The Mitral Valve in Hypertrophic Cardiomyopathy

It’s a Long Story

Anna Woo, MD, SM; Sean Jedrzkiewicz, MD

Hypertrophic cardiomyopathy (HCM) has evoked both fascination and controversy since its first modern description >50 years ago. Originally described as “functional aortic subvalvar stenosis” by Brock, the majority of articles about HCM in the ensuing first decade emanated from observations made in the operating room or in the cardiac catheterization laboratory. The actual cause of left ventricular outflow tract (LVOT) obstruction in patients with this condition had not yet been clarified. Ironically, the mechanisms of LVOT obstruction in HCM were only elucidated several years after surgery was first performed in these patients. In fact, an early report by Morrow described the septal myotomy procedure as surgical treatment for HCM and proposed that the myotomy interfered with the sphincter-like muscular contraction ring in the LVOT.

Noninvasive cardiovascular imaging studies have greatly advanced our knowledge about HCM. Hypertrophic cardiomyopathy is now felt to have tremendous genetic, clinical, morphological, and hemodynamic heterogeneity. Nevertheless, the presence of LVOT obstruction in patients with HCM has continued to inspire interest. The often contentious debates surrounding LVOT obstruction have centered on its very existence, its causes, its clinical impact and prognosis, and its optimal management. These issues have inextricably included the mitral valve, which has long been felt to play a pivotal role in the pathophysiology of LVOT obstruction in patients with HCM.

In the present issue of Circulation, Maron et al use cardiovascular magnetic resonance (CMR) imaging to characterize mitral valve leaflets in patients with HCM. This study assessed the lengths of the anterior mitral leaflet (AML) and posterior mitral leaflet in 172 consecutive patients with HCM. Their findings were compared with 172 normal control subjects matched for age, sex, and body surface area. In addition, the study included a small cohort of 15 subjects who were genotype-positive for a disease-causing mutation but who were free of hypertrophy (designated the phenotype negative or preclinical HCM group). Cardiovascular magnetic resonance imaging demonstrated that AML and posterior mitral leaflet lengths were significantly increased in patients with HCM compared with matched controls (26±5 mm versus 19±5 mm [P<0.001] and 14±4 mm versus 10±3 mm [P<0.001], respectively). There was no significant relationship between leaflet length and maximal left ventricular (LV) wall thickness, LV mass (indexed to body surface area), and other important clinical and morphological factors.

The relationship between mitral leaflet size and hemodynamic status was less clear. There was no significant difference in the lengths of the mitral leaflets in patients with resting LVOT obstruction (defined as an LVOT gradient ≥30 mm Hg at rest) compared with those without resting obstruction. There was no correlation between leaflet length and the magnitude of the resting LVOT gradient. The latter finding is not surprising, given the known variability of the LVOT gradient in individual patients. Furthermore, AML length was not an independent predictor of LVOT obstruction on multivariable logistic regression analysis. However, this study suggested a noteworthy relationship between AML length, LVOT size, and the occurrence of LVOT obstruction. The ratio of AML length to transverse LVOT diameter was significantly higher in patients with resting LVOT obstruction. There was a greater proportion of patients with resting LVOT obstruction who had an AML length/LVOT diameter ratio of >2.0 compared to patients with no resting obstruction (46% versus 15%, respectively; P=0.002).

Analyses of the group of 15 patients with preclinical HCM yielded important findings. The genotype-positive preclinical HCM group consisted of younger asymptomatic relatives (average age of 26 years, with an age range of 12 to 57 years), and the majority of these subjects (11 out of 15) carried a mutation of the myosin-binding protein C gene. The AML (but not the posterior mitral leaflet) length was significantly greater in the preclinical HCM group (21±3 mm) compared to matched controls (18±3 mm, P<0.01). Patients with overt LV hypertrophy had longer AMLs than the patients with preclinical HCM (P<0.001). The authors conclude that mitral leaflet lengths are increased in patients with HCM, and this process does not appear to be influenced by other clinical or morphological markers of disease severity. Because the AML was also increased in the preclinical HCM group, they also postulate that elongated mitral leaflets constitute a primary phenotypic expression of HCM. This article raises the intriguing possibility that HCM, which is caused by a mutation of the cardiac sarcomeric genes, may actually produce a primary abnormality of the mitral leaflets. The authors propose that basic molecular pathways other than (or...
in addition to) sarcomeric gene defects are responsible for the mitral leaflet abnormalities.4

This study by Maron and colleagues has many strengths. By using cine CMR imaging, which provides high spatial and temporal resolution,2 they were able to measure the lengths of the mitral leaflets. Cardiovascular magnetic resonance imaging was able to differentiate the leaflet border from contiguous chordae tendineae, which has been a technical limitation of transthoracic echocardiography.5,6 One of this study’s main contributions is that it demonstrates mitral leaflet elongation in a large and more contemporary consecutive cohort of patients with HCM. The study’s sample size of 172 patients with HCM (with 172 control subjects) was far greater than the small cohorts, consisting of 16 to 32 patients with HCM, assembled in previous studies that actually measured mitral leaflet lengths by echocardiography.5,7 In addition, the study by Maron et al includes a wider spectrum of patients. The vast majority (86%) of the overt HCM patients had New York Heart Association class I or II symptoms. They were fairly equally divided into patients with resting/provocable LVOT obstruction and patients with nonobstructive HCM. In contrast, previous echocardiographic and pathological studies examining the mitral valve included a preponderance of patients with symptomatic LVOT obstruction.1,5–9 The study by Maron et al addresses the important relationship between leaflet elongation, LVOT diameter, and its potential contribution to LVOT obstruction. Finally, this study includes a small but important number of genotype-positive relatives, which provides data for the first time on mitral leaflet morphology in asymptomatic carriers who have not yet manifested signs of pathological hypertrophy.

There are a few limitations with this study. Exercise testing was performed in 102 patients and was not systematically done in all of the 137 patients who did not have resting LVOT obstruction on Doppler echocardiography. Therefore, a complete hemodynamic assessment was lacking in 35 patients (20% of the overt HCM study group) in order to definitively classify patients as either obstructive or nonobstructive. Although the authors examine the effects of leaflet length, wall thickness, and LVOT size on the development on LVOT obstruction, they provide no information about other LV structures that might have an impact on the leaflet length or on the LVOT gradient, such as the position and geometry of the mitral and chordal apparatus or the position and size of the papillary muscles.1,2 In terms of the preclinical HCM group, although the mean AML length was greater in the preclinical HCM group compared with controls, it is not clear how many patients actually had an AML length that exceeded the range of normal (ie, 2 SDs from the mean value of the controls). Furthermore, because the LVOT diameter was not reported in the 15 controls, it is unknown if the LVOT diameter in the preclinical HCM group was smaller than in normal subjects, as was the case in the patients with overt HCM.4

**The Mitral Valve in Hypertrophic Cardiomyopathy: A Storied Past**

The mitral valve has long been a focus of interest for investigators of this condition. Initial observations that there were abnormalities involving the mitral valve in patients with HCM were made >4 decades ago. The pioneering hemodynamic and angiographic studies performed by investigators in the 1960s included the description of the AML encroaching toward the septum in the LVOT.10,11 This phenomenon was documented as a linear radiolucent area in the subaortic region,10 which is essentially the angiographic equivalent of systolic anterior motion (SAM) seen on echocardiography.1 Although these were the early days of cardiac imaging with cineangiography, these investigators drew attention to the abnormal geometry and morphology of the mitral leaflets, papillary muscles, LVOT, and LV cavity.11 They highlighted the elongation of the AML and postulated that the length and position of the AML likely contributed to obstruction. In addition, they noted enlargement and displacement of the papillary muscles. They hypothesized that the maldirection (or change in axis) of the papillary muscles, in addition to other factors, could cause abnormal traction on the AML and the chordae tendineae, leading to elongation of these structures.11 In a separate study, Wigle et al made fundamental observations about the development of mitral regurgitation, which occurred in late systole in patients with obstructive HCM, and which followed early aortic ejection and midsystolic AML-septal contact in the LVOT (henceforth recognized as the systolic sequence of eject-obstruct-leak).12

**Insights From Echocardiography**

Our understanding of HCM and, in particular, the mechanism of LVOT obstruction, has been greatly enhanced by the results of M-Mode and 2-dimensional echocardiographic studies.1,2 The first study using cardiac ultrasound to establish SAM of the mitral valve was published in 1969.1 Subsequent advances in echocardiography substantially increased our comprehension of the processes underlying LVOT obstruction. The determinants of SAM and LVOT obstruction are complex and can be generally categorized into (1) abnormal geometry of the LVOT and (2) hydrodynamic forces on the mitral valve causing SAM.1,2 Morphological abnormalities that cause narrowing of the outflow tract in HCM include the presence of sepal hypertrophy, anterior displacement of the mitral apparatus, and anterior displacement of the papillary muscles. The combination of elongation of the mitral leaflets and rapid LV ejection promotes SAM and LVOT obstruction.1

Detailed 2-dimensional echocardiographic studies have shown abnormalities of the morphology and motion of the mitral leaflets in patients with HCM. Two key echocardiographic studies have specifically assessed the lengths of the mitral leaflets in patients with HCM.5,7 In the study by Jiang et al, both mitral leaflets were shown by transthoracic echocardiographic measurements to be significantly longer (by an average of 1.5 to 1.7 cm) in 10 patients with obstructive HCM, as compared with 10 patients with either LV hypertrophy (nonobstructive type) and normal controls.5 There was actually no significant difference in the lengths of the mitral leaflets between the patients with nonobstructive HCM and the control subjects. In patients with HCM and SAM, the mitral leaflets coapt abnormally in the body (or central portion) of the leaflets rather than at the leaflet tips.5 Shah et al reported that the posterior mitral leaflet coapted...
with the mid portion of the anterior leaflet in patients with HCM and SAM, leaving the distal residual anterior leaflet tip in the LV cavity during systole. This resulted in a sharp angulation of the distal anterior leaflet toward the septum in mid systole. The authors suggested that the presence of a distal residual anterior leaflet and abnormal leaflet coaptation are prerequisites for the genesis of SAM and LVOT obstruction. Both groups of investigators acknowledged that there were difficulties in distinguishing the leaflet tips from the chordae tendineae with the transthoracic echocardiographic imaging that was available at the time (early to mid 1980s).

Transthoracic echocardiography, which provides better image resolution than the transthoracic echocardiographic approach, was used by Grigg et al to assess mitral leaflet morphology and coaptation and the mechanism of mitral regurgitation in 32 patients with obstructive HCM who underwent surgical myectomy. Both mitral leaflets were longer than those of control subjects (AML was 31 ± 4 mm in HCM versus 22 ± 3 mm in controls). The coaptation point was in the body of the leaflets at 9 ± 2 mm from the tip of the AML (compared to 2 ± 1 mm in controls). During early systole, the distal third to half of the AML developed SAM and angled sharply in an anterior and superior direction. This resulted in leaflet-septal contact and incomplete coaptation of the mitral leaflets in mid systole. Consequently, a funnel was formed by the distal portions of the leaflets and a jet of posteriorly directed mitral regurgitation arose from the interleaflet gap (in mid and late systole).

Finally, a recent study using real-time 3-dimensional echocardiography showed an increase in the mitral leaflet area and papillary muscle displacement in patients with obstructive HCM. During its >40-year history, cardiac ultrasound has thus provided the temporal and spatial resolution necessary to characterize and categorize SAM, leaflet coaptation, and mitral regurgitation. In addition, echocardiography has recognized other morphological abnormalities of the mitral leaflets and mitral apparatus associated with HCM, including leaflet thickening due to repetitive septal contact, mitral valve prolapse, infective endocarditis, chordal abnormalities, and anomalous insertion of the papillary muscles. Doppler imaging allows for the noninvasive assessment of LVOT obstruction and diastolic function. Current Doppler-echocardiographic techniques are essential in the evaluation, diagnosis, monitoring, and prognostication of patients with HCM.

**When Does the Story Begin?**

The major issue raised by Maron et al is whether mitral leaflet elongation is a primary morphological abnormality of HCM. The evidence that there are primary rather than acquired changes to the mitral leaflets mainly stems from the findings that (1) leaflet lengths were increased in the patients with HCM, (2) there was no difference in the AML lengths in the obstructive and nonobstructive HCM patients, and (3) increased AML lengths were identified in the preclinical HCM group. However, given the strong association between the AML length/LVOT diameter ratio and the presence of LVOT obstruction, this study lends support to the hypothesis that the combination of abnormal LVOT geometry, abnormal flow and hydrodynamic forces in the LVOT, and abnormal traction and tension on the mitral leaflets and chordae trigger or exacerbate the process of mitral leaflet elongation. Moreover, can we really say that the preclinical HCM group has a negative phenotype just because hypertrophy had not yet developed? We know from previous studies of genotype-positive individuals that abnormal diastolic indices and subtle findings of abnormal LV function and geometry have been detected in young HCM gene carriers and that they precede the onset of pathological hypertrophy. The CMR results in the preclinical HCM group are suggestive that changes to the anterior (and not the posterior) mitral leaflet tissue occur early in the disease process and are not necessarily caused by a direct effect of the sarcomeric gene mutation. As postulated by Maron et al, other mechanisms, such as growth factors, modifier genes, and environmental factors, likely play a major role in shaping the phenotype.

This study adds to the growing body of literature that has drawn attention to a number of abnormalities that can be identified before LV hypertrophy is expressed in carriers of disease-causing mutations. Electrocardiographic abnormalities (eg, repolarization abnormalities, T-wave inversion, pathological Q waves) may be seen before increased LV wall thickness is visualized on echocardiography. A number of studies have shown reduced early diastolic velocities on tissue Doppler imaging, compatible with derangements in LV relaxation, in genotype-positive HCM patients. Finally, in young HCM gene carriers and that they precede the onset of pathological hypertrophy. The CMR results in the preclinical HCM group are suggestive that changes to the anterior (and not the posterior) mitral leaflet tissue occur early in the disease process and are not necessarily caused by a direct effect of the sarcomeric gene mutation. As postulated by Maron et al, other mechanisms, such as growth factors, modifier genes, and environmental factors, likely play a major role in shaping the phenotype.

**Summary**

The short message is that the study by Maron et al definitively shows mitral leaflet elongation in a large study of patients with both overt and preclinical HCM. The study reinforces and extends the findings of previous angiographic, echocardiographic, and pathological studies. The results of this study imply a fundamental relationship between AML elongation, LVOT geometry, and LVOT obstruction. Recognition of abnormalities of the mitral leaflets or mitral apparatus has implications for the selection of the optimal treatment strategy for patients with obstructive HCM. Over the past 50 years, we have had to revise our thinking about HCM on numerous occasions. It is ironic that a disease that was first considered to be a mimicker of aortic stenosis may actually directly affect the mitral valve. However, given the twists and turns that have occurred in the history of our understanding and management of HCM, we can be sure that the final chapter has not yet been written on the mitral valve in patients with HCM.

**Disclosures**

None.

**References**


Key Words: Editorials ■ echocardiography ■ cardiomyopathy, hypertrophic ■ magnetic resonance imaging ■ mitral valve
The Mitral Valve in Hypertrophic Cardiomyopathy: It's a Long Story
Anna Woo and Sean Jedrzkiewicz

Circulation. 2011;124:9-12
doi: 10.1161/CIRCULATIONAHA.111.035568
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/124/1/9

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/