Dynamic Nature of the Aortic Regurgitant Orifice Area During Diastole in Patients With Chronic Aortic Regurgitation

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Background The effective aortic regurgitant orifice area varies with aortic pressure in animal models of acute aortic regurgitation. The purpose of this study was to determine whether the aortic regurgitant orifice area changes during diastole in patients with chronic aortic regurgitation.

Methods and Results Two-dimensional and Doppler echocardiography were performed immediately before and after magnetic resonance velocity mapping using a cine phase contrast sequence in 17 patients with chronic aortic regurgitation. ECG-gated continuous-wave Doppler velocity time integrals and magnetic resonance flow rates were measured 16 times per cardiac cycle. The mean aortic regurgitant orifice area (centimeters squared) was calculated by the continuity equation. The regurgitant orifice area was also determined for each diastolic acquisition interval. Changes in the regurgitant orifice area during diastole were modeled using an asymptotic exponential decay model to determine the static and dynamic components of the orifice. The regurgitant orifice area increased directly with regurgitant fraction \( y(\text{cm}^2) = 0.0072\text{cm}^2/\% \times x(\% ) - 0.0409[\text{cm}^2] \); \( r = .86, P < .0001 \). In 15 of 17 (88%) patients, the regurgitant orifice area decreased during diastole. The dynamic component of the regurgitant orifice area decreased with increasing regurgitant fraction \( y(\%) = -0.98x(\%) + 96.9\% \); \( r = -0.90, P < .0001 \). There were no significant differences in heart rate, systolic or diastolic blood pressures, or continuous-wave Doppler velocity time integrals measured before or after the magnetic resonance examination.

Conclusions The effective regurgitant orifice area decreases during diastole in patients with chronic aortic regurgitation. This phenomenon should be considered when evaluating aortic regurgit ant severity. (Circulation, 1994:89:2085-2092.)

Key Words • aorta • regurgitation • echocardiography • magnetic resonance imaging

Valvular heart diseases, including mitral stenosis, mitral regurgitation, and aortic stenosis, have been shown to be dynamic with changes in stenotic and regurgitant orifice areas in response to altered loading conditions.\(^1\)\(^2\) It has been suggested that the aortic regurgitant orifice area is a fixed area unresponsive to changes in aortic pressure.\(^3\) However, data from in vivo and in vitro animal models of acute aortic regurgitation indicate that the aortic regurgitant orifice area is load dependent.\(^4\)\(^5\) The regurgitant area increases directly with aortic distending pressure in the acute model, probably because increasing aortic pressure distends the aortic annulus, causing malap-portion of the aortic cusps.\(^3\)

Estimation of the aortic regurgitant orifice area is dependent on accurate determination of retrograde aortic flow and the velocity of this retrograde flow through the valve. Although estimating the regurgitant orifice area may be possible using echocardiography alone, small errors in any of several measurements may lead to significant inaccuracies.\(^6\) Velocity mapping with magnetic resonance (MR) phase contrast is a noninvasive, highly reproducible method of estimat-
ing 4+ aortic regurgitation before the MR study; this patient subsequently underwent replacement of the aortic root and aortic valve. Patients with aortic or mitral prostheses, atrial fibrillation, pregnancy, or other contraindications to an MR examination were excluded. Etiologies of aortic regurgitation were bicuspid, six; prior endocarditis, one; annular dilatation/hypertension, four; and degenerative aortic valve disease, six. Informed consent was obtained from patients before participation in the study. This study was approved by the Brigham and Women’s Committee for Protection of Humans from Research Risks.

Echocardiographic Study

Before MR imaging, blood pressure and heart rate were recorded. Two-dimensional and Doppler echocardiograms were performed with the patient in the left lateral position using a phased array system (Sonos 1000 or 1500, 2.5 MHz, Hewlett-Packard Co). Imaging continuous-wave Doppler spectra (QRS phase delay of 10 milliseconds) of the aortic regurgitant flow were obtained from the apical position and recorded on videotape for later analysis. In three patients, the continuous-wave Doppler spectra recorded from the second right intercostal space were superior to those obtained from the apical window and were used in the analysis. An example of an acceptable continuous-wave Doppler tracing with a clearly defined interface between the spectra and the surrounding background is shown in Fig 1. Blood pressure, heart rate, and continuous-wave Doppler recordings of the aortic regurgitant jet were also acquired immediately after MR imaging in all except two individuals.

Magnetic Resonance Imaging Study

MR imaging was performed on a 1.5-T whole-body scanner (SIGNA, General Electric). Patients were placed supine. Axial localizing images with a field of view of 40 cm were used. For velocity mapping based on the velocity dependent phase shift, a cine sequence (known as VINNIE) with retrospective electrocardiographic gating was used.\(^4\) The velocity sensitivity was set to 4 m/s per 360-degree phase shift. With a calibrated flow phan-

dom, the actual sensitivity was verified to differ less than 1% from this setting. Axial phase images with a field of view of 40 cm, a resolution of two averages, and an acquisition resolution of 256×128 points reconstructed to 256×256 points were acquired above the aortic annulus (≈4 cm) in an axial plane perpendicular to the ascending aorta. Axial velocity mapping closer to the aortic valve would require prescription of oblique slices, which was not possible with the available software and therefore not performed. The section thickness was 10 mm and the echo time 7 milliseconds. Excitation and signal acquisition occurred every 22 milliseconds, with a flip angle of 30 degrees. Phase maps were reconstructed for 16 evenly spaced different instants over the cardiac cycle, with the first phase map 15 milliseconds after the QRS trigger. An example of phase maps for one patient is shown in Fig 2.

The studies were downloaded to a Sun SparcStation (Sun Microsystems, Inc) equipped with dedicated software for the analysis of images. For each of the 16 intervals, vessel contours were manually drawn with a digitizing device on enlarged 64×64 subimages of the ascending aorta (Fig 3). Simultaneous depiction of the drawing procedure on a phase and a magnitude image facilitated accurate definition of the vessel contour. Each phase subimage was submitted to a zero-order phase correction based on the average phase value of pixels in and close to the stationary sternum; without this phase correction, an underestimation of the systolic blood flow would result. The systolic offset is introduced by the image reconstruction software, which adjusts the average phase of the image, disregarding phase shifts introduced by motion. Velocity was calculated based on the known relation between velocity and phase shift. For each image obtained, average velocity data are available for each pixel in the ascending aortic cross section.

Measurements and Calculations

Antegrade and retrograde flows were calculated by adding positive and negative axial velocity values for each pixel across the aortic cross-sectional area of all 16 instants per cycle. Thus, the antegrade flow includes diastolic forward
Fig 1. Example of continuous-wave Doppler spectrum from a patient with severe aortic regurgitation. Note the clear demarcation between the Doppler spectrum and the surrounding background. The solid black baseline represents 0 m/s. The time between the two vertical sets of marks is 1 second.

flow, which may be observed in normal individuals or individuals with mild aortic regurgitation. The regurgitant volume was determined for each of the 16 instants during diastole. Diastole composed 8 to 10 of the 16 acquisitions per cycle in the patients studied. By definition, the difference between antegrade and net forward stroke volume equals the regurgitant volume. Net forward cardiac output was determined by multiplying net forward stroke volume by the heart rate. Examples of aortic flow in two patients are shown in Fig 4. The regurgitant fraction was determined as

Fig 2. Example of cine velocity phase images acquired 16 times per cardiac cycle in a patient with severe aortic regurgitation.
The continuous-wave Doppler spectra of aortic regurgitation were traced offline using a software analysis program (Fig 4c and 4d). Spectra from five cycles were traced for each individual and matched for the QRS offset. The distance between QRS complexes was defined as a distance of 16 to allow division of the cardiac cycle into 16 equal intervals. All continuous-wave Doppler curves were imported into a software analysis program (ORIGIN 2.85) and averaged. The mean velocity time integral (VTI, in centimeters) of aortic regurgitation during the cardiac cycle was obtained by integrating the continuous-wave Doppler velocity spectra. The VTIs were then determined for each interval during diastole. Data from the initial diastolic interval and from the 16th interval (last in the cardiac cycle) were excluded from later analysis of interval changes since these intervals included isovolumic relaxation or contraction. This procedure was repeated for continuous-wave Doppler spectra obtained after each MR study. For the 14 of 17 patients in whom imaging continuous-wave Doppler was performed, the velocity time integral was corrected if the angle of incidence were >25 degrees (two patients) by dividing the velocity by the cosine of the incident angle for all velocities throughout diastole.

The mean regurgitant orifice area was determined using the continuity equation

\[
\text{Aortic Regurgitant Orifice Area (cm}^2) = \frac{\text{Regurgitant Volume (cm}^3)}{\text{Aortic VTI (cm)}}
\]

The interval orifice areas were determined for each diastolic instant by matching MR flow and echocardiographic velocity integrals. For each patient, the average and interval aortic VTIs obtained before the MR study were used in these calculations.

Each individual's data were analyzed using an asymptotic exponential decay model fit to each data set using a least-squares method (ORIGIN 2.85). An asymptotic exponential decay equation is expressed as

\[
y = Ae^{-kt} + B
\]

where \(A\) is the magnitude of the exponentially decaying time-dependent component of \(y\), and \(B\) represents the time-independent component. For the purposes of this analysis, the dynamic component of the orifice (D) was defined as \(A\), and the static component of the orifice (S) was defined as \(B\). Thus,

\[
\text{Aortic Regurgitant Orifice Area (cm}^2) = D\cdot e^{-kt} + S
\]

where \(D\) denotes dynamic component of the orifice area; \(t\), the time in seconds between acquisition intervals; \(k\), a constant for the rate of decay; and \(S\), the static component of the orifice area. The tolerance of the curve fit was a fractional \(\chi^2 < .05\).

The percent dynamic component was calculated as an index of changes in the orifice during diastole:

\[
\% \text{ Dynamic} = \frac{D}{D+S} \cdot 100
\]

For patients \((n=2)\) in whom the regurgitant flow was transient and decreased to zero in late diastole, the static component was equal to zero; thus, \% dynamic component = 100.

**Statistics**

Heart rate, blood pressure, and VTIs obtained before and after MR examination were compared using the Student's \(t\) test. The regurgitant fraction was compared with the \% dynamic component and the regurgitant orifice area using linear regression. Subgroups of patients with regurgitant fractions >10% \((n=13)\) and with audible aortic regurgitation \((n=16)\) were analyzed to exclude bias based on inclusion of patients with minimal aortic regurgitation. The regurgitant fraction, orifice area, and \% dynamic component were compared with systolic blood pressure, diastolic blood pressure, mean blood pressure, and pulse pressure using linear regression. A value of \(P \leq .05\) was considered statistically significant. Data are reported as mean±1 SD.

**Results**

For 15 of 17 patients, heart rate, blood pressure, and continuous-wave Doppler recordings of the aortic regurgitation were obtained before and after MR examination. The mean heart rate changed from 67.8 to 67.5
beats per minute (average difference, 0.3±3.8 beats per minute; \( P = \text{NS} \)). The mean systolic blood pressure was 143 mm Hg before and 144 mm Hg after MR (average difference, 0.5±9.5 mm Hg; \( P = \text{NS} \)). The mean diastolic blood pressure was 73 mm Hg before and 73 mm Hg after MR (average difference, 0.1±7.3 mm Hg; \( P = \text{NS} \)). The average aortic VTI increased from 379 to 383 cm (average change, -3.5±53.6 cm; \( P = \text{NS} \)). Net forward stroke volume measured by MR was 111.7±44.0 mL. The net forward cardiac output for patients enrolled in the study was 7.3±2.7 L/min. Regurgitant volume ranged from 1 to 209 mL (mean, 67±70 mL). Individual patient data are displayed in the Table.

The estimated mean regurgitant orifice area increased with regurgitant fraction \( (y[\text{cm}^2] = 0.0072[\text{cm}^2/\%] \times [\%] - 0.409[\text{cm}^2]; r = .86, P < .0001; \) Fig 5). In 15 of 17 (88%) patients, the regurgitant orifice area decreased during the diastolic data acquisition intervals. For those individuals with regurgitant fractions >10% \( (n = 13) \), the relation between the regurgitant fraction and regurgitant orifice area was similar \( (y[\text{cm}^2] = 0.0075 \text{ cm}^2/\% \times [\%] - 0.0705[\text{cm}^2]; r = .82, P < .0001) \). Fig 4e demonstrates a large change in regurgitant orifice area during diastole in a patient with moderate aortic regurgitation (mean regurgitant orifice area, 0.07 cm²). Fig 4f shows a small change in orifice area during diastole in a patient with severe aortic regurgitation (0.36 cm²).

Fig 4. a, Aortic flow for each acquisition interval from a patient with moderate aortic regurgitation (patient 7). Note that the maximal retrograde flow occurs in early diastole and decreases markedly throughout diastole. b, Aortic flow for each acquisition interval from a patient with severe aortic regurgitation (patient 17). While retrograde flow is maximal in early diastole, significant retrograde flow persists throughout diastole. c and d, Continuous-wave Doppler velocities (m/s) of the aortic regurgitant jet are shown for a patient with moderate aortic regurgitation (c) and severe aortic regurgitation (d). e, Interval regurgitant orifice areas throughout diastole for a patient with moderate aortic regurgitation. The areas decline markedly from early to late diastole. f, Interval regurgitant orifice areas throughout diastole for a patient with severe aortic regurgitation. Although the regurgitant orifice areas are larger earlier in diastole, the change throughout diastole is much smaller.
The asymptotic exponential decay model allowed determination of the dynamic and static components of the regurgitant orifice area during diastole for each patient. For the patient with moderate aortic regurgitation, D was much larger than S, with % dynamic component of 70.6 (Fig 6). The patient with severe aortic regurgitation had a much larger static component (% dynamic=35.9). For the group of patients studied, the % dynamic component varied inversely with the regurgitant fraction ($y/\% = -0.98 \times x/\% + 96.9/\%$; $r = -0.90, P < 0.001$; Fig 7). This relation was similar after patients with regurgitant fraction $<10\%$ were excluded ($y/\% = -0.85x/\% + 89.9/\%$; $r = -0.90, P < 0.001$) and when only those individuals with audible aortic regurgitation were analyzed.

The regurgitant orifice area varied inversely with the mean blood pressure ($y/\text{cm}^2 = -0.0075/\text{cm}^2/\text{mm Hg}$)\* mean blood pressure [mm Hg]+0.93 [cm$^2$]; $r = -0.69$, $P < 0.003$). There was a nonsignificant trend for mean arterial blood pressure to be directly related to the % dynamic component ($y/\% = 0.6/\%/\text{mm Hg}$)\* mean blood pressure [mm Hg]+78.2[\%]; $r = 0.41$, $P < 0.11$). There was no significant relation between the pulse pressure and the regurgitant fraction or regurgitant orifice area.

**Figure 7.** Plot of linear regression between the % dynamic component ($D/D+S$) and regurgitant fraction with 95% confidence intervals ($y/\% = -0.98x/\% + 96.9/\%$; $r = -0.90, P < 0.0001$).

**Discussion**

Use of Doppler echocardiographic and MR techniques allowed determination of mean and interval retrograde flow and regurgitant orifice area in this population with chronic aortic regurgitation. The regurgitant orifice decreased from early to late diastole, with significant changes occurring in 50- to 100-millisecond intervals. The diastolic change in the orifice area was particularly prominent in individuals with mild regurgitation (small regurgitant fractions).

Several anatomic factors may influence the nature of the regurgitant orifice area. The aortic leaflets normally have a large area of tissue overlap, extending from the central third to the edge of each leaflet. When there is a deformity of the leaflets leading to regurgitation, coaptation is impaired, usually along the edges of two or more cusps. If the damage to the leaflets is extensive, the size of the defect between the leaflets may change very little in response to changing aortic diastolic pressure. In addition, calcification of the leaflets may restrict the extent of leaflet overlap.

The degree of leaflet coaptation is affected by distension (and relaxation) of the aortic annulus and the aortic root. In the normal subject, the aortic annulus and root expand in systole and relax in diastole. As the aortic annulus and root diminish in size, more surface area of the aortic leaflets will be available for coaptation. In individuals with mild aortic regurgitation, this mechanism for improving leaflet coaptation toward the end of diastole may be intact. As the annulus decreases in size, leaflet coaptation improves, and the regurgitant orifice area decreases. Patients with more severe degrees of regurgitation may have failure of appropriate aortic annular relaxation and greater degrees of aortic leaflet destruction, leading to only small changes in the diastolic orifice area during diastole.

In addition to the interaction of the orifice and aortic annulus, the etiology of valvular dysfunction may influence the behavior of the orifice. Patients enrolled in this study had a wide variety of valvular pathology; we were unable to determine if this dynamic behavior was dependent on valve morphology or on duration of disease.
Other factors potentially influencing the regurgitant orifice include aortic distensibility, left ventricular compliance, left ventricular performance, and systemic blood pressure. Our results indicate that regurgitant orifice area and regurgitant fraction are related inversely to the diastolic and mean blood pressure, which is not unexpected given the known relation of diastolic blood pressure to disease severity. There was a nonsignificant trend for the dynamic nature of the orifice to be related to the mean blood pressure. Given the small population size, we cannot exclude the hypothesis that systemic arterial pressure influences the dynamics of the orifice.

The patients included have a large variation in regurgitant severity as determined by the regurgitant fraction. Even when those patients with minimal aortic regurgitation (regurgitant fraction <10%) were excluded from the analysis, the inverse relation between the regurgitant fraction and orifice dynamics was still present, suggesting that our initial observation was not due to inclusion of patients with minimal disease.

**Study Limitations**

Estimation of the regurgitant orifice area as described in the study is dependent on the accurate measurement of regurgitant volume and the velocity of blood flow through the valve. Since MR and echocardiographic data could not be collected simultaneously, echocardiographic examinations were performed immediately before and after the MR examination. There was no significant change in blood pressure, heart rate, or continuous-wave Doppler derived VTIIs before or after the MR study, suggesting that this was a reasonable approach. This approach is also supported by previous data demonstrating that continuous-wave Doppler velocities of the aortic regurgitant jet correlate well with the predicted velocity based on the diastolic aortic to left ventricular pressure gradient measured in the catheterization laboratory.22 Diastolic forward flow was quite small in this population; therefore, defining antegrade flow as forward flow over the entire cardiac cycle (16 images) was reasonable.

MR flow quantification may be subject to potential sources of variability. Phase subimages were subjected to a zero-order phase correction based on the average phase value of pixels in and close to a nonmoving structure, the sternum.23 This offset should alleviate potential underestimation of the magnitude of blood flow. The phase delay in MR acquisitions was 15 milliseconds after the QRS trigger and the continuous-wave phase delay was set at 10 milliseconds. It was assumed that the 5-millisecond difference in phases between MR and continuous-wave Doppler measurements was negligible. If one calculates the interval regurgitant orifice areas by comparing regurgitant volume/aortic VTI_{i-n}, where n = the interval number, the same pattern of change in the regurgitant orifice area throughout diastole is still seen, indicating that minor phase errors would not significantly alter the study results.

Since the MR-derived flows were made on images acquired above the aortic valve, retrograde flow included coronary flow as well as flow into the root due to aortic distension. The effect of aortic distension is minimal because the aorta is actually getting smaller during diastole. The inclusion of coronary flow in the measured flow will make the estimated regurgitant orifice area slightly larger than the true area but should lead to only a minor difference in this population with mean retrograde volumes of 67 mL per beat. In patients with aortic regurgitation, there is a shift from diastolic to systolic predominance in coronary flow, with an increase in total coronary flow.21,22 If one subtracted a constant value of coronary flow from each diastolic interval, the pattern of decrease in orifice area during diastole would not change, but the magnitude of that change would vary slightly.

The normal coronary artery flow velocity pattern, however, has the highest velocities early in diastole, with a decrease in velocity throughout diastole. In severe aortic regurgitation, the end-diastolic flow velocities approach zero.23 Total coronary flow patterns have been described using catheter thermodilution and coronary venous MR phase mapping.24,25 Based on quantitative data from these studies,22-25 the three patients with the smallest degree of aortic regurgitation would have negligible regurgitant aortic valve flow throughout part or most of diastole. For patients with moderate or severe aortic regurgitation, accounting for coronary flow decreases the magnitude of the dynamic component of the regurgitant orifice but will not eliminate the observed relation between the dynamic component of the orifice area and regurgitant fraction described in this study.

**Conclusions**

The regurgitant fraction, regurgitant volume, and regurgitant orifice area can be estimated noninvasively in patients with aortic regurgitation using these two imaging techniques. These data may be useful in patient management, especially when other imaging techniques are inadequate. While the decrease in regurgitant orifice area during diastole may be related to decreasing aortic annular distension with declining diastolic aortic pressure, the etiology of valvular dysfunction, aortic and left ventricular compliance, and systemic blood pressure may also influence the changes in the aortic orifice. In those individuals with a dynamic orifice, techniques that depend on the instantaneous maximal abnormal diastolic velocity disturbance in the left ventricular outflow tract (such as color Doppler echocardiography or the observation of signal voids on MR images) to determine aortic regurgitant severity may overestimate disease severity because the size of the velocity abnormality may reflect peak rather than the mean orifice area.11,26,27 Changes in the regurgitant orifice area throughout diastole may also explain, in part, the temporal variability in size and persistence of color Doppler jets in aortic regurgitation.28 Future work will be required to determine the importance of the dynamic component of the regurgitant orifice and the influence of medical therapy on the changes in the orifice area.

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