Dynamics of Mitral Regurgitant Flow and Orifice Area

Physiologic Application of the Proximal Flow Convergence Method: Clinical Data and Experimental Testing

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Background The proximal flow convergence method, a quantitative color Doppler flow technique, has been validated recently for calculating regurgitant flow and orifice area. We investigated the potential of the method as a tool to study different pathophysiological mechanisms of mitral valve incompetence by assessing the time course of regurgitant flow and orifice area and analyzed the implications for quantification of mitral regurgitation.

Methods and Results Fifty-six consecutive patients with mitral regurgitation of different etiologies were studied. The instantaneous regurgitant flow rate \( Q_0 \) was computed from color M-mode recordings of the proximal flow convergence region and divided by the corresponding orifice velocity \( V_0 \) to obtain the instantaneous orifice area \( A_0 \). Regurgitant stroke volume (RSV) was obtained by integrating \( Q_0 \). Mean regurgitant flow rate \( Q_{\text{m}} \) was calculated by RSV divided by regurgitation time. Peak-to-mean regurgitant flow rates \( Q_{\text{p}}/Q_{\text{m}} \) and orifice areas \( A_{\text{p}}/A_{\text{m}} \) were calculated to assess the phasic character of \( Q_0 \) and \( A_0 \). In the first 24 patients (group 1), computation of \( Q_{\text{m}} \) and RSV from the color Doppler recordings was compared with the conventional pulsed Doppler method (\( r=0.94, \text{SEE}=29.4 \text{mL/s} \) and \( r=0.95, \text{SEE}=9.7 \text{mL} \)) as well as with angiography (\( r=0.93 \) and \( r=0.94, \text{P}<0.001 \)). The temporal variation of \( Q_0 \) and \( A_0 \) was studied in the next 32 patients (group 2): In functional regurgitation in dilated cardiomyopathy (n=12), there was a constant decrease in \( A_0 \) throughout systole with an increase during left ventricular relaxation; \( A_{\text{p}}/A_{\text{m}} \) was 5.49±3.17. In mitral valve prolapse (n=6), \( A_0 \) was small in early systole, increasing substantially in midsystole, and decreasing mildly during left ventricular relaxation; \( A_{\text{p}}/A_{\text{m}} \) was 2.48±0.26. In rheumatic mitral regurgitation (n=14), a roughly constant regurgitant orifice area during most of systole was found in 4 patients. In the other patients there was significant variation of \( A_0 \) and the time of its maximum; \( A_{\text{p}}/A_{\text{m}} \) was 1.81±0.56. ANOVA demonstrated that the differences in \( A_{\text{p}}/A_{\text{m}} \) were related to the etiology of mitral regurgitation (\( P<0.0001 \)). To verify that the calculated variation in regurgitant orifice area during the cardiac cycle reflects an actual variation, the ability of the method to predict a constant orifice area throughout systole was tested experimentally in a canine model of mitral regurgitation. Five flow stages were produced by implanting fixed grommet orifices of different sizes into the anterior mitral leaflet. A constant regurgitant orifice area was correctly predicted throughout systole with a mean percent error of \( -1.8\pm4\% \) (from \(-6.9\% \) to +5.8\%); the standard deviation of the individual curves calculated at 10% intervals during systole averaged 13.3\% (from 3.6\% to 19.6\%). In addition, functional mitral regurgitation caused by ventricular dysfunction was produced pharmacologically in five dogs, and the color M-mode recordings of the proximal flow convergence region were obtained with the transducer placed directly on the heart instead of the chest, thus ruling out a significant effect of translational motion on the observed flow pattern. The pattern of regurgitant flow variation was identical to that observed in patients.

Conclusions The proximal flow convergence method demonstrates that regurgitant flow and orifice area vary throughout systole in distinct patterns characteristic of the underlying mechanism of mitral incompetence. Therefore, in addition to the potential of the method as a tool to quantify mitral regurgitation, it allows analysis of the pathophysiology of regurgitation in the individual patient, which may be helpful in clinical decision making. Calculating mitral regurgitant flow rate and volume from the time-varying proximal flow field (ie, without assuming a constant orifice area that would produce overestimation in individual patients) provides excellent agreement with independent techniques and agrees well with angiography. (Circulation. 1994;90:307-322.)

Key Words • mitral valve • Doppler flow

Mitral incompetence results from a mismatch between the leaflet area needed to occlude the orifice and the leaflet area available.\(^1\,\,^2\) The leaflet area needed is determined by the size of the mitral anulus,\(^2\,\,^3\) whereas the leaflet area available to participate in coaptation is critically dependent on the tension that is exerted on the leaflets\(^2\,\,^4\) and thus is not merely equivalent to anatomically defined total tissue leaflet area. Chordal and leaflet tension are a function of the position of the papillary muscles within the left ventricle (which varies with left ventricular chamber size), the size of the mitral anulus, and its distance from the papillary muscle tips. Since both ventricular and annular dimensions vary throughout the cardiac

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cycle, the regurgitant orifice area, too, may considerably vary throughout systole, depending on the underlying mechanism of regurgitation. In a canine model of acute mitral regurgitation created by excising a portion of the free edge of the anterior leaflet, a monotonic decrease in regurgitant orifice area, closely related to the decrease in ventricular size during systole, has been found.\(^5\) Chronic mitral regurgitation of different etiologies can be expected to be far more heterogeneous and complex because it involves pathological changes in tissue characteristics and geometry of the mitral annulus, leaflets, chordae tendineae, papillary muscles, and left ventricle.\(^6,7\) For lack of a clinical tool, the time course of mitral regurgitant orifice area previously could not be examined systematically in patients. The proximal flow convergence method, a color Doppler technique that visualizes acceleration of flow approaching a restrictive orifice,\(^8-12\) allows us for the first time to compute instantaneous regurgitant flow rates and orifice areas throughout systole in the clinical setting. Quantification of mitral regurgitation flow rates by the proximal flow convergence method has been validated in vitro for both steady and pulsatile flow,\(^14-19\) in vivo\(^20,21\) as well as in clinical studies by comparison to invasive and noninvasive standards.\(^22-26\)

The purpose of our study was therefore (1) to assess the temporal variation of regurgitant flow and orifice area in different forms of mitral insufficiency using the proximal flow convergence method, (2) to investigate whether different patterns, reflecting the specific pathological mechanisms leading to mitral valve incompetence, can be discriminated, and (3) to assess potential implications for the quantification of mitral regurgitant lesions from clinical data and experimental testing.

**Methods**

**Patients**

Fifty-six consecutive patients with mitral regurgitation of different etiologies were studied. All had adequate quality of echocardiographic recordings including clear visualization of the proximal flow convergence region on two-dimensional images and reliable M-mode measurements of the flow convergence radius throughout systole. In the first 24 patients (group 1), the accuracy of the color M-mode proximal flow convergence method for calculating regurgitant flow was determined by comparison to the standard pulsed Doppler echocardiographic method.\(^27,28\) Additionally, the proximal flow convergence measures were compared with angiographic grading of the severity of regurgitation.\(^29\) The mean age in group 1 was 52 ± 11 years (32 to 77). There were 11 women and 13 men. The etiology of the mitral regurgitation was defined by the patient's history and the initial two-dimensional echocardiographic study, which had been performed as part of the routine evaluation of the patient: It was rheumatic valvular disease in 7 patients, mitral valve prolapse in 8 patients, and functional mitral regurgitation caused by left ventricular dilation in 9 patients. In the following 32 patients (group 2), the temporal variation of regurgitant flow rate and orifice area was computed (see below) to study the underlying pathophysiology. The mean age was 54 ± 9 years (42 to 74). There were 14 women and 18 men. The etiology of mitral regurgitation was rheumatic valvular disease in 14 patients, mitral valve prolapse in 6 patients, and functional mitral regurgitation caused by left ventricular dilation in 12 patients. Forty-six patients were in sinus rhythm and 10 in atrial fibrillation at the time of the study.

**Echocardiographic Studies**

All studies were performed with a commercially available system (Hewlett-Packard SONOS 1000 or 500) equipped with a 2.5-MHz transducer.

**Pulsed-Wave Doppler Echocardiography**

Mitral and aortic flow was quantified as described previously.\(^27,28\) The mitral valve orifice was imaged in the parasternal short-axis view for planimetry of the maximal orifice area (at the leaflet tips). Two-dimensional echocardiographically guided M-mode echocardiograms of the mitral valve were recorded at the same level to obtain the mean-to-maximum opening ratio. The pulsed Doppler mitral flow profile at the tips of the mitral leaflets was obtained from the apical view. Mean mitral valve area was calculated from the product of maximal valve area and the mean-to-maximum opening ratio. Mitral stroke volume was calculated as mean mitral valve area times the mitral time-velocity integral. Two-dimensional echocardiography was performed in the parasternal long-axis view to measure the aortic diameter at the points of insertion of the valve at early systole and to calculate the corresponding aortic annulus area. The pulsed Doppler aortic flow profile was obtained from the apical view. Aortic stroke volume was calculated as annulus area times the time-velocity integral. Regurgitant stroke volume was calculated by subtracting aortic from mitral forward stroke volume. Mean mitral regurgitant flow rate was calculated by dividing regurgitant stroke volume by the duration of mitral regurgitation as determined by continuous-wave Doppler. Measurements were averaged from three cardiac cycles in sinus rhythm and from five cardiac cycles in atrial fibrillation.

**Color Doppler Flow Mapping**

Doppler color gain was adjusted to maximize signal without introducing spurious velocities in areas without flow. To minimize overestimation of the velocity by high color wall filter, a medium clutter filter was chosen for all studies, and zero-shifting below 50% of the Nyquist limit was avoided in 91% of the patients.\(^30\) The proximal convergence region was visualized in an apical view that allowed best alignment of flow to the Doppler beam throughout systole. The zoom function, which allows magnification of a predefined section of the image, was used to facilitate measurements when necessary. The pulse repetition frequency was typically between 3.8 and 4.6 kHz. Velocity of flow was measurable unambiguously until 58 cm/s (Nyquist limit velocity) at the depth of 16 cm. For each study, the point of first aliasing could be altered by zero shifting; alias velocity limits for flow away from the transducer between 16 and 58 cm/s were selected. For each patient, an alias velocity was selected in which the corresponding isovelocity shell appeared to be most hemispherical at the time of its maximal systolic extension; this occurred at higher alias velocities when regurgitation was more severe. Care was taken to avoid both inappropriate use of low alias velocities, causing visible elongation of the aliasing contour (because of the constraint of the flow field by adjacent solid boundaries far away from the orifice)\(^31,32\), and of high alias velocities, causing visible flattening of the isovelocity contours near the orifice (because of its finite size or noncircular shape).\(^11,14,18,33-35\)

**Computation of the Temporal Variation of Flow Rate and Orifice Area Based on the Proximal Flow Convergence Method**

Flow approaching a regurgitant orifice passes roughly hemispherical surfaces of decreasing area at an accelerating pace. By continuity (conservation of mass), regurgitant flow rates can be calculated at any hemisphere as the product of its
surface area and the velocity at that surface.\textsuperscript{10-25} Color Doppler flow mapping can visualize the hemisphere as a blue/red aliasing interface. Flow rate (Q) through the surface of the hemisphere is then calculated by

\[ Q = 2 \pi r^2 V_s \]

where \( 2 \pi r^2 \) is the surface area of the hemisphere at a given distance \( r \) from the mitral orifice, and \( V_s \) is the aliasing velocity,\textsuperscript{10-25} which can be read from the color velocity display scale. A color M-M mode echocardiogram, guided by the two-dimensional image, was recorded through the zenith of the iso-velocity hemisphere proximal to the orifice yielding the curve of instantaneous flow convergence radii \( r_0 \) (Fig 1). The instantaneous flow convergence radius, the distance from the alias contour to the presumed mitral regurgitant orifice, was operationally defined as the distance from the alias contour to the mitral leaflet leading edge, thus accounting for the axial motion of the mitral orifice during systole, which was 7\( \pm \)2.2 mm (range, 3 to 11 mm). Definition of the mitral leaflet edge was facilitated by removing the color Doppler signal from the frozen M-mode image when necessary. The curve was then digitized with a graphics tablet (Hidap Plus) attached to a conventional microcomputer (series 386 DX) with custom-written software for calculating the curve of instantaneous flow rates according to

\[ Q_{(t)} = 2 \pi r_{(t)}^2 V_s \]

Regurgitant stroke volume (RSV) was calculated integrating the instantaneous flow rates \( Q_{(t)} \)\textsuperscript{15-17,22}:

\[ RSV = \int Q_{(t)} dt = 2 \pi V_s \int r_{(t)}^2 dt \]

Mean regurgitant flow \( Q_m \) was calculated by dividing the regurgitant stroke volume by the duration of mitral regurgitation \( t_m \)\textsuperscript{17,22}. To assess the phasic character of the regurgitant orifice area, the ratio of peak to mean regurgitant flow, \( Q_p/Q_m \), was determined. Continuous-wave Doppler interrogation was performed through the mitral regurgitant orifice, and the position of the transducer was carefully adjusted to obtain a clearly defined envelope curve of the instantaneous orifice velocities, \( V_{0} \). This curve also was digitized and the curve of the instantaneous (effective) mitral regurgitant orifice area \( A_{(t)} \) was computed by dividing corresponding values of \( Q_{(t)} \) and \( V_{(t)} \) according to

\[ A_{(t)} = \frac{Q_{(t)}}{V_{(t)}} \]

Mean regurgitant orifice area \( A_m \) was calculated by integrating the instantaneous orifice areas and dividing by the duration of mitral regurgitation \( t_m \):

\[ A_m = \int A_{(t)} dt/t_m \]

To assess the phasic character of the regurgitant orifice area the ratio of peak to mean regurgitant orifice area, \( A_p/A_m \) was determined. Measurements were averaged from three cardiac cycles. When atrial fibrillation was present, three cardiac cycles representing the average heart rate were selected for averaging.

Cardiac Catheterization and Angiography

Biplane left cineventriculography was performed in all patients of group 1 (30° right and 60° left anterior oblique projections) with the injection of 40 to 50 mL Renografin at 13 to 16 mL/s. Severity of mitral regurgitation was graded using the classification of Sellers et al\textsuperscript{12} from I to IV (mild to severe). The angiograms were interpreted by consensus of two observers who were blinded to the results of the color Doppler examination.

Reproducibility of Measurements

Pulsed-wave Doppler and two-dimensional echocardiographic calculations of mitral inflow and aortic forward flow were performed in 20 normal subjects. The interobserver variability of regurgitant flow rate (and orifice area) calculations for the proximal flow convergence and the pulsed-wave method also was examined by two independent observers in group 1, with the mean percent difference expressing observer bias and the standard deviation expressing measurement variability.

Animal Experimental Testing

To test the ability of the method to predict a known fixed effective orifice area, a canine model of mitral regurgitation was designed. Eight adult dogs (25 to 35 kg) were anesthetized with 30 mg/kg IV sodium pentobarbital, intubated, and ventilated. Left thoracotomy was performed, and the pericardium was opened. Calibrated micromanometer-tipped catheters (Millar Mikro-tip, Millar Instruments) continuously recorded pressures with an ECG lead on an eight-channel strip-chart recorder (model 7700, Hewlett-Packard Co). Paper speed was increased to 100 mm/s when data for each stage were formally recorded. The dogs were placed on right heart bypass by draining all venous return from the superior and inferior venae cavae and coronary sinus and pumping the filtered and oxygenated blood by calibrated roller pump into the right atrium through a wide-bore cannula. Blood also could be pumped into or removed from the systemic arterial circuit through femoral cannulas to control left ventricular pressure independent of preload.\textsuperscript{36}

In 3 dogs, mitral regurgitation was created by inserting plastic grommets (fixed orifices) of known size into the anterior mitral leaflet between its midportion and tip, as previously reported\textsuperscript{20, 27, 38}: Effective orifice area (0.101, 0.128, and 0.25 cm\(^2\)) was determined in vitro as the ratio of peak flow rate and peak orifice velocity.\textsuperscript{29} Arterial pressure was changed by varying roller pump flow into or out of the femoral artery at various levels of cardiac output (controlled by the flow pumped into the right atrium), thereby producing five stable hemodynamic stages.

To demonstrate that the pattern of regurgitant flow rate variation in native mitral orifices can be reproduced in an experimental setting that rules out a significant effect of

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**Fig 1.** Schematic representation of an isovelocity hemisphere proximal to a mitral regurgitant orifice as visualized by two-dimensional (2D) color flow mapping at three different points in time (t1, t2, t3) (left side). Dashed line passing through the zenith of the hemispheres and the regurgitant orifice represents the position of the M-mode cursor. A color M-M mode echocardiogram (right side), guided by the two-dimensional image, yields the curve of instantaneous flow convergence radii \( r_0 \) with the radii \( r_1 \), \( r_2 \), and \( r_3 \) of the isovelocity hemisphere at \( t_1 \), \( t_2 \), and \( t_3 \) as well as the radius of the isovelocity hemisphere at \( t_1 \) at any other time during the regurgitation period. LA indicates left atrial side with the jet arising from the orifice; LV, left ventricular side with the proximal flow convergence region.
translational motion, color M-mode and two-dimensional recordings were obtained as in the patient studies in 5 dogs, but with the transducer directly placed on the heart: In contrast to transthoracic echocardiography with its fixed external reference system, the probe moves with the heart during epicardial imaging, giving a floating system of reference. Functional mitral regurgitation was produced by inducing global left ventricular dysfunction with dilatation pharmacologically (β-blockers, lidocaine) while maintaining physiological left ventricular pressures (phenylephrine, aortic clamping).

Statistical Analysis

Linear regression analysis using the least squares method was performed to compare color Doppler and pulsed-wave assessments of mitral regurgitation in group 1. Since a wide range of values may yield a high correlation coefficient even when data are in poor agreement, we additionally determined the difference between pairs of measurements by both methods according to Bland and Altman. The correlation between the angiographic degree of mitral regurgitation and the color Doppler assessment was examined using the Spearman rank-order test. Differences in clinical characteristics between groups 1 and 2 were subjected to Fisher’s exact test (categorical variables) or Student’s unpaired, two-sample t test (continuous variables). One-way ANOVA was used to examine the influence of different etiologies of mitral incompetence on the ratio of peak to mean regurgitant flow (Qp/Qm) and orifice area (Ao/An) in group 2. In the animal experimental studies, the error of regurgitant orifice area calculation was calculated at 10% intervals throughout systole and averaged for the five stages.

Results

Comparison Between Color Doppler, Pulsed Doppler, and Angiographic Estimates of Mitral Regurgitation (Group 1)

Patients in group 1 did not differ from those in group 2 regarding age, sex, distribution of etiology, and severity of mitral regurgitation by proximal flow convergence. In group 1, mean regurgitant flow rate by color Doppler ranged from 9 to 351 (125±88) mL/s and correlated well (r=.94, SEE=29.4 mL/s, P<.00001) with standard pulsed Doppler measurements (range, 23 to 325 mL/s; 116±83) (Fig 2, top left). Regurgitant stroke volumes by color Doppler (range, 9 to 130 mL; 40±33) and by the standard pulsed Doppler method (range, 7 to 103 mL; 38±28) correlated equally well (r=.95, SEE=9.7 mL, P<.00001) (Fig 2, top right). To determine the agreement between both methods, the differences between pairs of measurements were calculated and plotted with the 95% confidence interval (Fig 2, bottom). The mean difference was 1.9±25.4 mL/s for the mean regurgitant flow rate and 1.7±8.8 mL for the regurgitant stroke volume (not significantly different from zero).

Mean regurgitant flow rate and regurgitant stroke volume assessed by color Doppler echocardiography also correlated well with the angiographic grading of mitral regurgitation (r_s=.94 and r_c=.91, respectively, P<.001). The clinically important distinction between
grade II and grade III was facilitated by the lack of significant overlap between these groups (Fig 3).

Interobserver variability was 4.1±9.4% for mean regurgitant flow rates and regurgitant stroke volume calculated by the proximal flow convergence method and 4.2±7.7% for the pulsed-wave Doppler method. The interobserver variability for calculated regurgitant orifice area was 4.5±11.4%. The difference between aortic forward flow and mitral inflow obtained with the pulsed-wave Doppler method in patients without valvular heart disease was −6% to +9% of mitral inflow.

**Temporal Variation of Regurgitant Flow and Orifice Area in Different Etiologies of Mitral Insufficiency (Group 2)**

*Rheumatic Mitral Valve Disease*

Fig 4A shows an example of a color M-mode recording through the proximal flow convergence region in a patient with rheumatic mitral valve disease. A gradual, in most cases symmetric, increase and decrease of the instantaneous flow convergence radius was consistently found. Computer plots of the orifice velocity, the regurgitant flow, and orifice area are displayed in Fig 5A and 5B (also see Table). The ratio of peak-to-mean regurgitant flow (Qp/Qm) ranged from 1.51 to 3.00 (1.86±0.39). Four patients had a roughly constant regurgitant orifice area during most of systole (Fig 5A). Regurgitant orifice area varied throughout systole in 10 out of 14 patients (Fig 5B), with a ratio of maximal-to-mean regurgitant orifice area (Ap/Am) ranging from 1.19 to 3.14 (1.81±0.56): In 9 patients there was first an increase and then a decrease of the regurgitant orifice area, the maximum of the curve being reached in the first third of the regurgitation period in 2, in the second third in 5, and in the last third in 2 patients. In 1 patient there was a constant decrease in regurgitant orifice area during regurgitation resembling the pattern of functional mitral regurgitation (see below).

*Mitral Valve Prolapse*

Fig 4B shows a typical example of a color M-mode recording through the proximal flow convergence region of a patient with mitral valve prolapse; the corresponding computer plots of orifice velocity, regurgitant flow, and orifice area are displayed in Fig 5C. The flow convergence radius was small during early systole, reflecting mild regurgitant flow rates during this period, and rose substantially after mid-systole to reach a peak in late systole. Computation of the corresponding regurgitant orifice area showed a roughly constant and small regurgitant orifice area during the first half of the regurgitation period, with a sudden increase to substantial values in mid-systole. In all patients studied, a mild decrease in regurgitant orifice area was observed related to the decrease in driving pressure (orifice velocity) during left ventricular relaxation. The ratio of peak-to-mean regurgitant flow Qp/Qm ranged from 2.38 to 3.03 (2.61±0.29); the ratio of peak-to-mean regurgitant area Ap/Am ranged from 2.16 to 2.74 (2.48±0.26).

**Functional Mitral Regurgitation in Dilated Cardiomyopathy**

Fig 4C and 4D show typical examples of color M-mode recordings through the proximal flow convergence region of patients with mitral regurgitation in dilated cardiomyopathy; corresponding computer plots of orifice velocity, regurgitant flow, and orifice area are displayed in Fig 5D through 5F. The flow convergence radius showed a maximum very early during the regurgitation period followed by a rapid and constant decrease, reflecting a rapid decrease of regurgitant flow rates during this period. The ratio of peak-to-mean regurgitant flow Qp/Qm ranged from 2.17 to 5.35 (3.24±0.81); the ratio of peak-to-mean regurgitant area Ap/Am ranged from 2.82 to 13.8 (5.49±3.17). Values for Ap/Am over 5 reflected the regurgitant orifice area rapidly approaching zero during early to mid-systole. This was the case in patients with only mildly dilated or impaired ventricles in whom there was virtually no detectable regurgitant orifice area during mid-systole (Fig 5E and 5F), whereas in patients with moderately to severely dilated ventricles, a significant regurgitant orifice area could still be assessed at least during most of this period (Fig 5D). Two additional observations were made in this group: (1) As the orifice velocity continued to increase while the regurgitant flow rate was already decreasing (Fig 5D through 5F), the regurgitant orifice area usually decreased more rapidly than the regurgitant flow rate. This was most obvious in patients with a relatively steep rise in orifice velocity, reflecting a high
Fig 4. Examples of color M-mode recordings through the proximal flow convergence region in patients with rheumatic mitral valve disease (A), mitral valve prolapse (B), and functional mitral regurgitation (C and D). A, Symmetrical increase and decrease in the proximal flow convergence radius. Solid arrows point at the alias boundary; curved open arrow points at the mitral leaflet plane; B, the flow convergence radius is small during early systole (open arrows), reflecting low regurgitant flow rates during this period, and rises substantially after midsystole to reach a peak in late systole (solid arrows); C and D, the flow convergence radius shows a maximum very early during the regurgitation period (solid arrow) followed by a constant decrease, reflecting a constant decrease of regurgitant flow rates during this period. Late during the regurgitation period, an increase in the proximal flow convergence radius can be detected (open arrow), reflecting an increase in the regurgitant flow rate. Curved open arrow points at the mitral leaflet plane.
rate of pressure increase (Fig 5E and 5F). (2) In the 8 patients with the most severe left ventricular dilation, despite the fall in driving pressure (orifice velocity) during left ventricular relaxation, an increase in regurgitant flow occurred, implying a disproportionate increase in regurgitant orifice area. The increase in regurgitation also could be verified by two-dimensional visualization of the proximal flow convergence region in patients in whom a low heart rate permitted collection of sufficient frames in systole despite the limited temporal resolution of conventional color Doppler two-dimensional systems (Fig 6). ANOVA demonstrated a highly significant relation ($P<.0001$) between the etiology of mitral regurgitation and both $A_p/A_w$ ($F$ value, 11.64) and $Q_p/Q_w$ ($F$ value, 18.39); the null hypothesis that the sample come from populations with equal means could therefore be rejected.
Animal Experimental Testing

Fig 7 displays the curves of instantaneous effective regurgitant orifice area calculated by the proximal flow convergence method (expressed as percent of the actual effective orifice area) for five flow stages and their average. A constant effective regurgitant orifice area
was correctly predicted throughout systole. The error of regurgitant orifice area calculation determined at 10% intervals throughout systole was $-1.8 \pm 4\%$ (from $-6.9\%$ to $+5.8\%$); the variation of the individual curves about their mean was on average $2.3 \pm 10.4\%$. Thus, averaging substantially reduced scatter (Fig 8).

In all five dogs in which functional mitral regurgitation was produced by inducing ventricular dysfunction pharmacologically (and translational motion of the heart relative to the ultrasound beam was eliminated by placing the transducer directly on the heart), the color M-mode pattern of regurgitant flow variation was identical to that observed in patients with dilated cardiomyopathy (Fig 9).

Discussion

Dynamic Regurgitant Orifice Area

The traditional concept of assuming a fixed regurgitant orifice under different circulatory states\textsuperscript{44} has been challenged by studies of acute experimental mitral insufficiency in the dog.\textsuperscript{5,45,46} These studies described a monotonically decrease in regurgitant orifice area closely related to the decrease in left ventricular size during systole.\textsuperscript{5} Regurgitation was created by excising a portion of the free edge of an otherwise normal mitral valve; thus, the leaflet tissue area available to cover the mitral orifice was reduced without the complex pathological changes that can be observed in organic mitral valve disease, including leaflet, chordal and papillary muscle rigidity and deformity, commissural fusion, chordal rupture, prolapse, and flail.\textsuperscript{6,7} Hence, this model closely resembled the situation of functional mitral regurgitation in dilated cardiomyopathy\textsuperscript{4} yet may not represent regurgitation caused by structural mitral valve disease. In the present study, the temporal variation of regurgitant flow and orifice area could be examined for the first time in the clinical setting in a variety of pathological conditions. The results of this study support the concept of a dynamic regurgitant orifice.\textsuperscript{5,45,46}

However, we did not find one uniform pattern of temporal changes in regurgitant orifice area but various patterns, each reflecting the underlying mechanism of mitral incompetence.

**Functional Mitral Regurgitation in Dilated Cardiomyopathy**

The constant decrease in the regurgitant orifice area from early to mid or late systole in this patient group is consistent with the concept that mitral valve closure will be incomplete as long as large left ventricular and annular diameters prevent effective leaflet coaptation.\textsuperscript{2,4} Reduction of the mitral annulus area during ventricular contraction, in which the annulus participates,\textsuperscript{3,47} decreases the orifice area that has to be covered by the leaflets to achieve valve competence. Moreover, decreasing ventricular size reduces the tension on the leaflets resulting from the lateral, apical, and posterior displacement of the papillary muscles in the dilated cavity, allowing more effective leaflet coaptation. A simultaneous increase in ventricular-atrial pressure difference may also press the leaflets more tightly together.\textsuperscript{48} In fact, in patients with only moderately impaired and dilated left ventricles, the early systolic decrease in regurgitant orifice area was more rapid (Fig 5F) than could be explained exclusively on the basis of reduced annular and ventricular dimensions, which changed only little during that period. The concept that driving pressure contributes to effective leaflet coaptation in functional regurgitation is further supported by the divergent behavior of regurgitant flow and area on the one hand and the orifice velocity (driving pressure) on the other during left ventricular relaxation: In 8 of the 12 patients studied, an increase in regurgitation could be detected during left ventricular relaxation. This was due to an increase in regurgitant orifice area, presumably caused by the drop in ventricular pressure reducing effective leaflet coaptation. A simultaneous increase in mitral annulus area during ventricular relaxation\textsuperscript{3,47} also may contribute to the observed increase in regurgitant orifice area, although this increase was most prominent in patients with the most severe ventricular dysfunction and thus the least degree of mitral annulus motion and contraction. Thus, in patients with functional regurgitation, the ventricular-atrial pressure difference, although its square root is directly related to regurgitant flow by the Gorlin formula, may reduce regurgitant flow by decreasing regurgitant orifice area. Conformational changes of the ventricle (from more ellipsoidal at end systole to more spherical at the beginning of filling) might additionally impair leaflet coaptation by increasing tension on the valvular apparatus.

The pattern of phasic variation of the instantaneous regurgitant orifice area in functional regurgitation described in the present study has been confirmed by preliminary reports using a similar approach and an
Quantitative Parameters Computed From Proximal Flow Convergence Recordings in 32 Patients With Mitral Regurgitation of Different Etiologies (Group 2)

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<th>Qm, mL/s</th>
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RSV indicates regurgitant flow volume; Qp, peak regurgitant flow; Qm, mean regurgitant flow; Qp/Qm, peak-to-mean regurgitant flow; Ap, peak regurgitant orifice area; Am, mean regurgitant orifice area; Ap/Am, ratio of peak-to-mean regurgitant area; and MR, mitral regurgitation.

Independent technique that applies high-frame-rate, two-dimensional echocardiography to visualize the regurgitant orifice directly in suitable patients (severe regurgitation). 49, 50

**Mitral Regurgitation in Mitral Valve Prolapse**

Patients with mitral valve prolapse in this study showed a relatively constant and small regurgitant orifice area during the first half of the regurgitation period, suddenly rising in mid-systole. A mild decrease in regurgitant orifice area occurred during left ventricular relaxation, possibly because of decreased leaflet displacement above the annulus, as also seen on the M-mode echocardiogram. Again, this suggests that ventricular pressure can exert an effect of regurgitant orifice area independent of its direct hydraulic effect on regurgitant flow rate.
Rheumatic Mitral Valve Disease

Patients with a roughly constant regurgitant orifice area during most of systole were solely found in rheumatic valve disease. In many patients, however, there was substantial variation of the regurgitant orifice area and the time of its maximum. Thus, rheumatic mitral regurgitation, usually regarded as uniformly related to a fixed regurgitant orifice, was found to be heterogeneous. This can be attributed to the diversity of pathological changes that occur in rheumatic heart disease and that have been observed in this patient group studied: Severely deformed, fused and retracted leaflets may provide a regurgitant orifice that is roughly constant if the tissue is fibrotic and calcified or may be stretched by increases in pressure if sufficiently elastic. Less severe structural changes with preserved individual leaflet mobility can result in a functional type behavior, especially with significant ventricular volume overload. Asymmetry in leaflet length (with only one leaflet shortened and retracted) may result in a prolapselike situation. Thus, our data are consistent with the results of Jose et al., who studied the effect of vasoactive drugs on effective regurgitant orifice area determined by cardiac catheterization in organic mitral valve lesions: They found that mean orifice area remained unchanged only in lesions that showed severe fibrosis and calcification at surgery (predominant mitral stenosis and milder regurgitation). In patients with predominant mitral regurgitation, who tended to have relatively mobile leaflets with only one commissure fused, the regurgitant orifice area could substantially increase after infusion of noninotropic vasopressors and decrease after application of nitrates or after infusion of inotropic vasopressors (if the resulting decrease in ventricular size outweighed the effect of pressure increase).

Implications for the Quantification of Mitral Regurgitation by the Proximal Flow Convergence Method

Peak Flow Rate

Peak mitral regurgitant flow rates calculated from the proximal flow field have been shown to separate the angiographic grades of mitral regurgitation with a relatively good degree of overlap. However, discrepancies between invasive and noninvasive grades of mitral regurgitation based on peak flow rates occur in individual patients. Such discrepancies may relate in part to individual differences in the time course of flow throughout systole for the same peak flow rate. Grading severity of mitral regurgitation based on mean regurgitant flow rate or by regurgitant stroke volume may therefore be preferable, as supported by the good agreement between the proximal flow convergence, pulsed Doppler, and angiographic assessments of mitral regurgitation in this study.

Regurgitant Stroke Volume

Two different approaches have been proposed to calculate regurgitant stroke volume from proximal flow convergence measurements: (1) The continuous-wave Doppler method which calculates stroke volume as peak flow rate times the time velocity integral of the orifice velocities divided by the peak orifice velocity) assumes that the regurgitant orifice area is roughly constant so that changes in flow rate are in fixed proportion to changes in orifice velocity. (2) The color M-mode method, which integrates instantaneous flow rates and does not assume a constant orifice area. The present study demonstrates that regurgitant orifice area can vary considerably throughout systole and that different patterns of variation can be observed, since the regurgitant orifice can be created by completely different mechanisms. Therefore, assuming a constant area may cause errors in individual patients.

For example, patient 23 with functional regurgitation (Table) had a peak regurgitant orifice area comparable to patient 12 with rheumatic disease (0.56 versus 0.51 cm²) but a much smaller mean area (0.09 versus 0.33 cm²) and regurgitant stroke volume (8 versus 54 mL) because of a rapid decrease in orifice area with ventricular contraction. The differences in regurgitant stroke volume were in full agreement with clinical data. On the other hand, patient 29 with mitral valve prolapse and mainly late systolic regurgitation had a larger peak regurgitant orifice area than patient 12 with rheumatic disease (0.98 versus 0.56 cm²) but a comparable mean area (0.39 and 0.33 cm²) and regurgitant stroke volume (41 versus 54 mL, smaller because of a shorter regurgitation time). Therefore, grading mitral regurgitation by the peak orifice area or flow rate would have substantially overestimated the severity of the lesion in the patient with mitral prolapse.

Nevertheless, normalizing regurgitant flow rate throughout systole using the continuous-wave Doppler correction has been demonstrated to be accurate in a number of clinical studies. This can be explained by a variety of reasons: (1) Using continuous-wave Doppler, Rivera et al. normalized the midsystolic flow rate (which is not necessarily identical with peak systolic flow rate as shown in this study) to obtain regurgitant stroke volume. Since the midsystolic flow rate can be close to the mean flow rate, for example, when flow rate and orifice area decrease monotonically throughout systole, significant overestimation can frequently be avoided. (2) In rheumatic mitral valve disease, even when the regurgitant orifice area is not constant, a modest degree of variation will not necessarily result in an important error when calculating regurgitant stroke volume. (3) The spectrum of mitral valve prolapse, ranging from flail or near flail leaflets, also includes more pansystolic patterns than those described in this series. (4) In dilated cardiomyopathy, the more severe the incomplete valve closure, the less the decrease in regurgitant orifice area during left ventricular contraction. In addition, the burst of flow rate seen during the relaxation phase occurs for a short time, usually with a relatively small impact on regurgitant volume. These factors tend to minimize potential errors of the continuous-wave Doppler method in many patients, although care may need to be exercised in the individual patient. Some investigators, for example, have not used the envelope contour of the continuous-wave Doppler signal in patients with predominantly late systolic mitral valve prolapse but rather the sabre-shaped late systolic velocity spectrum of high intensity representing the bulk of regurgitant flow; correspondingly, in early systolic functional regurgitation, they used the early systolic high intensity signal only, thus applying an “eyeball” amplitude-weighted mean velocity correction factor.
Temporal Variability of Proximal and Distal Regurgitant Flow Fields

Smith et al. have recently emphasized the importance of assessing the temporal variability of mitral regurgitant jet areas by color Doppler for understanding the physiology of regurgitation and assessing its severity. They noticed that the timing of maximal jet area was related to the etiology of mitral regurgitation (e.g., the maximal jet area was recorded in the latter half of systole in two patients with mitral valve prolapse). The present data are in full accordance with those findings. We observed that jet area and proximal flow field showed concordant changes during systole (Fig 6); however, the proximal flow field is hydrodynamically better behaved for quantitation and is less dependent on Doppler instrument factors. Thus, it appears to be an ideal tool to study phasic changes in mitral regurgitation.

Clinical Implications of Orifice Area Variations

The results of this study suggest that changes in the ventricular-atrial pressure difference influence the temporal variation of mitral regurgitant orifice area depending on the mechanism of incompetence, and that in functional and even some structural regurgitant lesions, the systolic decrease in left ventricular and mitral annular size contributes to effective leaflet coaptation. These data, which support the concept of a dynamic regurgitant orifice even in structural mitral valve disease, imply that the regurgitant orifice area is not completely independent from momentary hemodynamic conditions. The regurgitant orifice area may reflect the level of systemic vascular resistance (deter-
mining the size and pressure of the left ventricle) as much as the severity of the valvular lesion itself. This would explain the beneficial effects of vasodilator therapy not only in functional mitral regurgitation but also in valvular heart disease, which cannot be sufficiently explained on the basis of changes in driving pressure alone. Some regurgitant orifices may be more apt to decrease with reduction in left ventricular size and pressure than others, depending on the lesion properties. Vandervoort et al have already demonstrated the value of assessing the regurgitant orifice area as a fundamental measure of valvular incompetence. As an extension of this concept, it may be necessary to relate a calculated regurgitant orifice area to the actual level of systemic resistance when assessing the severity of a valvular lesion. The degree and pattern of variation of the regurgitant orifice area within the cardiac cycle as well as the response of that area to acute vasodilator therapy may yield important information about the likelihood of successful chronic medical therapy and help to decide about indication and timing of surgery.

Limitations of the Study

Reference Methods

There is no satisfactory gold standard for quantifying mitral regurgitant volume and flow rate in patients. Both the combination of quantitative angiography and thermodilution and the combination of two-dimensional echocardiography and pulsed-wave Doppler have methodological limitations. The measurement error for cardiac output is 5% to 10% for thermodilution and 10% to 15% for angiography, with greater errors when they are combined to give mitral regurgitant volume. Because there was no simultaneous measurement of angiographic regurgitant flow, we chose pulsed Doppler integration of mitral inflow and aortic forward flow, which has been validated independently against true regurgitant flow in a canine model and has been demonstrated to have a comparatively low measurement variation, although this method is time consuming (several beats are averaged) and technically demanding. Its reliability is underscored by the comparatively small difference between aortic and mitral stroke volumes in normal subjects, found in this and our previous study, and has recently been confirmed by a large clinical series. As in our previous study, we found a good agreement between the color M-mode mean regurgitant flow rates and regurgitant stroke volumes and the standard pulsed Doppler measures as well as good correlation with the semiquantitative angiographic assessment of regurgitation. Moreover, using a true gold standard in the experimental part of our study, a good agreement between calculated and actual regurgitant orifice area was found throughout systole, with a relatively small error, especially when averaging several measurements.
M-Mode Recordings

Calculating instantaneous regurgitant flow rates from color M-mode recordings of the proximal flow convergence region faces two potential limitations: (1) The position of the regurgitant orifice and associated proximal flow convergence 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 proximal flow convergence 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 importantly affect measurements. Thus, for the purpose of this method, the problem of the limited lateral resolution actually becomes an advantage. Moreover, patients with functional mitral regurgitation usually show reduced translational motion caused by impaired left ventricular function. In fact, when reproducing functional mitral regurgitation experimentally while eliminating translational motion of the heart relative to the ultrasound beam by placing the transducer directly on the heart, the color M-mode pattern of regurgitant flow variation was identical to that observed in patients with dilated cardiomyopathy. When the proximal flow convergence region is small (in case of mild mitral regurgitation), its imaged extent can be appropriately enlarged by reducing the alias velocity with zero shifting. However, in those patients with severely hyperkinetic left ventricles whose translational heart movements happen to be almost perpendicular to the proximal flow convergence region, adequate M-mode echocardiographic assessment of the flow convergence radius throughout systole cannot be achieved. Indeed, in 25% of the patients originally considered for the study (6 patients for group 1 and 8 patients for group 2) the two-dimensional images showed significant lateral motion of the proximal flow convergence region relative to the M-mode cursor; those patients could therefore not be included in the study. (2) During periods of low driving pressure (very early and very late during systole), the isovelocity contour may flatten out, and a hemispherical formula will underestimate the surface area and thus regurgitant flow. As demonstrated in the experimental part of this study (Fig 7), this only affects calculations during the first and last 5% of systole (when flow rate is, in any event, low) with accuracy maintained at other times. Accordingly, in an effort to minimize potential sources of error the first and last 10 milliseconds of the regurgitation period were not included in the calculation of mean regurgitant flow rate and orifice area.

Proximal Flow Convergence Concept

Although the present method can account for the temporal variation of the proximal flow field, it does not solve other important problems of the proximal flow convergence method (nor does it propose to do so): Selection of the appropriate alias velocity and isovelocity shell, justifying the use of a hemispherical formula, was performed according to current practice in clinical studies. A more objective method with potential for automatization would certainly improve the reliability of the method. Since chamber size, regurgitant flow rate, and orifice area change during systole, different degrees of confinement and of the finite orifice effect can be expected. Therefore, the ideal alias velocity might also change during systole. However, these are second-order effects (modifying the temporal variation) and by definition neither invalidate a first-order (temporal) correction nor obviate the need for it. (For example, increasing confinement of the flow field as the ventricle shrinks during ejection might contribute to the observed midystolic increase in the proximal flow convergence radius in patients with mitral valve prolapse but not create this pattern, since the flow convergence radius decreases during the same period in the patients with rheumatic and functional mitral regurgitation). In addition, noncircular orifices represent a potential source of flow rate underestimation, although this can be minimized by avoiding measuring at high alias velocities close to the orifice. Both the results of the experimental part of the study as well as the close correlation and good agreement of the mean regurgitant flow rates and regurgitant stroke volumes...
calculated from the color M-mode and the standard pulsed Doppler techniques demonstrate that these limitations did not pose a major problem in the patients enrolled in the study. Therefore, these limitations should not affect our principal conclusions.

**Biological Variation**

Finally, given the complex functional anatomy of the mitral apparatus as well as the diversity of structural mitral valve disease, more patterns of variation (and combinations) may be found as the technique is more widely applied. Nevertheless, the present study demonstrates the value of the method for studying the pathophysiology of mitral regurgitation.

**Conclusions**

The questions raised in the introduction of this report can be answered as follows. The proximal flow convergence method demonstrates that regurgitant flow and orifice area vary throughout systole in distinct patterns characteristic of the underlying mechanism of mitral incompetence. Therefore, in addition to the potential of the method as a tool for quantifying mitral regurgitation, it allows us to analyze the pathophysiology of the lesion in the individual patient, which may be helpful in decision making and guiding medical therapy. Calculating mitral regurgitant flow rate and volume from the time-varying proximal flow field provides excellent agreement with independent techniques and agrees well with angiography.

**Acknowledgments**

Dr Schumannenthal was supported by a grant from the Deutsche Forschungsgemeinschaft, Bonn, Germany. This study was supported in part by a grant of the American Heart Association, Dallas, Tex, and by a gift of Rena M. Shulsky, New York, NY. Dr Levine is an Established Investigator of the American Heart Association, Dallas, Tex, with funds contributed in part by its Massachusetts Affiliate, Natick, Mass.

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Circulation. 1994;90:307-322
doi: 10.1161/01.CIR.90.1.307

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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