Mitrail Valve Abnormalities Identified by Cardiovascular Magnetic Resonance Represent a Primary Phenotypic Expression of Hypertrophic Cardiomyopathy

Martin S. Maron, MD; Iacopo Olivotto, MD; Caitlin Harrigan, BA; Evan Appelbaum, MD; C. Michael Gibson, MD; John R. Lesser, MD; Tammy S. Haas, RN; James E. Udelson, MD; Warren J. Manning, MD; Barry J. Maron, MD

Background—Whether morphological abnormalities of the mitral valve represent part of the hypertrophic cardiomyopathy (HCM) disease process is unresolved. Therefore, we applied cardiovascular magnetic resonance to characterize mitral valve morphology in a large HCM cohort.

Methods and Results—Cine cardiac magnetic resonance images were obtained in 172 HCM patients (age, 42±18 years; 62% men) and 172 control subjects. In addition, 15 HCM gene-positive/phenotype-negative relatives were studied. Anterior mitral leaflet (AML) and posterior mitral leaflet lengths were greater in HCM patients than in control subjects (26±5 versus 19±5 mm, P<0.001; and 14±4 versus 10±3 mm, P<0.001, respectively), including 59 patients (34%) in whom AML length alone, posterior mitral leaflet length alone, or both were particularly substantial (>2 SDs above controls). Leaflet length was increased compared with controls in virtually all HCM age groups, including young patients 15 to 20 years of age (AML, 26±5 versus 21±4 mm; P=0.0002) and those ≥60 years of age (AML, 26±4 versus 19±2 mm; P<0.001). No relation was evident between mitral leaflet length and LV thickness or mass index (P=0.09 and P=0.16, respectively). A ratio of AML length to LV outflow tract diameter of >2.0 was associated with subaortic obstruction (P=0.001). In addition, AML length in 15 genotype-positive relatives without LV hypertrophy exceeded that of matched control subjects (21±3 versus 18±3 mm; P<0.01).

Conclusions—In HCM, mitral valve leaflets are elongated independently of other disease variables, likely constituting a primary phenotypic expression of this heterogeneous disease, and are an important morphological abnormality responsible for LV outflow obstruction in combination with small outflow tract dimension. These findings suggest a novel role for cardiac magnetic resonance in the assessment of HCM. (Circulation. 2011;124:00-00.)

Key Words: cardiomyopathy, hypertrophic □ magnetic resonance imaging □ mitral valve

Hypertrophic cardiomyopathy (HCM) is a common genetic heart disease in which the predominant phenotypic expression is left ventricular (LV) hypertrophy.1-5 Previous reports of selected HCM populations studied at autopsy or after operative excision of the mitral valve have suggested that the mitral valvular apparatus may be structurally abnormal in some patients.6 However, data regarding the prevalence, functional characteristics, and significance of mitral valve abnormalities in a consecutive, clinically assessed HCM cohort are unavailable. Efforts at characterizing mitral leaflet size and length quantitatively with 2-dimensional echocardiography proved disappointing, although it is possible to appreciate greatly elongated leaflets in qualitative terms on routine clinical evaluations.7 However, cardiovascular magnetic resonance (CMR) imaging, with its high spatial and temporal resolution, provides a unique opportunity to characterize mitral valve structure in vivo.8-10 Therefore, in the present investigation, we used advanced imaging CMR to define morphological abnormalities of the mitral valve and to determine their relation to a number of demographic and clinical variables in a large HCM cohort.

Editorial see p ●●●
Clinical Perspective on p ●●●

Methods

Selection of Patients
We prospectively studied 172 consecutive HCM patients with CMR who presented to HCM referral centers at Tufts Medical Center.

Received September 1, 2010; accepted April 4, 2011.
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Guest Editor for this article was Catherine M. Otto, MD.

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Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.110.985812
by guest on May 2, 2017

intrinsic mitral valve disease, or confirmed anomalous insertion of mitral leaflet-septal contact.11 In patients without obstruction at rest ing from marked mitral valve systolic anterior motion with anterior/H11021/LV outflow tract obstruction, occurring in 42 of the 102 patients undergoing standard Bruce treadmill protocol.12

In addition, no patient had mitral valve prolapse,14 evidence of other alcohol septal ablation or surgical septal myectomy were excluded. CMR imaging was performed (Tufts Medical Center: Philips Gy-

Institute: Siemens Sonata 1.5 T, Erlangen, Germany) with an ECG gated steady-state, free precession breath-hold cines in 3 long-axis planes and sequential 10-mm short-axis slices from the atrioventric-

ular ring to apex. LV volumes, mass, and ejection fraction were measured with standard volumetric techniques and analyzed with commercially available software (MASS, version 6.1.6, Medis, Inc, the Netherlands). Left ventricular volume and mass data were indexed to body surface area. Maximum end-diastolic LV wall thickness measurements in each of the 16 segments were automatically calculated by commercially available software.

Late-gadolinium-enhancement images were acquired 10 to 15 minutes after intravenous administration of 0.2 mmol/kg gadolinium-DTPA (Magnevist, Schering, Berlin, Germany), with breath-held segmented inversion-recovery sequence acquired in the same orientations as the cine images. A threshold >6 SDs exceeding the mean for nonenhanced myocardium was used to define areas of late gadolinium enhancement.16

Anterior mitral leaflet (AML) and posterior mitral leaflet (PML) lengths were measured in diastole in only the 3-chamber view, with the leaflets maximally extended parallel to the anterior septum and LV free wall (Figure 1). The 3-chamber view was derived from an end-systolic short-axis view with the slice plane oriented along the aortic root parallel to the LV (ie, aortic) outflow tract. Leaflet length was defined as the distance from the most distal extent of anterior leaflet to its insertion into the posterior aortic wall and the most distal extent of posterior leaflet into the basal LV posterior free wall. Demarcation of mitral valve leaflet tip and contiguous chordae tendinae was made by visual inspection of valve motion during real-time analysis of the 3-chamber view cine, with measurements made in stop-frame mode using the internal calibration. Transverse LV outflow tract diameter was measured 1 cm below the aortic valve plane on the 3-chamber view image at end systole. The ratio of the transverse LV outflow tract diameter to AML length was constructed (range, 0.8 to 5.2; mean, 1.6).

Figure 1. The spectrum of mitral leaflet abnormalities in 6 hypertrophic cardiomyopathy (HCM) patients shown in left ventricular (LV) 3-chamber diastolic long-axis cardiac magnetic resonance images. Thick arrows denote anterior mitral leaflet (AML); thin arrows, posterior mitral leaflet (PML). A, An elderly man with an extraordinarily long AML measuring 33 mm; the PML is of normal length (although not well visualized in this frame). B, A 16-year-old boy with elongated PML (25 mm), 2-fold longer than the matched control subject (not shown here); the AML is of normal length. C, A 14-year-old boy with elongation of both the AML (33 mm) and PML (21 mm). D, A 34-year-old man with only mild ventricular septal (VS) thickness of 18 mm but particularly long AML (35 mm). E, A 31-year-old woman showing massive septal hypertrophy (thickness, 31 mm) but normal AML length. F, A 57-year-old man with preclinical HCM (myo-

sin binding protein C mutation) and normal LV wall thickness of 9 mm (asterisk) but greatly elongated AML (25 mm); the PML is of normal length. AO indicates aorta; LA, left atrium.

Cardiovascular Magnetic Resonance

CMR imaging was performed (Tufts Medical Center: Philips Gy-

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Results

Clinical and demographic characteristics of the 172 HCM study patients and control subjects are summarized in the Table. Mean age at evaluation was 42±18 years (range, 8 to 86 years); 106 patients (62%) were men. At the time of CMR study, 103 patients (60%) were asymptomatic in New York Heart Association functional class I, 45 (26%) had mild symptoms in class II, and 24 (14%) had severe heart failure symptoms in class III or IV. Left ventricular ejection fraction was 71±9% (range, 58% to 89%). Left ventricular outflow gradients ≥30 mm Hg at rest (range, 30 to 117 mm Hg) were present in 35 patients (20%), and a provokable (ie, exercise-induced) gradient was present in 42 other patients.

Mitrail Valve Morphology

In HCM patients, AML length was 26±5 mm (range, 17 to 41 mm), significantly greater than in control subjects (19±5 mm; range, 8 to 29 mm; P<0.001). The PML length in HCM was 14±4 mm (range, 6 to 28 mm), also significantly exceeding that of matched control subjects (10±3 mm; range, 2 to 17 mm; P<0.001; the Table). In 59 of the 172 HCM patients (34%), lengths of the AML alone (n=21; 12%), the PML alone (n=18; 10%), or both (n=20; 12%) exceeded 2 SDs from the mean of the control group (ie, ≥30 and ≥17 mm, respectively).

The AML and PML leaflet lengths were greater among HCM patients than control subjects across virtually all age groups (all adjusted P<0.0002; Figure 2), including children 15 to 20 years of age (AML, 26±5 versus 21±4 mm; P=0.0002) and older patients ≥60 years of age (AML, 26±4 versus 19±2 mm; P<0.0001). No differences in leaflet length were evident among HCM patients with respect to severity of mitral regurgitation (absent to mild [0 to 1+], 26±4 mm; moderate [2+], 25±5 mm; marked [3 to 4+], 26±4 mm; P=0.2 for AML), New York Heart Association class (overall P=0.45 for AML; P=0.94 for PML), or sex (P=0.32).

Relation of Mitrail Valve Morphology to Left Ventricular Hypertrophy and Late Gadolinium Enhancement

Among HCM patients, no relationship was evident between AML length and either LV mass index or maximal wall thickness (P=0.09 and P=0.16, respectively; Figures 3 and 4). Similarly, there was no relationship between PML length and mass index or wall thickness (P=0.9 and P=0.5, respectively; Figures 3 and 4).

The AML length did not differ between the 32 patients with mild LV hypertrophy (thickness, ≤18 mm) and 15 patients with extreme LV hypertrophy (thickness, ≥30 mm): 25±5 versus 26±5 mm, respectively (P=0.78). In addition, 7 of the 32 patients (22%) with mild hypertrophy had markedly elongated mitral leaflets (≥30 mm in length) compared with 3 patients (20%) with extreme LV hypertrophy (P=0.5). Late gadolinium enhancement was present in 83 HCM patients (48%). No differences were evident in either AML or PML leaflet length with respect to the presence or absence of late gadolinium enhancement (AML, 27±5 versus 26±4, P=0.33; PML, 14±4 versus 14±3 mm, P=0.9).

Relation of Mitrail Valve Morphology and Left Ventricular Outflow Tract Obstruction

There was no difference in AML or PML length among HCM patients with or without LV outflow tract gradients.

### Table. Demographics and Cardiac Magnetic Resonance Findings in Hypertrophic Cardiomyopathy Patients, Genotype-Positive/Phenotype-Negative Hypertrophic Cardiomyopathy Family Members, and Control Subjects

<table>
<thead>
<tr>
<th>Subjects</th>
<th>HCM Patients</th>
<th>Control Subjects</th>
<th>P</th>
<th>Genotype-Positive/Phenotype-Negative HCM Patients</th>
<th>Control Subjects</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>172</td>
<td>172</td>
<td>15</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at enrollment, y</td>
<td>42±18</td>
<td>42±18</td>
<td>0.95</td>
<td>26±15</td>
<td>26±15</td>
<td>0.98</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>106 (62)</td>
<td>106 (62)</td>
<td>1.0</td>
<td>7 (47)</td>
<td>7 (47)</td>
<td>1.0</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.95±0.27</td>
<td>1.96±0.27</td>
<td>0.76</td>
<td>1.86±0.26</td>
<td>1.83±0.27</td>
<td>0.65</td>
</tr>
<tr>
<td>Anterior leaflet length, mm</td>
<td>26±5</td>
<td>19±5</td>
<td>&lt;0.001</td>
<td>21±3</td>
<td>18±3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Posterior leaflet length, mm</td>
<td>14±4</td>
<td>10±3</td>
<td>&lt;0.001</td>
<td>11±2</td>
<td>10±2</td>
<td>0.17</td>
</tr>
<tr>
<td>LVOT diameter, mm</td>
<td>18±4</td>
<td>19±4</td>
<td>0.007</td>
<td>18±2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>71±9</td>
<td>66±5</td>
<td>&lt;0.001</td>
<td>65±8</td>
<td>64±5</td>
<td>0.24</td>
</tr>
<tr>
<td>Maximum LV thickness, mm</td>
<td>17±6</td>
<td>10±2</td>
<td>&lt;0.001</td>
<td>9±3</td>
<td>9±2</td>
<td>0.76</td>
</tr>
</tbody>
</table>

HCM indicates hypertrophic cardiomyopathy; LV, left ventricular; and LVOT, LV outflow tract.
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30 mm Hg at rest (AML, 27±4 versus 26±5 mm, \(P=0.57\); PML, 15±4 versus 14±4 mm, \(P=0.15\)), nor was there a correlation in the overall HCM group between AML or PML length and the magnitude of LV outflow gradient at rest (AML, \(P=0.10\); PML, \(P=0.12\)). Neither AML (\(P=0.27\)) or PML (\(P=0.5\)) length nor any other morphological variable was an independent predictor of outflow obstruction at rest. In addition, neither AML length nor PML length differed among HCM patients with LV outflow tract gradients \(\geq 30\) mm Hg induced by exercise and those patients with rest gradients \(\geq 30\) mm Hg (AML, 26±5 versus 27±4 mm, \(P=0.4\); PML, 14±3 versus 15±4 mm, \(P=0.3\)).

However, a ratio of AML length to transverse LV outflow tract diameter of \(2.0\) was significantly more common in patients with outflow gradients \(\geq 30\) mm Hg at rest (16 of 35, 46%) than in patients without obstruction (20 of 137, 15%; \(P=0.001\); Figure 5). The ratio of mean AML length to outflow tract diameter was also significantly greater in HCM patients with gradients \(\geq 30\) mm Hg at rest than in those without rest obstruction (2.16±0.89 versus 1.66±0.49; \(P=0.003\)). The ratio of mean AML length to outflow tract diameter showed a relatively weak but significant relation to magnitude of outflow gradient (\(P<0.01\)).

**Genotype-Positive/Phenotype-Negative HCM Patients**

Clinical and demographic characteristics of the 15 asymptomatic genotype-positive/phenotype-negative patients are summarized in the Table. The AML in these patients was significantly longer than in normal control subjects of the same age and body surface area (21±3 versus 18±3 mm, respectively; \(P<0.01\); Figure 1), with no difference in PML length (11±2 versus 10±2 mm, respectively; \(P=0.17\)).
AML length in HCM patients with LV hypertrophy exceeded that of preclinical patients \( (P<0.001) \).

**Reproducibility of Mitral Valve Leaflet Measurements**

Interobserver variability showed small differences in the measurements of AML and PML lengths between the 2 observers (−0.6 to 1.8 and 2.9 to 5.6, respectively). Analysis of intraobserver variability also showed small differences in the measurements of AML and PML lengths with an intra-class correlation coefficient of 0.5 for the AML and 0.6 for the PML.

**Discussion**

Since the initial contemporary report >50 years ago, the phenotypic expression of HCM has been reported largely in terms of LV hypertrophy and the cardiac sarcomere. However, a number of morphological features of HCM appear unrelated to disease-causing sarcomere mutations, including LV apical aneurysms, structurally abnormal intramural coronary arteries responsible for microvascular ischemia, segmental increase in LV wall thickness confined to only a portion of the chamber, and anomalous insertion of anterolateral papillary muscle into the mitral valve. In addition, previous studies of mitral valves removed at surgery or autopsy in relatively small and selected HCM subgroups have suggested that the mitral valve leaflets may be elongated in some patients, although these studies were compromised by inadequate controls. Therefore, in the present investigation, we have taken the opportunity to use CMR imaging, with its high spatial and temporal resolution, to characterize the morphology of the mitral valve and its relation to a number of demographic and clinical variables in a large consecutive HCM cohort.

Our data demonstrate that mitral valve leaflet length is significantly increased in HCM patients compared with an age-, sex-, and body size–matched control population without cardiovascular disease. In fact, in 30% of patients with HCM, elongation of the AML and/or PML was substantial, exceeding that of matched control subjects by >2 SDs. Furthermore, the mitral leaflet lengths reported here by CMR are virtually identical to the ex vivo measurements of valves excised from patients with HCM.
HCM patients postmortem or after surgical mitral valve replacement. In addition, those morphological studies demonstrated that mitral leaflet length was representative of total valve tissue area. Hence, it is reasonable to assume that CMR provides a reliable in vivo estimate of overall mitral valve size.

Our data also support the principle that morphological abnormalities of the mitral valve represent a primary phenotypic expression of HCM. Mitral valve leaflet elongation proved to be independent of a number of demographic and clinical variables relevant to HCM disease expression, including sex and heart failure symptoms. Leaflet length was also unrelated to patient age, and in fact was increased early in life; ie, in preadolescent HCM patients the lengths of both the AML and PML significantly exceeded that in age-, sex-, and body size–matched control subjects. In addition, not only was a significant relationship between mitral leaflet length and LV wall thickness (or mass) absent, but we also identified a subset of HCM patients with a unique phenotype in whom hypertrophy was particularly mild while the mitral valve was disproportionately enlarged with prominent leaflet elongation. Furthermore, we found no evidence that hemodynamic factors were responsible for the observed mitral valve structural abnormalities, given the similarity in leaflet lengths between HCM patients with or without LV outflow obstruction. Finally, the observation that anterior mitral valve leaflet lengths were greater among young preclinical HCM patients without LV hypertrophy than in normal control subjects further supports the principle that increased mitral valve size represents an independent and primary component of HCM disease expression.

Although the precise pathogenesis for elongation of the mitral valve leaflets in patients with HCM is uncertain, our findings, including the absence of myocytes from the leaflets, suggest that disease-causing mutations encoding proteins of the cardiac sarcomere are unlikely to account for the entire phenotypic expression of HCM. Indeed, other disease variables such as modifier genes and environmental factors may well play a role in the development of certain morphological abnormalities observed in HCM, including mitral valve enlargement. Although increased mitral valve leaflet length was identified in some children (as young as 13 years of age), our study design did not permit determination of whether mitral valve enlargement in HCM can represent a congenital malformation.

Increased mitral leaflet length proved to be an important, although not the sole determinant of LV outflow obstruction in our HCM patients. Indeed, on the basis of our analyses, the mechanism responsible for subaortic gradients is multifactorial, given that no single disease variable or outflow tract component tested in our multivariable model proved to be an independent predictor of rest outflow obstruction. However, LV geometry in which anterior mitral leaflet length exceeded 2-fold the transverse dimension of the outflow tract at end systole was an important morphological abnormality responsible for outflow obstruction at rest.

The observation that mitral valve length is associated with outflow obstruction in some patients has implications for management strategies in this disease. Elongated mitral leaflets create 2 potential problems. First, the mitral-septal contact point (and site of subaortic obstruction) can be displaced distal to its usual position, creating the necessity for an extended muscular resection. Second, an extremely elongated AML has the theoretical potential to produce mitral-septal contact (and obstruction) even after apparently adequate septal muscular resection. Indeed, a number of surgical reports of severely symptomatic obstructive HCM patients promote the combined approach of septal myectomy and AML repair, with leaflet extension or shortening reconstruction or plication. In this regard, van der Lee et al reported that 90% of their operated patients over an 8-year period were judged by the surgeon to have particularly elongated mitral leaflets that would have made myectomy alone unlikely to yield optimal hemodynamic results.

Taken together, these historical observations and the present data suggest that CMR assessment of mitral leaflet length may have a significant role in preoperative strategic planning to identify those HCM patients in whom mitral valve size and leaflet length can affect surgical management. Intraoperative decision-making with regard to LV outflow tract morphology may also rely on observations made with transesophageal echocardiography.

Finally, identification of elongated mitral valve leaflets by CMR can represent a clinical marker in HCM family members without LV hypertrophy (in whom the genotype is unknown). This assertion is substantiated by our data in genotype-positive/phenotype-negative relatives showing that mitral leaflet elongation was the sole overt clinical manifestation of an HCM-causing sarcomere protein mutation. Identification of an elongated mitral valve leaflet by CMR in such individuals also underscores the potential value of genotyping to achieve a definitive HCM diagnosis. These observations support an expanded role for CMR in earlier clinical diagnosis of relatives affected by HCM, although we recognize that it is also possible to appreciate greatly elongated mitral valve leaflets qualitatively by visual inspection with 2-dimensional echocardiography.

Conclusions

In this large HCM cohort, CMR demonstrates AML and PML elongation independently of other clinical variables of disease expression. These findings suggest that morphological valvular abnormalities likely represent a primary phenotypic expression of this complex disease, implying that basic molecular pathways other than (and/or in addition to) the disease-causing sarcomere mutation play a role in the development of HCM disease expression. In addition, elongated mitral valves in HCM may affect diagnosis and management considerations. Specifically, the enlarged mitral valve can represent a morphological marker for this disease, ultimately aiding in the identification of patients with an otherwise ambiguous diagnosis, including genetically affected HCM family members without LV hypertrophy. Elongated mitral leaflets (in association with small outflow tract diameter) represent a major contributor to dynamic LV outflow tract obstruction and may affect the selection of patients for the most appropriate septal reduction treatment strategy.
**Sources of Funding**
This work was supported in part by a grant from the Heerst Foundations (San Francisco, CA) to Dr B.J. Maron.

**Disclosures**
Dr M.S. Maron has been a consultant to PGx Health. Dr B.J. Maron has been a consultant to Gene Dx. The other authors report no conflicts.

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**CLINICAL PERSPECTIVE**

Mutations in genes encoding proteins of the cardiac sarcomere are responsible for left ventricular hypertrophy, the diagnostic *sine qua non* of hypertrophic cardiomyopathy (HCM). However, whether other morphological features of HCM, seemingly unrelated to sarcomere mutations, are part of the disease phenotype is uncertain. We used cardiovascular magnetic resonance to characterize mitral valve abnormalities in a cohort of patients with HCM. Both anterior and posterior mitral valve leaflet lengths were greater among HCM patients compared with an age- and sex-matched control population (26±5 versus 19±5 mm, P<0.001; and 14±4 versus 10±3 mm, P<0.001, respectively), including more than one third of HCM patients in whom one or both of the mitral leaflets were substantially increased in length. In HCM patients, there was no relationship between mitral valve leaflet length and a number of clinical and demographic variables, including age, maximal left ventricular wall thickness, or left ventricular mass. In addition, elongated mitral valve leaflets were often the only clinical manifestation present in HCM family members carrying a sarcomere mutation without left ventricular hypertrophy and can represent the sole clinical marker of genotype-positive status. Elongated mitral valve leaflets were an important determinant of left ventricular outflow obstruction, particularly in patients in whom anterior mitral valve leaflet length exceeded 2-fold the transverse dimension of the outflow tract. These cardiovascular magnetic resonance–based observations show that structural abnormalities of the mitral valve represent a primary expression of the HCM phenotype and a morphological marker that may aid in diagnostic and management strategies, including optimal planning for septal reduction therapy.
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Circulation. published online June 13, 2011;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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