 years) and 29 controls of similar ages (mean age 69±9 years) were evaluated by M-mode transthoracic echocardiography. Aortic cross-sectional compliance (CSC), Peterson's elastic modulus (index beta), aortic stiffness index (ASI) and aortic root distensibility (ARD) were calculated by M-mode echocardiography to evaluate the aortic root function. The findings of two groups of patients were compared by Mann-Whitney U test.
Results: The CSC and ARD were significantly decreased in patients with PEXS. The CSC was 12.2±6.3 cm^2/mmHg in patients with PEXS and 17.5±11.6 cm^2/mmHg in the control group (p=0.015). The ARD was 1.56±0.80 cm^2/dyne in patients with PEXS and 2.23±1.48 cm^2/dyne in the control group (p=0.021). The other two indices of aortic root function were not significantly different between the two groups.
Conclusion: Aortic root function decreases in patients with PEXS. PEXS may be regarded as a risk factor for cardiovascular and cerebrovascular events. *(Anadolu Kardiyol Derg 2012; 12: 483-7)*
Key words: Echocardiography, aortic root function, aorta, pseudoexfoliation syndrome

ÖZET

Amaç: Psödoeksfoliyasyon sendromu olan hastalarda aorta kökü fonksiyonlarını değerlendirmek.
Yöntemler: Bu gözlemsel, vaka kontrollü çalışmada, psödoeksfoliyasyon sendromu (PES) olan 31 hasta (ortalama yaş: 71±9 yıl) ve benzer yaştaki 29 kontrol (ortalama yaş±SD: 69±9 yıl) olguda aorta kök fonksiyonu değerlendirmesi için M-mod transtorasik ekokardiyografi yapıldı. Aorta kök fonksiyonu değerlendirmesinde, M-mod ekokardiyografi ile aortanın kesitsel kompliansı (AKK), Peterson elastik modülü (indeks beta), aorta sertlik indeksi (ASİ) ve aort kökü gerilme kapasitesi (AKG) hesaplandı. Bu iki grup hastanın bulguları, Mann-Whitney U testi ile karşılaştırıldı.
Bulgular: AKK ve AKG, psödoeksfoliyasyon sendromu olan hastalarda belirgin derecede azalmıştı. AKK, psödoeksfoliyasyonlu hastalarda 12.2±6.3 cm^2/mmHg iken, kontrol grupta17.5±11.6 cm^2/mmHg olarak bulundu (p=0.015). AKG, psödoeksfoliyasyon sendromu olan hastalarda 1.56±0.80 cm^2/dyne olarak, kontrol grubunda ise 2.23±1.48 cm^2/dyne olarak bulundu (p=0.021). Aorta kök fonksiyonu değerlendirmesinde iki grup arasında hesaplanan diğer iki indeks açısından belirgin fark bulunamadı.
Sonuç: Psödoeksfoliyasyon sendromu olan hastalarda aorta kök fonksiyonu azalmıştır. PES, kardiyovasküler ve serebrovasküler olaylar için bir risk faktörü olarak değerlendirilebilir. *(Anadolu Kardiyol Derg 2012; 12: 483-7)*
Anahtar kelimeler: Ekokardiyografi, aorta kök fonksiyonu, aorta, psödoeksfoliyasyon

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Accepted Date/Kabul Tarihi: 05.04.2012 **Available Online Date/Çevrimiçi Yayın Tarihi:** 07.06.2012

doi:10.5152/akd.2012.155

Introduction

Pseudoexfoliation syndrome (PEXS) is an age-related disorder of the extracellular matrix and is frequently associated with severe chronic secondary open-angle glaucoma and cataract (1). PEXS is characterized by the accumulation of dust-like pseudoexfoliation material in ocular tissues (2). The characteristic extracellular PEX fibrils are multifocally produced by various intraocular cell types and can be observed in the central retinal artery, short posterior ciliary arteries, vortex veins, ocular muscles, and orbital tissue. Loss of normal radial iris vasculature, neovascularization and narrowing and hypoperfusion of the iris vessels are associated with pseudoexfoliation glaucoma. The accumulation of pseudoexfoliation material in the vessel walls have been shown to be secondary to ischemia in some studies (2). Recently PEXS has also been reported to be positively associated with the risk for coronary artery disease among subjects 50 years or older (3). Cerebrovascular events and aneurysms of abdominal aorta are also reported to be more frequent in patients with PEXS (4, 5). However, some studies report that there is no association between systemic vascular diseases and pseudoexfoliation (6, 7).

The stiffening of aorta results in increased pulse pressure has adverse cardiac effects. Stiffening increases left ventricular afterload and causes left ventricular hypertrophy which in turn increases myocardial oxygen demand, thus may further increase the coronary artery disease (8). A thorough search of the literature identified no studies of changes in aortic root function in patients with PEXS.

Therefore, the present study sought to investigate the aortic root functions of this group of patients by transthoracic echocardiography.

Methods

Study design

This is a case - controlled observational study.

Study population

Overall, 31 patients with PEXS (Group 1) and 29 subjects of similar ages without PEXS (Group 2) were included in the study. The study population was chosen from the patients who admitted to the ophthalmology department for routine ophthalmic examination. Patients with aneurysm of the ascending aorta, left ventricular dysfunction, left ventricular dilatation, previous myocardial infarction, diabetes mellitus, dyslipidemia, or chronic renal failure and patients with history of smoking were excluded from the study. Characteristics of the subjects are presented in Table 1.

The study was approved by the Ethics Committee of the Başkent University and informed consent was obtained from all subjects.

Study protocol

All patients underwent a complete ocular examination by an ophthalmologist. The diagnosis of PEXS was based on the presence of typical pseudoexfoliation material on the anterior lens capsule in one or both eyes without glaucoma was based on the presence of typical pseudoexfoliation material on the anterior lens capsule in one or both eyes (1).

Echocardiographic examination

Two-dimensional M-mode echocardiography and blood pressure measurements were used to evaluate the aortic root function. M-mode tracings of the left ventricle and ascending aorta were obtained by a cardiologist and were recorded digitally on hard disk of the echocardiography device (Acuson, Sequoia, Mountain View, CA, USA) for further analysis. The measurements of the left ventricular end-diastolic and end-systolic dimensions, interventricular septal thickness and left ventricular posterior wall thickness were performed according to the criteria of the American Society of Echocardiography and the Penn Convention (9). The peak systolic aortic velocity was measured by pulsed-wave Doppler from the apical 4-chamber view at the level of the aortic valve. The peak systolic pulmonary velocity was measured at the parasternal short-axis view at the level of pulmonary valves. The systolic (SBP) and diastolic (DBP) blood pressures were measured at the time of echocardiographic examination by the same cardiologist. After the acquisition of all echocardiographic data, another cardiologist blinded to the diagnosis of the subjects, made the measurements from the recorded M-mode images. For each echocardiographic parameter, the mean value of 3 measurements was used in the statistical analysis.

Evaluation of aortic root function

The M-mode echocardiogram of the aortic root was obtained at least 3 cm distal to the aortic valve annulus. Aortic root function was evaluated noninvasively by echocardiography as described previously (9, 10): The end-diastolic (AoD) and end-systolic (AoS) dimensions of the aortic root were measured. Using the systolic (SBP) and diastolic blood pressure (DBP), and pulse pressure (PP=SBP-DBP) values, the following four aortic root function indexes were calculated: Aortic Cross-sectional Compliance (CSC)= π(AoS-AoD)AoD/2PP cm^2mmHg; Peterson's elastic modulus (index beta)= PP×AoD/(AoS-AoD) dynes/cm^2; Aortic stiffness index (ASI)=ln(SBP/DBP)/(AoS-AoD)/AoD; Aortic root distensibility (ARD)=2(AoS-AoD)/PPxAoD.

Statistical analysis

All data is presented as mean value$\pm$SD. Data was analyzed by SPSS 16.0 software for Windows (SPSS Inc, Chicago, Ill, USA). The unpaired t test and Mann-Whitney U test were used for statistical analysis and a p value less than 0.05 was considered statistically significant. Intra-observer and inter-observer variability was calculated by intraclass correlation coefficient. To determine intra-observer and inter-observer variability in the echocardiographic calculations, recordings of 12 subjects were reanalyzed by one of the authors on a separate day, and also by second cardiologist.

Results

There were no significant differences in terms of age, blood pressure values and aortic dimensions between the two groups (Table 1).

The dimensions of left atrium and right ventricle were not significantly different between Group 1 and Group 2 (Table 2). There were also no significant differences of left ventricular dimensions and wall thickness between the two groups. Among the Doppler measurements however, the aortic velocity was significantly higher in PEXS patients than in controls: 142±24 cm/sec in Group 1 and 127±19 cm/sec in Group 2 ($p<0.05$). On the other hand, pulmonary velocity was not significantly different between the two groups: 78±12 cm/sec in Group 1 and 72±11 cm/sec in Group 2 ($p=0.052$).

Among the indices of aortic root function, two of them were statistically significantly different between the two groups (Table 3): The CSC and ARD were significantly decreased in patients with PEXS. The CSC was 12.2±6.3 (10^{-3}) cm^2/mmHg in patients with PEXS and 17.5±11.6 (10^{-3}) cm^2/mmHg in the control group ($p=0.015$). The ARD was 1.56±0.80 cm^2/dyne in patients with PEXS and 2.23±1.48 cm^2/dyne in the control group ($p=0.021$). Regarding the other two indices of aortic root function, no significant difference was observed between the two groups. Peterson's elastic modulus (beta index) was 1827±756 dynes/cm^2 in Group 1 and 1477± 836 dynes/cm^2 in Group 2 ($p>0.05$). The aortic stiffness index was 6.5±2.4 in Group 1 and 5.5±3.0 in Group 2 ($p>0.05$) (Table 3).

We observed that the peak systolic aortic velocity was significantly increased in patients with PEXS (142±24 cm/sec) than the controls (127±19 cm/sec) ($p=0.013$), while the peak systolic pulmonary velocities were not significantly different between the two groups. This finding seems to be a result of impaired cushioning function of the aorta.

The intra-observer and inter-observer variability in the echocardiographic measurements was calculated as 5.2% and 3.6%, respectively.

Discussion

Among the four indices of aortic root function, the CSC and ARD were decreased in our PEXS patients. This observation may have important implications for PEXS since our results provide further evidence for the extraocular involvement in PEXS and may be an indicator of altered aortic root functions in PEXS patients.

Although PEXS is primarily an ocular disease, the accumulation of the abnormal pseudoexfoliation material has also been observed in extraocular tissues including the heart, lungs, kidneys, liver, gall bladder and brain (11, 12). When extraocular involvement occurs, the abnormal PEX material is frequently observed in the connective tissue of the above organs, with a preference for the periphery of the blood vessels. This observa-

Table 1. Characteristics of the subjects

Variables	Group 1 (n=31)	Group 2 (n=29)	*p
Age, years	71±9	69±9	0.398
Systolic blood pressure, mmHg	155±22	154±20	0.764
Diastolic blood pressure, mmHg	90±11	85±10	0.093
Pulse pressure, mmHg	66±16	69±15	0.481
Aortic dimension diastolic, mm	34.38±0.44	34.27±0.38	0.918
Aortic dimension systolic, mm	35.80±0.47	36.41±0.41	0.598
Aortic annulus dimension, mm	30±2.6	29.2±2.9	0.296

Data is presented as mean±SD
*Unpaired t-test

Table 2. Results of the 2-dimensional and Doppler echocardiographic measurements of the subjects

Variables	Group 1 (n=31)	Group 2 (n=29)	*p
Left atrium, mm	34.2±3.8	34.9±3.7	0.471
Right ventricle, mm	33.1±3.7	33.0±3.6	0.889
LVDED, mm	43.5±8.4	43.3±7.5	0.946
LVDES, mm	30.2±3.5	29.6±4.8	0.580
IVS, mm	10.9±1.3	11.8±6.4	0.448
PW, mm	10.3±1.1	10.6±3.8	0.645
Peak systolic aortic velocity, cm/sec	142±24	127±19	0.013
Peak systolic pulmonary velocity, cm/sec	78±12	72±11	0.052

Data is presented as mean±SD
*Unpaired t-test
IVS - interventricular septum, LVDED - left ventricular end-diastolic dimension, LVDES - left ventricular end-systolic dimension, PW - posterior wall

Table 3. Aortic root function indices of the subjects

Variables	Group 1 (n=31)	Group 2 (n=29)	*p
Cross-sectional compliance (10^{-3}), cm^2/mmHg			
Mean±SD	12.2±6.3	17.5±11.6	0.015
Range	4.55-27.08	5.72-53.38	
Peterson's elastic modulus, dynes/cm^2			
Mean±SD	1827±756	1477±836	0.067
Range	825-3145	340-2940	
Aortic stiffness index			
Mean±SD	6.5±2.4	5.5±3.0	0.058
Range	2.85-11.63	1.6-11.5	
Aortic root distensibility, cm^2/dyne			
Mean±SD	1.56±0.80	2.23±1.48	0.021
Range	0.58-3.45	0.72-6.80	

Data is presented as mean±SD
*Mann-Whitney U test

tion suggests that the abnormal PEX material may originate from the fibroblasts and muscle cells (striated, cardiac or smooth) and raises the possibility that PEXS may be part of a general disorder of extracellular matrix. Furthermore, several reports suggested an association of PEXS with cardiovascular and cerebrovascular diseases such as abdominal aortic aneurysm (13), asymptomatic myocardial dysfunction (14), angina pectoris, history of myocardial infarction (15), transient ischemic attacks (16), Alzheimer's disease (17), sensorineural hearing loss (18).

Our findings also have importance from the point of cardiovascular prognosis in patients with PEXS. It is well-known that elastic arteries dilate and stiffen with age, most noticeably in the ascending aorta and arcus aorta (19, 20). In the long term, decreased aortic elasticity has two important adverse effects on both the heart and the microcirculation (8). The stiffening of aorta results in increased pulse pressure (both increased systolic blood pressure and decreased diastolic blood pressure) which itself has adverse cardiac effects. Stiffening increases left ventricular afterload and causes left ventricular hypertrophy which in turn increases myocardial oxygen demand. Additionally, the decrease in diastolic blood pressure decreases coronary blood flow throughout diastole (8).

The second and frequently under-appreciated adverse effect of aortic stiffening is on the microcirculation of brain and kidneys (8). In addition to the conduit function, the aorta has a cushioning effect on cardiac pulsations. The cushioning effect prevents pulsatile cardiac flow to extend into the arterioles and capillaries. Due to this cushioning effect, the capillary flow is nearly continuous despite the cyclic cardiac pumping (8). In patients with decreased aortic elasticity, the loss of cushioning effect results in the extension of cardiac flow pulsations into the brain and kidney. The high flow and pressure pulsations in fragile microvasculature and increased energy loss can result in microhemorrhages and microinfarcts in these organs (8, 21, 22).

In the study of Ritland et al. (4), the acute (hemorrhages, embolus, thromboses) and chronic (cerebral atrophy, cerebral ischemia, senile dementia) cerebrovascular events are reported to be observed more frequently in PEXS patients. The decreased aortic root function in PEXS patients may explain at least some of the cerebrovascular diseases observed in this group of patients in previous studies (4, 15, 16).

Increased aortic stiffness has also been reported to affect the coronary arteries adversely. Fukuda et al. (23) studied brachial-ankle pulse wave velocity in subjects with and without coronary artery disease. They found a significant negative correlation of coronary flow reserve with brachial-ankle pulse wave velocity and concluded that coronary flow is altered with aortic stiffening in patients with coronary artery disease.

In the study of Andrikopoulos et al. (3) among subjects 50 years or older, PEXS was found to be positively associated with the risk for coronary artery disease. They suggested PEXS as a coronary artery disease risk factor.

In the study of Köz et al. (24) PEXS was reported to impair the endothelial function and cause structural vessel wall abnormality. The authors have observed increased levels of homocysteine, lipoprotein (a) and apolipoprotein A in the serum of PEXS patients, and they have suggested that these patients should also be evaluated for these additional cardiovascular risk factors. In our study, increased aortic stiffness findings also agree well with the structural changes in the vessel wall proposed in the study of Köz et al. (24).

The results of our study suggest that increased aortic stiffness may be at least partially responsible for the increased incidence of coronary artery disease observed in patients with PEXS.

In the current study, the exclusion criteria included aneurysm of the ascending aorta, left ventricular dysfunction, left ventricular dilatation, previous myocardial infarction, diabetes mellitus, dyslipidemia, or chronic renal failure and patients with history of smoking, which are all some additional factors to affect the vascular functions.

Study limitations

There are some limitations in our study. The relatively low number of subjects may be a limitation of our study. Further studies including large number of patients may disclose different results regarding the beta index and the aortic stiffness index.

Conclusion

To our knowledge, this is the first study to evaluate aortic root function in PEXS patients. Our results suggest that aortic root function is decreased in patients with PEXS. This novel observation contributes to the previous observations that PEXS may show systemic involvement.

Conflict of interest: None declared.

Authorship contributions. Concept - A.K.; Design - M.A.; Supervision - M.A., A.K.; Resource- M.B., A.K.; Materials - M.A.; Data collection&/or Processing- M.B., B.E.K.; Analysis &/or interpretation - M.A.; Literature search - B. E..K.; Writing - M.A., A.K.; Critical review - İ.H.M.

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