Mechanism of Mitral Regurgitation in Hypertrophic Cardiomyopathy

Mismatch of Posterior to Anterior Leaflet Length and Mobility

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Background—In hypertrophic cardiomyopathy, a spectrum of mitral leaflet abnormalities has been related to the mechanism of mitral systolic anterior motion (SAM), which causes both subaortic obstruction and mitral regurgitation. In the individual patient, SAM and regurgitation vary in parallel; clinically, however, great interindividual differences in mitral regurgitation can occur for comparable degrees of SAM. We hypothesized that these differences relate to variations in posterior leaflet length and mobility, restricting its ability to follow the anterior leaflet (participate in SAM) and coapt effectively.

Methods and Results—Different mitral geometries produced surgically in porcine valves were studied in vitro. Comparable degrees of SAM resulted in more severe mitral regurgitation for geometries characterized by limited posterior leaflet excursion. Mitral geometry was also analyzed in 23 patients with hypertrophic cardiomyopathy by intraoperative transesophageal echocardiography. All had typical anterior leaflet SAM with significant outflow tract gradients but considerably more variable mitral regurgitation; therefore, regurgitation did not correlate with obstruction. In contrast, mitral regurgitation correlated inversely with the length over which the leaflets coapted ($r = -0.89$), the most severe regurgitation occurring with a visible gap. Regurgitation increased with increasing mismatch of anterior to posterior leaflet length ($r = 0.77$) and decreasing posterior leaflet mobility ($r = -0.79$).

Conclusions—SAM produces greater mitral regurgitation if the posterior leaflet is limited in its ability to move anteriorly, participate in SAM, and coapt effectively. This can explain interindidual differences in regurgitation for comparable degrees of SAM. Thus, the spectrum of leaflet length and mobility that affects subaortic obstruction also influences mitral regurgitation in patients with SAM. (Circulation. 1998;98:856-865.)

Key Words: mitral valve ■ echocardiography ■ regurgitation ■ cardiomyopathy

Systolic anterior motion of the mitral valve (SAM) causes subaortic obstruction and mitral regurgitation.1-11 In patients with hypertrophic cardiomyopathy, a spectrum of morphological abnormalities of the mitral leaflets that has implications for the pathophysiological mechanism of subaortic obstruction by SAM has been described.7,12-15 This naturally leads to the question of whether these variations in the mitral leaflets also influence the presence and degree of mitral regurgitation.

The degree of SAM, obstruction, and regurgitation are closely related and have been shown to vary in parallel in the individual case.16 Clinically, however, great interindvidual differences in the degree of mitral regurgitation have been observed for comparable degrees of SAM. Even in the classic article by Wigle et al16, who demonstrated the direct quantitative relation of mitral regurgitation to outflow tract obstruction in the individual patient, no significant correlation between regurgitation and obstruction was found in the overall patient group. This apparent discrepancy has not yet been appropriately addressed.

Recent studies of mitral valve geometry in hypertrophic cardiomyopathy by use of transesophageal echocardiography have demonstrated that the regurgitant jet arises from a gap between the mitral leaflets. This gap results from severe systolic anterior motion of the distal anterior leaflet.17 In many cases, both distal leaflets created a funnel, directing the regurgitation through this gap.17 On the basis of these and similar clinical observations, we hypothesized that variations in leaflet length (posterior/anterior leaflet length mismatch) could restrict the ability of the posterior leaflet to follow the anterior leaflet as it moves toward the septum (participate in SAM) and to coapt effectively with it. Thus, disproportionate
degrees of anterior and posterior leaflet SAM, rather than SAM of the anterior leaflet alone, would determine the degree of mitral regurgitation. The purpose of the present study was to test the proposed mechanism in vitro and then to investigate its clinical relevance in a consecutive group of patients with hypertrophic cardiomyopathy by use of intraoperative transesophageal echocardiography.

Methods

In Vitro Model
We used a modification of a previously developed left heart flow model reproducing mitral valve motion in hypertrophic cardiomyopathy. A completely excised porcine mitral apparatus with intact papillary muscles and chordae was mounted on an elliptical annular ring (Figure 1). The papillary muscles were attached to small Plexiglas disks, which can pivot around the end of metal rods, permitting the muscles to reach their equilibrium position.

Clinical Studies

Patients
Thirty-four patients with obstructive hypertrophic cardiomyopathy consecutively undergoing surgery at the Cleveland Clinic Foundation were initially considered for the study. Two patients with significant mitral valve prolapse, 1 with a flail mitral leaflet, and 8 with severe mitral annular calcification were excluded. Thus, 23 patients with hypertrophic cardiomyopathy but without associated structural mitral valve disease were ultimately enrolled in the study. There were 12 women and 11 men. The mean age was 52 ± 18 years.

Figure 2. Diagram of transparent Plexiglas model, machined to produce an internal ellipsoidal cavity with typical shape and dimensions of left ventricle in hypertrophic cardiomyopathy. Mitral annulus covers an atrial outlet, which permits mitral regurgitation. Metal rods pass to the outside of the model through tubes at its apical end, allowing the papillary muscle position to be varied. Flow enters the ventricle from the apex and exits through an aortic tilting disk prosthesis or through a mitral regurgitant orifice into the atrial outlet.
Mitral Regurgitation in Hypertrophic Cardiomyopathy

Figure 3. Echocardiographic measurements performed in the in vitro model. SAM-AML indicates extent of anterior mitral leaflet motion with reference to line of coaptation; CL, contact length (distance over which both leaflets visibly coapt or gap between them); LA, model left atrium; and LV, model left ventricle.

Figure 4. Measurements obtained by transesophageal echocardiography in patients with hypertrophic cardiomyopathy. Left, Anterior and posterior mitral leaflets visibly coapt over a relatively long distance (contact length [C]). Right, Mitral leaflets fail to coapt, resulting in a visible gap (G). Shaded area in left atrium represents planimetered mitral regurgitant jet area. Ao indicates aorta; LA, left atrium; LV, left ventricle; α, angle between posterior left ventricular wall and basal part of posterior mitral leaflet; and β, angle between basal and apical (more distal) parts of posterior mitral leaflet.

(14 to 77 years). All patients had significant outflow tract obstruction with a systolic pressure gradient of 77±29 mm Hg (36 to 150 mm Hg) at the time of surgery.

Intraoperative Transesophageal Echocardiography

The studies were performed with a 2-dimensional and color-coded Doppler flow imaging system (Hewlett Packard Sonos 1500 and Acuson 128XP) and a 5-MHz phased-array transducer. The probe was passed after induction of general anesthesia, and the study was performed before the chest was opened. The following measurements were made in the frontal long-axis transesophageal view, which has been recommended for quantitative echocardiographic assessment of SAM geometry and mitral regurgitation17 (Figure 4): (1) maximal SAM-induced mitral regurgitant jet area by planimetry17, as well as width of the proximal jet (vena contracta width) as the jet emerged from between the leaflets17; (2) length of the anterior and posterior mitral leaflets and their ratio, where the length of each leaflet was measured in diastole from the annulus to its chordal insertion, identified by a change in echogenicity and thickness observed consistently during leaflet motion throughout the cardiac cycle17; (3) leaflet contact length, ie, the distance over which both leaflets visibly coapted or the gap between them (negative contact length); (4) sum of angle-α (between the posterior left ventricular wall and the basal part of the posterior leaflet) and angle-β (between the basal and distal parts of the posterior leaflet) as a measure of posterior leaflet mobility, with larger angles reflecting greater mobility; and (5) systolic outflow tract pressure gradient, calculated from the maximal outflow tract velocity as measured by continuous-wave Doppler echocardiography with a steerable beam. These velocities corresponded well with preoperative and epicardial measurements (within 0.3 m/s). As in the in vitro studies, each measurement was made 3 times on a calibrated computer from an optimal frame, and the average of these measurements was used for subsequent analysis. Observer variability, assessed as the SD of the differences in anterior and posterior leaflet length measurements made by 2 independent observers in 20 patients, was 3.3% of the mean, and intraobserver variability (1-month measurement interval) was 2.5%. Interobserver variability for jet area was 4.2%, with an intraobserver variability of 3.7%; for proximal jet width, the corresponding values were 3.9% and 3.5%.

Statistical Analysis

The dependence of mitral regurgitation on measures of mitral valve geometry and systolic outflow tract pressure gradient was studied by use of linear or nonlinear regression analysis as suggested by the data. In addition, we performed stepwise multiple linear regression analysis to assess the determinants of mitral regurgitation (regurgitant jet area and proximal width), entering into the regression model contact length, anterior and posterior leaflet lengths and their ratio, posterior leaflet mobility (sum of bending angles), and systolic pressure gradient. Because the likelihood of lack of coaptation (gap between the leaflets) is inversely related to the total available leaflet length, we also calculated the leaflet length ratio (anterior/posterior) divided by total leaflet length. Stepwise multiple linear regression analysis was also applied to assess the contributions of anterior and posterior leaflet length, posterior leaflet mobility, and pressure gradient to leaflet contact length. The univariate correlation coefficients for these variables were determined, and they were also entered into a multivariate model for predicting mitral regurgitation by use of the RS1 statistical package (Bolt, Beranek, and Newman, Inc, 1993). Forward stepping was used, with the F to enter and F to remove any variable selected so that the corresponding significance level (outer tail area) was <0.05. No variables were forced into the model.

Results

In Vitro Model

Although mitral regurgitant flow rate increased with increasing SAM for each individual mitral valve geometry, as expected, there was no correlation between the extent of SAM of the anterior mitral leaflet and mitral regurgitation over all the configurations studied (P>0.25; Figure 5, left), because the increase in mitral regurgitation with the induction of SAM varied with the baseline valve geometry. Elongation of both leaflets caused mitral regurgitation to increase slightly from 0.21 L/min with mild SAM to 0.3 L/min with severe SAM. Elongation of the anterior leaflet alone caused mitral regurgitation to increase from 0.1 to 1.1 L/min. Chordal shortening to further limit posterior leaflet excursion caused substantial mitral regurgitation (2.3 L/min) even with mild SAM, increasing to 9.0 L/min with severe SAM. In contrast to the lack of correlation between SAM and mitral regurgitation in the overall
group, a close inverse correlation was found between the mitral regurgitant flow rate and the contact length of the leaflets \(r=0.91, P<0.005\); Figure 5, right). Figure 6 demonstrates the impact of mitral leaflet length on the resulting mitral regurgitant geometry. Elongation of both leaflets permitted coaptation of the leaflets over a sufficient length not only at baseline (baseline geometry A) but also with maximal SAM of the anterior leaflet (SAM geometry A). Elongation of the anterior leaflet alone resulted in a reduced contact length of the leaflets with SAM (SAM geometry B). When the posterior leaflet was further restricted in its mobility, a visible gap was observed (SAM geometry C).

Clinical Studies

All patients had significant obstruction but considerably more variable degrees of mitral regurgitation; therefore, there was no correlation between the outflow tract gradient and mitral regurgitation, as anticipated \(P>0.25\); Figure 7, left). In contrast, as in the in vitro setting, a close inverse correlation between the contact length of the leaflets and mitral regurgitation was found \(r=-0.89, P<0.005\); Figure 7, right). Mitral regurgitant jet area increased with both decreased posterior leaflet mobility, as assessed by the sum of the angles \(\alpha\) and \(\beta\) \(r=-0.79, P<0.0001\); Figure 8, left), and decreased posterior leaflet length \(r=-0.71, P<0.005\); Figure 8, center). Mitral regurgitant jet area increased with the ratio of anterior to posterior leaflet length \(r=0.77, P<0.0001\); Figure 8, right), particularly when total leaflet area was taken into consideration (ratio of leaflet lengths/total leaflet length available; \(r=0.85, P=2\times10^{-7}\)). Similar results were found when proximal jet width was used to evaluate mitral regurgitation \(r=-0.82\) for posterior leaflet mobility, \(r=-0.64\) for posterior leaflet length, \(r=0.67\) for the ratio of anterior to posterior leaflet length, and \(r=0.76\) for that ratio/total available leaflet length; \(P<0.001\). Figure 9 illustrates the mechanism of the variability of mitral regurgitation in vivo. In the first case (Figure 9A and 9B), the anterior and posterior leaflets were considerably elongated. The posterior leaflet could thus follow the anterior leaflet even with maximal SAM, resulting in a relatively long contact length with virtually no mitral regurgitation. In the second case (Figure 9C and 9D), leaflet contact length was shorter, resulting in mitral regurgitation. In the third case (Figure 9E and 9F), the posterior leaflet was not sufficiently elongated to follow the anterior leaflet, resulting in a sizable gap with maximal SAM and associated severe mitral regurgitation.

Leaflet contact length, posterior leaflet length, ratio of anterior to posterior leaflet length, and posterior leaflet mobility (sum of angles) were significant univariate predictors of mitral regurgitation (Table 1). Stepwise multiple linear regression analysis identified contact length as the most powerful predictor \(F=94.4, r^2=0.83, P=3.2\times10^{-10}\), with a weaker contribution from the ratio of anterior to posterior leaflet length \(F=1.01, r^2=0.06, P=0.047\); including both in the model gave an \(r^2\) value of 0.88 \(P=6.7\times10^{-10}\). Similar results were obtained for proximal jet width, with the same significant univariate predictors; independent predictors in the multivariate analysis were coaptation length and posterior leaflet mobility \(r^2=0.77\). Leaflet mobility and posterior leaflet length were both significant univariate predictors of coaptation length (Table 2); only posterior leaflet mobility contributed independently in the stepwise multiple linear regression analysis \(F=35.1, r^2=0.62, P=0.000007\). In this population (patients with significant obstruction and outflow tract gradients), there were no significant correlations with systolic pressure gradient in these models.

Discussion

Failure of the mitral leaflets to coapt effectively results in the creation of a regurgitant orifice. In the case of obstructive hypertrophic cardiomyopathy, systolic anterior motion of the anterior leaflet causes subaortic obstruction and moves the anterior leaflet away from the posterior leaflet, disrupting their normal coaptation. Therefore, in the individual case, the degree of mitral regurgitation increases with increasing SAM \(2,16,17\). However, failure to meet and coapt effectively depends on the motion of both mitral leaflets, as demonstrated in the present study both in the controlled in vitro environment and in patients with hypertrophic cardiomyopathy undergoing quantitative analysis of mitral valve geometry by intraoperative transesophageal echocardiography.

The results of the present study show that SAM of the anterior leaflet produces greater mitral regurgitation if the posterior leaflet is limited in its ability to move anteriorly and to participate in SAM. This ability is determined both by the length of the posterior leaflet and by the range of motion dictated by its chordal and papillary muscle connections.
Thus, a close inverse correlation was found between the severity of mitral regurgitation and the length of the posterior leaflet and its mobility, expressed as the sum of the 2 angles that determine its net range of motion in the anterior direction. In none of the patients with significant mitral regurgitation was the posterior leaflet actually shortened; it simply was not sufficiently elongated to follow the anterior leaflet and to coapt effectively with it, which created a relative...
mismatch with reduced contact length or even a visible gap. Therefore, it is reasonable that the ratio of leaflet lengths was actually a stronger predictor of mitral regurgitation than posterior leaflet length itself, surviving as an independent determinant in the multivariate analysis. Anterior mitral leaflet length alone did not correlate with mitral regurgitation because once the anterior leaflet has reached the septum in these patients with obstruction, the length of effective coaptation depends primarily on posterior leaflet length and mobility. Angulation was used to assess posterior leaflet mobility because the restraining force of the subvalvular apparatus cannot be measured noninvasively but is ultimately reflected in this angular limitation (Figure 4). In patients with severe regurgitation, a more acute angle between the body of the posterior leaflet and its tip (pointing toward the posterior wall) was visible, with both distal leaflets creating a funnel leading to the regurgitant gap (Figure 4, right; Figure 9E and 9F). In patients with significant (moderate to severe) regurgitation, the sum of angles $\alpha$ and $\beta$ was consistently $<180^\circ$ (representing, on average, the sum of 2 acute angles), whereas the sum of these angles was $>180^\circ$ in patients with mild mitral regurgitation, with a sufficiently long and mobile posterior leaflet to follow the anterior leaflet and coapt effectively.

Integration With Previous Data

Recent evidence supports the concept that primary structural alterations of the mitral valve constitute an essential feature in many patients with obstructive hypertrophic cardiomyopathy, with leaflet elongation demonstrated by transthoracic\textsuperscript{9} and transesophageal echocardiography\textsuperscript{17} as well as pathological morphometry.\textsuperscript{12–14} Such analysis has shown considerable variability in leaflet elongation, including increased size of both anterior and posterior leaflets or asymmetrical enlargement of either the anterior leaflet or a posterior leaflet scallop,\textsuperscript{14} consistent with the variability demonstrated in the current study. These observations are of interest because they seem to describe a primary abnormality of the mitral leaflets in a disease characterized by mutations of muscle protein genes. The variable morphology of leaflet length has been identified as an important determinant of outflow tract obstruction\textsuperscript{14}; the present study has demonstrated its impact on the severity of mitral regurgitation. Our findings are also consistent with those of Klues et al,\textsuperscript{14} who found that no

Figure 7. Clinical results. Left, Lack of correlation between mitral regurgitation (MR jet area) and left ventricular outflow tract (LVOT) gradient in overall patient group. Right, Close inverse correlation between contact length of leaflets (CL) and mitral regurgitation (MR jet area).

Figure 8. Clinical results. Left, Inverse correlation between mitral regurgitation (MR jet area) and posterior leaflet mobility assessed by sum of the angles $\alpha$ and $\beta$ (Figure 4). Center, Inverse correlation between mitral regurgitation (MR jet area) and posterior mitral leaflet length (PML). Right, Correlation between mitral regurgitation (MR jet area) and ratio of anterior to posterior mitral leaflet length (AML/PML).
Figure 9. Clinical examples of different degrees of mitral regurgitation in 3 patients with comparable degrees of outflow tract obstruction. A, Two-dimensional transesophageal long-axis echocardiographic image (left atrium at top) depicting systolic mitral valve geometry. Arrowheads a and p point at the tips of anterior and posterior mitral leaflets, respectively. C indicates contact length of mitral leaflets, which is long in this patient, in whom both anterior and posterior mitral leaflets are elongated. Posterior leaflet could thus follow anterior leaflet even with maximal SAM, resulting in a relatively long contact length. As a result, there was virtually no mitral regurgitation, as seen in B, the corresponding color Doppler flow image in the same view. There is a turbulent outflow tract jet between mitral leaflets and interventricular septum but no mitral regurgitation. C and D, In second patient, leaflet contact length was shorter, resulting in mild mitral regurgitation (jet within left atrium, coming toward transducer at top of image). E and F, In third patient, posterior leaflet was not sufficiently elongated and mobile to follow anterior leaflet, resulting in a significant gap (G) with maximal SAM and, consequently, severe mitral regurgitation, with a large jet visibly emerging through gap between leaflets.
patients with importantly elongated leaflets had severe regurgitation. Although most patients typically have SAM involving at least the anterior leaflet, Maron et al\textsuperscript{15} reported a subset with isolated posterior leaflet SAM. Of 5 patients in that group for whom an angiogram was available (4 patients with severe and 1 with moderate posterior leaflet SAM), only 1 had mitral regurgitation, which was mild. This is consistent with the present study, demonstrating the least regurgitation with the most posterior leaflet elongation. In these cases, the outflow tract pressure gradient might actually contribute to effective coaptation by pressing the leaflets more tightly together. The present data are also in accordance with the findings of Grigg et al\textsuperscript{17} that the distal parts of both leaflets form a funnel directing the jet through a visible regurgitant gap in patients with significant mitral regurgitation. In the present study, this geometry could be quantitatively related to restricted posterior leaflet mobility and length.

The present study focused on SAM-induced mitral regurgitation in hypertrophic cardiomyopathy and hence excluded patients with other possible causes of mitral regurgitation, such as significant mitral valve prolapase. Nevertheless, the concepts resulting from the present study can be extended to patients with obstructive hypertrophic cardiomyopathy who also have mitral valve prolapase (~3% of all patients and 9% of those undergoing surgery).\textsuperscript{13,24–26} Bulging of the basal portion of the posterior leaflet beyond the anterior leaflet into the left atrium can reduce the amount of posterior leaflet area effectively available to follow the anterior mitral leaflet toward the septum (in a different direction) and meet with it. Thus, leaflet contact length is smaller for any given posterior leaflet length (Figure 10), which explains why mitral regurgitation is usually significant when prolapse is present in leaflet length (Figure 10), which explains why mitral regurgitation, which was mild. This is consistent with the present study, demonstrating the least regurgitation with the most posterior leaflet elongation. In these cases, the outflow tract pressure gradient might actually contribute to effective coaptation by pressing the leaflets more tightly together. The present data are also in accordance with the findings of Grigg et al\textsuperscript{17} that the distal parts of both leaflets form a funnel directing the jet through a visible regurgitant gap in patients with significant mitral regurgitation. In the present study, this geometry could be quantitatively related to restricted posterior leaflet mobility and length.

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Because the study patients were undergoing surgery and had significant resting gradients, it is reasonable that gradient did not contribute to models that explained the variation in mitral regurgitation among individuals (Tables 1 and 2). The inclusion of patients without obstruction would likely have shown a correlation between the gradient and mitral regurgitation, consistent with the literature\textsuperscript{1,16}, however, the purpose of the present study was to explain why there are differences in mitral regurgitation even within a group of patients with significant obstruction.

**Clinical Implications**

In the present study, we demonstrated the impact of mitral valve geometry on the severity of regurgitation in obstructive hypertrophic cardiomyopathy. The consideration of mitral valve geometry could be particularly helpful in predicting the reversibility of mitral regurgitation with reduction of SAM by subvalvular myectomy. When mitral regurgitation is severe in the presence of a relatively short posterior leaflet, posterior realignment of the anterior leaflet after myectomy can result in complete or almost complete abolishment of mitral regurgitation; in fact, this was the case in virtually all the patients with significant regurgitation studied in this series, which focused on SAM-induced mitral regurgitation. However, when mitral regurgitation is significant despite a substantially elongated posterior leaflet, other mechanisms (additional intrinsic abnormalities of the mitral valve) are likely to be present, and mitral regurgitation may remain significant despite adequate relief of SAM; conversely, mitral regurgitation has been shown to resolve when mitral valve repair is combined with septal myectomy.\textsuperscript{27} In addition, because correction of mitral valve geometry by anterior mitral leaflet plication or patching (to reduce mobility) has recently been introduced to relieve persistent mitral regurgitation, as well as outflow tract obstruction,\textsuperscript{28–30} assessment of mitral leaflet coaptation by transesophageal echocardiography as performed in the present study may help to identify patients suitable for these procedures.

**Limitations**

The use of a rigid, steady-flow, in vitro model cannot necessarily account for all features of the complex and dynamic in vivo situation, which is why the clinical relevance of the mechanism was also investigated in vivo after having been demonstrated in vitro. However, the ability to keep experimental conditions such as chamber dimensions and

### TABLE 1. Correlates of Mitral Regurgitant Jet Area

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<th>Multivariate</th>
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<tr>
<td></td>
<td>r</td>
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<tr>
<td>Coaptation length</td>
<td>-0.91</td>
<td>3 × 10⁻³</td>
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<tr>
<td>Anterior/posterior leaflet length</td>
<td>0.77</td>
<td>0.000016</td>
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<tr>
<td>Posterior leaflet length</td>
<td>-0.71</td>
<td>0.00016</td>
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<tr>
<td>Posterior leaflet mobility</td>
<td>-0.80</td>
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<tr>
<td>Net</td>
<td>0.88</td>
<td>6.7 × 10⁻¹⁰</td>
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### TABLE 2. Correlates of Coaptation Length

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<td></td>
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<tr>
<td>Posterior leaflet length</td>
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<td>Posterior leaflet mobility</td>
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toward the posterior portion of the left atrium). Nevertheless, we also used the proximal jet width or vena contracta width, which is a marker of regurgitant orifice size that is relatively independent of flow variables and instrument settings, and obtained similar results.

Conclusions

Variable leaflet length and mobility, which lead to a mismatch in coaptation of the posterior and anterior leaflets, can explain why interindividual differences in mitral regurgitation occur for comparable degrees of SAM despite the close relation of mitral regurgitation to SAM in the individual case. The present study demonstrates that this apparent contradiction can be reconciled by considering posterior leaflet motion, thus expanding the initial concept of the mechanism of mitral regurgitation in hypertrophic cardiomyopathy. According to this unifying model, variability in posterior leaflet length and mobility, rather than anterior leaflet SAM alone, result in insufficient contact length of the leaflets, which represents the final common pathway of mitral incompetence. Thus, the spectrum of variable morphological changes that affects subaortic obstruction also influences the degree of mitral regurgitation in patients with SAM.

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References


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