Mechanism of Dynamic Regurgitant Orifice Area Variation In Functional Mitral Regurgitation
Physiologic Insights From the Proximal Flow Convergence Technique

Judy Hung, MD,* Yutaka Otsuji, MD,* Mark D. Handschumacher, BS,* Ehud Schwammenthal, MD, PhD,† Robert A. Levine, MD, FACC*

Boston, Massachusetts and Tel Hashomer, Israel

OBJECTIVES
We used the Doppler proximal flow convergence technique as a physiologic tool to explore the effects of the time courses of mitral annular area and transmitral pressure on dynamic changes in regurgitant orifice area.

BACKGROUND
In functional mitral regurgitation (MR), regurgitant flow rate and orifice area display a unique pattern, with peaks in early and late systole and a midsystolic decrease. Phasic changes in both mitral annular area and the transmitral pressure acting to close the leaflets, which equals left ventricular-left atrial pressure, have been proposed to explain this dynamic pattern.

METHODS
In 30 patients with functional MR, regurgitant orifice area was obtained as flow (from M-mode proximal flow convergence traces) divided by orifice velocity (v) from the continuous wave Doppler trace of MR, transmitral pressure as 4v², and mitral annular area from two apical diameters.

RESULTS
All patients had midsystolic decreases in regurgitant orifice area that mirrored increases in transmitral pressure, while mitral annular area changed more gradually. By stepwise multiple regression analysis, both mitral annular area and transmitral pressure significantly affected regurgitant orifice area; however, transmitral pressure made a stronger contribution (r² = 0.441) than mitral annular area (added r² = 0.008). Similarly, the rate of change of regurgitant orifice area more strongly related to that of transmitral pressure (r² = 0.638) than to that of mitral annular area (added r² = 0.003). A similar regurgitant orifice area time course was observed in four patients with fixed mitral annuli due to Carpentier ring insertion.

CONCLUSIONS
In summary, the time course and rate of change of regurgitant orifice area in patients with functional MR are predominantly determined by dynamic changes in the transmitral pressure acting to close the valve. Thus, although mitral annular area helps determine the potential for MR, transmitral pressure appears important in driving the leaflets toward closure, and would be of value to consider in interventions aimed at reducing the severity of MR. (J Am Coll Cardiol 1999;33:538–45) © 1999 by the American College of Cardiology

The regurgitant orifice area (ROA) is a fundamental measure of mitral regurgitation (MR) that normalizes regurgitant flow rate for the pressure driving fluid into the left atrium (LA). The concept of ROA was introduced by Gorlin and Dexter (1) as a quantitative measure of MR that could also be of value in studying the mechanism of regurgitation and its response to therapy. Their initial calculation was based on hydraulic principles assuming a fixed regurgitant orifice. Subsequently, Borgenhagen et al. (2) and others (3–5) showed that the ROA changes dynamically in response to loading conditions and varies with changes in ventricular size and mitral annular dimensions as well as within the cardiac cycle. Further studies of orifice area changes have been limited by the invasive nature of the measurements required until the development of the proximal flow convergence (PFC) technique, a noninvasive Doppler echocardiographic method that provides instantaneous mitral regurgitant flow rate and orifice area. This technique uses Doppler color flow mapping to explore the region of flow convergence proximal to the regurgitant orifice, and calculates flow rate based on the pattern of velocities accelerating toward the orifice (see “Methods” section) (6–9).
Schwammenthal et al. (10), using this PFC technique, noted that the temporal patterns of mitral regurgitant flow and orifice area variation depend on the etiology of the regurgitant lesion, with a constant orifice in some patients with calcific rheumatic heart disease, and a mid to late systolic increase in patients with mitral valve prolapse. A unique biphasic pattern was observed in patients with functional regurgitation in dilated or ischemic left ventricles (LVs) with intrinsically normal mitral leaflets, with early and late systolic peaks and a midsystolic decrease. This initial observation has been confirmed subsequently by Shiota et al. (11) using an independent method with electromagnetic flow meters. This pattern had not been described previously and is of interest because of its potential to provide insights into the mechanism of functional MR and into potential therapeutic targets that would promote or lengthen the midsystolic decrease in orifice area, thereby decreasing the overall severity of regurgitation. Two explanations can be proposed for this pattern: 1) the regurgitant orifice area may vary in parallel with mitral annular area (MAA), which decreases to a minimum in midsystole and then increases in late systole with atrial filling (12); this would be consistent with early concepts relating orifice area to annular dimension (2–5); dilation of the mitral annulus, in fact, has been implicated in the development of functional MR (13), tethering the leaflets apart to limit effective coaptation (14–17); 2) another possibility is that ROA varies in response to phasic changes in the transmural pressure (TMP), which may act to close the mitral leaflets more effectively when it reaches its peak in midsystole (18,19).

The purpose of this study, therefore, was to use the proximal flow convergence technique as a noninvasive tool to examine whether the dynamic variation of ROA in functional MR is related primarily to temporal changes in MAA, TMP or both. One potential hypothesis, for example, is that the dynamic variation of ROA in functional MR is influenced by both TMP and MAA. This question is important because it may provide insights into the fundamental mechanism of functional MR and potentially improve our therapeutic approach to this problem in patients.

**METHODS**

**Patient population.** The patient population consisted of 30 consecutive patients with a LV ejection fraction of ≤30% and at least mild functional MR without intrinsic valvular disease, who had been referred for two-dimensional Doppler echocardiography and had images suitable for quantitative analysis. To determine the temporal pattern of ROA in the presence of a fixed annulus, we were able to include in this group four patients with Carpentier-Edwards mitral annular rings and persistent functional MR.

**Echocardiographic studies.** All studies were performed with a scanner (Hewlett-Packard SONOS 2500) equipped with a 2.5-MHz transducer. Two-dimensional echocardiography was performed in the standard apical four- and two-chamber views to visualize the mitral annulus in two orthogonal planes (20). The region of the mitral valve was magnified and the frame rate maximized by narrowing the sector angle to optimize measurement of mitral annular dimensions. The MR orifice velocity profile was obtained by continuous-wave Doppler with the beam aligned parallel to the regurgitant flow, and it was recorded digitally onto a magneto-optical disk for subsequent analysis.

**PFC technique.** The PFC technique has been validated as a quantitative Doppler method to calculate regurgitant flow rate and orifice area (6–9). As flow approaches an orifice, it forms concentric isovelocity shells of decreasing surface area and increasing velocity. By conservation of mass, flow through any shell must pass through the orifice. Doppler color flow mapping can depict such shells based on a selected velocity or provide a range of isovelocity contours as a digital map. The flow through any such shell equals its surface area times the velocity that defines the shell \((2\pi r^2 \cdot [\text{velocity}])\) for a hemispheric shape of the isovelocity shell (6–9).

The PFC region was imaged in the apical four-chamber view with the Doppler color gain adjusted to maximize signal without random noise velocities. The sector angle was narrowed and depth decreased to maximize the pulse repetition frequency for optimal velocity resolution. An M-mode cursor was aligned along the maximal diameter of the PFC region to obtain a color Doppler M-mode of the PFC region (tracing of color coded velocities vs time, Fig. 1), which was then digitally recorded.

**Echocardiographic measurements.** Mitral annular area. Two orthogonal mitral annular diameters were measured in the apical four- and two-chamber views using an analysis system (Sony Sum 1010). The mitral annulus was defined as the hinge points of the leaflets. Frame-by-frame measurements were made throughout systole and the MAA was calculated using \(\pi (a/2)(b/2)\) for an ellipse with a the diameter measured in the four-chamber view and b measured in the two-chamber view (20).

**Regurgitant orifice area.** Customized software developed on a work station (Silicon Graphics) was used to measure instantaneous mitral regurgitant flow rates and orifice areas from the digitized color M-mode images of the PFC region. To calculate regurgitant flow rate, the PFC technique

<table>
<thead>
<tr>
<th>Abbreviations and Acronyms</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA  = left atrium</td>
</tr>
<tr>
<td>LV  = left ventricle</td>
</tr>
<tr>
<td>MAA = mitral annular area</td>
</tr>
<tr>
<td>MR  = mitral regurgitation</td>
</tr>
<tr>
<td>PFC = proximal flow converg</td>
</tr>
<tr>
<td>ROA = regurgitant orifice a</td>
</tr>
<tr>
<td>TMP = transmitral pressure</td>
</tr>
</tbody>
</table>
requires measurement of the distance from the level of the leaflet orifice to the location at which a given velocity occurs. First, the LV edge of the mitral leaflet was traced to establish the location of the orifice. The definition of the mitral leaflets was facilitated by removal of the color signal from the display generated from the digital image. Then, the velocity contour defined by \( \frac{1}{2} \times \text{Nyquist velocity} \) was traced at each point in time from the digitized image. This velocity was chosen because studies in our laboratory have shown that digital color flow mapping in a converging calibration flow phantom designed by the American Society of Echocardiography accurately measures velocity from 0.5 to 1.5 times the Nyquist velocity, which is determined by the fundamental sampling frequency (pulse repetition frequency) of the Doppler technique. One-half the Nyquist velocity was chosen to maximize the size of the distance measured from the orifice to provide greatest accuracy. The traced contours were typically at a velocity of 25–35 cm/s. Finally, the instantaneous radii of the PFC were measured as the distance at each point in time between the velocity and leaflet contours, thus accounting for the axial motion of the mitral orifice during systole. Figure 2A shows a digital image of a color M-mode of the PFC region with small arrows pointing to the mitral leaflet and large arrows pointing to direction of regurgitant flow from LV to LA. Figure 2B shows the contour of the PFC region with the velocity set at \( \frac{1}{2} \times \text{Nyquist} \). This velocity contour and mitral leaflets were then traced to obtain instantaneous radii as shown in Figure 2C (see text for further details).

Mitral regurgitant flow rate \( Q \) was calculated as: 

\[
Q = 2\pi r^2 \text{velocity}
\]

where \( r \) is the radius of a hemispheric shell. The ROA was calculated as follows:

\[
\text{ROA} = \frac{Q}{\text{vel}_o}
\]

where \( Q \) is equal to regurgitant flow rate and \( \text{vel}_o \) is the mitral orifice velocity from continuous-wave Doppler.
**Transmirtal pressure.** The digitized images of the mitral regurgitant orifice velocities obtained from continuous-wave Doppler were also traced on the work station (Siicon Graphics). The TMP ( TMP = LV – LA pressure) was calculated using the simplified Bernoulli equation as: 4*(vel)^2 with vel, equal to the instantaneous velocity across the regurgitant orifice. This calculation has been validated extensively against invasive techniques using high-fidelity micromanometers in both experimental and patient studies (21,22).

**Comparison of time course.** The time courses of MAA, TMP and ROA were obtained for each patient by plotting the instantaneous values over systole, beginning with the peak of the QRS of the common electrocardiographic signal. Values for each variable were normalized to the maximum value for each patient to permit comparison of their time courses. Because the purpose of this study was to examine the midsystolic decrease in ROA and its subsequent rise, we analyzed the time course of all three variables during the interval between the early and late peaks of the ROA. This had the advantage of avoiding the intervals in early and in late systole during which both regurgitant flow rate and TMP were low, thereby avoiding the uncertainty in the calculated ratio of regurgitant flow rate and orifice velocity (orifice area) that comes from dividing two numbers close to zero, and avoiding the additional potential for flow rate underestimation by the Doppler technique (see “Discussion” section) (23,24). For the rates of change of these three variables, standard statistical software (Statview 4.5, 1996, Abacus Concepts, Inc., Berkeley, CA) was used to fit each time course to a polynomial equation, from which a first derivative or slope was calculated.

**Statistical analysis.** Univariate and multivariate stepwise regression analysis (Statview 4.5, 1996, Abacus Concepts, Inc., Berkeley, CA) was performed to examine the contribution of MAA and TMP to the values of ROA at individual time points. A similar analysis was performed to relate the rates of change of these three variables. Variables were entered in the order suggested by the regression model based on the F to enter or remove. Results were considered statistically significant for p value <0.05.

**Observer variability.** Interobserver variability was calculated as the SD of the differences in measurements by two independent observers over 25 traces for both ROA and TMP.

**RESULTS**

**Patient characteristics.** The mean age of the patient population was 65 ± 12 years. There were a total of 25 men and 5 women. The mean LV ejection fraction was 23 ± 7%. The average value among the patients of mean systolic MAA, TMP and ROA was 10 ± 2 cm², 49 ± 15 mm Hg and 25 ± 24 mm², respectively.

**Temporal pattern of MAA, TMP and ROA.** Figure 3 shows the normalized time courses of MAA, TMP and ROA in four representative patients. In all patients, ROA decreased rapidly from its early systolic peak and, in late systole, increased rapidly toward its second peak. Although MAA also peaked in early and late systole, its changes were far more gradual. In contrast, TMP showed similarly wide and rapid changes in early and late systole, mirroring the time course of ROA variations. This is also shown in Figure 4, in which ROA is seen to vary inversely with TMP over its full range in the upper two panels, in contrast to the wide variation of ROA over a narrow range of MAA values in the lower panels. A pattern similar to that of ROA was also observed for regurgitant flow rate itself, although the midsystolic decrease was less prominent in those with more severe MR.

**Carpentier-Edwards ring.** Figure 5 (left panel) shows the time course of MAA, TMP and ROA in a patient with functional MR and a Carpentier-Edwards mitral annular ring, which produces a fixed annular size. Despite this, ROA continued to display a biphasic pattern similar to that seen in patients without rings in place, with reciprocal variation of ROA and TMP (Fig. 5, right panel). This was observed in all four patients with Carpentier-Edwards mitral rings.

In the 30 patients studied (including those patients with Carpentier rings), univariate regression analysis showed that both TMP and MAA contributed significantly to ROA; however, TMP had a greater effect, with an r² of 0.441 versus 0.016 for MAA. The contribution of TMP to the time course of ROA was even more pronounced when the rates of change of TMP and MAA were entered into the regression analysis of the rate of change of ROA, with an r² value of 0.638 for TMP versus 0.046 for MAA. In a stepwise multivariate regression analysis of the contributions of TMP and MAA to ROA, TMP had the greater effect on ROA, accounting for most of its variation, with an r² of 0.441 from a total of 0.449, so that MAA contributed an additional r² of only 0.008. Similarly, in the stepwise multivariate regression analysis of the contribution of the rates of change of TMP and MAA to the rate of change of ROA, TMP had the predominant effect, with an r² of 0.638 from a total of 0.641, with MAA contributing an additional r² of only 0.003. When univariate and stepwise multivariate analyses were performed excluding patients with Carpentier-Edwards rings, the results were similar, with TMP having the dominant effect on ROA (multivariate r² = 0.483 from a total of 0.493; for slope of ROA, r² = 0.651 from a total of 0.654) and MAA providing only a minor contribution.

**Observer variability.** Interobserver variability for instantaneous ROAs and TMPs were 4.9% and 4.8% of the respective mean values.

**DISCUSSION**

Dynamic orifice area variation in functional MR. This study used the PFC technique to address a physiologic question directly in patients: the mechanism of dynamic...
variation in ROA observed in patients with functional MR. The results show that although both MAA and TMP contribute to this dynamic variation, TMP plays a predominant role. Changes in ROA most closely and reciprocally mirror those in TMP; both variables show rapid changes over a wide range in both early and late systole, whereas

**Figure 3.** The temporal pattern of the normalized values for MAA, TMP and ROA are shown for four representative patients. In all patients there is a biphasic pattern for ROA with a rapid decrease from its early systolic peak and a rapid increase toward its late systolic peak with a midsystolic decrease. Although MAA also peaked in early and late systole, its changes were more gradual and over a narrower range. In contrast, TMP showed wide and rapid changes in early and late systole mirroring the time course of ROA.

**Figure 4.** Relationship of ROA vs TMP and MAA. The upper panels show an inverse relationship over a full range for ROA and TMP whereas the bottom panels show that the ROA varies over a much narrower range with MAA.
changes in MAA are more gradual in slope and limited in range. This observation is strengthened by the persistence of similar dynamic changes in ROA in patients with mitral annuli fixed in size by insertion of a Carpentier-Edwards ring.

Mechanistic insights. Prior studies have emphasized the role of geometric factors (13,25–30), particularly mitral annular dilatation with insufficient leaflet area to cover the annulus (13), in determining the potential for functional MR. This study demonstrates that there is also an important contribution of the transmitral force required to drive the leaflets toward effective closure, consistent with the concepts derived from the models of global LV dysfunction studied by Kaul et al. (18) and Dent et al. (19). The importance of a closing force provided by TMP acting on leaflets that are tethered apart is compatible with the mechanism for functional MR illustrated schematically in Figure 6. The strong dependence of ROA on TMP, in fact, suggests the presence of opposing tethering forces in a dilated LV. In other words, it is precisely when tethering forces are increased, such as in functional MR, that variations in TMP can lead to important changes in ROA.

Leaflet tethering can be considered to delay effective coaptation until LV pressure has risen sufficiently to close the leaflets, in contrast to the rapid leaflet closure observed normally when the leaflets are not subject to increased tethering forces; this delayed closure may also reflect LV dysfunction with delayed pressure development (18,19). Similar findings of delayed leaflet closure, early and late systolic peaks of ROA and a midsystolic decrease mirroring the rise in LV pressure have also been observed in vitro in a model of tethered mitral leaflets subjected to physiologic pulsatile flow (31).

Clinical implications. The results of this study suggest that therapeutic interventions in patients with functional MR should ideally consider TMP in addition to changes in LV size and geometry. Traditional concepts have considered increasing afterload to have a detrimental effect on such MR, largely mediated through increases in LV size (2–5), and vasodilator therapy to have a beneficial effect, also mediated through changes in LV volume. These effects, however, may potentially be attenuated in patients with aneurysmally dilated and scarred ventricles, which may not importantly change shape or size in response to therapy; in such patients, one could speculate that increased LV pressure with increased afterload could increase TMP and thus act to reduce MR. Conversely, decreased LV pressure with vasodilator therapy could potentially exacerbate regurgitation. Further studies are necessary to examine whether these effects occur in clinical situations; and in fact, these factors deserve consideration in seeking an explanation for the recently reported and unexpected increases in ROA in some patients with MR receiving vasodilator therapy (32). Also, Chatterjee et al. (33) showed that sodium nitroprusside infusion in patients with severe heart failure reduced MR not only by decreasing LV size but also by increasing TMP by dramatically reducing LA pressure to a greater extent.
than LV pressure. In principle, inotropic agents would have the dual benefit of decreasing LV volume and mitral annular size as well as potentially increasing TMP by increasing LV pressure and decreasing LA pressure.

In evaluating the effects of such therapies, the results of the present study imply that standard measures of peak MR, such as maximal jet area, are insufficient because of the variable temporal pattern of regurgitant flow rate. This is the case in other conditions as well such as mitral valve prolapse (10,34), so that a large jet occurring only briefly during systole should not be overinterpreted in terms of the severity of regurgitation (35). The M-mode PFC method takes into account the temporal variation to determine total regurgitant stroke volume per beat (10).

Methods and limitations. The advantage of using the PFC method is that it is a noninvasive technique applied to increase our understanding of the mechanism of functional MR. Its limitation is that the isovelocity shells may not be strictly hemispheric, causing underestimation or overestimation of the flow rate (23,24). However, 1) throughout most of systole, the error of the flow calculation, as determined by the selected velocity for surface area calculation relative to the orifice velocity, was at most 5% based on the data of Rodriguez et al. (39), suggesting only mild estimation error; 2) overestimation of flow rates far from the orifice occurs primarily when the ventricular walls confine the PFC region and cause it to merge, in part, with vigorous aortic flow (23,36); because the patients studied had dilated LVs and low ejection fractions, such overestimation should be minimal and flow rate calculations accurate (36); 3) a similar technique used by Schwammenthal et al. (10) accurately integrated flow rate to give regurgitant stroke volume compared with both pulsed Doppler and quantitative angiographic techniques in patients, as well as in an in vivo model with implanted regurgitant orifices of known size; 4) it should be emphasized that our primary goal was not to obtain a more accurate determination of regurgitant flow and orifice area, but rather to describe the temporal pattern of the ROA, which should not be greatly affected by minor variations in quantification of regurgitant flow.

Calculating instantaneous regurgitant flow rates from color M-mode recordings of the PFC region also faces the potential limitation that the position of the regurgitant orifice and associated PFC zone can change due to translational movements of the heart while the M-mode beam is fixed. Therefore, the color M-mode cursor may not always pass exactly through both the zenith of the PFC region and the regurgitant orifice. However, at a depth of 16 cm and using a 2.5-MHz transducer, the finite ultrasound beam width results in a lateral resolution of 6 mm. The ultrasound beam therefore covers the whole pole rather than only the zenith of the isovelocity hemisphere, so that small translational movements should not affect measurements importantly. Thus, for the purpose of this method, the problem of the limited lateral resolution actually becomes an advantage, as validated and applied in clinical and experimental studies (10,34). Moreover, these patients with functional MR showed markedly reduced translational motion caused by impaired LV function, thereby minimizing any such potential effect.

The maximal value for r² explaining the variation in ROA is 0.449 using the normalized values of TMP and MAA, and is 0.64 using the rates of change of these variables, which are more likely to influence dynamic changes in ROA; other factors that could potentially explain the remaining variability include patient-to-patient variation in the absolute values and rates of change of TMP, MAA, mitral leaflet length and ventricular size, geometry and function.

The possibility can also be raised that the ROA might vary in patients with functional MR because of phasic changes not only in the mitral annulus but also in the tethering distances between the papillary muscles and the mitral annulus (37). To evaluate whether such an effect is likely, we measured the papillary muscle tethering distances to the anterior mitral annulus using three-dimensional echocardiography (37) in early systole, midsystole and late systole in four of the patients in this study. The tethering distances of both medial and lateral papillary muscles to the mitral annulus were measured at these time points and were not statistically different throughout systole by two-way analysis of variance (p = 0.52). Thus, there do not appear to be important phasic changes that could contribute to the observed and extensive variations in ROA. This is consistent as well with the observations of Sanfilippo et al. (38), who showed no significant variation in papillary muscle tip-to-annulus distance in patients without mitral valve prolapse, consistent with the concept that papillary muscle shortening offsets the systolic apex-to-base contraction of the heart.

Conclusions. In summary, the time course and rate of change of ROA in patients with functional MR are predominantly determined by dynamic changes in the TMP acting to close the valve. Thus, although MAA helps determine the potential for MR, TMP appears important in driving the leaflets toward closure, and would be of value to consider in interventions aimed at reducing the severity of MR.

Reprint requests and correspondence: Judy Hung, MD, Cardiac Ultrasound Laboratory-VBK 508, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114. E-mail: jhung@partners.org.

REFERENCES
3. Jose AD, Taylor RR, Bernstein L. The influence of arterial