Influence of Aortic Pressure on Effective Regurgitant Orifice Area in Aortic Regurgitation

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Background. The regurgitant volume in aortic regurgitation is determined by the diastolic filling period, the pressure gradient between the left ventricle and aorta, and the hemodynamic size of the regurgitant orifice area.

Methods and Results. To test the hypothesis that the aortic regurgitant orifice area is related to aortic pressure and aortic root size, 16 fresh calf heart and aorta specimens were studied in vitro using a continuous-flow system over a range of aortic pressures. Regurgitant orifice areas were calculated as the ratio of flow divided by peak velocity through the valve measured by image-guided continuous-wave Doppler, and aortic root areas were measured by two-dimensional echocardiography. When the defect was created at the edge of the noncoronary leaflet (n=10), regurgitant orifice area gradually increased 51±33% when aortic pressure was increased from approximately 40 to 152 cm of water (29.6 to 112.5 mm Hg) (p<0.0001). Similarly, the aortic root size increased 82±29% when the defect was created at the leaflet edge (p<0.0001). In contrast, when defects were created at the center of the noncoronary leaflet (n=6), only a small increase in regurgitant orifice area (9±7%) was observed with increasing pressure (p=0.043). The aortic root area remained strongly pressure dependent in specimens with defects at leaflet centers (p<0.0001).

Conclusions. The aortic regurgitant orifice area is dependent on both aortic pressure and the nature of the defect in the valve. Because not all regurgitant aortic valves are alike, further study of the nature of the regurgitant orifice area in humans may allow identification of patients who would benefit most from aggressive pharmacological therapy. (Circulation 1992;85:1565-1571)

KEY WORDS  • Doppler • echocardiography • hemodynamics • aortic valve disease

Evaluating the severity of aortic regurgitation is a common and difficult clinical problem. Several methods such as radionuclide ventriculography, Doppler echocardiography, and contrast aortography are currently used to provide quantitative or semiquantitative estimates of regurgitant fraction and volume.1-4 However, the regurgitant volume is influenced by several important variables including the pressure gradient between the aorta and left ventricle in diastole, the length of the diastolic filling period, and the hydrodynamic size of the aortic valve regurgitant orifice area,6 potentially limiting its clinical usefulness as a means of stratifying patients with aortic regurgitation.

It is possible that the regurgitant orifice area is a more reliable parameter than regurgitant volume for grading the clinical severity of aortic regurgitation. Advances in Doppler and magnetic resonance velocimetry techniques may allow estimation of the size of the regurgitant orifice area in patients with aortic regurgitation.6,6,7 Gaasch and Levine4 have proposed that “some patients with chronic aortic regurgitation (for example, those with aortic root diseases) may have a dynamic aortic regurgitant orifice area that responds to changes in aortic and/or ventricular dimensions.” Recently, a study of retrograde aortic flow in a sheep model of acute aortic regurgitation suggested that the regurgitant orifice area is, in fact, influenced by loading conditions; the pathophysiological mechanism for this effect is unclear.8 This study was designed to test the hypothesis that the aortic regurgitant orifice area is related to aortic pressure and aortic root size and to examine the effect of the position of the defect within the valve leaflet.

Methods

Specimens

Sixteen heart and aorta specimens from 2–3-month-old calves (35–45 kg) were obtained at the time of killing at a local slaughterhouse and studied within 2–24 hours of harvest. Part of the descending aorta was used to support the specimen because the ascending aorta of the calf is short. The aorta was cut to a length of 15 cm measured from the origin of the coronary arteries, and all branches were ligated. After dissecting free the atria, pericardium, and excess connective tissue, the coronary arteries were ligated at their origins. All specimens had a patent ductus arteriosus, which was suture-ligated and divided. The right ventricle was excised, leaving only the origin of the pulmonary artery. The left ventricle was
Experimental Apparatus

A continuous-flow system with normal saline solution maintained at 37°C and cornstarch (1%) for acoustic

FIGURE 1. Schematic diagram of the aortic valve with the two types of defects created. Shaded areas represent defects. RCA, right coronary artery; LCA, left coronary artery; RCC, right coronary cusp; LCC, left coronary cusp; NCC, noncoronary cusp.

opened by a vertical incision through the anterior wall leaving intact the papillary muscles, including the attachments of the anterior mitral leaflet. The specimen was then tested for leaks, which were ligated when present. Aortic regurgitation was created in 10 hearts by excising a portion of the edge of the noncoronary cusp (Figure 1). In six additional hearts, the defect was created at the center of the noncoronary cusp using circular punch biopsies with known diameters (0.2 cm, 0.3 cm, and 0.4 cm). Three rigid, precision-machined, acrylic models (Figure 2) with axisymmetric stenoses of known diameters (0.2 cm, 0.4 cm, and 0.6 cm) served as controls.

FIGURE 2. Schematic diagram of the rigid acrylic model used as control; d, known orifice diameter (0.2 cm, 0.4 cm, or 0.6 cm).

FIGURE 3. Schematic diagram of the continuous-flow system used to measure effective regurgitant orifice area (not drawn to scale). Arrows denote direction of fluid flow. Fluid used was normal saline-cornstarch (1%) solution.

reflection9,10 was used (Figure 3). The system consisted of three tanks; the highest tank was a supply reservoir providing a source of constant pressure for the models and specimens. A second tank served as the chamber where the rigid acrylic models and calf specimens were investigated, and the third tank served as a collection reservoir. The height of the fluid column between the tanks was altered to vary pressure and flow at the level of the aortic valve. To minimize errors caused by viscous pressure loss in the system, pressure was measured from a tube manometer (internal diameter, 1.25 cm) that was attached to the models or hearts via a T-connector. A 5-cm length of 1.0-cm internal diameter tubing and a 15-cm segment of aorta served as the "ascending aorta" above the aortic valve. At each pressure, the system was allowed to stabilize for at least 15 minutes before flow and velocity measurements were taken.

Measurements

Two-dimensional echocardiographic images of the aortic root were obtained by scanning down the aorta in the transverse plane (short axis) until the aortic leaflets were first noted. Volumetric flow (milliliters per second) through the control models and aortic valve defects was obtained by measuring the tank overflow. Because a pressure recovery effect caused by conservation of momentum can lead to a decrease in pressure in a jet relative to the static fluid pressure in the tank, the orifice areas were not calculated from velocities derived from the hydrostatic pressure gradient by the Bernoulli equation11; instead, peak velocities of flow through the rigid models and the aortic valve defects were directly measured with imaging continuous-wave Doppler using a Hewlett-Packard Sonos 1000 phased-array ultrasonoscope with a 2.5-MHz transducer. The optimal transducer position was obtained by scanning the color Doppler flow map and two-dimensional image in multiple planes to obtain the peak velocity of the aortic
regurgitant jet. Peak velocity and flow measurements were initially obtained at the highest pressure and subsequently obtained with sequential decreases to the lowest aortic pressure. Measurements were performed for each model and specimen at nine different pressures ranging from 40 to 152 cm of water (29.6 to 112.5 mm Hg) and recorded on standard half-inch videotape for later analysis.

In certain biomechanical studies of the stress-strain relation, particularly when testing a biological tissue in tension, the first set of measurements are different from succeeding sets. This phenomenon may be due, in part, to the rearranging of tissue fibers in response to changes in stress; energy stored as strain energy is therefore not completely recovered when stress is decreased. Each specimen in this study was preconditioned with two cycles from zero pressure to the highest pressure before measurements were taken. Ten of the specimens had additional measurements made during a third cycle by increasing pressure again from the lowest to highest level. This also allowed an evaluation of the stability of the system over the entire duration of the experiment (6–8 hours).

Calculations

Using an off-line digitizing computer system (GTI Freeland Medical Division, Indianapolis, Ind.), the aortic root area was measured by planimetry from the two-dimensional echocardiographic short-axis views. The mean of five measurements at each pressure was obtained from the inner border of the aorta. The mean of seven flow and three to seven velocity measurements at each pressure was obtained for all control models and calf specimens and was used to calculate the effective regurgitant orifice area

\[
\text{EROA} = \frac{Q}{V}
\]

where EROA=effective regurgitant orifice area in square centimeters, Q=flow in milliliters per second, and V=velocity in centimeters per second.

The pressure-strain elastic modulus (E_p) is a parameter that relates changes in arterial dimensions to changes in intra-arterial pressure; it is a measure of the stiffness of the vessel; as the stiffness of the vessel increases, the pressure-strain elastic modulus increases. For the purpose of comparison with previous studies of aortic elasticity, E_p was calculated as the ratio of the change in mean aortic pressure to the change in aortic root diameter

\[
E_p = \frac{\Delta P}{\Delta D/D}
\]

where \(\Delta P\)=change in pressure between the two measurements, \(\Delta D\)=change in diameter between the two pressures, and D=aortic root diameter at the highest pressure.

The change in pressure was obtained from the highest pressure (125–152 cm of water; 92.5–112.5 mm Hg) and the pressure midway (74–89 cm of water; 54.8–65.9 mm Hg) between the highest and lowest obtainable pressures.

FIGURE 4. Graph of calculated orifice area based on measured flow rate and velocity for the rigid models versus pressure. Filled circles (○) represent the model with 0.2-cm orifice diameter; filled squares (■), 0.4-cm orifice diameter; filled triangles (▲), 0.6-cm orifice diameter. EROA, effective regurgitant orifice area.

Statistics

Data from models, edge defect specimens, and center defect specimens were analyzed with a random-effects regression model using Program 5V of the BMDP statistical analysis software (BMDP Statistical Software, Inc., Los Angeles, Calif.). Orifice area and aortic root area were regressed on level of pressure. An additional random-effects regression analysis that included the interaction of pressure and type of defect (center versus edge) was performed to test the difference in slopes between the two types. To evaluate the reproducibility of measurements in the 10 specimens with an additional cycle of measurements, a repeated-measures regression model with a compound symmetry covariance matrix was used to evaluate the difference between the two sets of measurements. A probability value less than 0.05 was considered statistically significant.

Results

Rigid Models

For all pressures, the mean effective regurgitant orifice area was 0.032±0.001 cm² for the 0.2-cm-diameter model (anatomic defect area, 0.031 cm²). For the 0.4-cm-diameter model (anatomic defect area, 0.126 cm²), the mean regurgitant orifice area was 0.088±0.003 cm²; for the 0.6-cm-diameter model (anatomic defect area, 0.283 cm²), it was 0.248±0.007 cm². For these rigid models, there was no significant change in orifice area over the range of pressures tested (\(p=\text{NS}\)) (Figure 4).

Calf Heart Specimens

Leaflet edge defect. When defects were created at the edge of the noncoronary cusp, the effective regurgitant orifice area ranged from 0.078±0.045 cm² at the lowest
pressure to 0.109±0.064 cm$^2$ at the highest pressure. In the edge defects, there was a highly statistically significant change in effective regurgitant orifice area over the range of pressures studied (p<0.0001) (Figure 5A). The mean percent increase of the effective regurgitant orifice area from lowest to highest pressures was 51±33%. The results of random effect regression yielded the average regression line

$$\text{EROA (cm}^2\text{)} = 3.5 \times 10^{-4} \text{(pressure in cm of water)} + 0.061$$

Increases in aortic root size with increasing pressure were associated with increases in regurgitant orifice area in the edge defect specimens. There was a statistically significant increase in aortic root area from 4.0±1.0 cm$^2$ at the lowest pressure to 7.2±2.0 cm$^2$ at the highest pressure (p<0.0001) (Figure 5B). The mean percent increase of the aortic root area was 82±29%. The average relation of aortic root area to pressure was

$$\text{Aortic root area (cm}^2\text{)} = 0.03 \text{(pressure in cm of water)} + 2.6$$

Leaflet center defect. When defects were created at the center of the noncoronary cusp, the effective regurgitant orifice areas varied with the size of the bioplane punch. For each size of bioplane punch, two specimens were studied. For 0.2-cm-diameter punches, the effective orifice areas in the two specimens at the lowest pressures were 0.033 and 0.043 cm$^2$. For 0.3-cm-diameter punches, the effective orifice areas were 0.074 and 0.083 cm$^2$ and for 0.4-cm-diameter punches, the effective orifice areas were 0.154 and 0.176 cm$^2$. There was a borderline statistically significant change in the effective regurgitant orifice area over the range of pressures studied (p=0.043) (Figure 6A). The mean percent increase of the effective regurgitant orifice area for center defect specimens from lowest to highest pressures was 9±7%. The results of random-effects regression for center defects yielded the average regression line

$$\text{EROA (cm}^2\text{)} = 9 \times 10^{-5} \text{(pressure in cm of water)} + 0.092$$

In specimens with center defects, increases in aortic root size with increasing pressure were similar to increases in aortic root size in specimens with edge defects (Figure 6B). The aortic root area increased from 4.4±0.6 cm$^2$ at the lowest pressure to 8.7±1.6 cm$^2$ at the highest pressure (p<0.0001). The mean percent increase of the aortic root area was 89±30%. The average relation of aortic root area to pressure was

$$\text{Aortic root area (cm}^2\text{)} = 0.04 \text{(pressure in cm of water)} + 2.2$$

Pressure–Strain Elastic Modulus

$E_p$ was calculated for the aortic root in the edge defect specimens and center defect specimens. For edge defect specimens, $E_p$ was 400±119 g/cm$^2$. For center defect specimens, $E_p$ was 304±41 g/cm$^2$.

There was an excellent correlation between the continuous-wave Doppler velocity measurements and the calculated velocities using the modified Bernoulli equation for each change in pressure: calculated velocity in
centimeters per second=0.96(measured velocity in centimeters per second)+14 (r=0.98). To evaluate the reproducibility and stability over time of the system, additional measurements were made in 10 of the 16 heart specimens. Regression analysis of regurgitant orifice area versus pressure using a repeated-measures model demonstrated no statistically significant changes in the means or slopes when compared with the previous measurements in both center and edge defect types. In addition, similar analysis of aortic root area versus pressure demonstrated no significant changes when compared with the initial measurements.

**Discussion**

The effective orifice area may be calculated from Toricelli's equation as the ratio of flow to velocity through an orifice. Hemodynamic orifice area measurements in aortic stenosis have proven valuable in clinical cardiology; however, it has been well established that stenotic valve areas are influenced by pressure and flow conditions. Regurgitant orifice areas have not been easily quantitated in patients, primarily due to the lack of a reliable method of measuring total regurgitant flow (in contrast to peak regurgitant flow velocity, which can be readily measured by continuous-wave Doppler). Advances in magnetic resonance velocimetry and Doppler techniques may allow the estimation of the effective aortic regurgitant orifice area by measuring regurgitant flow in the ascending aorta and applying the continuity equation. The aortic regurgitant orifice area estimated with the ascending aorta Doppler catheter technique compares favorably with aortography as an indicator of the severity of aortic regurgitation; however, this technique is invasive and not suitable for serial evaluations in patients. In addition, the Doppler catheter technique assumes a blunt retrograde velocity profile; this assumption breaks down when the aorta is severely dilated. Velocity-encoded cine magnetic resonance has the unique capability of measuring ascending aortic regurgitant flow noninvasively. In addition, this method may allow description of complex flow profiles (such as in dilated aortas) and may be ideal for serial noninvasive evaluations of regurgitant flow in patients. At the current time, velocity-encoded cine magnetic resonance is a research tool that is not available for routine use.

It is important to note that the effective regurgitant orifice area is not the actual anatomic regurgitant orifice area; rather, it is the hemodynamic area that corresponds to the area of the vena contracta. The vena contracta is smaller than the anatomic orifice area because of streamline convergence through a constriction.

This study focused on the behavior of the effective regurgitant orifice area and its relation to aortic distending pressure, aortic root area, and the position of the defect in the valve leaflet. For defects at the tips of the aortic valve leaflet, the effective regurgitant orifice and aortic root areas varied with changes in distending pressure; an increase in aortic pressure increased both the effective regurgitant orifice area and aortic root size. It is likely that the effective regurgitant orifice area in leaflet edge lesions is influenced by aortic root dynam-
ics. At high pressures, the aortic root is distended, probably decreasing the amount of leaflet area available to seal the valve through leaflet coaptation. A critical pressure may be reached in which annular dilatation produces functional aortic insufficiency, presumably through ineffective coaptation. A defect at the tips of the leaflet is exposed maximally at high aortic pressures, leading to a larger effective regurgitant orifice area.

The present study demonstrated that lower aortic pressure may decrease the effective regurgitant orifice area by limiting aortic root distention and improving leaflet coaptation when the regurgitation occurs between leaflets; this may be one of two mechanisms of reducing the severity of aortic regurgitation through vasodilator therapy. The other mechanism, reduction of total regurgitant flow by reducing transvalvular pressure, will be important regardless of whether the regurgitant orifice area is pressure dependent or not.

In contrast, defects at the center of the leaflet demonstrated only a small (but statistically significant) dependence on aortic pressure despite significant changes in aortic root area. It is likely that defects at the center of the leaflet are not profoundly influenced by aortic root changes because these defects are farther from the area of leaflet coaptation. The small variations in regurgitant orifice area in response to aortic pressure may be due, in part, to strains at the boundary of the defect within the leaflet itself. Normal function of the aortic valve depends on the complex relation of several structures. The participation of the aortic root in allowing normal leaflet coaptation may be most apparent in patients with aortic root dilatation. Roman et al. noted that aortic root dilatation is a common cause of severe aortic regurgitation "in which greater degrees of root dilatation cause greater geometric distortion of the structures supporting the aortic valve cusps, leading to a larger regurgitant volume." In fact, Thubrikar and Brewer have demonstrated that aortic annular distention, aortic leaflet integrity, and leaflet mobility greatly influence one another. Furthermore, dynamic changes occurring superior to the aortic annulus as well as in the left ventricular outflow tract could affect aortic valve function. It is also important to consider that the natural history of the aortic regurgitant orifice area in patients has not been documented; it is possible that both the regurgitant orifice area and the regurgitant volume change over time. This may limit the value of these parameters for stratifying patients, particularly because the natural history of this disease may span several decades.

It is useful to compare the pressure–strain moduli of this study with previous studies of aortic biomechanics. In this study, the calculated \( E_p \) was 400 \pm 119 g/cm² for the aortas with edge defects and 304 \pm 41 g/cm² for aortas with center defects. These values are comparable with \( E_p \) values of 618 g/cm² obtained by Kalath et al. in the human aortic root and ascending aorta and 711 g/cm² obtained by Gozna et al. in the human ascending thoracic aorta. The lower \( E_p \) values indicate that the calf aortas are less stiff, probably because of the young age of the calf specimens, and \( E_p \) varies within species and with age.

**Limitations**

Several potential limitations in this study should be considered. First, a continuous-flow system was used; the experimental apparatus was not designed to evaluate viscoelastic properties of the effective regurgitant orifice. It is possible that the aortic valve apparatus behaves relatively elastically, so that the diastolic blood pressure dominates the stress–strain relation. However, if the system behaves in a viscoelastic manner, with long relaxation time constants, the mean blood pressure may dominate this relation. Further studies in a pulsatile-flow system or in vivo may be necessary to distinguish these possibilities.

Second, the specimen was suspended so that the natural curvature of the aorta was altered. It is possible that distorted retrograde flow profiles in patients with aortic regurgitation may influence the fluid dynamics of a diseased valve with a particular geometry; flow profiles in these patients have not been well described. Although at the Reynolds numbers in this study the flow was most likely relatively blunt, given the short entry region, it is possible that flow disturbances in this system (such as those caused by the tubing junctions) were present at the regurgitant orifice area. However, the experimental design for all models and specimens was identical, so that any effect of flow disturbances would be present in all experiments.

Finally, a saline–cornstarch solution such as the one used in this study has a different kinematic viscosity than blood. Under certain flow conditions, the effective orifice area will change despite no change in the actual orifice area; this effect is dependent on the Reynolds number and, therefore, the kinematic viscosity. However, at the Reynolds numbers (>3,000) in this study, changes in contraction or discharge coefficients could account for only a small portion of the changes observed in effective orifice area; this effect was not significant in the rigid models and was most likely trivial compared with changes in true orifice area in the specimens.

**Clinical Implications**

These data support the hypothesis that aortic root size and loading conditions influence the effective aortic regurgitant orifice area. Because the regurgitant orifice area and the driving pressure operating at the orifice are the determinants of the regurgitant volume, it is possible that in patients with aortic regurgitation, reduction of the regurgitant volume with vasodilators may be achieved through reduction of both the effective regurgitant orifice area and afterload. In fact, short-term studies by Miller et al. using sodium nitroprusside and Reske et al. using captopril have shown beneficial effects such as decreases in regurgitant and end-diastolic volumes in patients with aortic regurgitation. A long-term study by Scognamiglio et al. also showed reduction in left ventricular end-diastolic volume index and mass and reversal of left ventricular dilatation and hypertrophy after treatment with nifedipine.

Because not all regurgitant valves are alike, it is possible that some patients will benefit from afterload reduction more than others. Except for some congenitally deformed aortic valves or valves perforated by infective endocarditis, defects at the center of the leaflet are not common sites of aortic regurgitation. Aortic root dilatation is a common cause of chronic, severe aortic regurgitation, probably from edge defects caused by a distended aortic root and decreased aortic leaflet coap-
tation. It is therefore likely that the reduction in orifice area with vasodilators would be more apparent in patients with distensible aortic roots or with aortic leaflet edge defects or both. In contrast, the effective regurgitant orifice area in patients with aortic regurgitation from center defects may change little despite vasodilator therapy because the regurgitant orifice area may be less pressure dependent. It is also possible that the aortic regurgitant orifice areas in patients with bioprosthetic or heavily calcified aortic valves may be less pressure dependent and exhibit little change with vasodilator therapy because their annuli are rigid, although this was not investigated in this study. Furthermore, the behavior of the regurgitant orifice area in unstented homografts is not known. It is important to note that all patients may benefit significantly from vasodilator therapy because total regurgitant flow will decrease as the diastolic transvalvular pressure gradient is reduced. However, further characterization of the nature of the regurgitant orifice area in humans may allow identification of subsets of patients who will derive the additional benefit of a smaller regurgitant orifice area from aggressive pharmacological therapy.

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