Beneficial Effects of Vasodilator Agents in Severe Mitral Regurgitation Due to Dysfunction of Subvalvar Apparatus

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SUMMARY

To assess the potential beneficial effects of vasodilator agents in patients with severe mitral regurgitation, sodium nitroprusside was administered intravenously at a rate of 16 to 100 μg/min in eight patients with clinically significant mitral regurgitation presumably due to dysfunction of the subvalvar apparatus. In all patients there was a decrease in the magnitude of the peak ‘V’ wave (from 50 ± 4.5 to 19 ± 2.9 mm Hg) and in left ventricular filling pressure (33 ± 1.8 to 16 ± 1.4 mm Hg), together with a decreased intensity of the apical pansystolic murmur. There was a significant increase in forward cardiac index (2.2 ± 3.5 to 3.3 ± .47 liter/min/M²) and forward stroke volume index (23 ± 4.4 to 36 ± 6.8 ml/M²) along with a reduction in systemic vascular resistance (1802 ± 331 to 1102 ± 241 dynes/sec/cm⁻⁵). In the five patients in whom the therapy was continued, relief of symptoms of pulmonary venous congestion occurred. In the four patients in whom left ventricular volumes were determined angiographically, the observed increase in forward stroke volume was due to a reduction in the regurgitant fraction. These findings suggest that the use of vasodilator agents like nitroprusside can achieve the major objectives of treatment of patients with mitral regurgitation: an increase in forward stroke output, a reduction in regurgitant volume and a decrease in pulmonary venous pressure.

Additional Indexing Words:
Nitroprusside Outflow impedance

Surgical repair or replacement of the mitral valve apparatus can markedly benefit selected patients with severe and symptomatic mitral regurgitation. However, clinicians sometimes encounter situations where surgical therapy involves a prohibitively high risk and should be deferred. For example, in patients developing severe mitral regurgitation following acute myocardial infarction, the operative mortality associated with mitral valve replacement in the immediate postinfarction period is high, and a significantly better prognosis can be expected if surgical therapy can be deferred for a few weeks.1-3

In patients with mitral regurgitation, increased systemic vascular resistance augments the regurgitation.4-7 Therefore, reduction of systemic vascular resistance, i.e., reduction of aortic impedance to left ventricular ejection, should decrease the regurgitant volume and thereby increase forward cardiac output. Vasodilator agents like nitroprusside or phentolamine decrease systemic vascular resistance8-10 and should be useful in increasing forward output in patients with mitral regurgitation. It is also possible that increased left ventricular chamber size may further aggravate mitral regurgitation by causing either annular dilatation or derangement of function of the subvalvar apparatus, the functional integrity of which may substantially contribute to maintenance of mitral valve competence.

Increased forward stroke volume, resulting from the decreased systemic vascular resistance produced by vasodilator agents, should decrease end-systolic
and end-diastolic volumes. Decreased left ventricular chamber size if achieved should, therefore, at least partly restore the functional integrity of the subvalvar apparatus, improve the competence of the mitral valve, and decrease the severity of mitral regurgitation. Furthermore, nitroprusside and phen tolamine also reduce left ventricular filling pressure, presumably due to their venous pooling effects. Thus, such drugs should also be beneficial in relieving symptoms of pulmonary venous congestion. The purpose of the present study, therefore, was to evaluate the potential beneficial effects of such vasodilator agents as nitroprusside in hospitalized patients with severe mitral regurgitation.

**Patient Population**

Eight patients with severe mitral regurgitation (1 female and 7 males with an age range of 45 to 69 years) were studied. The etiologies of mitral insufficiency were probable papillary muscle dysfunction (and/or annular dilatation) in all 8 patients. Two patients developed severe mitral regurgitation following myocardial infarction and were studied in the immediate postinfarction period. All but one patient had clinical cardiomegaly and symptoms of congestive heart failure (duration 2 days to 2 years) and all had clinical signs of significant mitral regurgitation with associated pulmonary hypertension. All patients had cardiomegaly and pulmonary venous congestion and three showed frank pulmonary edema on chest X-ray at the time of the study. The clinical diagnosis was substantiated by the presence of giant ‘V’ waves in the pulmonary capillary wedge pressure (PCW) in all eight patients. Four patients had left ventriculograms for quantitation of regurgitant volumes. Seven patients were receiving diuretics and six were receiving digitalis at the time of study.

**Methods**

Arterial pressure was continuously monitored by inserting a 20 gauge arterial needle into the radial artery. Pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCW) and the magnitude of the ‘V’ wave in the pulmonary capillary wedge pressure and right atrial pressures were obtained from a Swan-Ganz balloon tip flow-directed catheter. All pressures were measured relative to a zero reference level 5 cm below the sternal angle. Four patients were studied in the Myocardial Infarction Research Unit where forward cardiac output was determined by the thermodilution technique. Indocyanine green was injected into the pulmonary artery with sampling from the radial artery, using a Gilford densitometer and a Harvard withdrawal pump. Any change in the intensity of the apical holosystolic murmur during nitroprusside administration was noted. In the four patients studied in the Cardiac Catheterization Laboratory, phonocardiograms were recorded from the left 5th intercostal space medial to the apex, both before and during nitroprusside administration without changing the gain setting. In the same four patients right anterior oblique left ventricular cineangiograms (60 frames/sec) were obtained both before and during nitroprusside administration to assess changes in regurgitant volume during impedance reduction. Left ventricular volumes were calculated from single plane cineangiograms and normalized for body surface area. The magnification factor was determined by measuring the ratio of the projected to the actual diameter of a metal ball placed at the mid-ventricular level. The outline of the left ventricle was traced from 90-120 consecutive frames from each cineangiogram, both before and during nitroprusside administration. Since calculated left ventricular volumes from single plane cineangiograms overestimate the actual volumes, appropriate corrections were made.

Left ventricular volumes were calculated from each frame, using an x-y digitizer and Sigma 3 computer. From each cineangiogram a volume curve covering at least two cardiac cycles was obtained. From such a volume curve the end-diastolic volume (EDV) and end-systolic volume (ESV) were obtained. The difference between the end-diastolic volume and end-systolic volume represents total left ventricular stroke volume (TSV), and the ratio of total left ventricular stroke volume to end-diastolic volume is the ejection fraction (EF). Forward left ventricular stroke volume (FSV) was calculated by dividing the dye forward cardiac output by the heart rate. Regurgitant volume (RV) was then calculated as the difference between total left ventricular stroke volume and forward left ventricular stroke volume and was expressed as the percentage of total left ventricular stroke volume

\[ RV(\%) = \left( \frac{TSV - FSV}{TSV} \right) \times 100 \]

**Stoke work index (SWI) and systemic vascular resistance (SVR)** were calculated as follows:

\[ SWI = \frac{(gm-m/beat/M^2) \times (MAP - PCW)}{0.0144} \]

where

- SWI = stroke work index (in ml/M²)
- MAP = mean arterial pressure (in mm Hg)
- PCW = mean pulmonary capillary wedge pressure, 0.0144 = correction fraction for the density of blood and the conversion of mm Hg to cm H₂O.

\[ SVR = \frac{MAP - RA}{F.C.O.} \times 80 \]

where

- RA = mean right atrial pressure in mm Hg.
Hemodynamic Effects of Nitroprusside in Patients with Mitral Regurgitation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>PAP (mm Hg)</th>
<th>PCW (mm Hg)</th>
<th>'V' (mm Hg)</th>
<th>FCI (L/min/M²)</th>
<th>FSVI (ml/M²)</th>
<th>SVR (dynes sec cm⁻⁵)</th>
<th>PVR (dynes sec cm⁻⁵)</th>
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Mean 101 95 83 70 45 29 33 16 50 19 2.2 3.3 23 36 16 29 1802 1102 263 163
SEM 5.9 4.9 3.8 3.3 2.4 2.4 1.8 1.4 4.5 2.9 .35 .47 4.4 6.6 3.0 6.0 331 241 45 26

P < .01 .005 .0005 .0005 .0005 .0005 .005 .01 .005 .025

Abbreviations: HR = Heart rate; MAP = mean arterial pressure; PAP = mean pulmonary artery pressure; PCW = mean pulmonary capillary wedge pressure; 'V' = peak 'V' wave in PCW; FCI = Forward cardiac index; FSVI = Forward stroke volume index; SVR = Systemic vascular resistance; PVR = Pulmonary vascular resistance; C = Control; NP = Nitroprusside.

*Mitral regurgitation following acute myocardial infarction.

F.C.O. = forward cardiac output in liter/min, 80 is the conversion factor for resistance units to dynes sec cm⁻⁵.

After control hemodynamic and angiographic studies, nitroprusside was administered through a peripheral vein at a rate of 16 to 100 μg/min. In all patients, nitroprusside was started at a low dose (16 μg/min) and increased gradually until either the mean arterial pressure decreased by approximately 20 mm Hg or there was a significant fall in pulmonary capillary wedge pressure. The infusion rate of nitroprusside was then kept constant throughout the study period. The hemodynamic effects could be reversed within 5-10 min of discontinuation of nitroprusside infusion.

Results

The hemodynamic effects of nitroprusside administration in all eight patients with mitral regurgitation are summarized in table 1. In general all patients showed directionally similar changes. There was a slight fall in heart rate (average -8%), a slight fall in mean arterial pressure (average -16%), and a greater fall in mean pulmonary artery pressure (average -36%). There was an increase in forward cardiac output (average +50%) and forward stroke volume (average +57%) (fig. 1), together with a reduction in systemic vascular resistance (average -39%) in all patients. Reduction in pulmonary vascular resistance occurred in 7 patients (average change for 8 patients -42%).

During nitroprusside administration, there was a dramatic decrease in the magnitude of the peak 'V' wave and mean capillary wedge pressure (figs. 2 and 3). In four patients in whom left ventricular (LV) and pulmonary capillary wedge pressures were recorded simultaneously, there was an increase in the systolic pressure gradient between left ventricular and pulmonary capillary wedge pressures (fig. 2) during nitroprusside infusion suggesting increased resistance at the mitral valve. Along with a decrease in the magnitude of the 'V' wave there was a decrease in the intensity of the apical pansystolic murmur in all patients. In five patients in whom nitroprusside infusion was continued, the symptoms of dyspnea improved significantly within a few hours. The volume data in the four patients studied in the Cardiac Catheterization Laboratory are summarized in table 2. In each patient there

Figure 1

Individual changes in cardiac output and forward stroke volume produced by nitroprusside (NP) infusion in eight patients with mitral regurgitation. In all patients, cardiac output and forward stroke volume increased during nitroprusside infusion. The solid rectangle indicates the mean of each group of measurements.
was a decrease in end-diastolic volume and end-systolic volume with no significant change in total stroke volume. Thus, there was a slight increase in the ejection fraction of the left ventricle (fig. 4). Although the total stroke volume remained relatively constant, forward stroke volume increased significantly because of the reduction in the regurgitant volume. This decrease in mitral regurgitation during nitroprusside infusion was also apparent from the more rapid downslope of the dye dilution curves (fig. 5).

**Discussion**

Clinical symptoms in patients with severe mitral regurgitation are primarily related to a decrease in forward cardiac output and an increase in pulmonary venous pressure. The major objective of therapy in such patients, therefore, is to increase forward output and decrease pulmonary venous pressure. The magnitude of the decrease in forward stroke volume in patients with mitral regurgitation is related to the severity of incompetence of the mitral valve apparatus and the resistance to ejection of blood into the aorta. Thus, an increase in systemic vascular resistance will increase mitral regurgitation and decrease forward stroke volume. Conversely, reduction in impedance to left ventricular ejection should decrease regurgitant volume and increase forward stroke volume. The present study demonstrates that such a reduction in systemic vascular resistance (decreased impedance to left ventricular ejection) achieved through the use of vasodilator agents like nitroprusside is indeed effective.
associated with increased forward output and decreased regurgitant volume. That a decrease in regurgitant volume occurred was apparent from the reduction in intensity of the apical pansystolic murmur, and from the marked decrease in the magnitude of the 'V' wave in the pulmonary capillary wedge pressure tracing. Finally, in all four patients in whom regurgitant volume was calculated, it was significantly reduced during nitroprusside infusion. Decreased regurgitant volume in these patients, however, might not be entirely due to decreased aortic impedance to left ventricular ejection; increased competence of the mitral valve will also decrease the regurgitant volume.

That there might have been increased competence of the mitral valve in these patients was suggested by the increased systolic pressure gradient between the left ventricle and pulmonary capillary wedge pressure during nitroprusside infusion (fig. 2) and the decrease in regurgitant flow. Increased competence of the mitral valve might have occurred due to improved function of the subvalvar structures caused by decreased left ventricular chamber size. Furthermore, decreased left ventricular end-diastolic volume (preload) along with decreased heart rate and arterial pressure (afterload) should decrease myocardial oxygen demand and thereby reduce myocardial ischemia. If myocardial and papillary muscle ischemia were contributory or aggravating factors for mitral regurgitation, then relief or decrease in ischemia should improve mitral valve competence and therefore help in reducing regurgitation.

Although the precise mechanisms of reduction in regurgitation were not clear, it is apparent from this study that forward output increases along with

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>EDV ml/M²</th>
<th>ESV ml/M²</th>
<th>TSV ml/M²</th>
<th>FSV ml/M²</th>
<th>RV %</th>
<th>EF</th>
<th>EDP mm Hg</th>
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<tbody>
<tr>
<td>Control</td>
<td>238 ± 51</td>
<td>140 ± 33</td>
<td>96 ± 24</td>
<td>31 ± 7</td>
<td>64 ± 8</td>
<td>.41 ± .07</td>
<td>30 ± 2.5</td>
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<td>Nitroprusside</td>
<td>206 ± 46</td>
<td>113 ± 32</td>
<td>93 ± 20</td>
<td>40 ± 9</td>
<td>44 ± 11</td>
<td>.47 ± .08</td>
<td>14 ± 2.3</td>
</tr>
<tr>
<td>P &lt;</td>
<td>.91</td>
<td>.905</td>
<td>NS</td>
<td>.025</td>
<td>.065</td>
<td>.05</td>
<td>.005</td>
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</tbody>
</table>

Abbreviations: EDV = End-diastolic volume; ESV = End-systolic volume; TSV = Total stroke volume; FSV = Forward stroke volume; RV = Regurgitant volume; EF = Ejection fraction; EDP = End-diastolic pressure.
decreased regurgitant volume—one of the important objectives of treatment of patients with mitral regurgitation.

The second beneficial effect was a reduction in pulmonary artery and pulmonary capillary wedge pressure. This reduction in pulmonary venous congestion was undoubtedly responsible for the decrease in dyspnea experienced by some patients.

This study demonstrates that vasodilator agents which reduce impedance can at least partially achieve the major objectives of treatment of patients with mitral regurgitation and congestive failure by increasing left ventricular forward output and decreasing regurgitant volume and pulmonary venous congestion. In clinical practice, therefore, vasodilator agents may be of value in the management of some patients with mitral regurgitation and congestive heart failure. This therapeutic approach may be particularly useful in the management of patients developing severe mitral regurgitation complicating myocardial infarction. In the immediate postinfarction period the operative mortality in such patients is high, although it decreases significantly if surgery can be delayed for a few weeks.1–3 Thus, if these patients could be maintained on vasodilator agents during the immediate postinfarction period, a better prognosis might be expected.

This study also demonstrates that administration of nitroprusside to such patients results in a modest reduction of heart rate, mean arterial pressure and left ventricular end-diastolic volume, all important determinants of myocardial oxygen demand.20 Furthermore, in experimental models it has been
shown that the improvement in ejection fraction produced by impedance reduction occurs without any change in contractility—another determinant of oxygen demand. Thus, it is reasonable to assume that the use of such therapy may decrease myocardial oxygen requirements and thereby prevent further myocardial ischemia and necrosis in such patients. It can also be postulated that such therapy might prevent progression of mitral insufficiency due to papillary muscle ischemia by reducing oxygen demand.

Although no complications occurred during nitropresside administration in these patients, caution must be observed to avoid a precipitous fall of arterial pressure which might compromise coronary perfusion. While instituting such therapy, therefore, careful hemodynamic monitoring is mandatory. Otherwise, a potentially beneficial therapeutic agent may turn out to be a hazardous one.

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References

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