Evaluation of left ventricular functions in patients with pseudoexfoliation syndrome using tissue Doppler echocardiography and its association with plasma BNP levels

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Abstract

Objective: Pseudoexfoliation syndrome (PES) is a systemic disorder that involves various visceral organs. In this observational cross-sectional study we aimed to investigate the left ventricular functions in patients with PES by using tissue Doppler imaging and correlations between B-type natriuretic peptide levels and cardiac functions.

Methods: The study enrolled 22 patients with PES (9 male, 41%), aged 57.0±8.8 years, and 23 control subjects (9 male, 39%), aged 52.8±4.9 years. Patients with any cardiovascular disease were excluded. Fasting blood samples were taken and tissue Doppler imaging was performed at the mitral annulus with echocardiographic examination. The independent t and Mann-Whitney U tests were used.

Results: The Em velocities at the basal septum and lateral annulus were significantly lower in patients with PES showing decreased diastolic functions (7.6±2.0 versus 9.1±1.6 cm/s, p=0.01 and 9.3±3.5 versus 11.5±3.1 cm/s, p=0.04 respectively). While global left ventricular systolic function assessed by ejection fraction was not significantly different between patients with PES and controls, the septum S-wave velocities of PES patients were lower (7.6±1.3 versus 8.5±1.2 cm/s, p=0.03). Total plasma B-type natriuretic peptide (BNP) levels were significantly higher in PES patients (129.04±99.38 pg/mL versus 59.64±53.69 pg/mL; p=0.005) and there was a negative correlation between plasma BNP concentration and mitral annulus average Em velocities (r=-0.554, p=0.009). E/Em ratio was also significantly higher in PES patients (7.85±2.01 versus 6.64±1.48, p=0.03).

Conclusion: In this study we showed decreased left ventricular diastolic functions correlated with plasma BNP levels in PES patients. Although further studies needed, evaluation and follow-up of PES patients in terms of left ventricular functions will be useful. *(Anadolu Kardiyol Derg 2014; 14: 422-6)*

Key words: pseudoexfoliation syndrome, diastolic function, left ventricle, echocardiography, tissue Doppler, BNP

Introduction

Pseudoexfoliation syndrome (PES) is an age-related disorder of the extracellular matrix, characterized by the production and progressive deposition of fibrillar extracellular material in many ocular and extraocular tissues. It may predispose to cataracts, zonular weakness and glaucoma in the eye. In the generalized process of exfoliation, the vessel walls, smooth and striated muscle cells, skin, heart, lung, liver, kidney, cerebral meninges, and gall bladder are involved. Microscopically, exfoliation material was shown to be present in the interstitial connective tissue of these organs, often close to elastic and collagen fibers, fibroblasts and blood vessel walls (1, 2).

No clear-cut association of PES with a cardiovascular disease has yet been shown. Although in some studies, systemic vascular associations including endothelial dysfunction, left ventricular dysfunction, coronary artery disease, abdominal aortic aneurysm and elevated plasma homocysteine levels have been reported, systemic clinical consequences of synthesis and accumulation of exfoliation material in PES have not been clearly identified (3-12). Furthermore in some studies, no association was found between PES and increased systemic vascular risk (13, 14).

In the literature, studies about left ventricular functions in patients with PES are limited and results are controversial (9-11). While in one study, asymptomatic diastolic dysfunction was shown (9), in other two studies, only systolic dysfunction was shown in PES patients (10, 11).

Therefore, in this study we aimed to investigate the left ventricular systolic and diastolic functions in patients with PES by using two-dimensional echocardiography with tissue Doppler imaging. Also, B-type natriuretic peptide (BNP) is a hormone released from cardiomyocytes in response to cell stretching and elevated in both systolic and diastolic myocardial dysfunctions

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(15). Therefore, we also aimed to measure BNP levels and investigate the correlations between BNP concentrations and cardiac functions in patients with PES.

Methods

Study design

Observational cross-sectional study.

Study population

In this prospective study, the study group comprised 22 PES patients with or without glaucoma, diagnosed during their routine ophthalmologic examinations at our Ophthalmology Department Faculty of Medicine, Mersin University, Mersin, and the control group comprised 23 patients without PES and glaucoma. The 2 groups were age and sex-matched.

Patients with ophthalmic diseases such as cataract, primary open-angle glaucoma, uveitis, age-related macular disease were not involved in the study or the control group. Having systemic hypertension, cardiovascular or cerebrovascular diseases, valvular or myocardial heart disease, any type of malignancies and diabetes mellitus were in exclusion criteria, either. Latent coronary artery disease was excluded after normal upright exercise testing. The control group consisted of subjects who were taking no medication, without a history of cardiac complaints and no significant past ocular history.

Study population was informed about the objectives of the study and proper informed consent was received for their participation in the research. This study was approved by the Institutional Review Board of Mersin University, Faculty of Medicine, and the study was performed following the guidelines of the Declaration of Helsinki and is in adherence to all laws in the authors' country.

Study protocol

Detailed ophthalmologic examination was made to all subjects. Fasting blood samples were taken from all patients and controls for BNP analysis. Echocardiographic examination including tissue Doppler imaging was performed.

Ophthalmologic evaluation

Pseudoexfoliation syndrome was diagnosed or ruled out by slit-lamp examination after the pupils were dilated by pharmacological agents. The diagnosis of PES was made when fibrillogranular exfoliation material was seen on the anterior lens capsule (1). During their routine ophthalmologic examinations, visual acuities and intraocular pressures of the patients and the controls were measured; anterior and posterior segments were evaluated by slit-lamp biomicroscopy.

BNP analysis

Serum of all cases was collected by a peripheral venous route. B-type natriuretic peptide levels were measured by Elecsys 1010/2010 device (Roche Diagnostics, Manheim, Germany) using electrochemoluminescence method. BNP normal levels are between 0-125 pg/mL.

Echocardiography

Two-dimensional echocardiography was performed by an experienced specialist with using Philips Sonograph (HD 11XE, Eindhoven, The Netherlands) with 3 MHz transducer. Images of heart were obtained in the standard parasternal long-axis, short-axis and apical four-chamber planes (16). M-mode echocardiograms in the parasternal long-axis were used for the measurement of left ventricule (LV) end-diastolic and systolic dimensions, left atrial diameter according to American Society of Echocardiography standards (17).

Left ventricle wall thickness was measured from 2 dimensional parasternal views at the end-diastol with the greatest measurement within the left ventricular wall defined as the maximal wall thickness. Diastolic function was previously evaluated with traditional ultrasound pulse Doppler recording at the distal margins of mitral valve leaflets. Early and late transmitral flow velocities, E velocity deceleration time and isovolumetric relaxation time were analyzed. Tissue Doppler imaging is a new technique for assessment of regional and myocardial systolic and diastolic functions (18). Therefore, we obtained peak systolic velocities and diastolic tissue Doppler indexes; early (Em) and late (Am) diastolic velocities from mitral septal and lateral annulus using a sample area of 5 mm. The analysis of tissue Doppler echocardiography is very angle dependent. However, the angle was tried to keep less than 25°. From combination of traditional and tissue Doppler indexes, we obtained E/Em ratio (Em is the average of the septal and lateral mitral annulus).

Statistical analysis

Data are expressed as mean±SD or median (min-max) values. Control of normal distribution of data was made with Shapiro-Wilks test. The values of patients and controls were compared using the independent t test and Mann-Whitney U test. Pearson and Spearman's correlation coefficient were performed to test univariate relations between BNP and echocardiographic parameters. Statistical analysis was performed using SPSS for windows (Release 11.5, SPSS Inc, Chicago, Illinois, USA). A p value <0.05 was considered statistically significant.

Results

The study enrolled 22 patients with PES (9 men, 41%), aged 57±9 years, and 23 control subjects (9 males, 39%), aged 53±5 years. Among PES patients, 9 patients had also pseudoexfoliative glaucoma (41%). We found bilateral involvement in 5 (23%) PES patients, 17 (77%) patients had unilateral involvement. Demographic characteristics of patients and controls are presented in Table 1.

Basal echocardiographic results

Global left ventricular systolic function assessed by ejection fraction was not significantly different between patients with PES and controls. Patients with PES had a significantly greater maximal left ventricular septal wall thickness (p=0.01). Left ventricular

posterior wall thickness was also higher in PES patients but it was not statistically significant (p=0.06). Left ventricular end-diastolic and end-systolic cavity sizes and left atrial diameters were similar between the two groups. Basal echocardiographic parameters of patients and controls are presented in Table 1.

Doppler echocardiographic results

In both groups, results of traditional pulse-wave Doppler showed no statistical difference in E and A velosities, deceleration time and isovolumetric relaxation time (Table 2). According to tissue Doppler investigation, the S-wave velocities of PES patients in the septum were lower than control subjects (7.6±1.3 versus 8.5±1.2 cm/s, p=0.03). Lateral wall S-wave velocities were also lower in PES patients but they didn't reach the statistical significance (9.0±2.3 versus 10.2±1.7 cm/s, p=0.07). The Em velocities at the septum and lateral wall were significantly lower in patients with PES syndrome (7.6±2.0 versus 9.1±1.6 cm/s, p=0.01 and 9.3±3.5 versus 11.5±3.1 cm/s, p=0.04 respectively). Therefore, in the patient group composed of PES, mitral annulus Em velocities (average of the septal and lateral mitral annuli Em velocities) were significantly lower compared to control subjects (8.5±2.1 versus 10.3±1.9 cm/s, p=0.007). Also, E/Em ratio was significantly higher in PES patients (7.85±2.01 versus 6.64±1.48, p=0.03) (Table 2).

Correlations between BNP levels and echocardiographic variables

Total plasma BNP levels were significantly higher in PES patients than in the controls (129.04±99.38 pg/mL versus 59.64±53.69 pg/mL; p=0.005) (Table 1). In the PES group, a negative correlation was found between plasma BNP concentration and mitral annulus average Em velocities (r=-0.554, p=0.009) and lateral wall Sm velocities (r=-0.452, p=0.04) (Fig. 1, 2) and there was a positive correlation between BNP concentration and left ventricle posterior wall thickness (r=0.499, p=0.021) (Fig. 3). Plasma BNP concentrations were higher in patients with pseudoexfoilative glaucoma compared with pseudoexfoiliative syndrome (181.37±118.85 pg/mL versus 92.81±66.26 pg/mL, p=0.04). There was no relation between pseudoexfoliative glaucoma and pseudoexfoliative syndrome patients in terms of tissue Doppler echocardiographic parameters. We found a significant negative correlation between BNP levels and mitral annulus Em velocities (r=-0.800, p=0.010) and a positive correlation between BNP and left atrium sizes (r=0.924, p=0.0001) in pseudoexfoliative glaucoma patients.

Table 1. Demographic and basal echocardiographic parameters of patients and controls

	Patients (n=22)	Controls (n=23)	*P*
Age, years	57±9	53±5	0.06
Men, n, %	9 (41%)	9 (39%)	0.91
BSA, m^2	26.3±2.6	28.4±5.2	0.11
BNP, pg/mL	129.04±99.38 90.16 (7.08-386.00)	59.64±53.69 36.71 (5.00-215.00)	0.005
LA, cm	3.84±0.33	3.69±0.39	0.18
LVEDD, cm	4.43±0.58	4.52±0.38	0.56
LVESD, cm	2.82±0.41	2.90±0.41	0.52
IVS, cm	0.98±0.14	0.87±0.12	0.01
PWD, cm	0.91±0.09	0.86±0.09	0.06
EF, %	64.5±6.3	63.8±5.2	0.71

Data are presented as number (percentage), mean±standard deviation and median (minimum-maximum) values. *Independent samples t-test and Mann-Whitney U test
BSA - body surface area; EF - ejection fraction; IVS - interventricular septal diameter during diastole; LA - left atrium; LVEDD - left ventricular end-diastolic diameter; LVESD - left ventricular end-sistolic diameter; NS - non-significant; PWD - posterior wall diameter during diastole

Discussion

Pseudoexfoiliation syndrome is a systemic disorder that involves various visceral organs in the body. In this study, we showed decreased diastolic left ventricular functions and increased BNP levels correlated with impaired diastolic functions in PES patients.

We have to emphasize that point: Early diastolic filling velocities of mitral annulus were significantly lower in PES patients than control subjects. But, E/Em ratio which was found directly correlated with impaired diastolic function was lower than 15 in all patients (19). Therefore, we could not claim significant diastolic dysfunction in patients with PES. We only showed decreased diastolic functions in PES patients. We eliminated patients having cardiovascular diseases which may also cause diastolic dysfunction. Therefore, we assumed that decreased diastolic functions may be the result of cardiac involvement with pseudoexfoliation materials. In the myocardium, the pseudoexfoliation materials were shown as closely apposed to the myocardial cells and their interrupted basement membranes (20). This accumulation of pseudoexfoliation material could probably alter the structures of the extracellular matrix of the myocardium, causing changes in myocardial relaxation. Although, increased left ventricular wall thickness in PES patients may support this hypothesis, we didn't apply cardiac biopsy to prove this accumulation.

Bojic et al. (9) studied the left ventricular diastolic functions in patients with PES with use of pulsed Doppler echocardiography of transmitral flow. They found decreased E and E/A ratio in PES patients and suggested the possibility of an association between patients with PES and a discrete asymptomatic myocardial diastolic dysfunction.

In the literature, there are only two studies about left ventricular functions studied with tissue Doppler echocardiographic investigation in patients with PES (10, 11). Demir et al. (10) used tissue Doppler echocardiography in patients with PES, but they primarily investigated myocardial ischemia. They found that peak systolic velocities of mitral annulus were lower in PES patients compared with controls and they suggested that these findings may indicate subclinical myocardial ischemia in patients with PES (10). Ulus et al. (11) also studied myocardial tissue Doppler investigation in PES patients and they also found that S-wave velocities at the septal and lateral annulus were signifi-

Table 2. Standard transmitral Doppler echocardiograhic data and assessment of mitral and tricuspid annuli spectral pulse Doppler velosities

	Patients (n=22)	Controls (n=23)	*P*
Transmitral Doppler			
Peak E velocity, cm/s	63.9±12.1	66.3±9.6	0.47
Peak A velocity, cm/s	74.7±20.5	73.9±12.8	0.89
E/A ratio	1.11±1.19	0.92±0.20	0.49
IVRT, ms	95.1±22.6	100.4±25.2	0.48
DT, ms	250.9±35.7	249.8±33.9	0.92
E/Em	7.85±2.01	6.64±1.48	0.03
DTI; Septum			
Sm peak, cm/s	7.6±1.3	8.5±1.2	0.03
Em peak, cm/s	7.6±2.0	9.1±1.6	0.01
Am peak, cm/s	9.9±2.1	10.4±1.4	0.30
Lateral wall			
Sm peak, cm/s	9.0±2.3	10.2±1.7	0.07
Em peak, cm/s	9.3±3.5	11.5±3.1	0.04
Am peak, cm/s	11.0±3.6	12.3±2.6	0.19
Mitral annulus Em, cm/s	8.5±2.1	10.3±1.9	0.007

Data are expressed as mean±SD. *Independent samples t-test, and chi-square test
A - late diastolic filling during atrial contraction; Am - late diastolic velocity; DT - deceleration time; DTI - Doppler tissue imaging; E - early diastolic filling; Em - early diastolic velocity; IVRT - isovolumetric relaxation time; Sm - systolic velocity

cantly lower in patients with PES than controls. In our study, septal systolic velocities with tissue Doppler were also lower in PES patients showing local decrease in systolic myocardial functions. Lateral wall systolic velocities were also lower in PES patients but they could not reach statistical significance. We could not find any difference in ejection fraction in PES patients which shows global left ventricular systolic functions.

In the previous two studies with tissue Doppler imaging, they could not find any difference in mitral annulus Ea velocities in PES patients. But, they included diabetic and hypertensive patients to the study which may also cause diastolic dysfunction. These diseases alone may also cause diastolic myocardial dysfunction. This may be the reason of diversity in results of diastolic functions.

B-type natriuretic peptide is a hormone that is secreted predominantly by the ventricles and reaches very high plasma concentrations in subjects with heart failure. Increased plasma BNP concentrations have been observed in diastolic dysfunction, left ventricular hypertrophy and systolic dysfunction (15). BNP is synthesized in the heart as a reaction to cardiac wall distension and stretching, and neurohormonal activation. In our study, BNP levels were significantly higher in PES patients compared with controls. There was a negative correlation between plasma BNP levels and mitral annulus avarage Em velocities and a positive correlation between BNP concentration and left ventricle posterior wall thickness. Therefore, we assumed that increased BNP levels may be result of decreased diastolic functions.

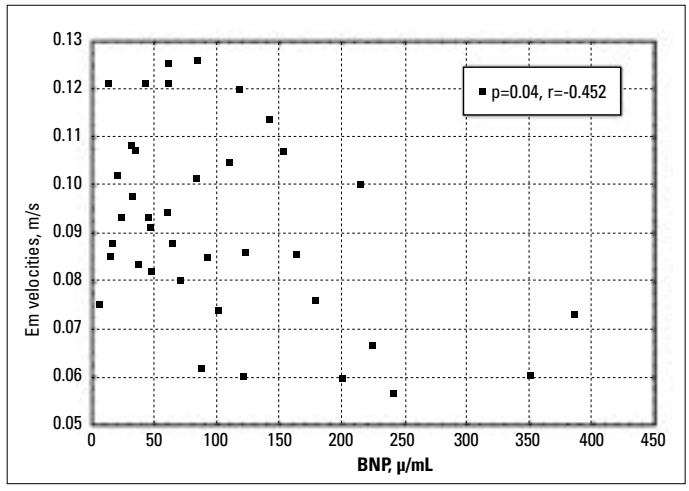

Figure 1. The relationship between plasma BNP concentrations and mitral annulus average Em velocities in PES patients

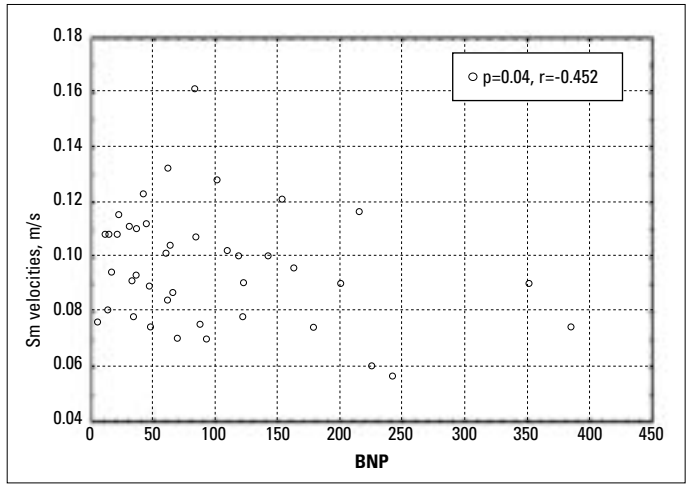

Figure 2. The relationship between plasma BNP concentrations and lateral wall Sm velocities in PES patients

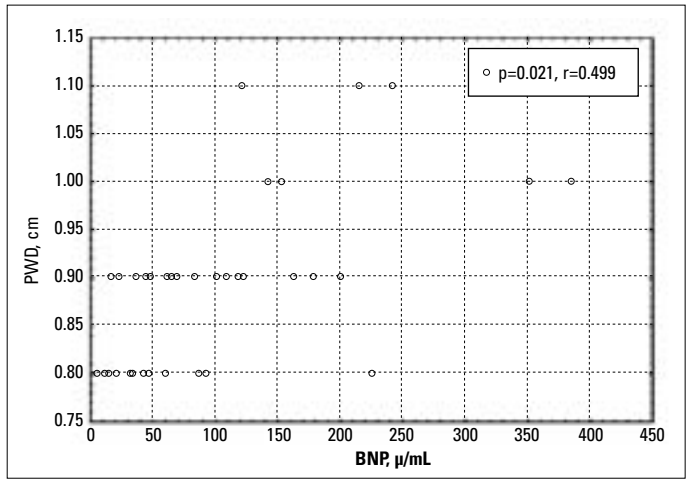

Figure 3. The relationship between plasma BNP concentrations and left ventricle posterior wall thickness (PWD) in PES patients

Pseudoexfoliation syndrome is the most common identifiable cause of open angle glaucoma, developing in about half of patients with PES over time (21). The cause of chronic pressure

elevation in PES eyes is an increased outflow resistance in the trabecular meshwork, most probably caused by a blockage of the outflow channels by exfoliative material followed by degenerative changes of Schlemm's canal wall (22). The risk of glaucomatous damage may be further increased by vascular factors and PES-associated alterations of blood vessels: many studies have reported on a general disturbance of ocular and retrobulber perfusion in PES patients with and without glaucoma (23).

Although there was no relation in terms of tissue Doppler parameters between pseudoexfoliative glaucoma and pseudoexfoliation syndrome patients, plasma BNP concentrations were higher in patients with pseudoexfoliative glaucoma compared with pseudoexfoliation syndrome. Further studies are needed to show the difference in cardiac functions between pseudoexfoliative glaucoma and pseudoexfoliation syndrome patients.

Study limitations

We did not perform coronary angiography in our patients. The 17 patients who may perform exercise testing had negative exercise stress testing, while the other patients had no clinical features or echocardiographic signs of coronary artery disease. Our study was performed on a relatively small number of patients. In these small, selected groups of patients, we may fail to show some correlations.

Conclusion

In this study we showed asymptomatic decreased left ventricular diastolic function in patients with PES. We also showed increased BNP levels correlated with impaired diastolic function. Early diagnosis and categorization of heart failure is very important for an effective therapy optimization and prognosis improvement. Although this study can not provide definite information about causality, evaluation and follow-up of PES patients in terms of left ventricular dysfunction will be useful.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - D.Ç.Y., A.Y.; Design - D.Ç.Y., A.Y.; Supervision - D.Ç.Y., A.Y.; Materials - A.Y., D.Ç.Y., L.T.; Data collection&/or processing - A.C., İ.G., L.T., F.Ş.; Analysis &/or interpretation - D.Ç.Y., A.Y., L.T.; Literature search - D.Ç.Y., A.Y.; Writing - D.Ç.Y., A.Y.; Critical review - D.Ç.Y., A.Y.

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