THE RELATIONSHIP BETWEEN ECHOCARDIOGRAPHIC FEATURES OF MITRAL VALVE AND ELASTIC PROPERTIES OF AORTIC WALL AND BEIGHTON HYPERMOBILITY SCORE IN PATIENTS WITH MITRAL VALVE PROLAPSE

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SUMMARY

The present study was designed to investigate the incidence of benign joint hypermobility syndrome (BJHMS) in mitral valve prolapse (MVP) and correlation between echocardiographic features of mitral valve and elastic properties of aortic wall and Beighton hypermobility score (BHS) in patients with MVP and BJHMS. Forty-six patients with nonrheumatic, uncomplicated and isolated mitral anterior leaflet prolapse (7 men and 39 women, mean age :26.1± 5.9) and 25 healthy subjects (3 men and 22 women, mean age 25.4 ± 4.3) were studied. Patients were divided into two groups according to their BHS (Group I, BHS ≥5; 5; Group II, BHS< 5). Individuals with accompanying cardiac or systemic disease were excluded. Echocaroliographic examination was done to all of the subjects. Presence of BJHMS was evaluated according to Beighton's criteria. The incidence of BJHMS in patients with MVP was found significantly higher than controls (45.6%, (21/46) vs. 12 % (3/25), p<0.0001). Group I (MVP+BJHMS) had significantly increased anterior mitral leaflet thickness (AMLT, 5.7± 0.6 ve 4.1± 0.5; p<0.001,) maximal leaflet displacement (MLD, 3.8 ± 0.7 vs. 2.9± 0.5; p<0.005) and degree of mitral regurgitation (DMR,17.1 ± 7.2 ve 11.2± 4.4 ;p<0.002) than those of group II. However, index of aortic stiffness (IAOS) was found to be lower (17.6± 6.9 vs. 23.9± 7.6; p<0.001) and aortic distensibility (AOD) was found to be higher (0.0035± 0.007 vs. 0.0024± 0.005; p<0.001) in group I. There was significant correlation between AMLT, MLD and DMR and BHS (r=0.57/p=0.007, r=0.55/p<0.009, r=0.51/p<0.01, respectively). In additon, AOD correlated positively with HMS (r=0.53/p<0.005), but index of aortic stifness correlated inversely with HMS (r=-0.49/p<0.007). Conclusion: The incidence of BJHMS in patients with MVP was more frequent than normal population and there was a significant correlation between severity of BJHMS (according to BHS) and echocardiographic features of mitral leaflet and elastic properties of aortic wall .

Key words: *Mitral valve prolapse, benign joint hypermobility syndrome*

ÖZET

MİTRAL KAPAK PROLAPSUSU OLAN HASTALARDA MİTRAL KAPAĞIN EKOKARDİYOGRAFİK VE AORT DUVARININ ELASTİK ÖZELLİKLERİ İLE BEIGHTON HİPERMOBİLİTE SKORU ARASINDAKİ İLİŞKİ

Mevcut çalışma mitral kapak prolapsusunda (MVP) benign eklem hipermobilitesi sendromu (BJHMS) sıklığı ve Beighton hipermobilite skoru (BHS) ile prolabe mitral kapağın ekokardiyografik, aort duvarının ise elastik özellikleri arasındaki ilişkiyi araştırmak amacıyla planlanmıştır. Çalışmaya romatizmal olmayan, komplikasyonsuz ve izole mitral ön yaprakçık prolapsusuna sahip 46 hasta (7 erkek ve 39 kadın, ortalama yaşları:26.1± 5.9) ve 25 sağlıklı birey (3 erkek ve 22 kadın, ortalama yaşları:26.1± 5.9) alındı. Hastalar BHS'larına göre iki gruba ayrıldılar. Birinci grup, BHS ≥5; 5 olan 21 hastadan, II. Grup, BHS< 5 olan 25 hastadan oluşmaktaydı. Çalışmaya katılan bireylerin hepsine transtorasik yolla ekokardiyografik inceleme yapıldı. Benign eklem hipermobilitesi sendromu varlığı Beighton kriterleri kullanılarak araştırıldı. Mitral kapak prolapsuslu hastalarda BJHMS sıklığı sağlıklı bireylere göre anlamlı düzeyde yüksek bulundu (45.6%, (21/46) ve 12 % (3/25), p<0.0001). 1.grupta mitral yaprakçığın kalınlığı (MYK, 5.7± 0.6 ve 4.1± 0.5; p<0.001), maksimal çökme miktarı (MÇM, 3.8 ± 0.7 ve 2.9± 0.5; p<0.005) ve mitral yetersizliğin derecesi (MYD, 17.1 ± 7.2 ve 11.2± 4.4 ;p<0.002) 2.gruba göre anlamlı ölçüde artmıştı. Diğer taraftan 1.grubta 2.gruba göre aortik stiffness indeksi (AOSI) daha düşük (17.6± 6.9 ve 23.9± 7.6; p<0.001), aortik distensibilite (AOD) ise daha yüksek bulundu (0.0035± 0.007 ve 0.0024± 0.005; p<0.001). MYK, MÇM,MYD ve AOD ile BHS arasında pozitif korelasyon (sırasıyla; r=0.57/p=0.007, r=0.55/p<0.009, r=0.51/p<0.01, r=0.53/p<0.005), fakat AOSI ile negatif bir korelasyon saptandı (r=-0.49 p<0.007). Sonuç: MVP'lu hastalarda BJHMS sağlıklı bireylere göre çok daha fazla ve BHS'na göre belirlenmiş BJHMS'nin ciddiyeti ile mitral kapağın ekokardiyografik, aort duvarının ise elastik özellikleri arasında anlamlı bir ilişki mevcuttur.

Anahtar kelimeler: *Mitral kapak prolapsusu, benign eklem hipermobilite sendromu*

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INTRODUCTION

Most frequently, mitral valve prolapse (MVP) occurs as a primary condition that is not associated with other diseases (1). However, MVP occurs quite commonly in heritable disorders of connective tissue that increase the size of the mitral leaflets and apparatus, including Marfan syndrome (2), Ehlers-Danlos syndrome (3) and pseudoxantoma elasticum (4). Increased joint laxity in patients with MVP was first reported in 1976 (5) and denied in 1977 (6). In following years, a high incidence of MVP has been reported in patients with benign joint hypermobility syndrome (BJHMS) (7-8), which, like MVP, is inherited mainly as a sex-influenced dominant trait (9-10). Abnormalities of collagen have been found in myxomatous or floppy valves of patients with MVP (11-13) that coincide with those identified in skin biopsies of patients with hypermobility syndrome (9) leading to the suggestion of a common pathogenetic mechanism of abnormal production or maturation of collagen (14). However, there has been a few studies on the relation between echocardiographic features of mitral valves [anterior mitral leaflet thickness (AMLT) (15) maximal leaflet displacement (MLD) (7), degree of mitral regurgitation (DMR)], and elastic properties of aortic wall [index of aortic systolic (AOSDI) and diastolic diameters (AODDI), index of aortic stiffness (IAOS) and aortic distensibility (AOD)] and Beighton hypermobility score (BHS) in MVP patients with BJHMS (9). In addition, previous studies have given conflicting results in the incidence of BJHMS in MVP (15,16).

The present study was designed to investigate both the incidence of BJHMS in MVP, and whether is a correlation between echocardiographic features of mitral valve and elastic properties of aortic wall and BHS in patients with MVP and BJHMS.

PATIENTS AND METHODS

The current study was carried out in the Department of Cardiology, Faculty of Medicine, Abant Izzet Baysal University between March 2000 and January 2002. Patients were recruited from those refered to our echocardiography laboratory with symptoms and/or signs consistent with a diagnosis of MVP. Patients with evidence of cardiomyopathy, congenital, or rheumatic heart disease and atrial fibrillation or conduction disturbances on resting electrocardiogram were excluded. We studied 46 patients with nonrheumatic, uncomplicated and isolated mitral anterior leaflet prolapse (7 men and 39 female, mean age 26.1± 5.9) and 25 healthy control subjects (4 men and 21 female, mean age 25.4± 4.3). None of the 46 subjects with mitral valve prolapse had a history of ischemic heart disease or any other cardiac or systemic disease. In addition, patients were excluded from study if they showed evidence of inflammatory joint disease or if they had typical features of one of the identical hereditary disorders of connective tissues.

Cardiological and Echocardiographic assesment: A full cardiological examination, including electrocardiography and echocardiography were performed by two blind independent observers. All individuals underwent full M-mode, two-dimensional and color-Doppler examinations with a commercially available system (Toshiba Diagnostic Ultrasound System Model SSA 270 A, Toshiba Corporation 1992, Tochigiken, Japan) that used a 2.5 MHz. Echocardiograms were recorded with a strip chart paper recorder (Toshiba line scan recorder LSR-20B) together with lead II electrocardiogram and phonocardiogram. The measurements were carried out according to recommendations of the American Society of Echocardiography (17). Classic MVP was defined as superior displacement of the mitral leaflets of more than 2 mm during systole and as a maximal leaflet thickness of at least 5 mm during dias-

tasis, and nonclassic prolapse was defined as displacement of more than 2 mm, with a maximal leaflet thickness of less 5 mm. We measured displacement of the mitral anterior leaflets in the parasternal and apical four chamber view. The anterior mitral leaflet thickness was evaluated during mid-diastole by measuring the distance from leading edge to the trailing edge of the thickness area of the midportion of the leaflet. The displacement of mitral leaflet were measured with both 2-D and M-mode echocardiography in parasternal long axis view. Color-Doppler echocardiographic examination was used for the detection and semiquantitaton of mitral regurgitation. The degree of mitral regurgitation was assesed as the ratio of the maximal regurgitant jet area to the area of the left atrium in the parasternal and apical long axis and apical four-chamber views. The degree of regurgitation was considered to be trace, mild, moderate, or severe on the basis of ratios of >0 to 10 , >10 to 20, >20 to 40, > 40 percent , respectively (18). Left ventricular end-diastolic dimension (LVEDD) and thickness of interventricular septum (IVST) and posterior wall (PWT) were measured at onset of the electrocardiographic Q wave. Left ventricular end-systolic dimension (LVESD) was measured at time of smallest left ventricular (LV) diameter. LV fractional shortening (LVFS) was defined as (LVEDD-LVESD)X 100/LVEDD. Left ventricular end-diastolic volume (LVEDV), end-systolic volume (LVESV) and ejection fraction (LVEF) were determined from apical two or four vievs using the Modified Simpson method. Cardiac output (CO) was measured as the product of stroke volume and heart rate. Systemic vascular resistance (SVR) was calculated as follows: SVR=(mPAO-mPRA/CO)X80, where mPRA is the mean right atrial pressure, considered equel to zero mm Hg in each subjects, and mPAO is mean aortic pressure , derived by cuff-sphygmomanometer, as diastolic blood pressure + 1/3 (systolic-diastolic blood pressure). Left ventricular myocardial weight (LVM) was calculated using the formula of Devereux et al.(19). BSA was determined from height and weight as described by Du Bois et al.(20). Left ventricular mass index (LVMI) was calculated as LVM/BSA. Systolic (AOSD) and diastolic (AODD) diameters of assending aorta were measured by M-mode in long axis wiev. Systolic (AOSDI=AODD/BSA) and diastolic diameter index (AODDI=AOSD/BSA) of aortic wall were calculated. Aortic stiffness (IAOS) was calculated according to this formula;(21-22)

Index of aortic stiffness = In (systolic/ diastolic blood pressure) / (systolic- diastolic aortic diameter/ diastolic aortic diameter)

Aortic distensibility (AOD) was calculated according to previously described formula; (23-24)

Aortic distensibility=2x(systolic-diastolic aortic diameter/ diastolic aortic diameter x aortic pulse pressure

Diagnosis of benign joint hypermobility syndrome: joint hypermobility was measured by using Beighton scale shown in Table I (25). In our study, BJHMS was mainly diagnosed using the draft criteria shown in Table II (25) but differently we accep-

Table I: Adapted from Beighton et al. (25)

The 9-point Beighton Scoring System for joint hypermobility scale
Scoring 1 point on each side • Passive dorsiflexion of the fifth MCP to 90° • Opposition of thumb to the flexor aspect of the forarm • Hyperextension of the elbow beyond 90° • Hyperextension of the knee beyond 90°
Scoring 1 point • Forward trunk flexion placing hands flat on floor with knees extended
Maximum score = 9

Table II: Proposed diagnostic criteria for benign joint hypermobility syndrome (25)

Major criteria
Beighton score of 4/9 or greater
Arthralgia for longer than 3 months in 4 or more joints
Minor criteria
Beighton score 1-3/9 (0-3 if aged >50)
Arthralgia 1-3 joints or back pain or spodylosis,spondylolisthesis
Dislocation in more than 1 joint, or in 1 joint or more on more than 1 occassion
Three or more soft tissue lesions (epicondylitis, tenosynovitis, bursitis)
Marfanoid habitus (tall, slim, span>height, upper segment:lower segment ratio< 0.89, arachnodactyly)
Skin striae, hyperextensibility , thin skin or abnormal scarring
Eye signs:drooping eyelids or myopia or antimongoloid slant
Varicose veins or hernia or uterine/rectal
Mitral valve prolapse (by echocardiography)
BJHMS diagnosis requires:
two major criteria or
one major+ two minor criteria or
four minor criteria or
two minor criteria and equivocally affected first-degree relative.
BHS: Beighton Hypermobility Score

ted BHS cut point as five and above (26) for BJHMS diagnosis. BJHMS is excluded by presence of Marfan or Ehlers-Danlos syndromes (as previously defined by the Berlin nosology)(27).

All subjects gave written informed consent, and the study protocol was approved by Ethical Comitee of the Abant İzzet Baysal Universty of Medical Faculty.

Statistical analysis:

Values were presented as mean ± standart deviation (sd). Unpaired t-test were used to compare groups. Pearson or Spearman's correlation tests was used to assess corrrelation between hypermobility score and echocardiographic parameters. P value was considered significant when it is less than 0.05. The tests were performed using SPSS 7.5 for Windows.

RESULTS

The incidence of BJHMS in patients with MVP was found significantly higher than controls (45.6%, (21/46) vs. 12 % (3/25), p<0.0001). Demographic, clinical and laboratory characteristics of two patient groups did not show statistically significant difference (p>0.05) (Table III). There were significant differences in AMLT (4.9± 0.9 vs. 2.2± 0.6; p<0.0001), MLD (5.3± 0.7 vs. 1.5± 0.4; p<0.0001) and DMR (13.9± 6.5 vs. 8.7± 3.2 ;p<0.001) bet- ween patients with MVP and controls. IAOS was found to be lower (21.3± 5.3 vs. 25.2± 4.9; p<0.005) and AOD was found to be higher in patients with MVP compared to controls (0.0029± 0.006 vs. 0.0021± 0.005; p<0.001) (Table IV). Group I had significant increased AMLT(5.7± 0.6 vs. 5.1± 0.5; p<0.001), MLD (3.8 ± 0.7 vs. 2.9± 0.5;p<0.001) and DMR (17.1± 7.2 vs. 11.2± 4.4;p<0.002) than those of group II. However, index of aortic stiffness (IAOS) was found to be lower (17.6± 6.9 vs. 21.3± 5.3; p<0.001) and aortic distensibility (AOD) was found to be higher in group I (0.0035± 0.007 vs. 0.0024± 0.005; p<0.001). In group I, there were significant correlations between AMLT, MLD and DMR and BHS (r=0.57/p=0.007, r=0.55/ p<0.009, r=0.51/ p<0.01, respectively) (Table VI). In additon, AOD correlated positively with HMS (r=0.53/ p<0.005), but index of aortic stiffness correlated inversely with HMS (r=-0.49/p<0.007) (Table IV). However , AODDI, AOSDI, LAD LVEDS, LVEDD, LVESV, LVEDV, LVEF and FS of all groups were similar and there were no correlation between any of these parameters and BHS (p>0.05) (Tables IV, V, VI).

Table III: Demographic, clinical and laboratory characteristics of control group and the two groups of patients with MVP

	CONTROLS, n =25	Group I, n = 21	Group II, n=25
Age (years)	25.4 ± 4.3	25.9 ± 5.6	26.5 ± 4.7
Men/Women, n	3/22	3/22	4/21
BSA (Body surface area;m^2)	1.68± 0.27	1.66± 0.31	1.67± 0.34
BMI (Body Mass Index :kg/m^2)	22.7 ± 3.5	21.9 ± 3.1	22.8 ± 3.9
Diastolic blood presure (mmHg)	72.9 ± 12.3	71.6 ± 11.2	70.8 ± 15.4
Systolic blood presure (mmHg)	124.7± 26.5	122.7± 22.5	123.9 ± 21.7
Heart rate (beat /minute)	72.9 ±13.3	72.3 ±13.3	73.8 ± 11.5
Symptoms			
Chest pain , n (%)	1/25	11(% 52)	12 (% 48)
Palpitations, n (%)	3/25	15 (%71)	16 (% 64)
Dizziness, n (%)	1/25	7 (%33)	8 (% 32)
Dispne, n(%)	0/25	7 (%33)	9 (% 36)
Clinical Examination			
Midsystolic click, n	0/25	16 (% 71)	17 (% 68)
Systolic murmur, n	1/25	11 (% 52)	12 (% 48)
Na (Meq/L)	137.5 ± 7.8	138.3 ± 8.1	139.2 ± 8.9
K (mEq/L)	4.2 ± 1.5	4.3 ± 1.4	4.3 ±1.7
Ca (mg/dl)	8.5 ± 1.1	8.7 ± 1.2	8.6 ± 1.0
Mg (mg/dl)	3.4 ± 0.9	3.3 ± 0.8	3.5± 0.7
Hb (g/dl)	13.4 ± 1.1	12.9 ± 1.5	13.2± 1.7
Htc (%)	39.8 ± 6.5	37.9 ± 7.3	38.7 ± 6.2

DISCUSSION

Mitral valve prolapse is the most commonly diagnosed valvuler heart disease, especially in the young, and affects 5% of the community (28). Most frequently, MVP occurs as a primary condition that is not associated with other diseases. However, it has also been reported to be associated with many conditions including connective tissue disorders (1-3). MVP is three-times more prevalent in patients with BJHMS than other patients and may be present in up to one third of all individuals with BJHMS (7-9, 29). However, there are a few reports with conflicting results on the incidence of BJHMS in MVP(15,16) and the relation between echocardiographic features of mitral valves and elastic properties of aortic wall and BHS in patients with both MVP and BJHMS (7,15). In this study, we investigated the incidence of BJHMS in patients with MVP and whether BHS in MVP patients is related to echocardiographic features of mitral valve prolapse and elastic properties of aortic wall.

In the present study, we found the incidence of BJHMS in patients with MVP to be 45%, slightly lower than that has been reported by Ondrasik et al (52%) (16), but it was quite lower than that has been reported by Coghlan (71.7%) (15). Our study population was younger than those of the two studies. In addition, in Ondrasik's study, the number of patients was quitely less than our study, and in both studies, they divided patients into three groups according to their of HMS (HMS, 0-2: controls; 3-4: mild BJHMS; 5-9:marked BJHMS). However,

Table IV: Conventional echocardiographic parameters, echocardiographic features of mitral leaflet, elastic properties of aortic wall and hypermobility score in controls and patients with MVP.

	CONTROLS, n =29	MVP, n = 46
Hypermobility Score	1.8 ± 1.5	4.9 ± 0.9 [a]
Anterior mitral leaflet thickness	2.2 ± 0.6	5.3 ± 0.7 [a]
Maximal leaflet displacement	1.5 ± 0.4	3.3 ± 0.8 [a]
Degree of mitral regurgitation	8.8 ± 4.3	13.9 ± 6.5 [b]
AOSDI (mm/m^2)	17.2 ± 2.6	18.3 ± 2.5
AODDI (mm/m^2)	16.7 ± 2.3	17.1 ± 2.1
Aortic distensibility ($mmHg^{-1}$)	0.0021 ± 0.005	0.0029 ± 0.006 [b]
Index of aortic stiffness	25.2 ± 4.9	21.3 ± 5.3 [c]
LAD (mm)	29.7 ± 5.2	31.3 ± 6.3
LVEDD (mm)	45.9 ± 5.9	47.9 ± 6.3
LVESD (mm)	31.3 ± 3.2	31.2 ± 4.3
LVMI (g/m^2)	83.4 ± 11.7	84.9 ± 9.7
LVFS (%)	33.4 ± 6.7.	35.5 ± 5.1
LVESV (ml)	38.9 ± 7.6	39.2 ± 6.2
LVEDV (ml)	91.7 ± 9.3	92.5 ± 9.3
LVEF (%)	62.7 ± 8.3	63.4 ± 6.3
CO (L/m^2)	3.29 ± 1.1	3.27 ± 0.9
SVR ($dyn.s.cm^{-5}$)	1354 ± 227	1337 ± 263

AODDI, diastolic diameter index of aortic wall; AOSDI, systolic diameter index of aortic wall; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-sytolic diameter; LVMI, left ventricular mass index; FS, left ventricular fractional shorthening; LVESV, left ventricular end-sytolic volume; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction;CO, cardiac output; SVR, systemic vascular resistance.
[a] P<0.0001 vs. controls, [b] P<0.001 vs. controls, [c] P<0.005 vs. controls.

because younger patients were more likely to have higher HMS and incidence of both MVP (25) and BJHMS are decreased with age (30, 31), we accepted HMS cut off point as five and above for BJHMS diagnosis and we divided our patients into two groups according to their HMS. Already, there is no universal agreement on a treshold for BJHMS; some researchers use a Beighton scale score of 5/9, other researchers 6/9, and still other researchers use a modified a Beighton score of 3/5 (26).

Extraarticular tissues and organs that rely upon the tensile strength of normal collagen may be affected in patients with BJHMS. Type I collagen is the most common type of collagen in the human body. With tensile strength, type I collagen is normally abundant in connective tissues such as tendon, ligament, joint capsule and skin. Type III collagen is found in the same tissues with type I collagen, but usually in lesser amounts. Thin and elastic compared with type I colagen, type III collagen is found in greater relative amounts extensible connective tissues, such as the vascular system, skin and lung (32). In patients with BJHMS, the ratio of type III collagen to type III + type I collagen is increased (9,14). The abnormal ratio of type III collagen to type I collagen is thought to cause the decreased tissue stiffness seen in patients with BJHMS. Decreased stiffnes of joint structures produces the joint hypermobility most obvious in patients with

Table V: Comparison of conventional echocardiographic parameters, echocardiographic features of mitral leaflet, elastic properties of aortic wall and hypermobility score in the two groups of patients with MVP.

	GROUP I (MVP+BJHMS) n=21	GROUP II (MVP- BJHMS) n= 25
Beighton hypermobility score	5.8 ± 0.7 [a]	4.1 ± 0.5
Anterior mitral leaflet thickness	5.7 ± 0.6 [b]	5.1 ± 0.5
Maximal leaflet displacement	3.8 ± 0.7 [b]	2.9 ± 0.5
Degree of mitral regurgitation	17.1 ± 7.2 [c]	11.2 ± 4.4
AOSDI (mm/m^2)	18.9 ± 2.6	17.8 ± 2.5
AODDI (mm/m^2)	17.4 ± 2.3	16.9 ± 2.1
Aortic distansibility ($mmHg^{-1}$)	0.0035 ± 0.007 [b]	0.0024 ± 0.005
Aortic stiffness index	17.6 ± 6.9 [b]	23.9 ± 7.6
LAD(mm)	31.7 ± 6.7	29.8 ± 6.3
LVEDD(mm)	48.3 ± 4.9	47.8 ± 5.6
LVESD (mm)	31.4 ± 3.7	30.9 ± 3.3
LVMI(g/m^2)	85.3 ± 9.3	84.6 ± 8.9
FS (%)	35.7 ± 4.5	35.3 ± 4.9
LVESV (ml)	38.7 ± 4.7	39.5 ± 5.3
LVEDV (ml)	91.7 ± 8.7	93.3 ± 9.8
LVEF(%)	63.8 ± 5.2	62.9 ± 4.9
CO (L/m^2)	3.29 ± 1.1	3.27 ± 0.9
SVR ($dyn.s.cm^{-5}$)	1328 ± 227	1371 ± 253

The abbreviations are as in Table IV.

[a] P<0.0001 vs. group II, [b] P<0.001 vs. group II, [c] P<0.002 vs. group II.

Table VI: The distribution of Beighton Hypermobility Scores and correlations with echocardiographic features of mitral leaflet and elastic properties of aortic wall.

	MVP, n=46 MVPB ± JHMS BHS= 4.9 ± 0.9	GROUP I, n=21 MVP+BJHMS BHS= 5.8 ± 0.7	GROUP II, n=25 MVP-BJHMS BHS= 4.1 ± 0.5	CONTROLS n=21 BHS= 1.8 ± 1.5
Anterior mitral leaflet thickness	r=0.62/p<0.001	r=0.57/p=0.007	r=0.47 / p<0.04	r=0.05/p>0.9
Maximal leaflet displacement	r=0.59/p<0.001	r=0.55/p<0.009	r=0.35/ p<0.05	r=0.24/p>0.2
Degree of mitral regurgitation	r=0.53/p<0.001	r=0.51/p<0.01	r=0.29/p>0.1	r=0.14/p>0.5
Index of aortic stiffness	r=0.47/p<0.003	r=0.53/p<0.005	r=0.23/p>0.3	r=0.18/p>0.4
Aortic distensibility	r=0.41/p<0.005	r=0.49/ p<0.007	r=0.21/p>0.5	r=0.27/ p>0.1

BJHMS; decreased stiffness of other tissues may result in prolapse seen other organs. Thus, MVP is caused by decreased stiffness of chordae tendineae that normally limit valve movement (26). On the other hand, Tamura et al. have shown that there was a haphazard arrengement of cells with disruption and fragmentation of collagen fibrils in electron microscopy of MVP (33). In another study, the concordance between inadequate production of type III collagen and echocardiographic findings of MVP in patients with type IV Ehler- Danlos syndrome have suggested that this collagen abnormality may be responsible in patients with this syndrome (34).

Abnormalities of collagen have been found in myxomatous or floppy valves of patients with MVP (11-13) that coincide with those identified in skin biopsies of patients with hypermobility syndrome (9) leading to the suggestion of a common pathogenetic mechanism of abnormal production or maturation of collagen (14). Several clinical observations have led to the speculation that primary MVP syndrome represents a generalized disorder of connective tissue. Thoracic skeletal abnormalities such as straight thoracic spine and pectus excavatum are commonly associated with this syndrome (35,36). The mitral valve undergoes differentiation between the thirty-fifth and forth-second days of fetal life, when the thoracic vertebra and thoracic cage are beginning to chondrification and ossification (37). Therefore, it has been postulated that primary MVP syndrome is a connective tissue disorder resulting from exposure to toxic agents during the early pregnancy (38). Some other investigators have suggested that MVP is a result of defective embryogenesis of cell lines of mesenchymal origin. This association of primary MVP with an increased incidence in patients with von Willebrand disease and other coagulopathies, primary hipomastia, and various connective tissue diseases has been used to support this concept (39,40).

Grahame et al. reported that there was a trend towards a positive correlation between anterior mitral leaflet excursion (e.g. displacement of anterior mitral leaflet) and hypermobility score but this did not reach statistical significance ($r = 0.23$, $p > 0.05$) (7). Moreover, they did not study the relationship between MLD, DMR IAOS and AOD and BHS. In the present study, BHS correlated positively with AMLT, MLD and DMR in patients with MVP, associated with or without BJHMS in both subgroups and all study group. This correlation was detected to be the strongest in the group I . Among echocardiographic features, mitral leaflet thickness had the strongest relation with BHS in both groups. There were significant differences in AMLT, MLD and DMR between patients with MVP and controls. Patients with MVP and BJHMS had significantly increased AMLT, MLD and DMR than those of patients with only MVP. There were significant corellations between AMLT, MLD and DMR and HMS in patients with MVP and BJHMS. In view of our findings, it could be hypothesized that patients with higher echocardiographic degree of MVP have increased BHS. Previous studies reported that both BJHMS and MVP are inherited as gender- influenced dominant traits and predominantly affect women (9,10). Most of our patients were also females who were mainly affected by both BJHMS and MVP.

Some studies reported that EDS and BJHMS are instances of a collagen deficiency diseases in which structural cardiovascular weakness (such as MVP) are associated with increased aortic compliance (9,41). We found that index of aortic stiffness (IAOS) was lower, but aortic distensibility (AOD) was higher in group I. In additon, AOD correlated positively with HMS, but index of aortic stiffness correlated inversely with HMS. Morever, three pairs of sisters had quite low IAOS and extremely high AOD. However, in this study no correlation

was found between any of echocardiographic parameters and BHS (LVEDS, LVEDD, LVESV LVEDV, LVEF,LVFS, AODDI, AOSDI, LAD). Handler et al. have shown that most of their patients had a raised aortic compliance indicating an increased distensibility of aortic wall. This is presumably related to abnormal collagen in the media. The results of our study generally accorded with and supported the results of Handler's.

Because our study rely on echocardiographic and clinical examinations, our results should be supported by findings of histo-pathological studies. The results of this study suggest that all patients, especially women, with mitral valve prolapse should have careful clinical assesment with Beighton hypermobility score because the frequency of BJHMS and other generalised connective tissue deficiency is likely to be higher.

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