Dynamic Changes in the Canine Mitral Regurgitant Orifice Area during Ventricular Ejection

Edward L. Yellin, Chaim Yoran, Edmund H. Sonnenblick, Shlomo Gabbay, and Robert W.M. Frater

SUMMARY We designed this study to test the hypothesis that in acute mitral regurgitation the mitral regurgitant area (MRA) is a dynamic quantity which varies with the time variation of ventricular volume. Mitral insufficiency was created in five open-chest dogs in which a portion of the anterior leaflet was excised. Phasic aortic and mitral flows were measured electromagnetically, along with left atrial and ventricular pressures. Filling, regurgitant, and stroke volumes, and systolic pressure gradient were determined by digital methods. MRA was calculated from the fluid dynamic equation of motion to give the temporal mean and the instantaneous value at three instants of time and at the time of peak flow (when inertia is negligible). Mean regurgitant fraction was 42 ± 12% with no indication of left ventricular failure due to volume overload. MRA decreased monotonically with time to 59% of its initial value and closely paralleled the decrease in ventricular volume during systole. In a control study using a tilting-disc prosthesis with a hole 5 mm in diameter in the occluder, the calculated MRA was time invariant and equal to the measured area for regurgitation. We conclude that in acute mitral regurgitation the MRA is a function of ventricular volume. Circ Res 45: 677-683, 1979

During mitral regurgitation, the distribution of flow between the forward and regurgitant paths is a dynamic process which depends on the driving pressure differences and the relative impedance of each path. Since energy losses across an incompetent valve vary with the square of the flow, the impedance of the regurgitant path is dominated by the effective A_r of the mitral valve. It is therefore of major interest to examine the possibility that the regurgitant A_r is not fixed. This study was designed to test the hypothesis that in acute mitral insufficiency the mitral regurgitant A_r decreases during ventricular ejection.

Previous studies from this laboratory (Yoran et al., 1979a; 1979b) and elsewhere (Borgenhagen et al., 1977) have demonstrated that the mean MRA during ventricular systole varies directly with the size and shape of the left ventricle. We have shown...
also that the mean $A_\text{m}$ can be calculated from the temporal mean pressure-flow relations and that an instantaneous area can be determined from the pressure-flow relations at peak flow (Gabbay et al., 1978). Thus, if the area changes with time (i.e., as the ventricular volume changes during systole), then the two methods will give different results. In this study, we also used the fluid dynamic equation of motion to estimate the MRA as a function of time during ventricular systole. We have shown that the calculated mitral regurgitant $A_\text{m}$ varies directly with the volume of the ventricle during ejection.

**Methods**

**Animal Preparations**

Six large mongrel dogs (20–30 kg) were anesthetized with sodium pentobarbitol (30 mg/kg, i.v.) and artificially ventilated with a mixture of room air and oxygen. The preparation has been described previously (Laniado et al., 1973). After a midline sternotomy and left thoracotomy at the 5th intercostal space, we opened the pericardium and supported the heart in a pericardial cradle. Millar catheter-tip micromanometers (PC-460 and PC-350) were introduced into the left ventricle and atrium via the apical dimple and pulmonary vein, respectively. The left carotid artery was catheterized for the heart in a pericardial cradle. Millar catheter-tip micromanometers (PC-460 and PC-350) were introduced into the left ventricle and atrium via the apical dimple and pulmonary vein, respectively. The left carotid artery was catheterized for

**Theory**

We treat the pressure-flow relations across the incompetent mitral valve as analogous to a stenosis or a hydraulic orifice (Yellin et al., 1976) and postulate a fluid equation of motion (see Glossary for definitions):

$$\Delta p = (A)\frac{dQ}{dt} + (AoB)^{-2}Q^2,$$

(1)

Where the first expression on the right-hand side is an inertial term and the second expression is a dissipative term due to viscous resistance and turbulent losses. Note that the constant, $B$, contains a discharge coefficient and appropriate conversion factors (see below). At peak flow, $\frac{dQ}{dt} = 0$, so that

$$Ao_p = Q_p/ B \sqrt{\Delta p_p}.$$

(2)

At any instant of time, if inertial forces are neglected, then Equation 1 can be written

$$Ao(t) = Q(t)/ B \sqrt{\Delta p(t)},$$

(3)

and the error in neglecting inertia is directly proportional to $\frac{dQ}{dt}$. The integration of Equation 1 over any time interval, where $Q_a = Q_b$ results in

$$\int_{t_1}^{t_2} (\frac{dQ}{dt}) dt = 0,$$

so that

$$Ao_m = \sqrt{Q_{rms}^2}/ B \sqrt{\Delta p_m}.$$

(4)

It is important to note that $\sqrt{Q_{rms}^2}$ is not equal to $Q_m$. The former term, the RMS value, is always greater than the mean. For example, for a sinusoidal flow: $Q_{rms} = 1.11Q_m$. $Q_{rms}$ can equal $Q_m$ only under the theoretical condition of uniform (i.e., square-wave) flow.

Equations 2–4 have been applied to this study as follows. The generalized terms have been replaced by specific variables defined in the Glossary (see also Figs. 1 and 2). Based on our previous work in mitral stenosis (Yellin et al., 1975), we let the discharge coefficient equal 0.6. When the $A_m$ is in mm$^2$ and when $\Delta p$ is the ventriculoatrial pressure difference measured in mm Hg, the conversion factor is 0.516. Thus, $B = 0.31$. Although it will be seen in Results that this value is reasonably good, that is of no major consequence in this study, since we will (1) analyze relative changes in the regurgitant area with time or we will (2) normalize all areas to the peak area. In the first case, the discharge coefficient will affect all the results equally, and in the second case, it will cancel from the ratio.

At peak flow, we apply Equation 2 and the MRA is

$$MRA_p = \frac{MiF_p/0.31 \sqrt{(LVP - LAP)_p}}{0.31 \sqrt{(LVP - LAP)_p}}.$$

(5)

At three instants of time, one preceding peak flow and two following the peak (Fig. 2), $\frac{dMiF}{dt}$ is
assumed to be negligibly small, and we calculate the area from

\[
MRA(t)_i = \frac{MRF}{0.31} \sqrt{(LVP - LAP)_i} (i = 1-3).
\]

Note that neglecting inertia before peak flow (time 1) results in an underestimated area, and neglecting inertia after peak flow (times 2 and 3) yields an overestimated area. Because peak flow occurs early (20% of RT, see Fig. 1 for a typical flow waveform), acceleration at time 1 is not insignificant, the measured pressure difference is too large, and Equation 6 underestimates the area. A more accurate estimate of the area at time 1 is made by assuming a maximal inertial effect. This occurs when mitral flow is zero, i.e., at the onset of flow reversal. The pressure difference at that time (arrow, Fig. 2) is due solely to inertia. We then subtract this value from the pressure difference at time 1 to get a new gradient which is due only to dissipation, and we calculate the MRA that is used in the Results. Although this calculation is subject to large measurement errors, due to rapid changes in pressure and flow at that time, it will be shown to be helpful in interpreting the results.

Finally, we assume that the flow waveform is nearly sinusoidal (Fig. 1), and we modify Equation 4 to calculate the mean area during the entire regurgitant period,

\[
MRA_m = \frac{1.1 (RV/RT)/0.31 \sqrt{(LVP - LAP)_m}}{QRMS = 1.10 Q_m}.
\]

Equation 7 is seen to be the Gorlin equation (Gorlin and Gorlin, 1951), corrected to account for $Q_{RMS} = 1.10 Q_m$. 

**Figure 1.** An oscillographic record with an atrial premature contraction showing an example of moderate mitral regurgitation (40% regurgitant fraction). The shaded areas indicate the pertinent calculations. $SV = 15.3 \text{ ml}$; $FV = 26 \text{ ml}$; $RV = 10.7 \text{ ml}$; $RT = 205 \text{ msec}$; $\Delta p = 53 \text{ mm Hg}$. $MRA = 26 \text{ mm}^2$. Time lines = one/sec.
FIGURE 2 Schematic of LVP and LAP, along with regurgitant flow (direction reversed), indicating the measurements required to calculate the instantaneous orifice areas at times 1, 2, 3, and P, where P is the time of maximum flow when inertia is nonexistent. The arrow points to the Δp at zero flow when there are no resistive forces, and is thus due solely to inertia at that time.

Data Processing and Analysis

FV, RV, SV, and systolic pressure gradient were calculated by digitizing the respective curves with a sonic digitizer (Science Accessories) coupled to a digital computer (PDP-11) which performs the integration. Zero flow was determined initially, just prior to cessation of bypass, at intervals during the experiment by slowing the heart and creating diastolic flow decay with vagal stimulation or postextrasystolic compensatory pause, and at termination with cardiac arrest (Yellin et al., 1976). The baseline determination was verified during the steady state when total inflow equals total outflow (FV = RV + SV).

Hemodynamic conditions (Table 1) are presented as mean ± SD to emphasize the divergent conditions studied. MRA calculations are presented as mean ± SE. For each dog: (1) time variations in MRA were investigated with a linear regression analysis of the coordinate pairs at times 1, P, 2, and 3; (2) the slopes were tested for significance against a null hypothesis of zero slope by analysis of variance; and (3) the paired t-test was used to test for differences between adjacent times (Daniel, 1978). The paired t-test not only removed the effects of an inherent correlation among the data from the same cardiac cycle, it also minimized the effects of possible nonrandom errors due to shifts in flow baseline. Thus, small baseline shifts influence the calculated areas equally in any single cardiac cycle, and the relative changes are not masked. (Note that the paired t-test was used only between adjacent times and was not applied indiscriminately to any two times.)

The data for all five natural valve experiments were analyzed for overall statistical significance, using the randomized complete block design (Daniel, 1978), with each dog considered a block and each time a treatment. This approach is designed to estimate the probability that any other dog with a similar lesion would behave in the same manner as those in this series. The paired t-test was also applied to the mean MRA values of each dog at adjacent times.

Because the data that are used to calculate the time variation of regurgitant area come from conditions of varying regurgitant periods and dissimilar actual A's, we made the results nondimensional to allow comparisons within and among dogs. Time was normalized by total regurgitant time (RT), and MRA was normalized by MRAa. We used the area calculated at peak flow for normalization because it is inherently the most accurate and subject to the

<table>
<thead>
<tr>
<th>Table 1 Hemodynamic Conditions</th>
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<tbody>
<tr>
<td>Dog</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
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<tr>
<td>5</td>
</tr>
</tbody>
</table>

Fixed orifice 120 ± 33 2.0 ± 0.42 15 ± 6 91 ± 13 40 ± 7 69 ± 24

Results are expressed as mean ± SD. HR = heart rate, CO = cardiac output, LVEDP = left ventricular end-diastolic pressure, PLVP = peak left ventricular pressure.
least measurement error. The normalized data then were investigated with linear regression and the slope tested for significant difference against a zero slope.

**Results**

**Hemodynamics**

Figure 1 is an oscillographic record taken at the time of an atrial premature contraction and is typical of the conditions studied in these experiments. We analyzed the control (C) and postextrasystolic (PES) beats because they provided an opportunity to calculate the MRA in the same dog at two different conditions of end-diastolic volume close together in time. Because the mitral flow was recorded at high gain, we attempted to avoid confusion in pattern recognition by delineating those portions of the records which were digitized to give the integrated areas shown shaded in Figure 1.

Table 1 presents the hemodynamic data for the five dogs with an excised portion of the natural leaflet and for the one dog with a fixed orifice and a nonfunctioning mitral apparatus. There is a reasonable consistency in the regurgitant fraction (RV/FV) among these six dogs, indicating a comparable level of cardiac function, the reproducibility of our method of creating insufficiency, and the appropriateness of the fixed-orifice model. The average level of function was normal for the anesthetized dog, and the standard deviation indicates that a large range of function was studied.

**MRA**

Preliminary calculations revealed that, although there were differences in the MRA related to end-diastolic volume, the relative changes of MRA with time were independent of end-diastolic volume, and the data for the C and PES beats were combined for the final calculations. Table 2 presents the calculated A₀'s based on Equations 5-7. In Figure 3 we have plotted the MRA(t), normalized by the MRA₀, against the time of measurement (t), normalized by the total RT, for the same beat. Because the fixed-orifice experiment was designed, in part, to test the applicability of the Gorlin equation, these results will be presented first.

**Table 2 Mitral Regurgitant Orifice Area (mm²)**

<table>
<thead>
<tr>
<th>Dog</th>
<th>MRA₀</th>
<th>P&lt; *</th>
<th>MRA₀</th>
<th>MRA(t₀)</th>
<th>P&lt; *</th>
<th>MRA(t₁)</th>
<th>P&lt; *</th>
<th>MRA(t₂)</th>
<th>P&lt; *</th>
<th>Slope‡</th>
<th>r</th>
<th>P&lt;§</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32 ± 4</td>
<td>NS</td>
<td>33 ± 4</td>
<td>42 ± 5</td>
<td>0.001</td>
<td>31 ± 3</td>
<td>0.01</td>
<td>30 ± 3</td>
<td>NS</td>
<td>-0.66</td>
<td>-0.33</td>
<td>NS</td>
</tr>
<tr>
<td>2</td>
<td>31 ± 2</td>
<td>0.001</td>
<td>36 ± 1</td>
<td>43 ± 4</td>
<td>0.02</td>
<td>32 ± 2</td>
<td>0.001</td>
<td>27 ± 3</td>
<td>0.001</td>
<td>-0.74</td>
<td>-0.27</td>
<td>0.05</td>
</tr>
<tr>
<td>3</td>
<td>28 ± 1</td>
<td>0.001</td>
<td>36 ± 1</td>
<td>39 ± 1</td>
<td>NS</td>
<td>27 ± 1</td>
<td>0.001</td>
<td>23 ± 1</td>
<td>0.001</td>
<td>-1.11</td>
<td>-0.88</td>
<td>0.001</td>
</tr>
<tr>
<td>4</td>
<td>12 ± 1</td>
<td>0.001</td>
<td>22 ± 1</td>
<td>25 ± 4</td>
<td>NS</td>
<td>16 ± 2</td>
<td>0.001</td>
<td>9 ± 1</td>
<td>0.01</td>
<td>-0.20</td>
<td>-0.68</td>
<td>0.001</td>
</tr>
<tr>
<td>5</td>
<td>43 ± 2</td>
<td>0.001</td>
<td>53 ± 2</td>
<td>62 ± 2</td>
<td>NS</td>
<td>39 ± 1</td>
<td>0.001</td>
<td>34 ± 1</td>
<td>0.02</td>
<td>-2.25</td>
<td>-0.84</td>
<td>0.001</td>
</tr>
<tr>
<td>Fixed orifice</td>
<td>26 ± 1</td>
<td>NS</td>
<td>27 ± 1</td>
<td>24 ± 0.4</td>
<td>NS</td>
<td>23 ± 0.4</td>
<td>NS</td>
<td>24 ± 0.4</td>
<td>NS</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± sd. MRA₀, MRA(t₀) = mean, instantaneous value at peak flow, and at times t₁, t₂, t₃. r = correlation coefficient for the linear regression based on analysis of variance. NS = not significant.

* Compared to MRA₀. ‡ Slope of regression line through the (MRA, t) coordinate pairs. § Compared to a zero slope based on analysis of variance. § P < 0.02 compared to MRA₀, based on paired t-test.

**Fixed Orifice**

There was no significant difference among the five results for the MRA calculated using the three methods (Table 2). The normalized results are plotted in Figure 3 (filled circles). Under the conditions of this study, Equations 5-7 gave consistent results,
and therefore, we conclude that the discharge coefficient did not change during the regurgitant period. The measured \( A_o \) was 25 mm\(^2\); and we added an estimated 5 mm\(^2\) for the perioccluder space in the Bjork-Shiley pivoting-disc prosthesis (based on 15.8 mm, i.d., and 0.1 mm of space) to arrive at an estimated 30 mm\(^2\) regurgitant \( A_o \). Thus, we may conclude that the value of the discharge coefficient was reasonably accurate.

**Natural Valve**

There was no significant difference between the mean and peak MRA for dog no. 1, although the time variation showed a significantly consistent fall in value (Table 2). The other four dogs (nos. 2–5) showed a significantly lower mean area than peak area and a decreasing area with time (Table 2). The two-way analysis of variance revealed a time variation in MRA significant at less than the 0.05 level. The paired \( t \)-test on the means of each dog also showed a significant difference at less than the 0.05 level. Thus, although dog no. 1 may not have had an MRA that changed in time, the overall variation indicated a better than 95% probability that a time variation would be seen in other dogs with similar lesions.

The normalized ensemble means for the pooled data are plotted in Figure 3 (filled squares). Since peak flow occurred early in the regurgitant period (20 ± 7%), the MRA calculated at that time can be greater than the mean only if the area decreases in time. The regression line showing that trend is plotted in Figure 3 and is based on the 187 individual observations. The slope of the regression line differs significantly from zero \((P < 0.001)\), which represents no change in time. Note that, because neglect of inertia tends to underestimate the area before the peak and overestimate it after the peak, the error inherent in our method tends to decrease the slope of the regression line and underestimate the rate of decrease in area with time.

It is interesting to note that the regression line intersects the time line midpoint at a value of 80% for the normalized area (arrow, Fig. 3). This is almost exactly equal to the normalized value of the ensemble mean regurgitant area (79%) and suggests that the decline in area is either linear, as shown, or symmetrical about the middle of the regurgitant period. To test this possibility, we integrated the aortic flow and regurgitant mitral flow curves and plotted the volume change as a function of time. A typical result is shown in Figure 4. It can be seen that the resulting curve is sigmoidal, with substantial linearity during midsystole. Thus, MRA decreases with time in proportion to the decrease in ventricular volume.

If we assume that the shape of the area-time curve is also sigmoidal, and if we employ the regression equation to determine the area change between the 10% and 80% time interval (i.e., over the linear portion), then we calculate a 41% reduction in MRA during ventricular systole. Or stated relative to the mean area: the regurgitant area was approximately 31% greater than the mean at the start of systole and was approximately 77% of the mean area at the end of systole.

**Discussion**

Previous investigations of acute mitral regurgitant dynamics have relied on models (Wiggers and Feil, 1922; Rodbard and Williams, 1954), shunts that bypass the mitral valve (Braunwald et al., 1957), and shunts that interfere with mitral valve motion (Braunwald et al., 1958). Although these methods are of value in understanding regurgitant dynamics, they are incapable of evaluating the role of the mitral apparatus. Since the effective area of the regurgitant orifice is a major determinant of the impedance to backflow, it is important to study its characteristics during ventricular systole. This is particularly important when the mitral cusps are mobile (Jose et al., 1964).

Recent studies using angiographic techniques have suggested that the MRA is a direct function of left ventricular chamber size (Chatterjee et al., 1973) or, more importantly, of the valvular and subvalvular dimensions (Borgenhagen et al., 1977). These are reasonable conclusions to expect from an intact and mobile mitral apparatus, and we were led to examine them further using directly measured phasic pressures and flows in the left heart chambers. Our initial results indicated that the mean MRA during ventricular systole varied directly with end-diastolic volume (Yoran et al., 1979a, 1979b). In those studies, end-diastolic volume changes were inferred from changes in end-diastolic pressure.

In the present study, we tested the hypothesis that the MRA changes with ventricular volume by examining the \( A_o \), during ventricular systole when the volume is decreasing monotonically with time (Fig. 4). Since the change in volume was calculated accurately from the simultaneous measurement of SV and RV, and because the measurement of phasic...
flows and pressures is the most accurate method of determining volume changes and effective A's, we conclude that our results are the primary standard by which to evaluate others.

An equation of motion containing an inertial and a square-law resistance term (Equation 1), previously has been used to calculate an A, that changes with time (Pierce et al., 1964). Their approach was somewhat different from ours, but the net effect was to include in the analysis an estimate of inertial influence. The fixed-orifice results (Table 2) indicate that our derived equations are appropriate and our choice of discharge coefficient (0.6) is reasonable. It should be noted, however, that the discharge coefficient used herein is not necessarily appropriate for the Gorlin equation when it is applied to studies on patients, since the sites and methods of measurement differ (Yellin et al., 1975). In the final analysis, the choice of discharge coefficient does not influence the results of this study because the calculated valve areas have been normalized (Fig. 3) and the constant terms cancel.

The hemodynamic data of Table 1 indicate that the dogs used in this study had moderate regurgitation (mean regurgitant fraction 42 ± 12%), maintained adequate ventricular function, and therefore were not volume overloaded. At autopsy, all five dogs used in the natural valve study had normal mitral leaflets, and the flow probe did not seem to interfere with cusp or annulus movement. Because the fixed-orifice study yielded a constant value for the regurgitant area and the natural valve study did not, we are confident that the probe did not significantly interfere with mitral apparatus function, although we cannot rule out this possibility in dog no. 1.

Furthermore, any impairment of annular mobility would have tended to minimize changes in the regurgitant area. Under the conditions of this study, we conclude that the effective MRA in acute mitral insufficiency decreases to an estimated 59% of its initial value during ventricular ejection and that this decrease is linear during the mid 70% of ejection. It is not unreasonable to assume that the anesthetized dog with moderate volume load will have an ejection fraction of 60%. Thus, the decrease in regurgitant area closely parallels the decrease in ventricular volume.

Finally, it is reasonable to expect that absolute values and relative changes in the MRA will differ with major differences in contractility, aortic impedance characteristics, initial ventricular volume, pericardial constraints, and lesion properties. We would like, therefore, to de-emphasize the quantified percent changes presented in this study in favor of emphasizing the concept that changes in regurgitant area do occur.

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