ORIGINAL ARTICLE

Evaluation of aortic distensibility in patients with mitral valve prolapse using echocardiography and applanation tonometry

Mitral kapak prolapsusunda aortik distensibilitenin ekokardiyografi ve aplanasyon tonometrisi ile değerlendirilmesi

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ABSTRACT

Objective: Mitral valve prolapse (MVP) is a heart valve anomaly that affects a considerable segment of the population. Studies of patients with isolated MVP have shown that aortic distensibility decreased as the aortic diameter increased. The aim of this study was to compare evaluations of aortic distensibility in MVP patients using both applanation tonometry and the conventional echocardiographic examination.

Methods: A total of 36 consecutive patients with MVP (16 male and 20 female) and 23 healthy controls (11 male and 12 female) were included in this study. The difference in aortic diameter and distensibility was examined using echocardiography and pulse wave velocity (PWV) was measured with applanation tonometry.

Results: According to the echocardiographic measurements, the aortic distensibility was lower in the MVP patients than in the control group (6.2±4.0 $cm^2.dyn^{-1}.10^{-6}$ vs. 10.0±5.2 $cm^2.dyn^{-1}.10^{-6}$; p=0.02). The PWV measured with applanation tonometry was significantly higher in the MVP patients than in the control group (9.0±2.4 m/s vs. 7.2±1.4 m/s; p=0.006).

Conclusion: The results of this study showed that aortic distensibility was reduced in patients with isolated MVP compared with a healthy control group. There was a moderate negative correlation between the results of both methods.

ÖZET

Amaç: Mitral kapak prolapsusu (MVP) popülasyonun büyük bir bölümünü etkileyen kalp kapak anomalisidir. Önceki çalışmalar, izole MVP hastalarında aort çapı arttıkça aort distensibilitesinin azaldığını göstermiştir. Bu çalışmanın amacı, konvansiyonel ekokardiyografik incelemeye ek olarak aort distensibilitesinin aplanasyon tonometrisi ile değerlendirilmesi ve MVP hastalarında her iki yöntemin karşılaştırılmasıdır.

Yöntemler: Bu çalışmaya 36 mitral kapak prolapsusu (16 erkek ve 20 kadın) ve 23 sağlıklı kontrol gruubu (11 erkek ve 12 kadın) dahil edildi. Tüm hastalarda ve kontrol grubunda; ekokardiyografi ile aort çapındaki değişiklik ve distensibilite incelendi ve aplanasyon tonometrisi ile nabız dalga hızı (NDH) ölçüldü.

Bulgular: Ekokardiyografik ölçümlere göre; aort distensibilitesi MVP hasta grubunda kontrol grubuna göre daha düşüktü (6.2±4.0 ve 10.0±5.2 $cm^2.dyn^{-1}.10^{-6}$, p=0.02). Aplanasyon tonometrisi ile ölçülen NDH, MVP hastalarında kontrol grubuna göre anlamlı olarak daha yüksekti (9.0±2.4 ve 7.2±1.4 m/s p=0.006).

Sonuç: Bu çalışma, izole MVP'li hastalarda aort distensibilitesinin sağlıklı kontrol grubuna göre azaldığını göstermiştir. Her iki yöntemin sonuçları arasında orta derecede negatif korelasyon vardı.

Mitral valve prolapse (MVP) is a disease that arises from the abnormal displacement of one or both of the mitral valve leaflets toward the left atrium during ventricular systole. MVP affects a significant portion of society; the prevalence has been found to be 2% to 3% in the general population.[1] While MVP

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Abbreviations:

2D	*Two-dimensional*
AoS	*Aortic systolic diameter*
AoD	*Aortic diastolic diameter*
BMI	*Body mass index*
CAD	*Coronary artery disease*
DM	*Diabetes mellitus*
IL	*Interleukin*
MMP	*Matrix metalloproteinase*
MVP	*Mitral valve prolapse*
PWV	*Pulse wave velocity*

is most often benign, it may lead to complications, such as mitral valve insufficiency, infective endocarditis, and arrhythmia. In developed nations, MVP is the most common cause of advanced mitral valve insufficiency, causing left atrial enlargement, atrial fibrillation, and heart failure. Therefore, it is important to determine those at risk and to follow up, particularly with patients who demonstrate mitral regurgitation.

Aortic stiffness and distensibility are indicators of the elasticity of the aortic wall. Over time, stiffness increases and elasticity and distensibility decrease. An increase in aortic stiffness is a natural feature of aging and also occurs as the result of many diseases, such as diabetes mellitus (DM), hypertension, atherosclerosis, and chronic kidney disease. Studies have shown that increased aortic stiffness is associated with cardiovascular events and total mortality.[2] It is also a risk indicator for stroke, dementia, and kidney disease.[3–10] Aortic stiffness can be measured with invasive methods as well as noninvasive methods, such as applanation tonometry, echocardiography, and magnetic resonance imaging. Currently, pulse wave velocity (PWV) is thought to be the most valid noninvasive method to measure arterial stiffness. It is considered the gold standard thanks to its simplicity, precision, reproducibility, and strong ability to predict negative events.[11–13]

MVP and a dilated aortic diameter are usually associated with connective tissue disorders. Nollen et al.[14] found that aortic diameter and aortic distensibility were independent predictors of progressive aortic dilatation in patients with Marfan syndrome. It has also been observed that isolated MVP, which is not associated with connective tissue disorders, was an independent predictor of aortic diameter increase.[15] In another study, it was determined that aortic distensibility was significantly reduced in patients with MVP compared with a control group.[16]

The aim of the present study was to assess aortic distensibility in MVP patients using applanation tonometry as well as the conventional echocardiographic examination to compare the 2 methods and examine the relationship between conventional (echocardiographic) and current diagnostic methods (PWV).

METHODS

Study population and protocol

In all, 36 consecutive patients with MVP and 23 healthy individuals who had comparable demographic features were included. The MVP patients had been diagnosed echocardiographically. In a parasternal long-axis echocardiographic evaluation, a prolapse of 2 mm or more toward the left atrium during systole of 1 or both of the mitral valve leaflets was accepted as the diagnostic criterion. The exclusion criteria were the presence of valve regurgitation that was more than mild, a history of coronary artery disease (CAD), coronary angiography, congenital connective tissue disorders (Marfan syndrome, Ehler-Danlos syndrome), systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, Behcet's disease, dilated or ischemic cardiomyopathy, congenital or rheumatic heart disease, atrial fibrillation, bundle branch block, and supraventricular or ventricular extrasystole. All of the participants provided written informed consent, and this study was approved by the local ethics committee (2014.1/8).

Blood pressure and anthropometric measurements

The weight and height of all of the study participants were measured with a manual ruler and analog bascule scale while they were wearing light clothing and without shoes. The body mass index (BMI) was calculated by dividing the weight by the square of the height (kg/m^2). Blood pressure measurements were performed in the supine position with a mercury sphygmomanometer at the same time as the echocardiographic examination. Korotkoff phases 2 and 5 were used to determine systolic and diastolic blood pressure. The average of 3 measurements was recorded as the clinical blood pressure value.

Echocardiography measurements

M-mode, 2-dimensional (2D) color Doppler measurements were recorded for all of the participants using a transducer with adjustable frequency (2.5–3.5 mHz, Vivid 7; GE Healthcare, Inc. Chicago, IL, USA). Ascending aortic M-mode measurements were recorded in the left lateral position. The recordings were performed within 3 cm of the aortic valve. The aortic

diameter was calculated by measuring the distance between the anterior and posterior walls of the aorta in systole and diastole. The aortic systolic diameter (AoS) was measured while the valve was open, and the diastolic diameter (AoD) was measured at the peak of the QRS wave observed on the electrocardiograph. Measurements were performed for 5 consecutive heart beats, and the mean was calculated. Aortic elastic parameters were considered the indicators of aortic function and were calculated with the following formula:

Pulse pressure (mmHg) = Systolic blood pressure - Diastolic blood pressure
Aortic strain (%) = 100 x (AoS-AoD) / AoD
Aortic distensibility ($cm^2.dyn^{-1}.10^{-3}$) = 2 x (AoS-AoD) / (Pulse pressure x AoD)

Applanation tonometry measurements

The PWV of all of the participants was automatically measured with a SphygmoCor device (AtCor Medical, Sydney, Australia) immediately following the echocardiographic evaluation. The distance between the right carotid communis bifurcation point and the origin of the common right femoral artery was measured over the body surface with a ruler. Carotid and femoral artery blood pressure waveforms were measured noninvasively using a pressure-sensitive pen transducer. The measurements were repeated for at least 10 cardiac cycles, and the mean value was used for the analysis. Aortic pulse waveform, augmentation index, and central aortic blood pressure values were obtained with the applanation tonometer placed over the right radial artery.

Statistical analysis

The data gathered from the study population of patients with MVP and a healthy control group were analyzed for statistical implications. Continuous variables are given as mean±SD. Categorical variables are expressed as percentages (%). An independent samples t-test was used to define the differences between continuous variables. A chi-squared or Fisher's exact test was used to determine the differences between categorical variables. For correlation analysis, the Spearman or Pearson tests were used. P values of <0.05 were considered significant. The statistical analyses were performed using SPSS for Windows, Version 11.5 software (SPSS Inc., Chicago, IL, USA).

RESULTS

The demographic characteristics of the patients with MVP and the control group are shown in Table 1. The mean age in the MVP group and in the control group was 38.5±16.9 years and 33±7.9 years, respectively (p=0.68). The history of hypertension (p=0.61), systolic blood pressure (p=0.18), diastolic blood pressure (p=0.07), smoking (p=0.42), DM (p=0.66), family history of CAD (p=0.56), BMI (0.21), and cardiovascular drug use (beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers) were similar between the 2 groups.

Echocardiographic features of the MVP patients and the control group are shown in Table 2. Aortic distensibility was significantly lower in the MVP group (6.2±4.0 $cm^2.dyn^{-1}.10^{-6}$) than in the control group (10.0±5.2 $cm^2.dyn^{-1}.10^{-6}$) (p=0.02). The left ventricular end systolic (p=0.36) and end diastolic diameter (p=0.49), left ventricular ejection fraction (p=0.45), left atrial diameter (p=0.39) and aortic strain (p=0.39) of the 2 groups were statistically similar.

The applanation tonometry measurements of the control group and the MVP patients are provided in Table 3. The PWV was significantly higher in the MVP group than in the control group (9.0±2.4 m/s

Table 1. Demographic features of the MVP patients and the control group

	MVP (n=36)	Control (n=23)	*p*-value
Age (years)	38.5±16.9	33±7.9	0.68
Gender (men)	16 (44.4)	11 (47.8)	0.50
Hypertension (%)	11 (30.6)	7 (30.4)	0.61
SBP (mmHg)	129±16.1	120.5±15.9	0.18
DBP (mmHg)	70.8±10.6	64.7±10.3	0.07
Smoker (%)	12 (33.3)	9 (39.1)	0.42
Family history (%)	10 (27.8)	6 (26.1)	0.56
DM (%)	2 (5.6)	1 (4.3)	0.66
BMI (kg/m^2)	24.0±3.8	25.0±3.5	0.21
Drug			
Beta blocker (%)	12 (33.3)	3 (13)	0.07
ACE/ARB (%)	9 (25)	3 (13)	0.22

ACE: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; BMI: Body mass index; DBP: Diastolic blood pressure; DM: Diabetes mellitus; MVP: Mitral valve prolapse; SBP: Systolic blood pressure.

Table 2. Echocardiographic features of the MVP patients and the control group

	MVP (n=36)	Control (n=23)	*p*-value
LVESD (cm)	2.8±0.45	2.9±0.4	0.36
LVEDD (cm)	4.7±0.5	4.8±0.4	0.49
LVEF (%)	60.8±6.1	60.9±6.0	0.95
LA (cm)	3.3±0.53	3.4±0.47	0.39
Ao strain (%)	8.6±5.2	10.3±4.3	0.39
Aortic distensibility ($cm^2.dyn^{-1}.10^{-6}$)	6.2 ±4.0	10.0 ±5.2	0.02

Ao strain: Aortic strain; LA: Left atrium; LVEDD: Left ventricular end diastolic diameter; LVEF: Left ventricular ejection fraction; LVESD: Left ventricular end systolic diameter.

Table 3. Applanation tonometry measurements of the MVP patients and the control group

	MVP (n=36)	Control (n=23)	*p*-value
PWV (m/s)	9.0±2.4	7.2±1.4	0.006
PP (mmHg)	39.3±9.2	32.2±11.5	0.86
CABP (mmHg)	112.7±15.8	100.5±13.2	0.33
AIx (%)	10.7±13.1	10.5±7.1	0.45

AIx: Augmentation index; CABP: Central aortic blood pressure; PP: Pulse pressure; PWV: Pulse wave velocity.

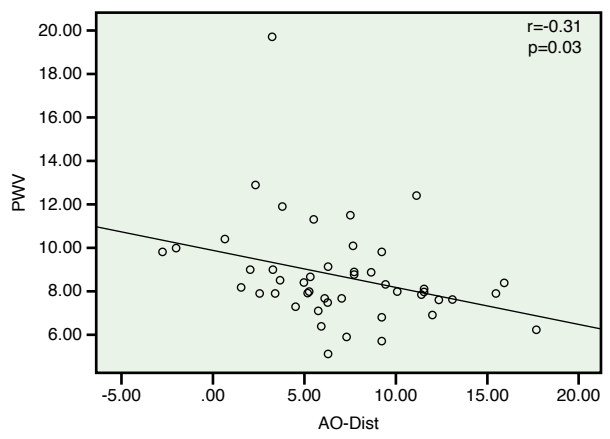

Figure 1. Correlation between aortic distensibility and pulse wave velocity in MVP patients. Ao-Dist: Aortic distensibility; MVP: Mitral valve prolapse; PWV: Pulse wave velocity.

and 7.2±1.4 m/s, respectively; p=0.006).The pulse pressure, central aortic blood pressure, and augmentation index values were statistically similar. There was a moderate negative correlation between the aortic distensibility measured using echocardiography and the PWV measured with applanation tonometry in patients with MVP (r=-0.31; p=0.03) (Fig. 1).

DISCUSSION

The findings of our study can be summarized in the following 4 points: a) echocardiographic evaluation determined a significant decrease in aortic distensibility in the MVP group in comparison with the control group, b) carotid-femoral applanation tonometry PWV assessment showed a significant elevation in the MVP group compared with the control group, c) statistical analysis of the data obtained with 2 methods revealed a moderate negative correlation between aortic distensibility and carotid-femoral PWV, and d) measurement of the augmentation index did not yield a significant difference between the MVP group and the control group. The primary finding of our study is the reduced aortic distensibility in patients with MVP.

MVP is a common cardiac anomaly that may cause serious complications, such as mitral regurgitation and arrhythmia. Histological evaluations of the cardiac valve of MVP patients have demonstrated proliferation of the mitral valve leaflets and increased acid mucopolysaccharide in the spongiotic portion of the cardiac valve.[17–19] As a result, the center of the leaflet becomes slack. The cardiac valves and chorda tendinea myxomatosis can also be a part of the process. Electron microscopy reveals a random sequence of disrupted cells and fragmented collagen fibrils. In an immunohistochemical study carried out on patients with MVP and mitral regurgitation, increased release of catabolic enzymes, such as matrix metalloproteinase, endoproteinase, and interleukin (IL) 1 beta from interstitial cells, including active myofibroblasts, was detected.[20] Myofibroblast cells present in myxomatous valves are known to secrete not only collagen, but collagenase (matrix metalloproteinase [MMP] 1-MMP 13), gelatinase (MMP 2-MMP 9), cysteine protease (cathepsin C and M), and IL-1B, a cytokine that leads to proteolytic enzyme secretion.

The main pathophysiology of the decrease in aortic distensibility is disruption in the balance of the production and destruction of collagen and elastin, which are the supporting structures, as a result of various factors (lipids, angiotensin, sympathetic hormones, glucose

balance, hypertension) that damage this vascular wall structure. Disruption of this balance is primarily triggered by an inflammatory environment and leads to an abnormal increase in collagen production and a decrease in the amount of elastin, resulting in increased vascular stiffness. Cytokines, intracellular adhesion molecules, transforming growth factor beta, elevated levels of MMPs, mononuclear cells, macrophages, infiltrative vascular smooth muscle cells, damaged and fragile elastin molecules, increased collagen, and abnormal endothelial cells have been observed in the intima of stiffened vessels in histological evaluations.[21]

MVP and a dilated aortic diameter are frequently associated with congenital connective tissue disease. The most common cause of early death in Marfan syndrome is aortic dissection due to aortic dilatation; distensibility and diameter measurements are important in these patients. Vitarelli et al.[22] found that patients with Marfan syndrome had reduced distensibility and increased stiffness. The quantity and irregular structure of the elastin fibers in the ascending aorta in Marfan syndrome may adversely affect aortic compliance.[23]

The fact that isolated MVP, which is not associated with connective tissue disease, is an independent predictor of a larger aortic size was demonstrated in a study of 1254 patients, and it was noted that this result supported the view that mitral valve and aortic structural changes may represent phenotypic integration.[15] Similarly, in patients with isolated MVP, increased inflammatory processes and increased MMP activity are not just limited to mitral valves but may also cause similar pathologies in the aorta. It may be the cause of the reduction in aortic distensibility in patients with isolated MVP, as observed in our study. However, histopathological studies are needed to further support this view.

Other studies have found beta-1 adrenergic receptor polymorphism[24] and elevated adrenergic activity[25] in patients with MVP. It has been reported that increased adrenergic activity might have an adverse effect on aortic functions by affecting the vasa vasorum flow.[26] During this physiopathologic process, there might be another explanation for decreased aortic distensibility in patients with MVP.

Assessment of aorta flexibility in patients with MVP has been performed in many studies. Kardesoglu et al.[16] showed that aortic distensibility was decreased in 20 male patients with MVP. In another study published in 2013, the aortic distensibility of 63 young, male, classic and non-classic patients with MVP was compared, and it was observed that the aortic distensibility was greater in the classic MVP patients compared with the non-classic MVP group.[27] In research focusing on pediatric patients diagnosed with MVP, Erolu et al.[28] compared MVP patients with a control group, and it was determined that aortic distensibility was higher whereas stiffness was lower in patients with MVP. In the same study, the aortic stiffness was higher and distensibility was lower in the classic MVP group in contrast with the non-classic MVP group. In another study published in 2018, 17 patients with MVP and significant MY were compared with a control group, and aortic distensibility was shown to be decreased in the patient group.[27] The results of these studies, which seem to be contradictory, give rise to the thought that numerous variables, such as age, gender, the structure of cardiac valve, degree of deficiency, and coexisting diseases might have an effect on the assessment of aortic distensibility in MVP patients, and that processes affecting the structure of the aorta in MVP patients might be more complicated than previously thought. In the aforementioned studies, aortic distensibility was evaluated using echocardiography, the conventional technique. In the present study, we used both echocardiography and applanation tonometry, the gold standard method for measuring aortic distensibility.

Conclusion

The findings of our study showed that both echocardiography and applanation tonometry demonstrated that aortic distensibility was reduced in patients with isolated MVP. There was a moderate negative correlation between the results of the two methods.

Limitations

The number of patients in our study was limited because only patients with isolated MVP were included. Factors such as smoking and use of a beta-blocker, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker, which may affect aortic distensibility in patients with MVP, also represent a limitation; however, this effect was reduced in part due to a control group with similar characteristics.

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Anahtar sözcükler: Aortik distensibilite; mitral kapak prolapsusu; nabız dalga hızı.