A Mathematical Model for the Quantification of Mitral Regurgitation

Experimental Validation in the Canine Model Using Contrast Echocardiography

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Background. Because the clearance of contrast from the left atrium (LA) relative to the left ventricle (LV) depends on the degree of mitral regurgitation (MR), we hypothesized that a mathematical model can be developed that would provide a quantitative estimation of MR from the washout of contrast from these chambers.

Methods and Results. After mathematically developing the model, we performed experiments in two groups of dogs with the use of contrast echocardiography. Group 1 consisted of nine dogs in which different degrees of MR were produced by creating ischemic LV dysfunction. Contrast was injected into the LV, and MR was graded visually on a scale of from 0 to 4+. Videointensity plots generated from the LA and LV were provided to the model. There was excellent correlation between visual assessment of MR and model-derived regurgitant fraction in the 33 stages: \( y = 0.16x + 0.002 \) (r=0.97, \( p < 0.001 \), SEE=0.06). To obtain a more quantitative validation, we placed electromagnetic flow probes on the aorta and just cephalad to the mitral annulus in six dogs (group 2) during cardiopulmonary bypass. Different degrees of MR were produced by chordal traction and/or myocardial ischemia. Regurgitant fraction was calculated at each stage from the flow probe and videointensity data. There was excellent correlation between flow probe and model-derived regurgitant fraction (\( y = 0.96x + 0.03; r = 0.96, p < 0.001 \), SEE=0.06), and close interobserver and intraobserver correlations were noted using flow probe and contrast echocardiographic data.

Conclusions. A mathematical model that uses the clearance of contrast from the LA relative to the LV can be used to accurately measure the severity of MR. These findings may have important practical implications for the quantification of MR. (Circulation 1992;86:553–562)

KEY WORDS • mitral regurgitation • model, mathematical

There are major limitations to currently available methods of assessing the severity of mitral regurgitation (MR). For example, Doppler echocardiography (both pulsed and color flow mapping) is, at best, semiquantitative.\(^1,2\) Although radionuclide angiography has the potential of providing quantitative information, it is limited by its inability to clearly separate overlapping cardiac chambers.\(^3\) For these reasons, clinicians still rely on cineangiography to estimate the severity of MR. In addition to being semiquantitative,\(^4\) this technique has other limitations. Because the assessment of the severity of MR is based on the degree of opacification and rate of clearance of dye from the left atrium (LA), variations in factors such as LA size and cardiac output influence this determination. Although theoretically regurgitant fraction (RF) can be derived from measurements of chamber volumes and cardiac output during cardiac catheterization,\(^5\) these measurements frequently are erroneous. Furthermore, because it is an invasive procedure, cardiac catheterization is limited in the serial assessment of MR.

Because the clearance of contrast from the LA relative to the left ventricle (LV) depends on the degree of MR, we hypothesized that a mathematical model can be developed that would provide a quantitative estimation of MR from time–intensity plots obtained simultaneously from the LA and LV. The model was first tested in a group of dogs undergoing contrast echocardiography for the assessment of MR, in which contrast was injected into the LV and MR was estimated visually.\(^6\) On obtaining encouraging results, this model was again tested with
contrast echocardiography in a second series of dogs in which contrast was injected into the LV and RF was calculated from flows through the mitral and aortic valves using electromagnetic flow probes. Our results indicate that our mathematical model provides an accurate quantitative estimation of the severity of MR.

Methods

Mathematical Model

The model assumes that the relative clearance of contrast from the LV and LA indicates the severity of MR. It assumes that other factors that might also affect contrast washout from these chambers, such as cardiac output, affects clearance of contrast from both chambers to similar extents. If after the contrast has been adequately mixed with blood, Ca and Cv are the end-systolic concentrations of contrast in the LA and LV, respectively, then the concentrations of contrast in the LA (Ca) and LV (Cv) at next end systole can be determined by the following equations (see “Appendix”):

\[
Ca_2 = [1 - f' \cdot (1 - b)] \cdot Ca_1 + [(1 - b - f) \cdot (b/V)] \cdot Cv_1
\]

\[
Cv_2 = f' \cdot V \cdot Ca_1 + [1 - b - f] \cdot Cv_1
\]

where \( f \) is the forward LV ejection fraction, \( b \) is the backward LV ejection fraction, \( V \) is the ratio of LA to LV volumes, and \( f' \) is the fraction of blood going from the LA to the LV during each diastole (Figure 1A).

These recurring relations can be applied to data from several successive end-systolic frames to obtain optimal fits between experimental and model-derived data. The greater the number of frames available for analysis, the better is the estimation of the parameters. Because four parameters (\( f, b, f', \) and \( V \)) are used to estimate these relations, the model creates a four-dimensional matrix.

To better conceptualize this model, assume that the ratio of LA to LV volume (\( V \)) is known and these relations must be derived using only the other three parameters. In such an instance, the experimental data are fitted to the model by varying the remaining three parameters in three-dimensional space. A least-squares fit is performed at each step until an optimal fit is obtained between model-derived and experimental data (Figure 1B).

For these iterations, \( f \) (forward LV ejection fraction) is varied each time by 0.02 within a range of 0.1–0.8, which would be the expected outer limits of this variable. Similarly, \( b \) (backward LV ejection fraction) is changed by the same increments within a range of 0–0.7, with the total ejection fraction \( f + b \) limited to 0.1 and 0.8. The value of \( f' \) (volume of blood going from LA to LV in each diastole) is adjusted between 0.2 and 1.0. The value of each parameter is altered for each step until the best fit is obtained between the experimental and the model-derived data (indicated by \( P1 \) in the three-dimensional matrix shown in Figure 1B).

Animal Preparations

The dogs were anesthetized with 30 mg/kg sodium pentobarbital i.v. (Abbott Laboratories, North Chicago, Ill.), intubated, and ventilated using a dual-phase control respirator pump (model 607, Harvard Apparatus, South Natick, Mass.). An 8F catheter was placed in the left femoral artery for monitoring of arterial pressure and blood gases. This catheter was connected to a physiological recorder (model 4568C, Hewlett-Packard, Waltham, Mass.) via a fluid-filled pressure transducer (model 1280C, Hewlett-Packard). A similar catheter was placed in the left femoral vein for administration of fluids and drugs as needed. Blood gases were monitored, and fractional inspired oxygen and respiratory rate were adjusted accordingly. Intravenous sodium bicarbonate (Abbott Laboratories) was used to maintain pH between 7.3 and 7.5.

In group 1 dogs, a median sternotomy or a left lateral thoracotomy was performed, whereas in group 2 dogs, a median sternotomy with extension to a left thoracotomy was performed. The heart was suspended in a pericardial cradle. The proximal portions of the left anterior descending coronary artery (LAD) and left circumflex artery (LCx) were dissected free from surrounding tissues, and snares were placed loosely around them. A catheter was placed in the LA to measure LA pressure and connected to the physiological recorder via a fluid-filled transducer.

Group 1 dogs. In the nine group 1 dogs, a micromanometer-tipped catheter (model PC-484B, Millar Instruments, Houston, Tex.) was inserted into the LV cavity via a stab wound in the apex and secured in place with a purse-string suture (see Figure 2). This catheter was used to measure LV pressures and inject contrast into the LV cavity. The left main coronary artery was dissected free from surrounding tissues, and a snares was placed loosely around it. The right femoral artery was cannulated with a 12F catheter (Bard, USCI, Billerica, Mass.), which was attached to plastic tubing (Tygon, Norton Plastics, Akron, Ohio) placed in a constant-flow roller pump (Varistaltic Series S, Manostat Corp., New York). The other end of this tubing was connected to a Gregg cannula. After the tubing was primed with arterial blood, the tip of the Gregg cannula was inserted into the ascending aorta via an incision made in the left innominate artery, and it was advanced into the left.
main lumen, where it was secured with the preplaced snare. In this manner, blood flow to the entire LV myocardium was controlled using the roller pump.

**Group 2 dogs.** A 6-in. 8F catheter was placed in the LV to measure LV pressures and inject contrast into the LV cavity (see Figure 3). The proximal portions of the ascending and descending aortas were dissected free from surrounding tissues. An electromagnetic flow probe (model EP250, Carolina Instruments, King, N.C.) was positioned snugly around the proximal portion of the ascending aorta and was connected to a flowmeter (model FM 501, Carolina Instruments), which in turn was connected to the physiological recorder. A snare was placed loosely around the descending aorta just distal to the left brachiocephalic artery to alter afterload during the experiment.

After administration of 20,000 units heparin sodium (Elkins-Sinn, Inc., Cherry Hill, N.J.), the right femoral artery was cannulated with a 14F catheter (USCI), and the superior vena cava and right ventricle were cannulated with two 28F venous cannulae (Sherwood Medical Inc., St. Louis, Mo.). These cannulae were connected to the arterial and venous tubing of the bypass pump, respectively. A cannula (DLP Inc., Grand Rapids, Mich.) was placed in the aortic root to allow delivery of cardioplegia and for measurement of central aortic pressure. The dogs were placed on cardiopulmonary bypass using a roller pump (model 6002, Sarns Inc., Ann Arbor, Mich.) and a bubble oxygenator (model S-100A, Shiley, Irvine, Calif.). They were cooled to a rectal temperature of 25°C using a heat pump (Blanketrol 200 HL, Sub-Zero Products, Inc., Cincinnati, Ohio). The aorta was cross-clamped proximal to the origin of the right brachiocephalic artery, and cardiac arrest was induced by the delivery of cardioplegia to the aortic root.

The LA was incised, and an electromagnetic flow probe (model EP-455C, Carolina Instruments) was sutured to the LA wall immediately cephalad to the mitral annulus as described previously. The flow probe was connected to a flowmeter, which in turn was connected to the physiological recorder. Two heavy silk ties were placed around groups of mitral valve chordae tendineae and externalized through the LV free wall near the apex. The atriotomy was closed, and the dog was rewarmed, defibrillated, and weaned from cardiopulmonary bypass with the aid of an intravenous infusion of dobutamine (5 μg/kg·min⁻¹, Eli Lilly Co., Indianapolis, Ind.).

**Contrast Echocardiography**

Two-dimensional echocardiographic images were obtained using 5-MHz transducers placed over the surface of the heart (Mark III, Advanced Technology Laboratories, Seattle, Wash., for the group 1 dogs; XP128, Acuson Corp., Mountain View, Calif., for the group 2 dogs). A saline-filled bath acted as an acoustic interface between the heart and the handheld transducer. To obtain optimal quality images with homogeneous brightness in the entire field, the power output settings and time-gain compensation were adjusted at the beginning of each experiment and kept constant throughout. Images were recorded on videotape using a VHS recorder (Panasonic model NV 8950, Matsushita Corp.).

Contrast was injected through the catheter positioned in the LV cavity. For the group 1 dogs, it consisted of an agitated mixture of 2 ml Renografin-76 (Squibb Diagnostics, New Brunswick, N.J.) and 2 ml saline. For the group 2 dogs, it consisted of 0.5 ml of albumin mi-
crobubbles (450 million/ml, 4.5-μm diameter) (Albunex, Molecular Biosystems, Inc., San Diego, Calif.) mixed with an equal amount of saline. Images were acquired using a modified apical four-chamber view or a parasternal long-axis view.

In the group 1 dogs, the severity of MR was assessed visually by two blinded observers. It was graded on a scale of from 0 to 4+. If contrast never entered the LA, MR was graded as 0. If it entered the LA but cleared within 3 beats, it was graded as 1+. If it took as long for the contrast to clear from the LA as from the LV, MR was graded as 4+. Intermediate stages were graded as 2+ and 3+: half grades also were used.

An off-line image analysis computer (Mipron System, Kontron, Eching, FRG) was used for quantification of the echocardiographic data. A sequence of images from just before contrast injection and until its disappearance from the LV cavity was transferred from videotape to video memory of the computer. The end-systolic frames were identified in computer memory by the observer, who then placed regions of interest over the LA and LV. To increase signal-to-noise ratio, these regions were made as large as possible while excluding surrounding structures. Figure 4 shows examples of these regions placed over images where trace (left panel) and severe (right panel) MR was noted. Plots of mean pixel intensity versus frame number then were derived for each stage.

These data were transferred to RS/1 (Bolt, Beranek, and Newman, Cambridge, Mass.) on a minicomputer (VAX 8250, Digital Equipment Corp., Maynard, Mass.). The videointensity data before the appearance of contrast were subtracted from all subsequent frames to obtain background-subtracted data. After adequate mixing of contrast and after maximal opacification of the LA and LV, an initial set of data was provided to the model to generate the succeeding values. The data were closely assessed for the occurrence of attenuation; if it occurred, only those images obtained after its disappearance were selected. From six to 12 end-systolic frames were provided for calculation, depending on the clearance rate of contrast from the LV cavity. To expedite computation of RF, the observer provided the model with a rough estimate of the LA-to-LV volume ratio (V) as assessed on echocardiography. This value was adjusted by the model by no more than ±0.05 before deriving RF.

**Figure 4. Method of placement of regions of interest over the left atrium and left ventricle. These examples are taken from two stages from the same dog depicting trace (0.5+) (panel A) and moderately severe (3+) (panel B) mitral regurgitation. The regions of interest occupy most of the left atrium without encroaching on surrounding structures. (See text for details.)**

**Measurement of RF**

The flow signals were acquired directly onto an 80386-based personal computer (Kontron Electronics) using an eight-channel analog-to-digital convertor (DAS-16, Metabyte Corp., Taunton, Mass.). All data were sampled at 200 Hz and formatted and displayed using Labtech Notebook (Labtech Technologies Corp., Wilmington, Mass.). These data were transferred to RS/1 for further analysis. Data also were acquired on a strip-chart recorder.

When there was no MR or only mild MR, it was easy to discern the zero-level baseline on the mitral flow signal from where the area subtended by forward flow could be measured (Figure 5A). In severe MR, however, the mitral flow signal appeared as a sine wave (Figure 5B), not allowing a confident estimation of the zero-level baseline. Because the forward mitral volume minus the backward mitral volume (integral of instantaneous flow over time) equals forward aortic volume, we developed a program that used this relation to determine the zero-level baseline on the mitral flow signal. To accomplish this, the zero-level baseline was first arbitrarily adjusted below the entire mitral signal (depicted by the horizontal dashed line in Figure 5C),...
and the areas under the curves for mitral and aortic signals were calculated. The zero-level baseline then was automatically adjusted to a slightly higher level, and the areas under the curve were calculated again. These iterations were repeated until the forward minus the backward mitral volume equaled the forward aortic volume. The zero-level baseline was adjusted at this level (depicted as a solid horizontal line in Figure 5C), and forward mitral volume was automatically calculated. Because the forward mitral volume includes the forward LV stroke volume as well as the regurgitant volume, RF was calculated as backward mitral volume divided by forward mitral volume.

**Measurement of Hemodynamics**

Hemodynamic data in the group 1 dogs were recorded at a paper speed of 100 mm/sec using a strip-chart recorder. In group 2 dogs, all hemodynamic data were acquired in digital format as described above. In both groups of dogs, 10 consecutive cycles were analyzed to determine values for each stage.

**Protocol**

After acquiring data at baseline, different severities of MR were produced. In the group 1 dogs, MR was produced by creating varying degrees of ischemic LV dysfunction through occlusion of the LAD or LCx or by reducing left main flow. In the group 2 dogs, varying severities of MR were produced by creating different degrees of outward traction on the chordae tendineae or by occluding the LAD, LCx, or both. At each stage, contrast echocardiographic and hemodynamic data were acquired simultaneously. In six stages in each group of dogs, measurements were repeated for the same stage to assess reproducibility of the methods. In six stages with moderate MR in the group 2 dogs, afterload was increased by tightening the snare on the descending aorta, whereas preload was increased by infusing 300–500 ml of oxygenated blood from the bypass pump over 1 minute. At the end of the experiment, the dogs were killed.

**Statistical Analysis**

Data analysis was performed using RS/1. Data were expressed as mean±1 SD, and differences between stages were compared using ANOVA. Differences were considered significant at p<0.05 (two-sided). In the group 1 dogs, visual assessment of MR was correlated with model-derived RF using Spearman’s rank correlation. In the group 2 dogs, model-derived RF was correlated with that measured from flow probes using linear regression analysis. Linear regression also was performed for estimation of reproducibility of both contrast echocardiographic and flowmetric measurements and to determine interobserver and intraobserver variabilities.

**Results**

**Group 1 Dogs**

A mean of four stages (range of two to six) was obtained in the nine group 1 dogs. The hemodynamic data for different degrees of ischemic MR (0 to 4+) are depicted in Table 1. The severity of MR is related to the

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**FIGURE 5. Method of determining zero-flow baseline level on the mitral flow signal.** Panel A: Tracing of mitral flow signal in which there is little mitral regurgitation and the zero-flow baseline is easily discernable. Panel B: Tracing of mitral flow signal in which there is moderate mitral regurgitation and it is impossible to determine the zero-flow baseline. Panel C: Algorithm for determining zero-flow baseline using the aortic flow signal. The dashed horizontal line represents the first level of iteration to define zero-level baseline, whereas the horizontal solid line depicts the final zero-level baseline where the forward aortic flow equals the forward minus backward mitral flows. (See text for details.) SV, stroke volume; MFV, mitral forward volume; MBV, mitral backward volume.
degree of LV systolic dysfunction as evidenced by LV systolic pressure, mean aortic pressure, and peak positive dP/dt.

Figure 6 illustrates time–intensity plots obtained from three stages in one of the group 1 dogs. A close association can be noted between the model-derived and actual data. In Figure 6A, where the LA curve is flat and the slopes of the LA and LV curves are highly divergent, MR was graded visually as 0 and the model calculated a RF of 0. In Figure 6B, where the slopes of the curves from the LV and LA are closer and where visually MR was graded as 2.5+, the model calculated a RF of 0.39. In Figure 6C, where the slopes of the LA and LV curves are almost identical and MR was visually assessed as 4+, the model calculated a RF of 0.62. Figure 7 illustrates the relation between the degree of MR assessed visually and the model-derived RF from 33 stages in the nine group 1 dogs. The correlation is good, the slope of the curve is not significantly different from the line of identity, and the SEE is small.

**Group 2 Dogs**

A mean of five stages (range of three to eight) was obtained in the six group 2 dogs. The hemodynamic data for different degrees of MR, arbitrarily defined based on the RF, are given in Table 2. Despite worse hemodynamics with severe MR, unlike the group 1 dogs, the severity of MR in this group of dogs was not related primarily to a decrease in LV systolic function.

Figure 8 illustrates digitally acquired aortic and mitral flow data from three different stages in one of the group 2 dogs as well as the calculated RF for each stage. The more severe was the MR, the lower was the forward aortic stroke volume. Figure 9 illustrates the relation between RF derived using the flow probes and that derived from the model from 29 stages in all six dogs. The correlation is good, the slope of the curve is not significantly different from the line of identity, and the SEE is small.

**Reproducibility of the Methods**

The same observer measured six duplicate data sets (flow probe and contrast echocardiography) in group 2 dogs. The model-derived RF was determined from the contrast echocardiographic data, and actual RF was calculated from the flow data. There was close reproducibility of both methods with correlation coefficients of $r=0.86$ and $r=0.99$ for contrast echocardiographically derived and flow probe–calculated RF values, respectively.

**Interobserver and Intrarobserver Errors**

The same observer repeated measurements from six stages in both groups of dogs, whereas a second ob-

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**Table 1. Hemodynamic Results From the Group 1 Dogs**

<table>
<thead>
<tr>
<th>Severity of MR</th>
<th>Heart rate (bpm)</th>
<th>AOP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>LAP (mm Hg)</th>
<th>LV dP/dt</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>131±19</td>
<td>77±26</td>
<td>6±11</td>
<td>4±4</td>
<td>1,317±523</td>
</tr>
<tr>
<td>1+</td>
<td>114±28</td>
<td>80±38</td>
<td>17±8</td>
<td>17±13</td>
<td>1,500±649</td>
</tr>
<tr>
<td>2+ to 3+</td>
<td>119±20</td>
<td>65±24</td>
<td>19±7</td>
<td>20±15</td>
<td>1,322±387</td>
</tr>
<tr>
<td>4+</td>
<td>132±20</td>
<td>39±18*</td>
<td>19±9</td>
<td>21±7</td>
<td>1,107±821</td>
</tr>
</tbody>
</table>

MR, mitral regurgitation; bpm, beats per minute; LVEDP, left ventricular end-diastolic pressure; LAP, mean left atrial pressure; LV, left ventricular; AOP, mean aortic pressure.

*p=0.07, ′p=0.06, ′′p=0.05.
server also made measurements on two separate occasions on the same six data sets. The interobserver and intraobserver correlations were close for visual assessment of the severity of MR in the group 1 dogs (r = 0.99 and r = 0.99). The correlations also were close for both flow probe–calculated RF (r = 0.99 and r = 0.99) and contrast echocardiographically derived RF (r = 0.97 and r = 0.99) in the group 2 dogs. In the group 2 dogs, the regions of interest were placed on separate occasions in a blinded manner to derive time–intensity plots.

Discussion

We have described a mathematical model for assessing the severity of MR and demonstrated that this model can be used accurately and reproducibly. We have validated this model in canine preparations in which MR was assessed both visually as well as quantitatively with electromagnetic flow probes. Although we used contrast echocardiography to validate this model, cineangiography could provide similar results. To our knowledge, this is the first study that has actually validated in vivo a clinically applicable technique for the assessment of the severity of MR.

Value of the Mathematical Model

Even during cineangiography, the determination of MR is qualitative because it is assessed based on the degree of LA opacification and the time it takes for the dye to clear from the LA. Several obvious factors confound such an assessment. For example, if the LA is very large, the opacification may not be impressive despite significant MR, whereas with the same amount of MR occurring in a small LA, the degree of opacification might appear to be more striking. Similarly, dye might go as far back as the pulmonary veins in the setting of moderate MR when the LA is small, whereas with a very large LA even severe MR might not result in pulmonary vein opacification. Finally, if cardiac output is low, dye will clear slowly from the LA even in the absence of severe MR.

Our model is based on the assumption that the relative clearance of contrast from the LV and LA is related to the severity of MR. For the model to work appropriately, it is not required that the entire LA be filled with dye in systole because a large region of interest in the LA will detect a small jet (Figure 4A). Similarly, the model does not depend on the degree of opacification of the LA relative to the LV. Even subtle changes in LA contrast, not visually apparent, are detected on videointensity measurements. Finally, the model is not influenced by cardiac output because it evaluates the relative clearance of contrast from both chambers. If cardiac output is low, the absolute rate of clearance of contrast from both chambers will be equally affected, whereas the relative clearance will still depend on the degree of MR.

Because in the group 1 dogs the severity of MR was related to the severity of LV dysfunction, it could be argued that we had not demonstrated that the model assessed the severity of MR independent of cardiac output. In the group 2 dogs, however, in which MR was produced by applying chordal traction (where LV function is normal) and/or by producing ischemic dysfunction (where LV function is reduced), the model accurately predicted the severity of MR, suggesting its independence from cardiac output.

This model is unique because it is developed on physiological principles and does not use a retrospective fit of data to empirically derived parameters. The model is based on indicator dilution principles and there are no “fudge factors” involved; although not tested in this study, it conceivably could be used to measure other forms of valvular regurgitation as well.

Model Limitations

Certain steps have to be taken for the model to work appropriately. First, the correct frames have to be selected, and at least six end-systolic frames are required for data fitting. The greater the number of frames, the greater will be the statistical certainty. Second, regions of interest have to be placed with care and should include as much of the LA as possible to increase the signal-to-noise ratio without encroaching on surrounding structures (Figure 4). The model is very sensitive to noise and can produce erroneous results if the regions of interest are not placed accurately. Viewing the selected frames in cine-loop format helps to

<table>
<thead>
<tr>
<th>Severity of MR (RF)</th>
<th>Heart rate (bpm)</th>
<th>AOP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>LAP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–0.10</td>
<td>131±15</td>
<td>105±27</td>
<td>14±6</td>
<td>11±6</td>
</tr>
<tr>
<td>0.11–0.30</td>
<td>137±14</td>
<td>96±20</td>
<td>15±13</td>
<td>14±8</td>
</tr>
<tr>
<td>0.31–0.50</td>
<td>122±28</td>
<td>70±31</td>
<td>23±15</td>
<td>16±8</td>
</tr>
<tr>
<td>&gt;0.50</td>
<td>118±28</td>
<td>78±16</td>
<td>20±6</td>
<td>19±8</td>
</tr>
</tbody>
</table>

MR, mitral regurgitation; RF, regurgitant fraction; bpm, beats per minute; AOP, mean aortic pressure; LVEDP, left ventricular end-diastolic pressure; LAP, mean left atrial pressure.

No significant differences were noted in the hemodynamic data among the different severities of mitral regurgitation.
appropriately define the regions of interest. Alignment of images is sometimes required if significant motion artifacts are present. Finally, fitting the model to experimental data is computer intensive because many iterations must be performed to generate various values for each parameter. In this era, however, the need for such computational power should not be considered a serious limitation.

Critique of the Methods
Application of the mathematical model depends on a linear relation between cavitary microbubble concentration and measured videointensity. If the relation between these variables is significantly nonlinear over the range of microbubble concentrations used, then the derived RF could be inaccurate. To minimize this problem, we used microbubble concentrations sufficiently low to avoid attenuation. When attenuation was present, we selected frames after it had disappeared and confirmed the absence of attenuation from the quantitative data. We also used postprocessing curves in our echocardiographic instruments, which provided the most linear transformation of echo signal to videointensity. Consequently, we believe that for the range of bubble concentrations used in our study, the relation between microbubble-mediated backscatter and videointensity should not be a major source of error.

Stability of the contrast agent is an additional concern. Recent reports suggest that albumin microbubbles may be destroyed or altered by systolic pressures generated by the LV. These reports are based on peripheral venous injection of contrast, where transpulmonary transit conceivably could alter microbubble characteristics. In the present study, we did not observe less contrast effect in the LV during systole, suggesting that bubble destruction or alteration is not a significant problem when contrast is injected directly into the LV.

Other than the microbubbles themselves, the correlation of the backscatter data with flows is limited by factors such as acoustic power, carrier frequency, and postprocessing algorithms. We optimized the image quality by adjusting power output and time-gain compensation at the beginning of each experiment and did not change these settings during the rest of the experi-

![AORTIC FLOWS](image1)

![MITRAL FLOWS](image2)

**FIGURE 8.** Examples of digitally acquired aortic and mitral flow signals from three different stages from one of the group 2 dogs where mitral regurgitation was produced by a combination of chordal traction and left ventricular ischemia. As the severity of mitral regurgitation increases, the aortic flow signal amplitude (indicative of forward stroke volume) decreases. Although the total forward flow decreases with increasing severity of ischemia-induced mitral regurgitation, the fraction of backward mitral flow compared with forward mitral flow increases. (See text for details.) REG FRAC, regurgitation fraction.

![REG FRAC = 0.08](image3)

![REG FRAC = 0.34](image4)

![REG FRAC = 0.53](image5)

**FIGURE 9.** Plot of data from 29 stages from six group 2 dogs depicting excellent correlation between model-derived (x axis) and flow probe–measured (y axis) regurgitant fractions. (See text for details.)
ment. Furthermore, because we used background-subtracted videointensity data, any spatial heterogeneity in video signal would not affect the results significantly. In addition, because our model evaluates LA opacification relative to LV opacification, it tends to minimize the confounding influence of instrument-related factors.

Because only an approximation of the ratio of LA to LV volumes is required for our model, errors introduced by actual volume measurements, required for other methods for estimating the severity of MR, also are avoided. After fitting the three other parameters, the model also adjusts the ratio of LA to LV volume (V) to derive RF. Providing a rough estimate of this value is, however, useful in reducing computational time.

We used electromagnetic flowmetry as the gold standard for the quantification of RF in our group 2 dogs. Despite the superiority of this technique in terms of providing actual flow information, certain limitations must be considered. If the flow is extremely eccentric, the measured flow will vary from the actual flow. MR created by global ischemia, such as in the group 1 dogs, usually is a centrally directed jet.14 Because we produced MR in the group 2 dogs by placing tension simultaneously on chordae tendineae attached to both mitral leaflets, we believe that MR in these dogs also was centrally directed.

A significant practical problem associated with the use of electromagnetic flow probes is baseline drift.15 If the signal drifts over time, determination of the timing of zero-level baseline flow is difficult, thus the measurement of forward and backward flows may be inaccurate. To overcome this problem, we used a unique computer-assisted approach in which the aortic flow was used to determine where the zero-level baseline flow occurred on the mitral flow signal. Because the forward aortic flow volume is equal to the forward minus the backward mitral flow volume, forward aortic flow signals can be used to determine the timing of zero-level baseline mitral flow (Figure 5). In the study dogs, there was no aortic regurgitation, so zero-flow baseline was easy to determine on the aortic flow signal (Figure 8). Furthermore, the snug placement of the aortic flow probe over the ascending aorta provided a very reliable signal. Other factors that influence measurements using electromagnetic flow probes, such as hematocrit,15 probably did not influence our results because we did not measure absolute flows.

Finally, one can argue that because we had an excellent relation between the model and visually assessed MR in the group 1 dogs, visual assessment could be used alone. Several counterpoints can be provided for such an argument. First, "expert" visual analysis was performed for these data, which may not be available in every situation. Second, LV ischemia, the method of producing MR in this group of dogs, results in slower contrast washout; therefore, reading more MR with more ischemia may have influenced the results. Finally, during 4+ MR, RF varied from 0.52 to 0.80, values that in the clinical setting may have different prognostic implications. Quantification of the severity of MR is, therefore, better than visual assessment alone.

**Comparison With Previous Attempts at Quantification of MR**

Digital subtraction cineangiography with videodensitometry has been attempted for the quantification of MR.16 For this method, the indicator can be injected peripherally or centrally, and indicator–dilution curves can be acquired as time–intensity plots from the angiographic images. This method, however, has technical limitations and has not been validated with a gold standard. The routine method of obtaining RF from measurements of chamber volumes and cardiac output during cardiac catheterization5 is prone to errors and has never been validated experimentally.

Among the noninvasive tests available, radionuclide angiography with first-pass imaging is limited by inherent difficulties in resolving overlapping cardiac chambers.2 Range-gated pulsed Doppler mapping of the extent of regurgitant jets into the LA has been reported to correspond well to visual grading of angiographic contrast ventriculograms, but the technique is time consuming, highly operator dependent, and only semi-quantitative.3 Initial enthusiasm for the use of color flow Doppler imaging in this role17,18 has been tempered by limitations in translating velocity mapping into flow data. The spatial distribution of MR jets imaged by color Doppler is dependent on multiple factors, including operator and machine characteristics,19 geometry of the regurgitant orifice,20 and receiving chamber compliance.21

In comparison with these techniques, because microbubbles are mixed rapidly with blood and serve as blood flow indicators that can be sampled by ultrasound over time,22 accurate measurement of blood flow can be achieved. This has been demonstrated for the quantification of myocardial blood flow with this technique.9,23 The imaging and quantification of regurgitant flows rather than spatial velocity patterns also should allow contrast echocardiography to be less dependent on variables such as orifice geometry and machine settings. Although this technique has been attempted previously for the assessment of MR,24,25 it has been used qualitatively in a manner similar to cineangiography.

**Clinical Implications**

It is sobering to realize that no method used clinically to assess the severity of MR, including cineangiography, has been validated in vivo against actual measurements of flows or RF. Our model provides an opportunity to quantify MR using almost any method that is based on indicator dilution principles. As such, direct LV injection of contrast during two-dimensional echocardiography can be performed in the catheterization laboratory24 or the operating room25 to assess the severity of MR. This technique may find particular application in patients with renal disease, those with allergies to dyes, and those with poor LV function. The same principles also can be applied to data obtained during cineangiography.

The LV now can be opacified from a venous injection of contrast.26,27 It is thus possible that contrast echocardiography could provide an estimation of the severity of MR during routine echocardiographic examinations. The mathematical model used would obviously be different and more complex than our current model, but the principles would remain the same. It is in this regard that the application of a mathematical model for the estimation of the severity of MR during contrast echocardiography appears particularly promising.
Appendix

After contrast has mixed adequately with blood, at the end of any systole, let \( C_a \) be concentration of contrast in the LA, \( C_v \) be concentration of contrast in the LV, \( v \) be LA volume, and \( v \) be LV volume.

If during the next diastole, \( f' \) is the fraction of contrast in the LA that flows into the LV, then the concentration of contrast in the LA at the end of that diastole will be

\[
C_a' = (1-f') \cdot v \cdot C_a/(v-v_d)
\]

(1)

where \( v_d \) is the decrease in the LA volume during ventricular diastole (atrial systole).

The corresponding concentration of contrast in the LV will be

\[
C_v' = (V' \cdot C_v + f' \cdot v \cdot C_a)/(V'e)
\]

(2)

where \( V' \) is the LV volume at end diastole.

If \( f \) is the forward LV ejection fraction and \( b \) is the backward LV ejection fraction, then \( V_e \) is related to \( V \) by the following equation:

\[
V = V_e \cdot (1-b-f)
\]

(3)

Substituting for \( V \) from Equation 3 in Equation 2, we get the following:

\[
C_v' = f' \cdot (v/V_e) \cdot C_a + (1-b-f)C_v
\]

which is also equal to the concentration of contrast in the LV (\( C_v \)) at the end of the next systole. Therefore

\[
C_v = f' \cdot (v/V_e) \cdot C_a + (1-b-f)C_v
\]

(4)

The concentration of contrast in the LA at the end of the next systole will be

\[
C_a = [C_a' \cdot (v-v_d) + V_e \cdot b \cdot C_v']/v
\]

(5)

Substituting for \( C_a' \) from Equation 1 and for \( C_v' \) from Equation 4, we get the following:

\[
C_a = [1-f' \cdot (1-b)] \cdot C_a + [b \cdot (1-b-f)/(v/v_d)] \cdot C_v
\]

(6)

By defining \( (v/v_d)=V \), Equations 6 and 4 can be rewritten in the following forms:

\[
C_a = [1-f' \cdot (1-b)] \cdot C_a + [(1-b-f) \cdot (b/V)] \cdot C_v
\]

(7)

\[
C_v = f' \cdot V \cdot C_a + (1-b-f) \cdot C_v
\]

(8)

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