Acknowledgments

The authors gratefully acknowledge Marie Coscia for preparing the manuscript; we thank the technicians in the Cardiac Electrophysiology Laboratory; and especially thank John A. Kastor, M.D., Chief of the Cardiovascular Section, for his continued support and encouragement.

References

Quantification of Aortic Valvular Regurgitation in Dogs by Nuclear Imaging

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SUMMARY Radionuclide gated cardiac blood pool (GBP) imaging was used to quantitatively assess the severity of acute aortic valvular regurgitation produced experimentally in 10 anesthetized dogs. Right ventricular (RV) and left ventricular (LV) stroke counts (end-diastolic minus end-systolic counts in RV and LV regions of interest) were used as indices of the stroke volumes of the two ventricles. Regurgitant fraction (RFGBP) was derived by assuming that an excess of LV stroke counts compared to RV stroke counts was due to regurgitant flow: RFGBP = LV stroke counts - RV stroke counts/LV stroke counts × 100. Regurgitant fraction (RFEMF) was also estimated directly from an electromagnetic flowmeter (EMF) on the ascending aorta. Mean RFEMF was 55.8 ± 17.9% (±SD). Close agreement was found between regurgitant fractions measured by GBP and EMF (RFGBP = 1.09, RFEMF - 4.7%, r = 0.88, p < 0.001, SEE = 9.98%). The severity of regurgitation from blood pool images also correlated closely with aortic pulse pressure (r = 0.89) and the length of the tear in the aortic valve (r = 0.84). These results suggest that blood pool imaging may be useful for noninvasive quantification of regurgitant flow in patients with valvular insufficiency.

NONINVASIVE ASSESSMENT of the severity of aortic and mitral regurgitation in patients is usually based on clinical evaluation, supplemented by indirect techniques such as electrocardiography, chest radiography, and echocardiography, which assess the effects of regurgitation and other factors on ventricular myocardium and chamber size, but which do not measure regurgitation directly. Quantification of regurgitation in man is most often based on measurements of total left ventricular stroke volume and effective forward stroke volume. This requires invasive cardiac catheterization with biplane cineangiography and measurement of forward cardiac output by indicator dilution or Fick techniques. Unfortunately, this quantitative ventriculographic approach is technically difficult and most angiographers therefore use some form of subjective grading of the severity of regurgitation.

A new, noninvasive method for measuring the severity of mitral and aortic regurgitation based on nuclear imaging has been recently described. The difference in activity measured within end-systolic and end-diastolic areas of interest over the left and right ventricles are measured from a gated blood pool image. Since the blood pool activity is proportional to blood volume, a left ventricular/right ventricular...
(LV/RV) stroke volume ratio can be derived from the differences in counts. The LV/RV ratio was found to be only slightly greater than 1 in the absence of mitral and/or aortic regurgitation, whereas a significantly elevated ratio was obtained in the presence of regurgitation. The degree of elevation of the ratio corresponded to the degree of regurgitation assessed subjectively from ventriculography in the same patients. In the current study, the method was examined in an experimental model of aortic regurgitation. The imaging technique was compared directly to flow probe measurements, aortic pulse pressures and the size of the experimentally produced lesions in the aortic valve.

Methods

Ten adult mongrel dogs were anesthetized with 30 mg/kg sodium pentobarbital and maintained on intermittent positive pressure ventilation with room air. After left thoracotomy, acute aortic valve regurgitation was produced using an adaptation of the technique of Williams. A polyurethane tube (internal diameter 0.070 inches) was advanced from the right carotid artery until the tip was on the aortic valve cusp. In initial experiments, its position was verified with hand injection of meglumine diatrizoate (Renografin 76) during fluoroscopy. In later experiments, manipulation of the polyurethane catheter into the supra-aortic position was achieved simply by palpation of the ascending aorta without using fluoroscopy. After positioning, an instrument (fig. 1) composed of three pieces of wire (25 inches long with diameter of 0.014 inches) soldered at one end to an 18-gauge needle, was passed through the polyurethane tube until it punctured the cusp and passed into the left ventricle. One of the three wires was then withdrawn slightly, causing the others to bulge. This bulging wire assembly was then withdrawn through the narrow slit in the aortic valve, tearing the aortic cusp. Regurgitation was confirmed by observing retrograde flow of a supra-aortic hand injection of contrast material into the left ventricle.

Peak aortic systolic and end diastolic pressures were measured through a polyurethane catheter in the ascending aorta, connected to a Statham P23Db transducer and calibrated against a mercury manometer. Aortic pulse pressure was determined as peak systolic minus end diastolic pressures (mm Hg).

Aortic blood flow was obtained from a sine wave electromagnetic flowmeter (Biotronix BL-613) with cuff-type flow transducers placed snugly around the ascending aorta immediately above the aortic valve. Zero flow was obtained mechanically by brief cross-clamping of the aorta downstream from the flow probe before and after inducing aortic regurgitation. Aortic flow, pressure, and a limb lead ECG were recorded simultaneously on a Brush 200 direct writing recorder (Gould, Inc.) at paper speeds of 25, 100 and 200 mm/sec.

Regurgitant fraction was estimated from the aortic flow tracings as the ratio of the area below the zero line (i.e., negative or regurgitant flow) to the area above the zero line during the preceding systolic ejection period (total forward stroke volume) (fig. 2). Because coronary blood flow was ignored, the measured regurgitant fraction probably slightly overestimated the true amount of aortic regurgitation. Results were expressed as the mean of five successive cardiac cycles, measured by planimetry using a Hewlett-Packard digitizer. Observer reproducibility of the planimetric method was good; in 10 repeated measurements on one cardiac cycle the coefficient of variation was 2%. Beat-to-beat variation in regurgitant fraction calculated over 10 consecutive cycles in two dogs was small (coefficient of variation 6%). Reproducibility of the regurgitant fraction measured by flow probe was tested in one dog using five aortic cross-clamp zero reference measurements during separate 20 minute periods after creation of mild and severe regurgitation, and was small (coefficients of variation 9% and 9%, respectively).

After equilibration of 10 mCi technetium-99m-labeled human serum albumin, gated blood pool images were acquired in the anterior and 10° left anterior oblique views with the dog in the supine position. A mobile Ohio-Nuclear Series 420 scintillation camera

Figure 1. The device used to create aortic valve rupture. Tightening of one of the three wires after the instrument has pierced the cusp causes a loop to form that ruptures the leaflet as it is withdrawn.
interfaced to a Medical Data Systems computer (MUGA Cart) and an R-wave triggering device (Brattle Instrument Corporation) was used to obtain images at a framing rate of 14 frames/RR interval and a counting rate of 300,000 counts/frame. Cinematic images were examined to determine the best view for separation of left and right ventricles (usually the anterior view in these dogs). Regions of interest were created with a light pen over the left and right ventricles in the end diastolic image, taking care to avoid the atria and major vessels (fig. 3). This was done by switching back and forth between end-diastolic image, end-systolic image, difference image (end-diastolic minus end-systolic), and the cinematic display to maximize definition of the ventricular areas. The atria and great vessels were recognized by their anatomic appearance, and in addition, the atria demonstrated an increase in activity during ventricular systole. Care was also taken to make the lower edges of the ventricular regions of interest generous, so as to include all of the respective ventricular activity. The difference between end-diastolic and end-systolic counts was calculated and expressed as the LV/RV stroke volume ratio

\[
\frac{(LV \text{ diastolic} - LV \text{ systolic counts})}{(RV \text{ diastolic} - RV \text{ systolic counts})}.
\]

Regurgitant fraction was calculated by the formula:

\[
\frac{LV \text{ count difference} - RV \text{ count difference}}{LV \text{ count difference}} \times 100
\]

Regions of interest were outlined twice in each image and the mean of the two regurgitant fractions calculated. In one dog, the image was outlined by a single observer 10 times to determine reproducibility of the regurgitant fraction. The coefficient of variation was 8%. Interobserver variation was calculated from independent measurements by two observers, without knowledge of the flow probe data or whether the images were pre- or postregurgitation. The correlation coefficient was 0.89 \((y = 1.06x - 0.18)\). Areas of interest were also outlined in the left and right lung adjacent to the heart to determine whether there were any changes in extracardiac background counts during the cardiac cycle that might affect the LV/RV ratio.

In seven dogs a single tear was made in the aortic valve and blood pool images were obtained. In three dogs, mild aortic regurgitation was created with one tear, followed by more severe regurgitation with a second tear. Blood pool images were recorded at each level of severity.

After sacrifice of the dogs, the hearts were examined to measure the dimensions of the aortic cusp defect and the inner circumference of the aorta. Congenital intracardiac shunts were excluded. In one dog, a technical fault with the electromagnetic aortic probe precluded any flow measurements, but the data from the images were included in comparisons with pulse pressure changes and the autopsy dimensions of the valve defects.

**Results**

Table 1 summarizes the pressure, flow and radionuclide measurements in each dog.

Acute aortic regurgitation produced a rise in mean \((\pm SD)\) aortic pulse pressure from 23 ± 4 to 61 ± 22 mm Hg. In three dogs the initial valve defect was small, producing a change in mean pulse pressure from 25 ± 2 to 41 ± 2 mm Hg, and regurgitation was increased by rupturing a second cusp (two dogs) or enlarging the initial defect (one dog). This produced an increase in mean pulse pressure to 82 ± 9 mm Hg.

The mean regurgitant fraction measured by flow probe was 56 ± 18% (range of 16–79%). Simultaneous mean regurgitant fraction by blood pool imaging was similar (59 ± 20%). There was a highly significant correlation between the radionuclide and the flow probe technique for quantitating regurgitant flow \((r = 0.88, p < 0.001, \text{SEE} = 9.98)\) (fig. 4). There was

![Figure 2](http://circ.ahajournals.org/lookup/suppl/doi:10.1161/01.CIR.61.2.406/-/DC1/fig2.jpg)

**Figure 2.** Aortic flow tracing from a dog after moderate aortic regurgitation. Zero flow is obtained by aortic cross clamp. Regurgitant flow volume is represented by area R and total forward flow or stroke volume by area F.
also a significant correlation between the degree of regurgitation measured by the LV/RV ratio and the magnitude of the aortic pulse pressure ($r = 0.89$, $p < 0.001$) (fig. 5). There was no significant difference in background activity between end-diasstole and end-systole in either the left (3551 ± 705 to 3529 ± 659 counts) or right (3082 ± 895 to 3115 ± 921 counts) lung adjacent to the heart. Thus, the changes in counts in the left and right ventricular areas of interest used to derive the regurgitant fraction did not appear to be influenced by fluctuation in background activity during the cardiac cycle.

Autopsies showed varying degrees of valve defects, ranging from a small central hole to complete severance of the cusp from its aortic attachment. The defects usually consisted of a linear tear either in the middle of the cusp or at its junction with the aortic wall, producing a defect that was probably elliptical in vivo (fig. 6). The maximum length of each defect was measured and normalized for the mean internal aortic circumference at the aortic ring, which was 42.6 ± 2.8 mm for all dogs. The normalized defect length varied from 1–19 mm. The regurgitant fraction determined from the blood pool images correlated well with this anatomic measurement of aortic insufficiency ($r = 0.84$, $p < 0.001$) (fig. 7).

**Discussion**

The results of this study indicate that aortic valvular regurgitation can be quantified noninvasively from radionuclide gated blood pool images by comparing the stroke volumes, determined by activity measurements, of the left and right ventricles. Close agreement was found between regurgitant fractions calculated by this method and those measured from electromagnetic flowmeter tracings. Regurgitation measured from blood pool images also correlated closely with aortic pulse pressure and with the length of the tear produced in the aortic valve. The results of

<table>
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<tr>
<th>Dog</th>
<th>LV/RV ratio</th>
<th>Regurgitant fraction (GBP) %</th>
<th>Regurgitant fraction (flow probe) %</th>
<th>Aortic pulse pressure (mm Hg)</th>
<th>Normalized length of aortic cusp defect (mm)</th>
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<td>Postregurgitation</td>
<td></td>
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<td>Postregurgitation</td>
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Dogs 7, 9, and 10 had an initial valve defect created (a), followed by a larger defect (b). Abbreviations: LV/RV = left ventricular/right ventricular; GBP = gated blood pool; NR = no regurgitation.
this study extend our previous experience in patients with left-sided valvular regurgitation.

In dogs, the mean LV/RV ratio before aortic regurgitation was higher than the theoretical expected value of 1.0, an observation similar to one made in patients without valvular regurgitation. This discrepancy is attributable to an inappropriately low value for RV stroke volume. Because of partial inclusion of the right atrium within the RV region of interest, RV systolic counts are probably overestimated and RV stroke counts underestimated. In addition, because of partial overlap of the RV outflow tract and aortic root, the superior portion of the RV cannot be included in the RV region of interest. To obtain ideal LV/RV stroke volume ratios, our method theoretically requires that selected regions of interest include all activity coming from the respective ventricle, but at the same time exclude any nonventricular activity that changes during the cardiac cycle. We used a fixed region of interest constructed on the end-diastolic image rather than variable regions for end-diastole and end-systole. This approach was chosen because of its simplicity and also because of the poor edge definition of the right ventricle at end systole in dogs. The fixed region of interest method assumes that during the cardiac cycle, the background activity surrounding each ventricle does not change significantly. This was confirmed in the current study, as well as in our previous study in patients. Using a fixed region of interest, the contribution of background activity to total activity is essentially equal at end-diastole and end-systole. Thus, the difference in activity between these two times represents the change in ventricular volume. Using variable regions of interest has the theoretical advantage of more precise definition of ventricular borders, but the complexity is increased considerably because six regions of interest must be outlined (LV and RV end-diastolic regions, LV and RV end-systolic regions, and LV and RV background regions) instead of two. This approach requires proper background subtraction to measure correctly the change in ventricular activity because the number of matrix points in the end-diastolic and end-systolic images are not the same.

Clinical assessment of valvular regurgitation is often unreliable and several methods for quantitating regurgitant flow have been described, including indicator dilution techniques, contrast radiography, and analysis of aortic and peripheral pulses. More recently, Doppler echocardiography and radionuclide techniques have been suggested. None has been completely satisfactory.

Most widely used are the radiologic techniques that are based on measurement of total stroke volume from biplane cineangiography and effective stroke volume from cardiac output determinations. The cineangiographic volume determinations are based on geometric assumptions that are not always valid. Honey et al. reported that ventricular cineangiography was inaccurate in quantitating mitral regurgitation, and many prefer to make only a subjective assessment of the severity of regurgitation.

Indicator dilution techniques have problems related primarily to inadequate mixing of the tracer. In methods using left atrial sampling with left ventricular injection or left ventricular sampling with aortic root injection, mixing problems are especially great, although this has been partially overcome by continuous infusions of Xe as the indicator. These techniques are also invasive and unsuitable for repeated measurements.

Doppler echocardiography has been used for quantitative measurements of regurgitation, although echocardiographic measurements of LV volume, essential for this method, involve major assumptions...
about ventricular shape. Kirch et al. have presented a technique based on computerized first-pass radionuclide angiocardiography. Advantages of this approach include the possibility of quantifying individual lesions in the presence of mixed valvular disease. Disadvantages include the need to inject a discrete bolus delivered into the proximal atrium. For left-sided lesions, the tracer must be injected through a wedged pulmonary artery catheter.

Another noninvasive approach making use of radioisotopes compares the cardiac output and stroke volume determination made during first-pass angiography to the total stroke volume determination calculated from the LV ejection fraction and end-diastolic volume. Although this approach is attractive in that it is similar in principle to the classic angiographic approach, it suffers from the uncertainties of scintigraphic evaluation of left ventricular end-diastolic volume using the area-length method. More recently, methods for measuring left ventricular volumes from equilibrium blood pool scintigrams have been described that avoid geometric assumptions by using left ventricular time-activity data. A combination of first-pass and equilibrium techniques may therefore be useful for measuring regurgitant fraction by allowing separate determinations of forward and total left ventricular stroke volume.

The technique that we have studied in the present experiments should be applicable to any disease process causing selective stroke volume increases in one ventricle compared with the other. We have examined only aortic regurgitation in this study, but our previous experience in patients suggests that mitral regurgitation can be quantified by the same method. In patients with combined aortic and mitral regurgitation, the method cannot separate the amount of regurgitation of each valve, but should accurately reflect the total LV regurgitant fraction. Because of this, results could theoretically be similar in patients with moderate involvement of both valves, or severe involvement of one valve combined with mild involvement of the other. In both cases, however, the method should indicate the overall hemodynamic burden on the left ventricle resulting from valvular insufficiency. The method is also applicable to unidirectional shunts and to isolated right-sided valvular regurgitation, although as in left-sided lesions, the individual contributions from two regurgitant valves cannot be separated. Its usefulness in assessing left-sided valvular regurgitation assumes that no significant right-sided regurgitation is present. When right- and left-sided regurgitation coexist, the method can only reflect the amount by which one ventricle is volume overloaded relative to the other.

The ability to quantitate regurgitant flow noninvasively should prove clinically useful in several groups of patients. For example, patients with acute endocarditis of the aortic and/or mitral valves can have the severity of regurgitation ascertained without intravascular catheterization. In patients with acute myocardial infarction complicated by mitral insufficiency, gated cardiac blood pool imaging can be used to measure both the severity of regurgitant flow and the adequacy of LV function. The technique should also be valuable for noninvasive evaluation of periprosthetic valvular leaks and for evaluation of patients with acute intermittent heart failure who may have auscultatorily silent mitral regurgitation. The experimental and clinical results obtained with this technique suggest that it is well-suited for serial measurements of regurgitant flow, either to assess the effect of therapy or as part of a study of natural history.

It should be cautioned that this method has not yet been validated in the setting of severe heart failure with marked dilatation of left and/or right ventricles. Although there is no theoretical reason why the method should break down, practical considerations of ventricular chamber definition could produce inaccuracies. Particularly with marked right-sided cardiac dilatation, overlap between the respective atrial

**Figure 6.** Example of a linear tear in left aortic cusp.

**Figure 7.** Comparison of aortic regurgitation measured by the left ventricular/right ventricular (LV/RV) ratio and the size of the aortic valve defect at autopsy.
and ventricular chambers, or between left and right ventricles, could result in a diminished ability to accurately separate and measure left and right stroke activities. This potential pitfall will require further investigation in patients and animal models.

Acknowledgment

The authors thank William Montgomery, Greg Shindledeker, and John Clulow for technical assistance in nuclear imaging; Alexander Wright and Anthony DiPaola for laboratory expertise; and Rosemary Hopkins for her expert secretarial work.

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Quantification of aortic valvular regurgitation in dogs by nuclear imaging.
R H Baxter, L C Becker, P O Alderson, P Rigo, H N Wagner, Jr and M L Weisfeldt

Circulation. 1980;61:404-410
doi: 10.1161/01.CIR.61.2.404
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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