Dynamic Aspects of Acute Mitral Regurgitation:
Effects of Ventricular Volume, Pressure
and Contractility on the Effective
Regurgitant Orifice Area

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SUMMARY  The dynamics of acute mitral regurgitation were studied in six open-chest dogs in whom a portion of the anterior leaflet was excised. Phasic mitral and aortic flows were measured electromagnetically and left ventricular filling volume, regurgitant volume (RV) and forward stroke volume (SV) were calculated. The systolic pressure gradient (SPG) between the left ventricle (LV) and left atrium (LA) was obtained from high-fidelity pressure transducers. The effective mitral regurgitant orifice area (MRA) was calculated from the hydraulic equation of Gorlin.

Volume infusion resulted in significant increases in both left atrial and left ventricular pressures; thus, the SPG was unchanged and the increase in RV was due primarily to the increase in MRA. Angiotensin infused to raise arterial pressure resulted in greater increments in left ventricular than left atrial pressure, so that SPG rose significantly. The increase in RV was due to increases in both MRA and SPG. Norepinephrine infusion increased systolic left ventricular pressure and SPG, while left ventricular end-diastolic pressure and left atrial pressure diminished. Despite a significant increase in SPG, RV did not increase, due to a substantial decrease in MRA. Thus, angiotensin and volume infusion induced a substantial increase in regurgitation due to the increase in MRA, while augmentation of contractility after norepinephrine infusion resulted in a decrease in regurgitation through reduction of MRA. These findings support the clinical view that maintaining a small LV with sustained myocardial contractility will reduce mitral regurgitation. Alternatively, left ventricular dilatation can enhance mitral regurgitation by increasing the effective regurgitant orifice independent of SPG.

NORMAL MITRAL VALVE FUNCTION depends on the mechanical integrity of the mitral annulus, valve leaflets, chordae tendineae, papillary muscles and the contraction of the free left ventricular (LV) wall. The factors that determine the regurgitant flow in mitral insufficiency are the systolic pressure gradient (SPG) between the left ventricle and left atrium, the size of the regurgitant orifice or the area of the defect in mitral closure, and the duration of the regurgitation or the length of ventricular systole.1 2 It has been traditionally accepted that the regurgitant orifice is fixed under different circulatory states,1 except in the clinical syndrome of papillary muscle dysfunction in which the properties of the supporting structures may change with time.3 6 However, recent studies of experimental acute mitral insufficiency in the dog have suggested that the size of the regurgitant orifice is not fixed.7 The present study was designed to define the effects of alterations in ventricular volume, pressure loading and myocardial contractility on the regurgitation of experimental acute mitral insufficiency, and to determine if the size of the regurgitant orifice is altered by these interventions.

Materials and Methods

Six mongrel dogs weighing 20–30 kg were anesthetized with sodium pentobarbital (25 mg/kg) and placed on artificial ventilation. The animal preparation has been described previously.6 Briefly, after a midline sternotomy and bilateral thoracotomy in the fifth intercostal space, the pericardium was opened and the heart supported in a pericardial cradle. High-fidelity catheter-tip pressure transducers (Millar Instruments) were introduced into the left ventricle and left atrium through the apical dimple and pulmonary vein, respectively. A short catheter (30 cm) was introduced into the right carotid artery and connected to a Statham pressure transducer to measure aortic pressure. All three transducers were adjusted to equal sensitivity and common zero. The first derivative of the LV pressure was obtained with an R-C differentiator. An electromagnetic flow transducer was placed around the ascending aorta.

During cardiopulmonary bypass, the left atrium was opened and an electromagnetic flow probe was sutured around the mitral annulus. Special care was taken not to suture the sewing ring of the probe to the annulus of the mitral valve in order to avoid interference with mitral ring mobility and cusp movement. Thus, the mitral valve apparatus remained intact. Phasic mitral and aortic flows were measured with a two-channel, square-wave flowmeter (Carolina Medical Electronics). Under direct vision, acute mitral regurgitation was produced by excising a portion of the free edge of the anterior leaflet. The left atrium was then closed, normal sinus rhythm was

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restored with DC defibrillation and the animal was weaned from circulatory bypass.

Filling volume (FV), regurgitant volume (RV) and forward stroke volume (SV) were calculated by digitizing the flow curves with a sonic digitizer (Science Accessories) coupled to a programmable calculator (Hewlett-Packard 9820). The average of three to five determinations was used for each calculation. Zero mitral flow was determined initially while the animal was still in ventricular fibrillation, during the experiment by producing long postextrasystolic diastolic periods, and again at the end of each experiment by arresting the heart with KCl. RV was calculated from the flow curve (fig. 1). In the steady state, SV plus RV equals FV, which is equal to the total LV stroke volume (SV total). The regurgitant fraction is defined by the ratio RV/SV total. The mean SPG between the left ventricle and left atrium was determined from simultaneous LV and left atrial pressure curves, and was calculated using the same digitizing system.

The mean mitral regurgitant orifice area (MRA) during ventricular systole was calculated from the revised Gorlin equation:

\[ \text{MRA} = \frac{\text{RV}}{\text{RT}} \cdot C \cdot \sqrt{\text{SPG}} \]

where RV = regurgitant volume (ml), RT = regurgitant time (sec), measured directly from the mitral flow curve (fig. 1) and SPG = systolic pressure gradient. C is a constant, which is 37.9.

Thirty to 45 minutes after completing the surgical preparation, the dogs were stable and hemodynamic data were collected for analysis. The hemodynamic effects of the following interventions were tested: 1) volume infusion: 200–400 ml of blood or dextran, rapidly infused to increase the LV end-diastolic pressure (LVEDP) to approximately 18 mm Hg; 2) angiotensin: i.v. infusion (5–10 μg/min); and 3) norepinephrine: i.v. infusion (4–10 μg/min). Pressures, flows, ECG and dp/dt were recorded on an oscillographic recorder (Electronics for Medicine DR-12) at a paper speed of 100 mm/sec. Each intervention was preceded by a stable control period. The standard t test on the paired data was used for statistical analysis.

Results

Volume Expansion

The acute hemodynamic effects of volume expansion are shown in table 1 and figures 1 and 2. Increases were found in peak LV pressure (12%), LVEDP (88%), forward cardiac output (41%), forward LVSV (45%) (there was no change in heart rate), and left atrial v-wave amplitude (113%) (table 1). RV rose by

![Figure 1. Oscillographic records during control period (left) and volume expansion (right). Note the large increase in regurgitant volume (RV) despite no change in systolic pressure gradient (SPG) after volume loading. AoF = aortic blood flow; MiF = mitral blood flow; LVP = left ventricular pressure; AoP = aortic pressure; LAP = left atrial pressure; SV = forward left ventricular stroke volume; FV = filling volume; RT = regurgitant time.](image-url)
Table 1. Hemodynamic Effects of Volume Loading, Increased Arterial Pressure and Contractility

<table>
<thead>
<tr>
<th>Volume loading</th>
<th>LVSP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>LA &quot;V&quot; (mm Hg)</th>
<th>CO (l/min)</th>
<th>SV (ml)</th>
<th>SV/RV</th>
<th>dp/dt (mm Hg/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>108.2 ± 5.6</td>
<td>8.9 ± 0.8</td>
<td>20.2 ± 1.7</td>
<td>1.79 ± 0.16</td>
<td>10.8 ± 0.9</td>
<td>1.65 ± 0.24</td>
<td>2660 ± 260</td>
</tr>
<tr>
<td>V</td>
<td>120.7 ± 5.7</td>
<td>16.7 ± 1.3</td>
<td>43.1 ± 3.3</td>
<td>2.53 ± 0.20</td>
<td>15.7 ± 1.2</td>
<td>1.55 ± 0.19</td>
<td>2680 ± 220</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>NS</td>
</tr>
</tbody>
</table>

Angiotensin

| C              | 101.8 ± 7.7  | 11.0 ± 1.0    | 26.2 ± 1.7     | 2.08 ± 0.25| 13.1 ± 1.4| 1.44 ± 0.37| 2330 ± 350       |
| A              | 135.7 ± 9.1  | 16.3 ± 1.9    | 31.5 ± 3.6     | 1.37 ± 0.19| 10.4 ± 1.0| 0.85 ± 0.21| 3130 ± 390       |
|                | p < 0.01     | p < 0.01      | NS             | p < 0.05   | NS       | p < 0.05  | p < 0.01         |

Norepinephrine

| C              | 94.1 ± 3.4   | 12.0 ± 2.3    | 24.9 ± 3.9     | 1.66 ± 0.14| 10.2 ± 1.0| 1.21 ± 0.29| 2050 ± 160       |
| NE             | 126.6 ± 5.2  | 8.6 ± 1.9     | 20.0 ± 2.7     | 2.17 ± 0.12| 12.7 ± 0.8| 1.70 ± 0.34| 3760 ± 290       |
|                | p < 0.01     | p < 0.01      | p < 0.02       | p < 0.01   | p < 0.05  | p < 0.001| p < 0.001        |

Values are mean ± SEM.
Abbreviations: LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; LA "V" = left atrial v-wave amplitude; CO = forward cardiac output; SV = forward stroke volume; RV = regurgitant volume; dp/dt = maximum derivative of left ventricular pressure; C = control; V = volume loading; A = angiotensin; N = norepinephrine.

44% and regurgitant fraction increased slightly, but significantly, by 8% (fig. 2, panels A and B).

Since the increase in peak LV pressure was accompanied by a nearly parallel rise in left atrial pressure (fig. 1), the ventriculatrial systolic pressure gradient increased by only 5% (fig. 2, panel C). MRA increased by 31% (fig. 2, panel D). If the regurgitant area had remained unaltered by the volume load, the small increase in SPG would have accounted for only 23% of the total increase in RV.

Increment of Systolic Pressure with Angiotensin

The hemodynamic effects of angiotensin infusion are shown in table 1 and figures 3 and 4. Peak systolic pressure increased by 33% and LVEDP rose 45%. Forward cardiac output was reduced by 25%, and since there was no change in heart rate, forward SV also decreased (23%). The forward SV/RV ratio decreased by 41%, and left atrial v-wave amplitude increased 23%.

During angiotensin infusion there was a 41% increase in RV and a 35% increase in regurgitant fraction (fig. 4, panels A and B). SPG rose markedly by 39% (fig. 4, panel C). MRA increased by 14%. If the orifice area had remained unchanged, then the calculated RV associated with the increase in SPG of 21 mm Hg (39%) would have been only 14.3 ml. Thus, the increase in RV from 11.6 to 14.3 ml was due only to an increase in SPG, and the further increase in RV to 16.3 ml was due to the increase in MRA.

Increased Myocardial Contractility with Norepinephrine

Table 1 and figures 5 and 6 show the hemodynamic effects of norepinephrine infusion. Systolic blood pressure and dp/dt both increased by 35%, while LVEDP decreased 28%. Both forward cardiac output and SV increased substantially (31% and 25%, respectively). The ratio of forward SV to RV increased by 40% and the left atrial v wave fell 20%.

Despite the 51% increase in SPG after norepinephrine infusion, there was a statistically insignificant 12% decrease in RV (fig. 6, panels A and C) and the orifice area had remained unchanged, then the calculated RV associated with the rise in pressure gradient (51%) would have increased 6%, rather than decreased 12%.

Discussion

In 1922, Wiggers and Feil demonstrated the relationship between the arterial pressure and the severity of experimental mitral regurgitation in dogs. Their conclusions were based on changes in left atrial pressure, since RV was not measured. Increases in arterial pressure were associated with elevations in left atrial pressure. Conversely, when arterial resistance was diminished as a result of aortic decompression or the administration of nitrates, left atrial pressure, and presumably regurgitation, decreased. In their experimental preparation, the mechanism involved in the regulation of the amount of the mitral regurgitation could not be defined. In other experimental studies of mitral regurgitation, Braunwald et al. used an extracardiac cannula between the left atrium and the left ventricle or a perforated tube placed through the left atrial appendage and advanced through the mitral valve into the left ventricle. The former method, using a shunt between the left ventricle and left atrium, was also used by Urschel et al.
methods of experimental mitral regurgitation eliminate the role of the entire mitral apparatus in mitral regurgitation. Others have calculated the amount of mitral regurgitation as the difference between the forward cardiac output (determined by dye dilution) and the total cardiac output (determined angiographically). This method is limited by the fact that the regurgitant flow was not measured directly, and cardiac output was measured by two methods which provide only mean flows with wide limits of potential error. Additionally, the RV was calculated from two non-simultaneous cardiac outputs.

We have overcome these limitations by measuring phasic inflow to the left ventricle across the mitral valve, outflow across the aortic valve and regurgitation into the left atrium. From these data, the forward SV, RV and FV were calculated in the same cardiac cycle (figs. 1, 3 and 5).

Regurgitant flow across the incompetent mitral valve is generally related to the SPG between the left ventricle and the left atrium, the size of the regurgitant orifice (or the size of the defect of mitral closure), and the duration of ventricular systole. Except in the clinical syndrome of papillary muscle dysfunction, the MRA is considered to be fixed. Thus, the RV should be a function only of the SPG between the left ventricle and atrium. However, our study demonstrates that in acute mitral regurgitation, experimentally produced in the normal canine heart, the mitral regurgitant orifice does not have a fixed area. The effective area of the regurgitant orifice varies under different hemodynamic conditions.

During volume expansion, the amount of regurgitation increased significantly (44%), despite a small or insignificant increase in the SPG (fig. 2, panel A). The increase in RV which was measured directly from the mitral valve flow probe, could not be derived from the hydraulic formula if the orifice area was unchanged. Only 23% of the 44% increase in the RV during volume expansion could be attributed to a rise in SPG, if the MRA was taken as constant. Seventy-seven percent of the increase in RV was therefore due to a significant increase in the effective MRA (fig. 2, panel D). Thus, our findings indicate that during volume expansion the increased mitral regurgitation is due primarily to an increase in the effective MRA, secondary to an increase in ventricular volume as inferred from an increase in LVEDP. These findings are in agreement with those of Borgenhagen et al., who applied angiographic methods and found that the subvalvular region of the end-diastolic ventricular cavity and the end-diastolic diameter of the mitral annulus were increased by volume expansion.

The increase in systemic blood pressure produced by angiotensin infusion resulted in a significant increase in the RV (fig. 4 and table 1). Our findings are in agreement with those reported earlier by Wiggers and Feil, Braunwald et al., Jose et al., and Borgenhagen et al. The increased impedance to ventricular ejection was associated with a decrease in the forward cardiac output and an increase in the RV (fig. 4 and table 1). The measured RV averaged 16.3 ml. Had the regurgitant area remained constant, it would, by calculation from the SPG, have been only 14.3 ml. The difference between these two figures is explained by a significant increase of the area of the effective regurgitant orifice (fig. 4, panel D).

The infusion of angiotensin caused a significant rise in LVEDP, from 11 to 16 mm Hg (table 1). Accompanying this there must also have been changes in ventricular geometry. Leidtke et al. found that an increase in LV afterload by methoxamine produced a marked diminution of LV contraction, especially in the apex. At end-diastole the LV configuration became globular and the length-to-width ratio approached unity. Tsakiris et al. and Carleton and Clark showed that end-diastolic chamber volume and midventricular diameter varied directly with afterload, while ejection fraction varied inversely. With increased end-diastolic pressure, and presumably end-diastolic volume and reduced ejection fraction, the end-systolic volume increased, perhaps preventing complete systolic coaptation of the mitral valve leaflets.

The increase in systemic blood pressure with norepinephrine was associated with a significant reduction of LVEDP and a significant increase in
dp/dt (table 1), indicating a substantial enhancement of the contractile state of the left ventricle. Since the magnitude of mitral regurgitation is related directly to the product of the regurgitant orifice size and to the square root of the SPG between the left ventricle and atrium, factors altering the regurgitant orifice size will affect the regurgitation relatively more than similar changes in the SPG. This is well demonstrated after the administration of norepinephrine.

Despite a substantial increase in ventriculoatrial SPG, RV decreased (fig. 6). If the regurgitant area had been fixed, the increase in the SPG (from 47 to 72 mm Hg; fig. 6, panel C) would have resulted, as calculated by the hydraulic formula, in an increase of RV from 9.9 to 10.5 ml. In fact, the directly measured RV decreased slightly (fig. 6, panel A), due to a significant decrease in MRA. Our findings are in agreement with other studies of acute mitral insufficiency, and observations in patients with mitral valve disease and mobile mitral structures. Based on angiographic studies, Borgenhagen et al. observed significant reductions in end-diastolic subvalvular region and in mitral annular diameter and speculated that enhanced ventricular contractility decreased both the end-diastolic and end-systolic ventricular volume, which led to the decrease in regurgitant orifice size.

It has been shown that at least two-thirds of the mitral valve ring is attached to the base of the left ventricle and that the mitral leaflets contain muscle fibers which contract synchronously with atrial systole. It is therefore reasonable to assume that the mitral annulus participates in LV contraction and relaxation, and that norepinephrine may have a direct effect on the size of the mitral annulus. If the diameter of the annulus is significantly less in systole than in diastole, this would help ensure that cusps of a given dimension will coapt effectively in systole to prevent regurgitation. It follows that if a cusp has a defect based on the free edge, its failure to meet the opposite cusp will be enhanced by a larger annulus diameter.

Tsakiris et al. have noted in addition a decrease in the mitral annular size during both atrial and ventricular systole. They also suggested that the size and
shape of the left ventricle may affect mitral valve closure. When LV end-diastolic volume was increased and the ejection fraction was reduced, as in acute elevation of aortic pressure, the presystolic narrowing of the annulus associated with atrial contraction was not followed by further reduction in size during ventricular systole. Under these conditions the mitral valve closure was less adequate.

The reduction of mitral regurgitation by nitroprusside has been described by other investigators, and is thought to be due to the reduction in systemic vascular resistance (decreased impedance to LV ejection). In a recent investigation of the mechanism of reduction of mitral regurgitation with vasodilator therapy, we found that nitroprusside caused a significant decrease in mitral regurgitation. However, the mechanism by which nitroprusside reduces the severity of mitral regurgitation is different from that in previous studies. In our studies nitroprusside caused significant reductions in both the systemic blood pressure and LV filling pressure, and therefore the SPG changed only slightly and could not account for the significant reduction of regurgitation. The reduction in mitral regurgitation by nitroprusside was primarily due to a significant decrease in the effective MRA, which we conclude was secondary to a reduction of ventricular volumes.

In this study, ventricular volumes were not measured directly but changes were inferred from changes in LVEDP. End-diastolic pressure has long been used as an index of end-diastolic volume, especially under acute conditions with an open pericardium, where compliance is not altered, and has also been shown to be an accurate index of LV end-diastolic volume during nitroprusside administration, volume loading and augmentation of systolic pressure. Finally, we conclude that since in this study the ven-

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**Figure 6.** Oscillographic records during control period (left) and norepinephrine infusion (right). Note the unchanged regurgitant volume (RV) despite a large increase in systolic pressure gradient (SPG) with norepinephrine infusion. Other abbreviations as in figure 1.

**Figure 5.** Oscillographic records during control period (left) and norepinephrine infusion (right). Note the unchanged regurgitant volume (RV) despite a large increase in systolic pressure gradient (SPG) with norepinephrine infusion. Other abbreviations as in figure 1.

**Figure 6.** Effects of norepinephrine infusion. NE = norepinephrine; other abbreviations as in figure 2.
tricles were not on the steep portion of their pressure-volume curves, the relatively large changes in LVEDP reflect similar changes in LV end-diastolic volume.

The findings in this study of acute mitral regurgitation indicate that when the mitral valve apparatus is not rigid, the size of the effective MRA can be altered by different hemodynamic factors. Augmentation of ventricular afterload and/or preload enlarges the ventricle, widens the annulus and the regurgitant orifice, and increases regurgitant flow. Conversely, reduction in ventricular volume and increased contractility narrows the mitral annulus and the regurgitant orifice and decreases the regurgitant flow. This study supports the clinical view that maintaining a small left ventricle with sustained myocardial contractility will reduce the amount of mitral regurgitation for a given lesion, particularly when the leaflets are mobile. Alternatively, ventricular dilatation can enhance regurgitation, primarily by increasing the effective orifice for regurgitation, independent of changing pressure gradients.

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