The Relationship Between Echocardiographic Features of Mitral Valve and Elastic Proporties 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 the correlation between the echocardiographic features of the mitral valve and elastic properties of the aortic wall and Beighton hypermobility score (BHS) in patients with MVP and BJHMS.

Fourty-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, MVP+BJHMS; group II, MVP-BJHMS). Individuals with accompanying cardiac or systemic disease were excluded. Echocardiographic examination was performed in all subjects. The presence of BJHMS was evaluated according to Beighton's criteria.

The incidence of BJHMS in patients with MVP was found to be significantly higher than that of controls (45.6%, (21/46) vs 12% (3/25), $P < 0.0001$). Group I (MVP + BJHMS) had significantly increased anterior mitral leaflet thickness (AMLT, 3.4 ± 0.4 vs 3.1 ± 0.3; $P < 0.005$), maximal leaflet displacement (MLD, 2.4 ± 0.4 vs 1.7 ± 0.4; $P < 0.005$), and degree of mitral regurgitation (DMR, 17.1 ± 7.2 vs 11.2 ± 4.4; $P < 0.01$) compared to group II. However, the index of aortic stiffness (IAOS) was found to be lower (17.6 ± 6.9 vs 23.9 ± 7.6; $P < 0.005$) and aortic distensibility (AOD) to be higher (0.0035 ± 0.007 vs 0.0024 ± 0.005; $P < 0.005$) in group I. There was a 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 addition, AOD correlated positively with BHS (r = 0.53/$P < 0.005$), but the index of aortic stiffness correlated inversely with BHS (r = -0.49/$P < 0.007$).

The incidence of BJHMS in patients with MVP was more frequent than the normal population and there was a significant correlation between the severity of BJHMS

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(according to BHS) and echocardiographic features of the mitral leaflets and elastic properties of the aortic wall. (Jpn Heart J 2004; 45: 447-460)

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MITRAL valve prolapse (MVP) occurs most frequently 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 the 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 have been a few studies on the relation between the echocardiographic features of mitral valves [anterior mitral leaflet thickness (AMLT),[15] maximal leaflet displacement (MLD),[7] degree of mitral regurgitation (DMR)], elastic properties of the 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 with respect to the incidence of BJHMS in MVP.[15,16]

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

METHODS

The 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 referred 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 a resting electrocardiogram were excluded. We studied 46 patients with nonrheumatic, uncomplicated, and isolated

mitral anterior leaflet prolapse (7 men and 39 women, mean age, 26.1 ± 5.9) and 25 healthy control subjects (3 men and 22 women, mean age, 25.4 ± 4.3). None of the 46 subjects with mitral valve prolapse had a history of ischemic heart disease or other cardiac or systemic disease. In addition, patients were excluded from the study if they showed evidence of inflammatory joint disease or if they had typical features of one of similar hereditary disorders of connective tissues.

Cardiological and echocardiographic assessment: A full cardiological examination, including electrocardiography and echocardiography, were performed by two independent, blinded 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, Tochigi, Japan) that used 2.5 MHz. Echocardiograms were recorded with a strip chart paper recorder (Toshiba line scan recorder LSR-20B) together with a lead II electrocardiogram and phonocardiogram. The measurements were carried out according to the 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 diastasis, and nonclassic prolapse was defined as displacement of more than 2 mm, with a maximal leaflet thickness of less than 5 mm (Figure 1A and B). The maximal displacement of the anterior mitral leaflet was measured with both 2-D echocardiography in parasternal long-axis and apical four-chamber views and M-mode echocardiography (Figure 1C). The anterior mitral leaflet thickness was evaluated during mid-diastole by measuring the distance from the leading edge to the trailing edge of the thick area of the mid-portion of the leaflet and thickness of the rough zone of the anterior mitral leaflet (Figure 1D). Color-Doppler echocardiography was used for the detection and semiquantitation of mitral regurgitation. The degree of mitral regurgitation was assessed 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 (Figure 1E). Grading was performed from one of these echocardiographic windows in which the regurgitant flow was best visualized. 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, and > 40 percent, respectively.[18] Left ventricular end-diastolic dimension (LVEDD) and thicknesses of the interventricular septum (IVST) and posterior wall (PWT) were measured at onset of the electrocardiographic Q wave. 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) X 80, where mPRA is the mean right atrial pressure, considered equal to zero mm Hg in each subject, and mPAO is mean aortic pressure, derived using a cuff-sphygmomanometer, as diastolic blood pres-

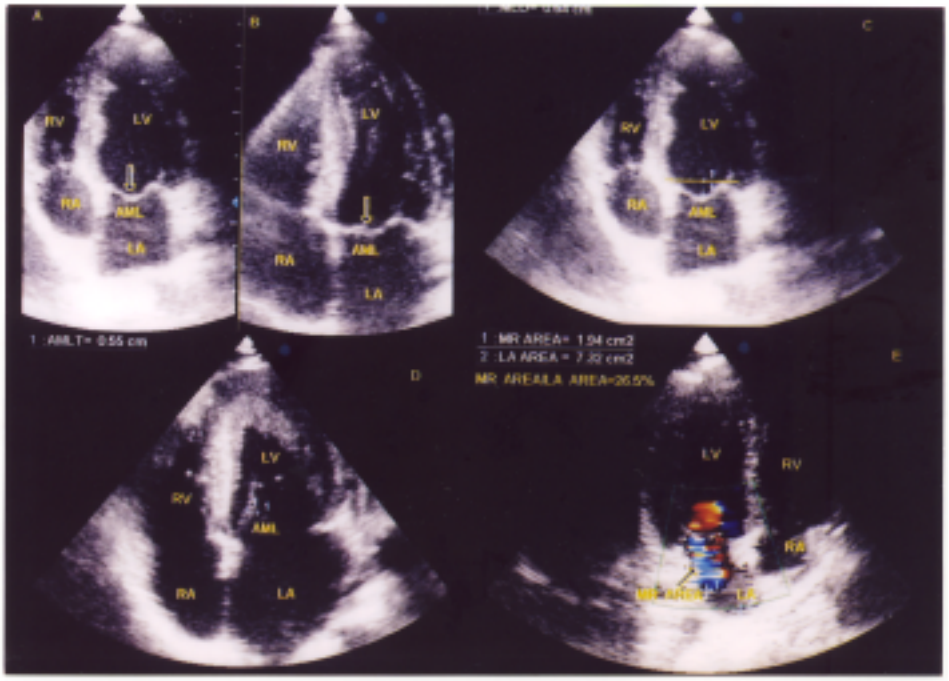

Figure 1. **A:** Echocardiogram of a patient with mitral valve prolapse (MVP) and benign joint hypermobility syndrome (group I) in apical four-chamber view. **B:** Echocardiogram of a patient with only MVP (group II); **C:** Measurement of maximal leaflet displacement (MLD); apical four chamber echocardiogram of a patient with MVP demonstrating a curved anterior mitral leaflet that extends beyond the plane mitral annulus (yellow-dotted line) **D:** Measurement of the anterior mitral leaflet thickness (AMLT). AMLT was evaluated during mid-diastole by measuring the distance from the leading edge to the trailing edge of the thickness of the rough zone of the anterior mitral leaflet; **E:** Grading of the severity of mitral regurgitation. The degree of mitral regurgitation (DMR) was assessed as the ratio of the maximal regurgitant jet area (MR area) to the area of the left atrium (LA area) in the apical four-chamber view. **Abbreviations:** AML = anterior mitral leaflet; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; MR = mitral regurgitation.

sure + 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 the ascending aorta (aortic root) were measured by M-mode in a long axis view (Figure 2). Systolic (AOSDI=AODD/BSA) and diastolic diameter indices (AODDI=AOSD/BSA) of the aortic wall were calculated. Aortic stiffness (IAOS) was calculated according to the following 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 a previously described formula;[23,24]

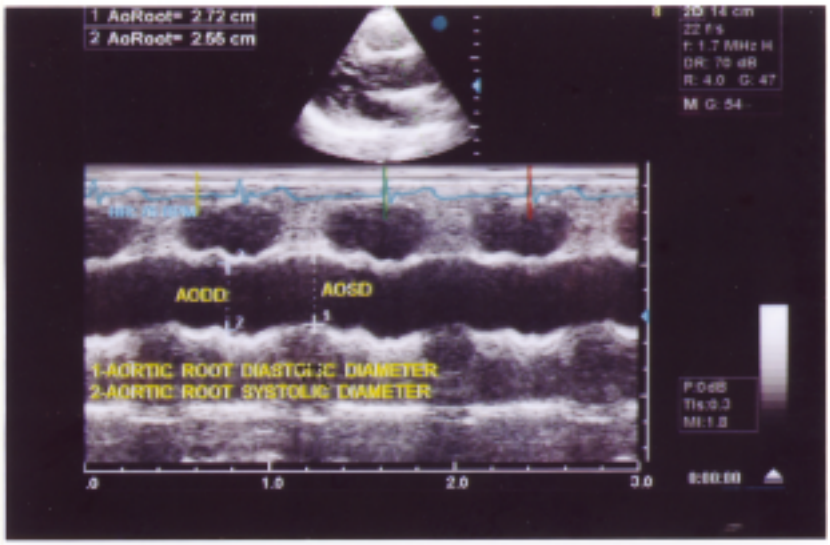

Figure 2. Measurement of diameters of the ascending aorta (aortic root) from two dimensional guided M-mode cursor on long axis parasternal two-dimensional echocardiogram is directed approximately 3 cm above aortic valve. Electrocardiogram is also shown. AODD = aortic root diastolic diameter; AOSD = aortic root systolic diameter.

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

Diagnosis of benign joint hypermobility syndrome: Joint hypermobility was measured using the Beighton scale shown in Table I.[25] In our study, BJHMS was mainly diagnosed using the draft criteria shown in Table II[25], but we also accepted a BHS cut-off point of five and above[26] for a BJHMS diagnosis. BJHMS is excluded by the 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 the Ethics Committee of the Medical Faculty of Abant Izzet Baysal University.

Statistical analysis: Values are presented as the mean ± standard deviation (SD). An unpaired t-test was used to compare the control and patients with MVP. One-way ANOVA was used to compare the groups (controls, group I, and group II). Nonparametric ratios between groups were compared with the χ^2-test. Pearson or Spearmen's correlation test was used to assess the correlation between the hypermobility score and echocardiographic parameters. A *P* value was considered significant when it was less than 0.05. The "r" value was the correlation coefficient. The tests were performed using SPSS 7.5 for Windows.

Table I. The 9-point Beighton Scoring System for Joint Hypermobility Scale

Scoring 1 point on each side
• Passive dorsiflexion of the fifth MCP to 90°
• Apposition of thumb to the flexor aspect of the forearm
• 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

Adapted from Beighton, *et al*.[25]

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 spondylosis, spondylolisthesis
Dislocation in more than 1 joint, or in 1 joint or more on more than 1 occasion
Three or more soft tissue lesions (epycondlylitis, tenosynovitis, bursitis)
Marfanoid habitus (tall, slim, span > height, upper segment: to 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 prolapse
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

RESULTS

The incidence of BJHMS in patients with MVP was found to be significantly higher than controls (45.6%, (21/46) vs 12% (3/25), $P < 0.0001$). Statistically significant differences in demographic, clinical, and laboratory characteristics between the two patient groups were not observed ($P > 0.05$) (Table III). There were significant differences in AMLT (mid-portion; 3.2 ± 0.4 vs 1.3 ± 0.4; $P < 0.0001$, rough-zone; 3.3 ± 0.5 vs 1.3 ± 0.4; $P < 0.0001$), MLD (2.0 ± 0.5 vs 0.9 ± 0.3; $P < 0.0001$) and DMR (13.9 ± 6.5 vs 8.8 ± 4.3; $P < 0.001$)

Table III. Demographic, Clinical, and Laboratory Characteristics of Controls 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 pressure (mmHg)	72.9 ± 12.3	71.6 ± 11.2	70.8 ± 15.4
Systolic blood pressure (mmHg)	124.7 ± 26.5	122.7 ± 22.5	123.9 ± 21.7
Heart rate (beats/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%)
Dyspnea, *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%)

between 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 with controls (0.0029 ± 0.006 vs 0.0021 ± 0.005; $P < 0.001$) (Table IV). Group I had significantly increased AMLT (mid-portion; 3.4 ± 0.4 vs 3.1 ± 0.3; $P < 0.005$, rough-zone; 3.6 ± 0.6 vs 3.2 ± 0.4; $P < 0.005$), MLD (2.4 ± 0.4 vs 1.7 ± 0.4; $P < 0.005$), and DMR (17.1 ± 7.2 vs 11.2 ± 4.4; $P < 0.01$) than those of group II. However, the index of aortic stiffness (IAOS) was found to be lower (17.6 ± 6.9 vs 23.9 ± 7.6; $P < 0.005$) and aortic distensibility (AOD) was found to be higher in group I (0.0035 ± 0.007 vs 0.0024 ± 0.005; $P < 0.005$) (Table V). In group I, there were significant correlations between the AMLT-mid-portion, AMLT-rough zone MLD, DMR, and BHS ($r = 0.57/P = 0.007$, $r = 0.59/P = 0.005$, $r = 0.55/P < 0.009$, $r = 0.51/P < 0.01$, respectively) (Table VI). In addition, AOD correlated positively with HMS ($r = 0.53/P < 0.005$), but the index of aortic stiffness correlated inversely with HMS ($r = -0.49/P < 0.007$)(Table VI). However, AODDI, AOSDI, LAD LVEDS, LVEDD, LVESV, LVEDV, LVEF, and FS in all groups were similar and there were no correlations between any of these parameters and BHS ($P > 0.05$) (Tables IV, V and VI).

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 (± BJHMS) n = 46
Hypermobility score	1.8 ± 1.5	4.9 ± 0.9[a]
AMLT-mid-portion (mm/m^2)*	1.3 ± 0.4	3.2 ± 0.4[a]
AMLT-rough zone (mm/m^2)*¶	1.3 ± 0.4	3.3 ± 0.5[a]
MLD (mm/m^2)*	0.9 ± 0.3	2.0 ± 0.5[a]
DMR (%)	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/m^2)*	17.8 ± 2.9	18.7 ± 3.9
LVEDD (mm/m^2)*	27.2 ± 3.7	28.7 ± 4.1
LVESD (mm/m^2)*	18.5 ± 2.1	18.8 ± 2.9
LVMI (g/m^2)	83.4 ± 11.7	84.9 ± 9.7
LVFS (%)	33.4 ± 6.7	35.5 ± 5.1
LVESV (mL/m^2)*	23.1 ± 4.7	33.7 ± 4.1
LVEDV (mL/m^2)*	54.7 ± 5.9	55.6 ± 5.8
LVEF (%)	62.7 ± 8.3	63.4 ± 6.3
CO (L/m^2)*	1.96 ± 0.7	1.97 ± 0.6
SVR ($dyn{\cdot}s{\cdot}cm^{-5}$)	1354 ± 227	1337 ± 263

AMLT = anterior mitral leaflet thickness; MLD = maximal leaflet displacement; DMR = degree of mitral regurgitation; 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-systolic diameter; LVMI = left ventricular mass index; FS = left ventricular fractional shortening; LVESV = left ventricular end-systolic volume; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; CO = cardiac output; SVR = systemic vascular resistance.

* These parameters were indexed by body surface area

¶ AMLT was also measured as the thickness of rough zone of anterior mitral leaflet

[a] $P < 0.0001$ vs controls, [b] $P < 0.001$ vs controls, [c] $P < 0.005$ vs controls

Table V. Conventional Echocardiographic Parameters, Echocardiographic Features of Mitral Leaflet, Elastic Properties of Aortic Wall, and Hypermobility Score in Controls and Patients With MVP (Group I and II)

	Controls $n = 29$	Group I (MVP+BJHMS) $n = 21$	Group II (MVP-BJHMS) $n = 25$
Hypermobility score	1.8 ± 1.5	5.8 ± 0.7[a†]	4.1 ± 0.5[a]
AMLT-mid-portion (mm/m^2)*	1.3 ± 0.4	3.4 ± 0.4[a‡]	3.1 ± 0.3[a]
AMLT-rough zone (mm/m^2)*¶	1.3 ± 0.4	3.6 ± 0.6[a‡]	3.2 ± 0.4[a]
MLD (mm/m^2)*	0.9 ± 0.3	2.4 ± 0.4[a‡]	1.7 ± 0.4[a]
DMR (%)	8.8 ± 4.3	17.1 ± 7.2[b◊]	11.2 ± 4.4
AOSDI (mm/m^2)	17.2 ± 2.6	18.9 ± 2.6	17.8 ± 2.5
AODDI (mm/m^2)	16.7 ± 2.3	17.4 ± 2.3	16.9 ± 2.1
Aortic distensibility ($mmHg^{-1}$)	0.0021 ± 0.005	0.0035 ± 0.007[a‡]	0.0024 ± 0.005[c]
Index of aortic stiffness	25.2 ± 4.9	17.6 ± 6.9[b‡]	23.9 ± 7.6
LAD (mm/m^2)*	17.8 ± 2.9	19.2 ± 4.3	17.9 ± 4.1
LVEDD (mm/m^2)*	27.2 ± 3.7	29.2 ± 3.2	28.7 ± 2.9
LVESD (mm/m^2)*	18.5 ± 2.1	18.9 ± 3.1	18.5 ± 2.9
LVMI (g/m^2)	83.4 ± 11.7	85.3 ± 9.3	84.6 ± 8.9
LVFS (%)	33.4 ± 6.7	35.7 ± 4.5	35.3 ± 4.9
LVESV (mL/m^2)*	23.1 ± 4.7	23.2 ± 3.4	23.7 ± 3.6
LVEDV (mL/m^2)*	54.7 ± 5.9	55.1 ± 5.6	55.9 ± 6.3
LVEF (%)	62.7 ± 8.3	63.8 ± 5.2	62.9 ± 4.9
CO (L/m^2)*	1.96 ± 0.7	1.98 ± 0.7	1.96 ± 0.5
SVR ($dyn{\cdot}s{\cdot}cm^{-5}$)	1354 ± 227	1328 ± 227	1371 ± 253

Abbreviations same as Table IV.

* These parameters were indexed by body surface area (BSA)

¶ AMLT was also measured as the thickness of rough zone of anterior mitral leaflet

[a] $P < 0.0001$ vs controls, [b] $P < 0.001$ vs controls, [c] $P < 0.01$ vs controls

[†] $P < 0.001$ vs group II, [‡] $P < 0.005$ vs group II, [◊] $P < 0.01$ 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, $n = 46$ MVP ± BJHMS 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 $n = 29$ BHS = 1.8 ± 1.5
Anterior mitral leaflet thickness*	$r = 0.62/P < 0.001$	$r = 0.57/P = 0.007$	$r = 0.47/P < 0.04$	$r = 0.05/P > 0.9$
Anterior mitral leaflet thickness ¶	$r = 0.63/P < 0.001$	$r = 0.59/P < 0.005$	$r = 0.48/P < 0.04$	$r = 0.05/P > 0.9$
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	$r = -0.41/P < 0.005$	$r = -0.49/P < 0.007$	$r = 0.21/P > 0.5$	$r = 0.27/P > 0.1$

* AMLT was measured as thickness of mid-portion of anterior mitral leaflet.

¶ AMLT was also measured as thickness of rough zone of anterior mitral leaflet.

DISCUSSION

Mitral valve prolapse is the most commonly diagnosed valvular heart disease, especially in the young, and affects 5% of the population.[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 the echocardiographic features of mitral valves and elastic properties of the 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 the echocardiographic features of mitral valve prolapse and elastic properties of the aortic wall.

In the present study, we found the incidence of BJHMS in patients with MVP to be 45%, which was slightly lower than that has been reported by Ondrasik, *et al* (52%),[16] but it was considerably lower than the 71.7% reported by Coghlan and Natello.[15] Our study population was younger than those of both of these studies. In addition, in the Ondrasik, *et al* study, the number of patients was substantially less than ours, and in both studies, they divided the patients into three groups according to their HMS (HMS, 0-2: controls; 3-4: mild BJHMS; 5-9: marked BJHMS). However, because younger patients were more likely to have a higher HMS, the incidences of both MVP[25] and BJHMS decreased with age.[30,31] Therefore, we accepted the HMS cut-off point as five and above for the diagnosis of BJHMS and we divided our patients into two groups according to their HMS. In fact, there is no universal agreement on a threshold for BJHMS; some researchers use a Beighton scale score of 5/9, other researchers use a Beighton scale score of 6/9, and still other researchers use a modified 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 tendons, ligaments, joint capsules, and skin. Type III collagen is found in the same tissues as type I collagen, but usually in lesser amounts. Thin and elastic compared with type I collagen, type III collagen is found in greater relative amounts in expandable 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 stiffness of joint structures produces the joint hypermobility most obvious in patients with BJHMS; decreased stiffness of other tissues may result in the prolapse seen in 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 arrangement of cells with disruption and fragmentation of collagen fibrils in electron microcopy 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 the responsible factor 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 forty-second days of fetal life, when the thoracic vertebra and thoracic cage are beginning 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 part of 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 hypomastia, 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 (eg, 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 groups. This correlation was detected to be the strongest in 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 compared to those of patients with only MVP. There were significant

correlations between AMLT, MLD, DMR, and HMS in patients with MVP and BJHMS. In view of our findings, it could be hypothesized that patients with a 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 have reported that EDS and BJHMS are examples of collagen deficiency diseases in which a structural cardiovascular weakness (such as MVP) is associated with increased aortic compliance.[9,41] We found that the index of aortic stiffness (IAOS) was lower but aortic distensibility (AOD) was higher in group I. In addition, AOD correlated positively with HMS, but the index of aortic stiffness correlated inversely with HMS. Moreover, three pairs of sisters had quite low IAOS and extremely high AOD. However, in this study no correlation was found between any of the 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 the 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, *et al*.

Because our study relies on echocardiographic and clinical examinations, our results should be supported by histopathological findings. The results of this study suggest that all patients, especially women, with mitral valve prolapse should undergo careful clinical assessment with the Beighton hypermobility score because the frequency of BJHMS and other generalised connective tissue deficiencies is likely to be higher.

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