Mitral Valve Dimensions and Motion in Marfan Patients With and Without Mitral Valve Prolapse
Comparison to Primary Mitral Valve Prolapse and Normal Subjects

Riccardo Pini, MD, Mary J. Roman, MD, Randi Kramer-Fox, MS, and Richard B. Devereux, MD

To determine mitral valve and extravalvular findings associated with mitral valve prolapse (MVP) in patients with the Marfan syndrome, we compared mitral leaflet and anular dimensions and motion by computerized two-dimensional echocardiography in 53 Marfan patients (28 with M-mode echocardiographic MVP) to those in 48 adults with primary MVP and in 35 normal subjects. Mitral leaflet billowing occurred in 28 of 28 Marfan patients with M-mode MVP versus 24 of 48 with primary MVP ($p<0.00005$), 0 of 25 Marfan patients without M-mode MVP, and 0 of 35 normal subjects (both, $p<0.00001$). Billowing occurred on the first systolic frame in 8 of 28 Marfan-MVP patients, in whom posterior leaflet chordae arose abnormally from the posterior ventricular wall, and in no other subjects. These patients had large mitral valves and normal anular dynamics, whereas the remaining 20 Marfan-MVP patients had increased systolic anular expansion. Marfan-MVP patients were younger than those without MVP (29±12 vs. 38±15 years, $p<0.02$) and had lower body mass index (19.8±2.7 vs. 23.9±2.9 kg/m², $p<0.00005$) and systolic blood pressure (120±20 vs. 133±20 mm Hg, $p<0.05$), similar to differences between primary MVP and normal subjects in body mass index (21.5±3.0 vs. 23.9±4.8 kg/m², $p<0.01$) and systolic pressure (118±14 vs. 125±18 mm Hg, $p<0.05$). Marfan patients with and without MVP had similar arm span, arm span to height ratio, upper to lower segment ratio, and prevalence of ectopia lentis and thoracic bony abnormalities, but arachnodactyly was more frequent in those with MVP (82% and 48%, respectively; $p<0.02$). We conclude that 1) leaflet billowing occurs more uniformly in Marfan patients with MVP than in primary MVP, 2) MVP in Marfan patients may be due to either valve enlargement with distinctively abnormal chordal architecture or abnormal mitral anular distensibility, 3) Marfan patients with MVP have low body weight and systolic blood pressure, similar to primary MVP, and 4) Marfan patients with MVP more commonly have arachnodactyly but otherwise have similar skeletal and anthropometriccharacteristics to other Marfan patients. (Circulation 1989;80:915–924)

Mitral valve prolapse (MVP) occurs commonly as a primary, dominantly inherited condition and also as a secondary manifestation of a number of conditions, most notably the Marfan syndrome. Although primary MVP and the Marfan syndrome are etiologically distinct, they resemble each other in being associated with extracardiac features including altered body habitus and certain thoracic bony abnormalities. Aside from evidence that MVP in the Marfan syndrome is associated more frequently with complications at an early age, little is known of the structural or functional abnormalities of the mitral valve underlying MVP in the Marfan syndrome or of whether differences in mitral valve abnormalities exist between MVP secondary to the Marfan syndrome and primary MVP. Accordingly, the present study was undertaken to compare mitral valve structure and function as revealed by quan-
titative two-dimensional echocardiography and extracardiac findings in Marfan patients with and without MVP to those in normal adults and subjects with uncomplicated primary MVP.

Methods

Subjects

All subjects underwent an extensive clinical evaluation as participants in prospective studies of MVP and the Marfan syndrome. This evaluation included a complete history, physical examination with auscultation in multiple positions, examination for thoracic bony abnormalities, blood pressure, height, weight, a 12-lead electrocardiogram, and M-mode and two-dimensional echocardiograms.

From October 1983 to November 1987, 61 adult patients with the Marfan syndrome and who had not undergone previous cardiac surgery were enrolled in the study. In 53 of these 61 consecutive patients (87%), we obtained technically excellent two-dimensional echocardiograms in which the mitral valve leaflets were clearly visualized on each frame during stopframe review of the entire cardiac cycle. The eight Marfan patients excluded from further analyses were similar in age (mean = 40 years), sex distribution (38% women), prevalence of MVP (50%) by both M-mode and qualitative two-dimensional criteria with typical auscultatory features in all cases), and characteristics of body habitus to the 53 patients with technically excellent two-dimensional echocardiograms who comprised the study population. Marfan patients underwent a comprehensive skeletal, anthropometric, and ocular evaluation. According to criteria adapted from those of Pyeritz and McKusick, the diagnosis of the Marfan syndrome was made only when cardiac manifestations were present in at least two of the following four areas: a) the skeletal system (arachnodactyly, abnormal segment ratio, or marked kyphoscoliosis), b) the cardiovascular system (aortic root dilatation by two-dimensional echocardiography), c) the eyes (ectopia lentis), and d) the family history (positive diagnosis or death in a first-degree relative due to aortic dissection).

A group of normal adults and subjects with uncomplicated MVP who have been previously reported in part were used as comparison groups in the present study. These subjects were adults selected from the file of our large prospective study of MVP based on the availability of two-dimensional echocardiograms suitable for stopframe analysis of mitral valve dimensions on each frame throughout the cardiac cycle. Subjects with uncomplicated MVP met M-mode echocardiographic criteria for diagnosis of this condition, supported by typical auscultatory features on the present (88%) or previous (12%) auscultatory examinations, without clinical or echocardiographic evidence of hemodynamically significant mitral regurgitation by criteria previously reported from this laboratory, whereas control subjects had normal mitral valves by M-mode echocardiogram and normal auscultatory examinations.

Echocardiographic Methods

Echocardiograms were performed by an experienced research technician with subjects in the partial left decubitus position, with the head of the bed elevated approximately 30°. Two-dimensional echocardiograms were recorded on 0.5-in. videotape using a Diasonics DRF 400 echocardiograph (Diasonics, Inc., Milpitas, California) or an HP 77020 echocardiograph (Hewlett-Packard, Andover, Massachusetts) with a 3.5 MHz transducer; M-mode tracings made using the same transducer were recorded on black and white strip-chart paper at 50 mm/sec. The accuracy of both horizontal and vertical calibrations of these machines was verified using an RMI phantom (Radiation Measurements, Inc., Middleton, Wisconsin). In patients with narrow intercostal spaces, additional M-mode recordings were made with a smaller independent transducer (Aerotech 2.25 MHz 13-mm diameter focused at 2–16 cm) using a Picker 80C echocardiograph (Picker, Inc, Northford, Connecticut).

Extensive recordings of the mitral valve were made from all available parasternal acoustic windows. M-mode tracings included multiple sweeps across the mitral valve from left ventricle to aorta along differently oriented paths as well as transverse scans of the valve, analogous to the T-scan introduced for left ventricular measurements by Henry et al. Two-dimensional recordings of the mitral valve were made in multiple projections of parasternal long- and short-axis and apical four-chamber views in all subjects. Extensive Doppler recordings in both pulsed (3.5 mHz carrier frequency) and continuous wave (1.9 mHz carrier frequency) mode were performed from parasternal and apical windows to evaluate the presence and severity (by mapping the extent of regurgitant flow) of mitral and aortic regurgitation in 47 of 53 Marfan patients.

Computerized Analysis

Videotaped two-dimensional echocardiograms were reviewed using a Diasonics Cardio Review Center (option 4) that provided real-time and stopframe viewing formats. Analyses reported here used the parasternal long-axis view because of evidence that normal mitral valves may present an artifactual appearance of mitral prolapse in the apical four-chamber view due to the saddle shape of the mitral anulus. After repeated review of the study, a cardiac cycle was selected that allowed the best visualization of the anterior and posterior mitral leaflets from base to tip and the chord across the mitral anulus from the base of one leaflet to that of the other throughout the cardiac cycle. The entire systolic period (from the beginning of the R wave to the next opening of the mitral valve) of this cycle was examined frame by frame in stop-action format in long-axis view. In each frame, the mitral anular
diameter was defined as extending between the hinge points at the base of each leaflet. The anterior and posterior leaflet positions in each frame were manually digitized using a graphic tablet. Digital data from each frame and appropriate calibration factors were stored on diskette for further analysis. Tracings were made by an operator who had no knowledge of clinical or strip-chart M-mode findings. A computer program was written in UCSD Pascal by one of the investigators (R.P.) for the quantitative analyses described below. The analysis program presented a sequential frame-by-frame
graphic display of mitral valve motion in the original spatial orientation (Figure 1A). Data obtained from the digitized mitral images included length of the anterior and posterior leaflets and anular diameter. The length of anterior and posterior leaflets was measured just prior to mitral valve closure. Mitral anular diameter was measured in 12 frames, from the beginning of the R wave to the frame just prior to mitral valve opening.

**Diagnosis of Mitral Valve Prolapse**

All diagnostic and quantitative evaluation of the mitral valve was performed blindly, with no knowledge of either clinical findings or the results of the alternate two-dimensional or M-mode echocardiographic technique. Standard criteria for M-mode echocardiographic diagnosis of mitral prolapse, which primarily detect posterior systolic displacement of mitral leaflets, were used with two-dimensional echocardiographic verification of correct beam angulation. As previously described, diagnosis of MVP is made purely by M-mode echocardiography when continuous mitral leaflet interfaces were displaced more than 2 mm behind the valve’s C-D line in late systole, with “turning around” of leaflet interfaces with motion away from the transducer. More than 3 mm posterior displacement throughout systole on M-mode echocardiography was accepted as diagnostic of holosystolic MVP only when confirmed by detection of systolic billowing of one or both leaflets across the line connecting the hinging points of the anterior and posterior mitral leaflets in stopframe review of the two-dimensional parasternal long-axis view. The diagnosis of MVP by these criteria in our laboratory has proved to be highly reproducible (57 of 60 or 95%) in studies performed 19–54 months apart. In our laboratory studies, these echo criteria were associated with typical systolic clicks and/or murmurs in 166 of 176, or 94%, of patients with mitral prolapse, and were closely related to biological features of mitral valve prolapse, including inheritance and low body weight.

Diagnosis of mitral leaflet billowing was made by two-dimensional echocardiography if one or both mitral leaflets were demonstrated by our computer-assisted analysis to protrude across the line connecting the hinging points of the anterior and posterior mitral leaflets into the left atrium at any point during systole. This criterion is in accord with recommendations by previous investigators for qualitative interpretation of two-dimensional echocardiograms. Leaflet billowing detected by these criteria reflects superior as well as posterior displacement of mitral leaflets during systole. As suggested by Levine et al, only the parasternal long-axis view was examined for the diagnosis of MVP because a nonplanar shape of the mitral anulus can produce the appearance of mitral leaflet billowing in the apical four-chamber view in normal subjects.

**Statistical Analysis**

Differences between two frequencies are evaluated by the \( \chi^2 \) test with Yate’s continuity correction or Fisher’s exact test. Data are reported as mean±SD; means are compared by unpaired Student’s \( t \) tests or analysis of variance followed by the Scheffé test. Normal limits for mitral valve measurements were derived as the mean value±1.96 SD in our normal subjects. A \( p \) value of less than 0.05 was considered statistically significant.

**Results**

**Subjects**

A total of 136 subjects comprises the present study population, including 28 with Marfan syndrome with M-mode echocardiographic MVP, 25 with Marfan syndrome without echocardiographic MVP, and comparison groups of 35 normal individuals and 48 with uncomplicated primary mitral valve prolapse.

<table>
<thead>
<tr>
<th>TABLE 1. Demographic and Clinical Findings</th>
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<tr>
<td>Normal (n=35)</td>
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<tr>
<td>Mean age (yr)</td>
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<tr>
<td>Women (%)</td>
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<tr>
<td>Midsystolic clicks (%)</td>
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<tr>
<td>Late/holosystolic murmurs (%)</td>
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<td>Height (m)</td>
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<td>Body surface area (m²)</td>
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<td>Body mass index (kg/m²)</td>
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<td>Systolic blood pressure (mm Hg)</td>
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<tr>
<td>Diastolic blood pressure (mm Hg)</td>
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<tr>
<td>Thoracic bony abnormalities (%)</td>
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MVP, mitral valve prolapse.

*Pectus excavatum or carinatum, scoliosis, straight thoracic spine.*
TABLE 2. Differences in Mitral Valve Dimensions Between Normal, Mitral Valve Prolapse Subjects, and Marfan Patients

<table>
<thead>
<tr>
<th></th>
<th>Normal (n=35)</th>
<th>MVP with billowing (n=24)</th>
<th>MVP without billowing (n=24)</th>
<th>Marfan with billowing (n=28)</th>
<th>Marfan without billowing (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior leaflet (cm)</td>
<td>2.00±0.31</td>
<td>2.08±0.31</td>
<td>1.95±0.28</td>
<td>2.07±0.30</td>
<td>1.99±0.35</td>
</tr>
<tr>
<td>Posterior leaflet (cm)</td>
<td>1.45±0.22</td>
<td>1.54±0.30</td>
<td>1.35±0.22</td>
<td>1.39±0.25</td>
<td>1.34±0.29</td>
</tr>
<tr>
<td>End-diastolic anulus (cm)</td>
<td>2.68±0.39</td>
<td>2.83±0.36</td>
<td>2.59±0.32</td>
<td>2.87±0.50</td>
<td>2.90±0.50</td>
</tr>
<tr>
<td>End-systolic anulus (cm)</td>
<td>2.91±0.34</td>
<td>3.02±0.45</td>
<td>3.03±0.40</td>
<td>3.04±0.39</td>
<td>2.96±0.34</td>
</tr>
<tr>
<td>Systolic anular diameter variation (%)</td>
<td>27±12</td>
<td>22±11</td>
<td>41±14*</td>
<td>28±13</td>
<td>21±14</td>
</tr>
</tbody>
</table>

MVP, mitral valve prolapse.
*p<0.001 vs. normal.

The same proportion of probands was present in the Marfan and the primary MVP groups (34 of 53 or 64% and 30 of 48 or 63%, respectively). As shown in Table 1, no difference was found in age or gender among subject groups. Midsystolic clicks, late systolic murmurs, or both were present in a higher percentage of subjects with uncomplicated mitral prolapse than in Marfan patients. Marfan patients had larger body surface areas than either controls or subjects with uncomplicated MVP. No difference was found in body mass index between Marfan patients and subjects with MVP, whereas both groups had lower body mass indexes than controls. Thoracic bony abnormalities (pectus excavatum or carinatum, scoliosis, or straight thoracic spine) were present in nearly all patients with Marfan syndrome, whereas 56% of subjects with primary MVP and only 11% of controls had one or more of these abnormal findings. Among subjects who underwent slit-lamp examination, ectopia lentis was present in 34 of 52, or 65%, of Marfan patients and was absent in four of four, or 100%, of MVP and one of one, or 100%, of normal subjects. Of the 53 Marfan patients, 35, or 66%, had positive family histories, three, or 6%, appeared to represent new mutations, and 15, or 28%, had incomplete family evaluations due to adoption or other circumstances. In the 26 families of subjects with MVP that were evaluated, one or more additional relatives was found to be affected in 24 (92%), among whom were six additional subjects in the present report.

**Pattern of MVP**

Billowing of one or both mitral leaflets into the left atrium during systole was demonstrated by analysis of two-dimensional recordings in 28 of 28, or 100%, of Marfan patients with M-mode echocardiographic MVP and 24 of 48, or 50%, of patients with primary MVP (p<0.00005). The remaining 24 patients with primary MVP (50%) demonstrated systolic anular expansion, as recently described.13 Two-dimensional echocardiograms in the latter group demonstrated posterior displacement of mitral leaflets both on qualitative review of the recordings and when points spaced equidistantly from base to free edge of the leaflets had their motion in the anteroposterior axis tracked by our computerized system. Leaflet billowing did not occur in any of the 25 Marfan patients or 35 normal subjects without M-mode echo or clinical evidence of MVP.

Computerized frame-by-frame two-dimensional echocardiographic examination of systolic mitral leaflet movements demonstrated that eight of 28 (29%) Marfan patients with MVP exhibited marked leaflet billowing on the first systolic frame, suggesting a lack of support by the subvalvular apparatus (Figure 1A). Further, qualitative analysis of the two-dimensional recordings of these eight patients demonstrated the origin of all visualized posterior leaflet chordae to be from the left ventricular posterior wall rather than from a major papillary muscle (Figure 1B); no patients with primary MVP exhibited these abnormalities. Marfan patients with MVP had left ventricular, left atrial, and aortic dimensions similar to Marfan patients without MVP; the subgroup of Marfan patients with early systolic billowing did not differ from Marfan patients with mid- to late systolic billowing in left ventricular and atrial dimensions or in aortic diameter. No difference was found in age and sex distribution or in anthropometric and skeletal findings between Marfan patients with and without early systolic billowing, but mitral systolic murmurs were more frequent in Marfan-MVP patients with early, as opposed to midsystolic or late systolic billowing (75% vs. 25%, p<0.05). Aortic dilatation and/or dissection were equally prevalent in the two subgroups.

Doppler examination revealed mild mitral regurgitation in six of 26 Marfan patients with MVP, including four of eight, or 50%, of those with early systolic billowing, two of 18, or 11%, of those with mild to late systolic billowing, and in one of 21, or 5%, of Marfan patients without MVP. Aortic regurgitation by Doppler was equally prevalent in Marfan patients with and without MVP (12% vs. 38%, NS). Late systolic murmurs suggestive of mild mitral regurgitation were audible in one of two, or 50%, of Marfan-MVP patients and in one of four, or 25%, of Marfan patients without MVP who did not undergo Doppler evaluation. A murmur of aortic regurgitation, subsequently demonstrated by cardiac catheterization before aortic surgery to be severe, was detected in one of two, or 50%, of Marfan patients with MVP who did not have Doppler evaluation.
Mitral Leaflet Dimensions

The entire group of Marfan patients exhibited normal anterior and posterior leaflet lengths (2.03±0.32 and 1.37±0.27 cm, respectively, NS), as did the 28 Marfan patients with MVP (Table 2, Figure 2). However, the subgroup of Marfan patients with early systolic billowing had increased anterior leaflet length (2.33±0.28 vs. 1.97±0.24 cm in Marfan patients without early systolic billowing, p<0.01; p<0.02 vs. controls), with one value outside normal limits and the remaining seven patients toward the upper end of the normal distribution. Also, although anterior and posterior mitral leaflets in the entire group with uncomplicated MVP were similar to those in normal subjects, posterior leaflet length was greater in MVP subjects with systolic billowing than in those without (p<0.05).

Mitral Anular Diameter

Mitral anular diameter at end diastole was slightly increased in Marfan patients compared with normal subjects (2.88±0.50 vs. 2.68±0.39 cm, p<0.05), but only four of 53, or 8%, of Marfan patients had end-diastolic anular diameter above the upper confidence limit derived from normal subjects (Figure 3A). However, the subgroup of Marfan patients with early systolic billowing had significantly increased end-diastolic anular dimensions (3.26±0.69 cm, p<0.005 vs. controls). The remaining 20 Marfan patients without early systolic billowing had normal anular diameter at end diastole (2.72±0.30 cm, NS vs. controls; p<0.01 vs. patients with early systolic billowing). The entire group of subjects with primary mitral prolapse showed normal end-diastolic anular diameter (2.71±0.36 cm, NS vs. controls; p<0.05 vs. Marfan patients). The end-diastolic anular diameter was normal in both the Marfan and the primary MVP groups (3.01±0.36 and 3.03±0.42 cm, respectively, vs. 2.91±0.34 cm, NS), but the Marfan patients with early systolic billowing exhibited an increased end-diastolic anular diameter (3.38±0.41 cm, p<0.002 vs. controls). As shown in Figure 3B, anular dimensions were outside normal limits in three of these eight patients and were toward the upper end of the normal distribution in the other five, whereas the remaining Marfan patients with and without MVP were within the normal range.

Although the entire group of Marfan patients had a normal percent increase in anular diameter from the minimum diameter attained in early systole to end systole (25±14% vs. 27±12%, NS), the patients without early systolic billowing exhibited increased anular expansion in midsystole to late systole compared with normal subjects, whereas the eight
patients with early systolic billowing had normal anular dynamics (Figure 4). Among primary MVP subjects, only those without billowing had an increased anular expansion during systole (41±14%, p<0.001, vs. controls).

**TABLE 3. Relation of Clinical Findings to Presence or Absence of Mitral Leaflet Billowing in Marfan Patients**

<table>
<thead>
<tr>
<th></th>
<th>Billowing (n=28)</th>
<th>p</th>
<th>No billowing (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>29±12</td>
<td>&lt;0.02</td>
<td>38±15</td>
</tr>
<tr>
<td>Women (%)</td>
<td>17 (61)</td>
<td>NS</td>
<td>9 (36)</td>
</tr>
<tr>
<td>Midsystolic clicks (%)</td>
<td>17 (61)</td>
<td>&lt;0.001</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Late/holosystolic murmur (%)</td>
<td>11 (39)</td>
<td>&lt;0.02</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.82±0.14</td>
<td>NS</td>
<td>1.86±0.12</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.5±12.3</td>
<td>&lt;0.00005</td>
<td>83.0±11.9</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.84±0.05</td>
<td>&lt;0.0005</td>
<td>2.08±0.21</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>19.8±2.7</td>
<td>&lt;0.00005</td>
<td>23.9±2.9</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>120±20</td>
<td>&lt;0.05</td>
<td>133±20</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>72±10</td>
<td>NS</td>
<td>77±13</td>
</tr>
<tr>
<td>Arm span (m)</td>
<td>1.85±0.17</td>
<td>NS</td>
<td>1.91±0.15</td>
</tr>
<tr>
<td>Arm span/height</td>
<td>1.02±0.04</td>
<td>NS</td>
<td>1.03±0.04</td>
</tr>
<tr>
<td>Upper segment/lower segment</td>
<td>0.84±0.06</td>
<td>NS</td>
<td>0.84±0.07</td>
</tr>
<tr>
<td>Ectopia lentis (%)</td>
<td>20 (71)</td>
<td>NS</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Arachnodactyly (%)</td>
<td>23 (82)</td>
<td>&lt;0.02</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Thoracic bony abnormalities (%)</td>
<td>28 (100)</td>
<td>NS</td>
<td>21 (84)</td>
</tr>
<tr>
<td>Pectus excavatum (%)</td>
<td>16 (57)</td>
<td>NS</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Pectus carinatum (%)</td>
<td>10 (36)</td>
<td>NS</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Scoliosis (%)</td>
<td>21 (75)</td>
<td>NS</td>
<td>15 (60)</td>
</tr>
<tr>
<td>Straight back (%)</td>
<td>1 (4)</td>
<td>NS</td>
<td>1 (4)</td>
</tr>
</tbody>
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**Relation of Clinical Findings to Presence or Absence of Mitral Leaflet Billowing in Marfan Patients**

Marfan patients with mitral leaflet billowing were younger than those without leaflet billowing (29±12 vs. 38±15 years, p<0.02), whereas the female predominance among Marfan patients with MVP (61% vs. 36% among patients without MVP, p=0.13) did not attain statistical significance (Table 3).

Midsystolic clicks, late systolic murmurs, or both were present in 22 of 28, or 79%, of Marfan patients with leaflet billowing, but also in five of 25, or 20%, of Marfan patients without MVP. Patients with leaflet billowing had strikingly lower body mass indexes than those without billowing (19.8±2.7 vs. 23.9±2.9 kg/m², p<0.000005) and a lower systolic blood pressure (120±20 vs. 133±20 mm Hg, p<0.05). No difference was found in arm span, arm span to height ratio, upper to lower segment ratio, and ectopia lentis between patients with and without leaflet billowing, whereas arachnodactyly was more frequent in patients with billowing than in those without (82% vs. 48%, p<0.02). The two subgroups of Marfan patients exhibited the same frequency of thoracic bony abnormalities, scoliosis, and straight back.

**Discussion**

The present study confirms the occurrence of MVP in a majority of patients with Marfan syndrome that has been reported by previous investigators and sheds new light on the pathophysologic basis of this feature of the Marfan syndrome. Our findings demonstrate that MVP in Marfan
patients may be related to either mitral valve enlargement or to abnormal anular and possibly leaflet distensibility. Frame-by-frame analysis of mitral leaflet motion revealed the presence of marked leaflet billowing on the first systolic frame associated with the origin of all visualized posterior chordae from the left ventricular posterior wall in eight of 28 (29%) Marfan patients with MVP, a pattern seen in no patient with primary MVP. The apparent abnormal architecture of the subvalvular apparatus in these patients was associated with significant enlargement of the mitral leaflets and anulus compared with Marfan patients without MVP or with normal adults. In the remaining Marfan patients in whom MVP occurred in midsystole, mitral leaflet and anular dimensions were normal, but supernormal expansion of the mitral anulus occurred during systole.

These findings exhibit both parallelisms and differences with the results we have obtained in patients with primary MVP.13 When primary MVP patients were subdivided on the basis of systolic leaflet billowing, those with leaflet billowing exhibited subtle leaflet expansion and normal anular dynamics (partially analogous to the Marfan patients with early systolic prolapse), whereas those without leaflet billowing exhibited exaggerated anular distensibility (similar to the exaggerated mitral anular expansion seen in Marfan patients with midsystolic leaflet billowing). However, fundamental differences between MVP due to the Marfan syndrome and primary MVP were also evident, as early systolic prolapse in one Marfan subgroup was associated with an abnormal origin of posterior mitral leaflet chordae not seen in any patient with primary MVP, and increased mitral anular distension was associated with the presence of leaflet billowing in Marfan patients and with its absence in those with primary MVP. Although these differences in the mitral valve phenotype of primary MVP and MVP secondary to the Marfan syndrome are likely to reflect differences in the molecular bases of these conditions, attempts to identify the responsible genes have so far been futile.36,37

Marfan patients with MVP were younger and tended disproportionately to be women (61% vs. 36%, NS) than patients without MVP, a difference that partially explains the observation that Marfan patients with MVP had lower weight and body surface area than patients without MVP. However, Marfan patients with MVP were significantly leaner and had lower systolic blood pressure than Marfan patients without MVP, similar to differences in body mass index and systolic blood pressure between subjects with primary MVP and normal subjects. These differences were not attributable to a gender imbalance between Marfan patients with and without MVP, as body mass index was equally reduced among men and women with MVP (19.2±3.0 vs. 20.1±2.6 kg/m², NS), parallel to the similarity in body mass indexes of normal men and women.38 Further, Marfan patients with MVP presented a similar prevalence of typical auscultatory findings (midsystolic clicks, late systolic murmurs, or both) as subjects with primary MVP. However, the typical auscultatory features that were detected in a surprising percentage (five of 25, or 20%) of Marfan patients without echocardiographic MVP appeared to have a variety of causes. One woman, age 58 years, had mitral anular calcification, associated with mild mitral regurgitation on one of two Doppler studies; one man, age 25 years, had imaging echocardiograms that were suggestive but never diagnostic of MVP, with minimal mitral regurgitation on three of six Doppler studies; one man, age 24 years, may have had a false-negative echocardiogram for MVP in this study as one of three subsequent studies barely met diagnostic criteria. Another man, age 28 years, had four normal imaging studies of the mitral valve at New York Hospital but developed mild mitral regurgitation on serial Doppler examinations, as left ventricular dilatation developed parallel with the onset of aortic regurgitation due to aortic root dilatation; and the final man, age 41 years, with a late systolic murmur but normal imaging study of the mitral valve, had separated from his family and declined follow-up in our institution or elsewhere.

Despite the difference in body build between Marfan patients with and without MVP, anthropometric, skeletal, and ocular examinations did not differ between the subgroups defined by the presence or absence of MVP; only arachnodactyly was more frequent in Marfan patients with MVP than in those without. The primary MVP patients exhibited a significantly higher prevalence of thoracic bony abnormalities than normal subjects but a lower one than among Marfan patients.

Computerized analyses of two-dimensional echocardiograms demonstrates that the MVP occurring as a secondary feature in a majority of Marfan patients differs from primary MVP, both with regard to the pattern of mitral leaflet motion (billowing in 100% versus 50% of subjects with primary MVP) and with regard to a distinctive disturbance of valvular architecture, with the origin of all visualized posterior leaflet chordae directly from the posterior left ventricular wall, in a subset of Marfan patients with MVP. This observation adds abnormal chordal support as a fourth in vivo mechanism of MVP to the three mechanisms that have been documented by previous echocardiographic studies: mitral leaflet and anular enlargement,12,39 abnormal mitral anular distensibility,13 and reduction in left ventricular size due to conditions such as atrial septal defect40 and anorexia nervosa.41 Similar to observations in non-Marfan subjects, Marfan patients with MVP were strikingly thinner and had lower systolic arterial pressure than those without MVP. At present the biologic basis of these differences is unknown both in the Marfan syndrome and in primary MVP. Further, our data demonstrated that although arachnodactyly was statistically more common in Marfan patients with MVP, the anthro-
pometric and skeletal examination does not clearly differentiate Marfan patients with and without MVP.

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References


**KEY WORDS** • echocardiography, M-mode • Marfan syndrome • valvular prolapse • echocardiography, two-dimensional
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R Pini, M J Roman, R Kramer-Fox and R B Devereux

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