Diversity of Structural Mitral Valve Alterations in Hypertrophic Cardiomyopathy

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Background. Hypertrophic cardiomyopathy (HCM) is characterized by an asymmetrically hypertrophied left ventricle and is regarded as a disease of cardiac muscle.

Methods and Results. To assess the possibility that the mitral valve itself may be involved in the disease process, we studied mitral valves from 94 patients with HCM and 45 normal control subjects. The area of the mitral leaflets was increased in patients with HCM compared with control subjects (12.9±3.7 versus 8.7±2.0 cm²; p<0.001). For the overall group of patients, this increase was largely caused by an increase in anterior leaflet length (2.2±0.5 cm for HCM versus 1.8±0.3 cm for control subjects; p<0.001), because circumference did not differ between the two groups. Mitral leaflet area was increased (≥12.0 cm²) in 55 (58%) of the 94 valves. In 12 of these 55 valves, both the anterior and posterior leaflets were enlarged; the other 43 valves had asymmetrical or segmental enlargement of either the anterior leaflet (36 patients) or a portion of posterior leaflet (seven patients). In addition, nine patients had a congenital malformation of the mitral apparatus in which one or both papillary muscles inserted directly into anterior mitral leaflet (mitral valve area was normal in seven of the nine).

Conclusions. Sixty-two (66%) of 94 mitral valves had a constellation of structural malformations, including increased leaflet area and elongation of the leaflets or anomalous papillary muscle insertion directly into anterior mitral leaflet. These findings expand the morphological definition of HCM by demonstrating that the disease process is not confined to cardiac muscle but rather many patients also have structural abnormalities of the mitral valve that are unlikely to be acquired or secondary to mechanical factors. (Circulation 1992;85:1651–1660)

Keywords • hypotrophy • cardiomyopathies • valves • genetics • left ventricle

Hypertrophic cardiomyopathy (HCM) is considered to be a primary disease of cardiac muscle characterized by a diverse morphological and clinical spectrum.1–7 It is generally accepted as a basic tenet of HCM that left ventricular hypertrophy represents both the gross anatomic marker and is probably the principal determinant of the clinical and pathophysiological features of the disease.2–8 Most morphological reports of HCM have described the mitral valve as being intrinsically normal, with only focal secondary thickening of the leaflets and chordae tendineae.1,2,6,9,10 Anecdotal descriptions, however, have suggested that the mitral valve may be congenitally abnormal in some patients with HCM.11–16 To resolve this issue, we systematically examined mitral valves in a large number of patients with HCM.

Methods

Selection of Case Material

Patients with HCM. The files of the Pathology Branch from 1982 to 1989 were reviewed. Eighty-two mitral valves previously excised surgically from patients with HCM had been accessioned; 66 had been removed intact and were in suitable condition for study. Of the 66 valves, one had morphological features of mitral prolapse17–21 and was excluded, reducing the number of operative specimens to 65. These valves had been surgically excised from severely symptomatic patients with HCM undergoing mitral valve replacement to relieve obstruction to left ventricular outflow15,22–24; each operation had been performed by the same surgeon (Dr. Charles L. McIntosh). Each mitral valve specimen consisted of both leaflets, the attached chordae tendineae, and in some instances portions of the papillary muscles. To include mitral valves from patients with nonobstructive HCM, as well as patients with obstruction who had not undergone mitral valve replacement, 29 heart specimens with HCM also were selected from the files of the Pathology Branch by virtue of suitable condition for study and a recent complete hemodynamic or echocardiographic evaluation. Of these 29 patients, seven died after ventricular septal myotomy/myectomy (four within 30 days of operation and three later). None of the other 22 had a cardiac operation; 11 died suddenly, seven of progressive congestive heart failure and four of noncardiac causes. Mitral valves were excised from these 29 hearts (as well as 45 controls), with care taken to remove the leaflets from their circumferential attachments along the annular margin, leaving a 2–3-mm border as done by the
surgeon in excising the valves at operation. Thus, the 65 mitral valves removed at surgery and the 29 removed after death constitute the overall study group of 94 valves.

In each study patient, diagnosis of HCM was based on the presence of a hypertrophied nondilated left ventricle in the absence of another cardiac or systemic disease capable of producing the magnitude of hypertrophy present in that patient7; in addition, each patient had typical necropsy and/or clinical features of HCM.2–8 The magnitude of the left ventricular outflow gradient was assessed at cardiac catheterization in 89 of 94 patients, including all 65 with mitral valve replacement. In the other five patients, basal left ventricular outflow gradients were estimated by Doppler echocardiography.25,26 Of these five patients, four had no evidence of basal outflow obstruction; each was also judged to be free of significant provokable obstruction on the basis of the absence of ventricular septal endocardial plaque and the presence of nonthickened mitral leaflets at necropsy.2,4,6

Patients were classified as obstructive if the subaortic peak systolic pressure gradient was >30 mm Hg under basal conditions and/or with provocative maneuvers or as nonobstructive if the subaortic gradient was absent under basal conditions and <30 mm Hg with provocation (Table 1).

Control patients. Mitral valves from 45 consecutively studied patients with entirely normal hearts, both functionally and anatomically, were chosen as control subjects (Table 1). All 45 patients died from noncardiac conditions. In each control patient, heart weight was ≤350 g in men and ≤300 g in women. The 45 patients ranged in age from 15 to 74 years (mean, 45); 24 were men, and 21 were women.

Morphometry

Mitral valves were fixed in 10% buffered formalin after their removal at operation. Valves were introduced to the fixative freely without stretching or manipulation. Tissue specimens were placed in an opened position on a cutting board and extended to full length (i.e., circumference) with the atrial aspect exposed. Usually it was necessary to affix the opened valve directly to the board with pins to flatten the specimen.

The following morphological measurements (Figure 1)27 were made directly from the mitral valve specimen: 1) circumference of the valve annulus measured along its margin of attachment; 2) and 3) maximum lengths of anterior and posterior leaflets (from attachment margin to free edge); 4) thickness of the anterior leaflet; 5) weight of the excised valve; and 6) areas of the leaflets, both together and separately. To assess mitral leaflet area (in square centimeters), borders of the opened valves were traced with a fine-tipped pen on an acetate overlay. The areas of the leaflets were then planimeterized. Maximal thickness of anterior leaflet was measured with an adjustable caliper. Mitral valves were weighed on a scale accurate to 0.1 g.

Reproducibility

Interobserver and intraobserver variability for measurement of mitral leaflet area was tested in a subset of 20 valves (14 with HCM and six normal control sub-

jects). To determine interobserver variability, two observers (H.G.K. and A.L.D.) independently measured the mitral valves. To determine intraobserver variability, one observer (H.G.K.) measured mitral leaflet area on two occasions 4 months apart.

Histology

Twenty-two mitral valves from patients with HCM (10 obstructive and 12 nonobstructive) and 12 from normal control subjects were studied by light microscopy. Longitudinal sections were taken in the midportion of the anterior leaflet as well as in the most elongated portion of the posterior leaflet in 22 valves. Tissue was embedded in paraffin and sectioned at 6 μm. Two histology sections were prepared: one was stained by the Movat method and one with hematoxylin and eosin. The extent of mucopolysaccharide deposition was assessed in qualitative terms from the histological sections.

Statistical Analyses

Data were expressed as mean ± SD. Differences in morphological measurements between groups of patients were assessed by unpaired Student’s t test. Proportions were compared by the χ² test, and other selected comparisons were assessed with one-way ANOVA. Relations between selected parameters or variables were assessed by linear regression analysis. A stepwise regression analysis28 was used to determine the association between mitral leaflet area and several clinical and morphological variables in patients with HCM and in normal controls (i.e., age, sex, body height and weight, heart weight, previous ventricular septal myotomy/myectomy, left ventricular wall thickness and end-diastolic cavity dimension, magnitude of mitral regurgitation, left ventricular systolic pressure, and outflow gradient).

Results

Group Analysis of Mitral Valve Morphology

Mitral leaflet area. In the 94 patients with HCM, the mitral leaflet area ranged from 6.3 to 23.0 cm² (mean, 12.9±3.7 cm²) and significantly exceeded that of normal control subjects (4.7–13.0 cm²; mean, 8.7±2.0 cm²; p < 0.001) (Figures 2 and 3; Table 1). In 44 (47%) of the 94 valves, total leaflet area exceeded that of the largest control valve. Mitral leaflet area was significantly smaller in valves removed from patients at surgery (12.0±3.5 cm²) than in those obtained at necropsy (14.6±3.3 cm²; p < 0.001) (Tables 2 and 3).

Valve length. In patients with HCM, the lengths of the anterior and posterior leaflets were 1.0–3.4 cm (mean, 2.2±0.5 cm) and 0.7–2.4 cm (mean, 1.4±0.4 cm), respectively, and both significantly exceeded values for normal controls (Figure 4; Table 1).

Valve circumference. Mitral valve circumference was similar in the overall group of 94 patients with HCM (5.5–12.8 cm; mean, 8.5±1.7 cm) and in normal controls (6.4–9.5 cm; mean, 8.2±2.8 cm; p > 0.05) (Figure 5; Table 1).

Mitral valve weight and thickness. Mitral valves from patients with HCM were thicker and heavier than those from controls (by about 2:1) (Table 1).
TABLE 1. Clinical, Hemodynamic, and Morphometric Data in Patients With HCM and in Normal Controls

<table>
<thead>
<tr>
<th></th>
<th>All HCM patients</th>
<th>Control subjects</th>
<th>p</th>
<th>Obstructive group</th>
<th>Nonobstructive group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>94</td>
<td>45</td>
<td>...</td>
<td>77 (82%)</td>
<td>17 (18%)</td>
<td>...</td>
</tr>
<tr>
<td>Surgically excised valves</td>
<td>65</td>
<td>0</td>
<td>...</td>
<td>65</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Age (mean±SD years)</td>
<td>43±15</td>
<td>45±17</td>
<td>NS</td>
<td>45±15</td>
<td>34±12</td>
<td>NS</td>
</tr>
<tr>
<td>(range)</td>
<td>(15–77)</td>
<td>(15–74)</td>
<td></td>
<td>(15–77)</td>
<td>(18–54)</td>
<td></td>
</tr>
<tr>
<td>Male:female, n (%)</td>
<td>48 (51%):</td>
<td>24 (53%):</td>
<td>NS</td>
<td>41 (53%):</td>
<td>7 (41%):</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>46 (49%):</td>
<td>21 (47%):</td>
<td></td>
<td>36 (47%):</td>
<td>10 (59%):</td>
<td></td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>6 (6%)</td>
<td>0</td>
<td>NS</td>
<td>5 (6%)</td>
<td>1 (6%):</td>
<td>NS</td>
</tr>
<tr>
<td>One or more major coronary arteries narrowed &gt;50% (angiography), n (%)</td>
<td>13 (14%)</td>
<td>0</td>
<td>&lt;0.01</td>
<td>12 (16%)</td>
<td>1 (6%):</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LV-SA gradient (mm Hg)*</td>
<td>52±47</td>
<td>...</td>
<td>...</td>
<td>69±43</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Basal</td>
<td>85±55</td>
<td>...</td>
<td>...</td>
<td>110±36</td>
<td>5±8</td>
<td>&lt;0.001</td>
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<tr>
<td>Provoked</td>
<td></td>
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<tr>
<td>Operation</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MVR</td>
<td>52 (55%)</td>
<td>0</td>
<td>...</td>
<td>52 (68%)</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>M&amp;M</td>
<td>7 (7%)†</td>
<td>0</td>
<td>...</td>
<td>7 (9%)†</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>M&amp;M plus MVR</td>
<td>13 (10%)†</td>
<td>0</td>
<td>...</td>
<td>13 (17%)†</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>New York Heart Association functional class:</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>I</td>
<td>7 (7%)</td>
<td>45</td>
<td>&lt;0.001</td>
<td>1 (1%)</td>
<td>6 (35%):</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>II</td>
<td>8 (9%)</td>
<td>0</td>
<td></td>
<td>6 (8%):</td>
<td>2 (12%):</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>70 (74%)</td>
<td>0</td>
<td></td>
<td>61 (79%):</td>
<td>9 (53%):</td>
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<td>IV</td>
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<td>0</td>
<td></td>
<td>9 (12%):</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Echo measurements (mm)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Septal thickness</td>
<td>21±6</td>
<td>...</td>
<td>...</td>
<td>20±5</td>
<td>24±8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Free wall thickness</td>
<td>14±4</td>
<td>...</td>
<td>...</td>
<td>13±4</td>
<td>16±5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mitral valve measurements</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Areas (cm²)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Anterior leaflet</td>
<td>5.9±1.7</td>
<td>4.3±1.0</td>
<td>&lt;0.001</td>
<td>5.7±1.7</td>
<td>6.7±1.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Posterior leaflet</td>
<td>2.6±1.1</td>
<td>1.7±0.5</td>
<td>&lt;0.001</td>
<td>2.5±1.1</td>
<td>2.9±1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Total leaflet</td>
<td>12.9±3.7</td>
<td>8.7±2.0</td>
<td>&lt;0.001</td>
<td>12.4±3.7</td>
<td>14.4±3.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Circumference (cm)</td>
<td>8.5±1.7</td>
<td>8.2±2.8</td>
<td>NS</td>
<td>8.2±1.6</td>
<td>9.8±1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lengths (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior leaflet</td>
<td>2.2±0.5</td>
<td>1.8±0.3</td>
<td>&lt;0.001</td>
<td>2.1±0.5</td>
<td>2.4±0.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Posterior leaflet</td>
<td>1.4±0.4</td>
<td>1.1±0.2</td>
<td>&lt;0.001</td>
<td>1.4±0.4</td>
<td>1.6±0.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>2.0±0.7</td>
<td>1.0±0.3</td>
<td>&lt;0.001</td>
<td>2.1±0.7</td>
<td>1.3±0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thickness, anterior leaflet (mm)</td>
<td>2.1±0.9</td>
<td>1.1±0.4</td>
<td>&lt;0.001</td>
<td>2.4±0.8</td>
<td>1.0±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Valves with increased area (&gt;12.0 cm²), n (%)</td>
<td>55 (59%)</td>
<td>1 (2%)</td>
<td>&lt;0.001</td>
<td>40 (52%)</td>
<td>15 (88%):</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Valves with papillary muscle insertion, n (%)</td>
<td>9 (10%)</td>
<td>1 (2%)</td>
<td>&lt;0.01</td>
<td>9 (12%):</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Heart weight (g)†*</td>
<td>597±164</td>
<td>271±45</td>
<td>&lt;0.001</td>
<td>673±127</td>
<td>543±167</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

HCM, hypertrophic cardiomyopathy; LV-SA, left ventricle to systemic artery; MVR, mitral valve replacement; M&M, ventricular septal myotomy/myectomy.

* Determined by cardiac catheterization in 89 patients (95%) and by Doppler echocardiography in five patients (5%).
† Twenty patients with a previous ventricular septal myotomy/myectomy showed no difference in anterior, posterior, and total mitral leaflet area, circumference, lengths of anterior and posterior leaflets, valve weight, and thickness of anterior leaflet compared with the remaining 57 obstructed patients without myotomy/myectomy.
‡ Heart weight available only in the 29 necropsy patients.

Individual Patient Analysis of Mitral Valve Morphology

Mitral valve size. Mitral leaflet area exceeded the 95th percentile of the normal control valves (>12.0 cm²) in 55 (59%) of 94 patients and was <12.0 cm² in the other 39 (41%). Consequently, the 55 mitral valves ≥12.0 cm² were considered to be increased in size, while the other valves were judged to be of normal size. Also, mitral leaflet area exceeded the greatest value in the control group (i.e., 13.0 cm²) in 44 (47%) of 94 patients (Figure 3). In 36 of the 55 enlarged valves, only the anterior leaflet was increased in size (area >5.0 cm²; normal <4.6
patients with posterior sural chordae between showing scallops and Posterior 2.

1. Total circumference of valve along annular margin; 2 and 3, lengths of anterior and posterior leaflets. Anatomic demarcation of anterior mitral leaflet from posterior leaflet was made visually, usually by identification of insertion of a fanlike arrangement of commissural chordae between the two.27 PM, papillary muscle.

cm2); in seven other valves, only the posterior leaflet was increased in size (area >2.5 cm2; normal <1.9 cm2), often caused by segmental elongation of one scallop of the leaflet (length 85–113% of anterior leaflet length); in the remaining 12 valves both mitral leaflets were enlarged.

Mitral valves were without the morphological features of mitral valve prolapse,17–21 such as ballooning and redundancy of the leaflets, increased annular circumference, and apparent elongation of the chordae tendineae. Analysis of Movat-stained histological sections showed that none of the patients with HCM studied had increased amounts of mucopolysaccharide compared with normal control subjects.

Anomalous papillary muscle insertion. In nine of the 94 patients with HCM (each with basal outflow obstruction), the head of one or both papillary muscles inserted directly into the ventricular aspect of anterior mitral leaflet, involving the anterolateral or posteromedial commissural region but also extending to adjacent portions of the leaflets (Figure 6).29 Chordae tendineae were absent in the region of anomalous papillary muscle insertion but appeared normal in other areas. Mitral leaflet size was normal (<12.0 cm2) in seven and mildly increased in two (12.2 and 13.0 cm2).

Reproducibility

Analysis of interobserver variability showed small differences in mitral leaflet area between the two observers (0.56±1.4 cm2). Linear regression analysis relating the two measurements showed a correlation coefficient of 0.91. Analysis of intraobserver variability also showed small differences in mitral leaflet area between the two observations (0.25±0.9 cm2); linear regression analysis showed a correlation coefficient of 0.97.

Other Valvular Abnormalities

Scallops. Of the 94 mitral valves, 34 (36%) had an increased number of posterior leaflet scallops (either four or five) that were of similar size; the circumference and mitral valve area of these 34 valves (8.9±1.6 cm and 12.9±3.4 cm2, respectively) did not differ significantly from those of the other 60 valves (8.4±1.6 cm and 12.3±3.2 cm2, respectively). In contrast, only two of the 45 control valves (4%) had more than three posterior leaflet scallops (p<0.001).

Fibrous thickening. Of the 94 patients, 38 had no or only focal thickening of the anterior mitral leaflet (usually at the free leaflet edge) that occupied <50% of total leaflet area. In the other 56 valves, the fibrous thickening was more diffuse, often involved most of the leaflet, and was judged to be of secondary origin.2,6,9

Markedly different patterns of fibrous thickening were observed in obstructive and nonobstructive patients. The 17 nonobstructive patients had either no or only mild focal thickening; each of the 77 patients with obstruction had mild or diffuse thickening (p<0.001). In the subgroup of 38 study patients with no or mild focal anterior leaflet thickening, mitral leaflet area (13.9±3.7 cm2) exceeded that of normal control subjects (8.7±2.0 cm2; p<0.001) (Table 4).

Comparison of Obstructive and Nonobstructive Patients

When the 17 patients without outflow obstruction were compared with the combined obstructive group of 77 patients (12 necropsy and 65 surgical), nonobstructive patients proved to have larger leaflet area, circumference, and length (Table 1).

Relation of Mitral Valve Size to Clinical and Morphological Features

The relation of mitral valve area to clinical and pathological variables was analyzed by stepwise regression analysis separately for patients with mitral valve replacement and those studied at necropsy. In patients with mitral valve replacement, leaflet area was inversely related to female sex and directly related to body height (p=0.041 and p=0.014, respectively; multiple r2=0.24); in necropsy patients, leaflet area was inversely related only to female sex (p<0.001). In both analyses, the body

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**FIGURE 1.** Schematic of an opened normal mitral valve showing anterior (AML) and posterior (PML) mitral valve leaflets. Posterior leaflet is composed of two lateral (LAT) scallops and a middle (MID) scallop. 1, Total circumference of valve along annular margin; 2 and 3, lengths of anterior and posterior leaflets. Anatomic demarcation of anterior mitral leaflet from posterior leaflet was made visually, usually by identification of insertion of a fanlike arrangement of commissural chordae between the two.27 PM, papillary muscle.

**FIGURE 2.** Scatterplot of total area of mitral valve leaflets in patients with hypertrophic cardiomyopathy (HCM) and normal controls.
FIGURE 3. Photographs of mitral valves from three patients with obstructive hypertrophic cardiomyopathy aged 31, 29, and 60 years (I, II, and III) and from a normal control patient without cardiovascular disease (IV) showing variation in valvular size and structure. Valves have been opened with the circumference displayed in a horizontal orientation, exposing the atrial surface. I, Large valve (area, 22 cm²) in which both the anterior (A) and posterior (P) leaflets are greatly elongated and increased in area. II, Large valve in which increased valve size (area, 18 cm²) is caused primarily by elongation and enlargement of the anterior leaflet. III, Segmental elongation and increased area confined to a lateral scallop of posterior mitral leaflet, which has virtually the same length as the normal-size anterior leaflet. IV, Valve is normal in area (i.e., 11 cm²), length, and thickness.
Histological Findings

Valves from patients with obstructive HCM had histological changes judged to be secondary in origin. Normal leaflet architecture remained largely intact, although the thickness of the fibrosa was markedly increased because of increased amounts of fibrous tissue that appeared in a pattern of parallel layers with varying density. In contrast, the spongiosa layer was decreased in thickness, with reduced amounts of elastic fibers. Patients with nonobstructive HCM had a histological mitral valve structure similar to that of the control subjects.

Discussion

Hypertrophic cardiomyopathy is generally regarded as an inheritable disease of cardiac muscle.3–5,80 Most pathophysiological consequences of HCM have been ascribed largely to the asymmetrically thickened left ventricular muscle, which is the most characteristic morphological marker of this disease.1,2,4–6,31–33 For many years, the mitral valve has been known to play an important role in hemodynamic alterations by producing systolic anterior motion, midsystolic contact with the ventricular septum, and consequently dynamic obstruction to left ventricular outflow.11,16,34–40 The question of whether or not the mitral valve is altered as part of the basic disease process in HCM has never been studied systematically or resolved. Indeed, most previously reported observations made either at necropsy or surgery have described the mitral valve as virtually free of intrinsic disease (although often secondarily thickened).1,2,6,9,10 Isolated observations in selected patients with HCM, however, have described structural abnormalities of the mitral valve that appear to be congenital and are associated with systolic anterior motion and outflow obstruction.11–16

The findings of the present study of almost 100 mitral valves removed at necropsy or at surgery provide substantial evidence for important structural abnormalities of the mitral valve in HCM that do not appear to be of

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**Table 2. Comparison of Patients With HCM Who Had Mitral Valves Removed Surgically With Those With Mitral Valves Removed at Necropsy**

<table>
<thead>
<tr>
<th></th>
<th>Mitral valves removed surgically</th>
<th>Mitral valves removed at necropsy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>65 (69%)</td>
<td>29 (31%)</td>
<td>...</td>
</tr>
<tr>
<td>Age (mean ± SD years)</td>
<td>47 ± 14</td>
<td>36 ± 14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male:female, n (%)</td>
<td>32 (49%):33 (51%)</td>
<td>17 (59%):12 (41%)</td>
<td>NS</td>
</tr>
<tr>
<td>LV-SA peak systolic gradient (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>71 ± 45</td>
<td>24 ± 34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Provoked</td>
<td>111 ± 37</td>
<td>33 ± 48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New York Heart Association functional class</td>
<td></td>
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<td>I</td>
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<td>7</td>
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</tr>
<tr>
<td>II</td>
<td>3</td>
<td>5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>III/IV</td>
<td>62</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Echo measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septal thickness (mm)</td>
<td>19 ± 4</td>
<td>25 ± 7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Free wall thickness (mm)</td>
<td>13 ± 3</td>
<td>16 ± 5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral valve measurements</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Areas (cm²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior mitral leaflet</td>
<td>5.4 ± 1.5</td>
<td>7.0 ± 1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Posterior mitral leaflet</td>
<td>2.4 ± 1.1</td>
<td>3.0 ± 1.0</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Total leaflets</td>
<td>12.0 ± 3.5</td>
<td>14.6 ± 3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Circumference (cm)</td>
<td>8.0 ± 1.5</td>
<td>9.7 ± 1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lengths (cm)</td>
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<td></td>
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</tr>
<tr>
<td>Anterior mitral leaflet</td>
<td>2.0 ± 0.5</td>
<td>2.5 ± 0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Posterior mitral leaflet</td>
<td>1.3 ± 0.4</td>
<td>1.6 ± 0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>2.2 ± 0.7</td>
<td>1.6 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>2.4 ± 0.8</td>
<td>1.4 ± 0.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HCM, hypertrophic cardiomyopathy; LV-SA, left ventricle to systemic artery.

. . . , Not applicable.

height and/or gender accounted for only 24% of the observed variability in mitral valve area.

The relation between mitral leaflet area and heart weight in patients with HCM was not significant; correlation coefficients were 0.36 (p = 0.054), although there was a significant correlation between these two parameters in normal controls (correlation coefficient, 0.40; p = 0.01). For the overall group, there was no linear relation between mitral leaflet area and either age, magnitude of mitral regurgitation or outflow tract gradient, left ventricular cavity size, or wall thickness. Sixteen female patients >50 years old had the smallest mitral valves, with leaflet areas significantly less than those for the other 78 patients (11.0 ± 2.5 versus 13.2 ± 3.8 cm², p < 0.05).
TABLE 3. Patients With HCM and Obstruction to Left Ventricular Outflow: Comparison of Mitral Valves Removed Surgically With Those Removed at Necropsy

<table>
<thead>
<tr>
<th></th>
<th>Mitral valves removed surgically</th>
<th>Mitral valves removed at necropsy</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Patients (n)</td>
<td>65</td>
<td>12</td>
<td>...</td>
</tr>
<tr>
<td>Age (mean±SD years)</td>
<td>47±14</td>
<td>38±16</td>
<td>NS</td>
</tr>
<tr>
<td>Male:female, n (%)</td>
<td>32 (49%):33 (51%)</td>
<td>9 (75%):3 (25%)</td>
<td>NS</td>
</tr>
<tr>
<td>LV-SA peak systolic gradient (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>71±45</td>
<td>60±26</td>
<td>NS</td>
</tr>
<tr>
<td>Provoked</td>
<td>111±37</td>
<td>102±26</td>
<td>NS</td>
</tr>
<tr>
<td>New York Heart Association functional class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0</td>
<td>1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>II</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>III/IV</td>
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<td>8</td>
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</tr>
<tr>
<td>Posterior mitral leaflet</td>
<td>2.4±1.1</td>
<td>3.1±1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Total leaflets</td>
<td>12.0±3.5</td>
<td>14.8±3.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Circumference (cm)</td>
<td>8.0±1.5</td>
<td>9.6±1.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lengths (cm)</td>
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</tr>
<tr>
<td>Weight (g)</td>
<td>2.2±0.7</td>
<td>2.1±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Thickness (mm) (anterior leaflet)</td>
<td>2.4±0.8</td>
<td>2.0±1.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

HCM, hypertrophic cardiomyopathy; LV-SA, left ventricle to systemic artery.

...., Not applicable.

acquired origin. Indeed, these observations would appear to expand the basic morphological definition of HCM, and representing an evolution of the precept that this disease is structurally confined to cardiac muscle. Mitral leaflet area was significantly greater in our patients with HCM than in control patients without car-

FIGURE 4. Scatterplot of mitral valve leaflet lengths shown separately for both anterior (AML) and posterior mitral leaflets (PML) in patients with hypertrophic cardiomyopathy (HCM) and normal controls.

FIGURE 5. Scatterplot of mitral valve circumference in patients with hypertrophic cardiomyopathy (HCM) and normal controls.
diovascular disease. The patients with HCM also showed considerable variability with respect to mitral valve structure and size. About 60% of all mitral valves were enlarged (some up to twice the normal leaflet area), and only about 40% were within the 95% confidence limits of the normal control valves (<12.0 cm²). For the overall group of patients with HCM, the increased mitral leaflet size was largely a result of an increase in leaflet length (from margin of attachment to free margin).

In addition to increased overall mitral valve size, leaflet elongation, and asymmetrical (segmental) enlargement of either the anterior or a portion of the posterior leaflet, other structural malformations of the

<table>
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<tr>
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<tr>
<td>Patients (n)</td>
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<tr>
<td>Weight (g)</td>
</tr>
<tr>
<td>Thickness (mm) (anterior leaflet)</td>
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... Not applicable.
mitral valve were found that are not readily explained as secondary or acquired abnormalities. About 10% of the patients studied had a congenital malformation of the mitral apparatus characterized by direct insertion of one or both papillary muscles into anterior mitral leaflet. Thus, two thirds of our study patients had increased mitral leaflet size or a structural valve malformation that is likely to have been present from birth. Furthermore, mitral leaflet size or leaflet enlargement could not be explained on the basis of fibrous thickening alone (secondary to traumatic septal contact), because our subset of 38 study patients appear to be the sole determinant of outflow obstruction in some patients with enlarged valves, and there was no identifiable morphological feature not present in our HCM valves, such as leaflet ballooning, elongated chordae, and excessive mucopolysaccharide deposition.

thermore, valves producing mitral prolapse also show a marked increase in circumference not characteristic of most mitral valves in HCM. Finally, preoperative echocardiograms recorded in each of our 65 patients with mitral valve replacement did not show evidence of mitral valve prolapse motion pattern. Therefore, there is no convincing evidence that the structurally abnormal mitral valves present in our patients represent examples of the primary floppy mitral valve, itself an uncommon occurrence in patients with HCM.

The findings of the present study also have potentially relevant implications with regard to the pathogenesis of HCM. Recently, mutations in the gene that encodes for the heavy chains of cardiac myosin (localized to chromosome 14) have been identified in members of families with HCM. However, to date, not all families with HCM studied appear to show this abnormality, and therefore the broad morphological spectrum and clinical heterogeneity of HCM ultimately may not be explained solely by a myosin defect. Indeed, the findings of the present study that focus on structural valve abnormalities represent an evolution in our understanding of the complex nature of HCM and raise the possibility that the disease process is not limited to myocardium (and a defect in myosin) in all patients.

Acknowledgment

We wish to recognize the expert photographic assistance of Mr. Michael Spencer.

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