Effect of Nitroprusside on Left Ventricular Dynamics in Mitral Regurgitation

By Daniel J. Goodman, M.D., Ronald M. Rossen, M.D., Earl L. Holloway, M.D., Edwin L. Alderman, M.D., and Donald C. Harrison, M.D.

SUMMARY
In order to evaluate the circulatory action of vasodilator therapy in patients with significant mitral regurgitation, sodium nitroprusside was infused intravenously in 14 patients who had mitral regurgitation due to a variety of causes. In 13 of these patients, valvular insufficiency had been present for several years. The mean arterial pressure fall from 88 ± 1.2 to 71 ± 2.1 mm Hg was accompanied by a significant decrease in pulmonary artery pressure (from 27.4 ± 2.7 to 19.1 ± 2.4 mm Hg), pulmonary artery wedge v wave (from 31.7 ± 3.3 to 17.0 ± 1.9 mm Hg), and left ventricular end-diastolic pressure (from 16.7 ± 1.6 to 9.3 ± 1.2 mm Hg). In 10 patients significant decreases in angiographic end-diastolic volumes (from 196 ± 10 to 177 ± 10 ml) and end-systolic volumes (from 90 ± 10 to 77 ± 9 ml) were accompanied by slight decreases in the total stroke volume and slight increases in the ejection fraction. The improved forward stroke volume index (from 27 ± 3.0 to 33 ± 2.1 ml) was due to a very significant reduction in the regurgitant fraction (from 57 ± 6 to 42 ± 6%). Nitroprusside, therefore, has beneficial hemodynamic effects in patients with chronic mitral regurgitation.

Additional Indexing Words:
Hemodynamics  Vasodilator therapy  Angiographic studies

IN THE PATIENT WITH MITRAL REGURGITATION, two avenues are available for the ejection of blood from the left ventricle: 1) antegrade, through the aortic valve and 2) retrograde, through the mitral valve. Depending on the severity of the mitral regurgitation, hemodynamics may be altered significantly. The left ventricle is presented with a volume overload, while the left atrium, pulmonary vessels, and right heart may work at higher pressures. The forward cardiac output can be reduced. Because left ventricular blood is ejected via two different pathways, it should be possible to vary the volume of blood ejected into each by adjusting the impedance to ejection in either pathway independently. Increasing the resistance to ejection of blood into the aorta by raising the systemic vascular resistance has been shown to increase the severity of mitral insufficiency.1,2 Similarly, reduction of the systemic vascular resistance has been shown to augment forward ejection and reduce regurgitation in patients with severe valvular disease.3 In order to quantify the changes which occur and to relate them to the severity of disease in a larger group of patients with chronic mitral regurgitation of moderate degree, we studied 14 patients at the time of diagnostic cardiac catheterization during control periods and during infusion of nitroprusside in doses large enough to profoundly influence the circulatory state of the patient.

Methods
Patients Studied
Fourteen patients with significant mitral insufficiency were studied at the time of diagnostic cardiac catheterization. The nature of the study and all risks were explained to each patient and informed consent was obtained. There were eight females and six males, ranging in age from 31 to 68 years, with a mean of 54 years. The etiology of the mitral regurgitation was rheumatic in eight, idiopathic ruptured chordae tendineae in two, papillary muscle dysfunction related to coronary artery disease in two, prolapse of the posterior leaflet of the mitral valve in one, and bacterial endocarditis with perforation of the anterior leaflet of the mitral valve in one. In all patients, except one with bacterial endocarditis, the valvular insufficiency was chronic, being of greater than three years' duration. Clinically, all patients were class III, New York Heart Association functional classification, and had clinical evidence of cardiomegaly. All were taking digitalis and diuretics at the time of the study. The clinical diagnosis of mitral insufficiency was confirmed in all patients by a left ventriculogram performed by the retrograde arterial approach. In 10 patients, a second left ventriculogram was performed during nitroprusside infusion for evaluation of changes in ventricular volumes. Nine
patients to date have had cardiac operations, with mitral valve replacement performed in all.

At the time of diagnostic cardiac catheterization right atrial, right ventricular, pulmonary artery, and pulmonary capillary wedge pressures were determined with a 7 or 8 F end-hole catheter connected to a Statham P23Db pressure transducer. Arterial and left ventricular pressure tracings were recorded in 10 cases by percutaneous catheterization of the femoral artery with a 6.7 F end-hole catheter connected to a Micron MP-15 transducer. The frequency response of the entire system was demonstrated to be flat to 14 Hz. The zero pressure reference level was taken at mid-chest. In the other four patients, arterial and left ventricular catheterization was accomplished by brachial arteriotomy and the use of an 8 F catheter-tipped manometer (Millar).

Cardiac output was determined by the Fick technique, utilizing the arterial-venous O2 difference and a 5 min collection of expired air.

Angiographic Methods

Left ventriculography was performed in the right anterior oblique projection using a 50 cc bolus of meglumine diatrizoate and sodium diatrizoate administered over three to four cardiac cycles. The ventriculograms were recorded simultaneously on 35 mm cine film and on a video disc. Quantitative angiographic measurements were obtained utilizing a light-pen computer system which employs the area-length method of Sandler and Dodge to compute the ventricular volumes.4,5 Volumes were calculated for those beats earliest in the ventriculogram which were adequately visualized. Premature beats and beats following premature beats were excluded. For those patients in atrial fibrillation, three cardiac cycles were averaged. Magnification factors were computed using a grid of 1 cm squares set at varying heights above the table top and employing a fixed tube-to-image intensifier distance. Regurgitant volume was calculated as the difference between the forward cardiac output, determined by the Fick method, and the angiographically determined ventricular output.

After control studies were completed, nitroprusside was initially infused at a rate of 15 μg/min through a peripheral vein. The rate of infusion was increased every 2 min by 10-15 μg/min, until the mean arterial pressure had decreased by 10-20 mm Hg. To maintain this circulatory response, nitroprusside infusion rates of 15 to 50 μg/min were needed. In some cases, infusion of 15 μg/min or very small increments in the infusion rate resulted in such large blood pressure changes that it was mandatory to constantly monitor the arterial pressure. After the desired pressure had been attained, hemodynamic measurements were repeated after 10 min of constant nitroprusside infusion. Then, a second left ventriculogram was performed while the infusion was maintained.

Results

Tables 1 and 2 summarize the hemodynamic effects of nitroprusside in the 14 patients, including changes in ventricular volume in 10 patients. While in general all patients had the same directional changes, occasional minor deviations including no change in the parameter studied were noted. Nitroprusside infusion produced a fall in mean arterial pressure of 20%, accompanied by a fall in systemic vascular resistance of 35% (fig. 1). Although heart rate was not significantly changed (+5%), three patients exhibited marked increases. There was a tendency for those individuals who increased their heart rate following nitroprusside to have mean wedge pressures below 20 mm (6 of 7) and for those patients whose heart rate fell following nitroprusside to have mean wedge pressures of 20 mm or greater (5 of 6). The left ventricular end-diastolic pressure (−40%), the pulmonary capillary wedge mean (−40%) and v wave (−46%), and the pulmonary artery mean pressure (−30%) fell significantly and by a similar magnitude (figs. 2 and 3). The pulmonary vascular resistance (−12%) and right atrial mean pressure (−33%) also declined. Both the forward cardiac index (+27%) and the forward stroke volume index (+34%) increased significantly (fig. 1).

In 10 patients, left ventricular volume studies were
Table 1

Summary of Clinical and Hemodynamic Data in 14 Patients Receiving Nitroprusside

<table>
<thead>
<tr>
<th>Pt no.</th>
<th>Dx</th>
<th>Sex</th>
<th>HR beats/min C</th>
<th>RA mm Hg C</th>
<th>PA mm Hg NP</th>
<th>PCW mm Hg C</th>
<th>V mm Hg C</th>
<th>MAP mm Hg C</th>
<th>LVEDP mm Hg NP</th>
<th>FCI L/min/m² C</th>
<th>PVR R.U. C</th>
<th>SVR R.U. C</th>
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</thead>
<tbody>
<tr>
<td>1/M</td>
<td>RHD</td>
<td>M</td>
<td>82</td>
<td>88</td>
<td>3</td>
<td>2</td>
<td>19</td>
<td>15</td>
<td>16</td>
<td>12</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>2/F</td>
<td>RHD</td>
<td>F</td>
<td>93</td>
<td>139</td>
<td>6</td>
<td>5</td>
<td>23</td>
<td>19</td>
<td>18</td>
<td>17</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>3/F</td>
<td>RHD</td>
<td>F</td>
<td>93</td>
<td>117</td>
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<td>5</td>
<td>19</td>
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<td>15</td>
<td>9</td>
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<tr>
<td>4/F</td>
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<td>F</td>
<td>85</td>
<td>77</td>
<td>6</td>
<td>3</td>
<td>44</td>
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<td>90</td>
<td>7</td>
<td>5</td>
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<td>75</td>
<td>8</td>
<td>6</td>
<td>29</td>
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<td>38</td>
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<tr>
<td>8/M</td>
<td>ABE</td>
<td>M</td>
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<td>72</td>
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<td>2</td>
<td>24</td>
<td>14</td>
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<td>PMD/CAD</td>
<td>M</td>
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<td>75</td>
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<td>1</td>
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<tr>
<td>10/M</td>
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<td>92</td>
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<td>5</td>
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<td>11/M</td>
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<td>M</td>
<td>64</td>
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<td>1</td>
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<td>9</td>
<td>14</td>
<td>7</td>
<td>22</td>
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<tr>
<td>13/F</td>
<td>RHD</td>
<td>F</td>
<td>117</td>
<td>103</td>
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<td>5</td>
<td>32</td>
<td>20</td>
<td>26</td>
<td>17</td>
<td>48</td>
<td>20</td>
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<tr>
<td>14/F</td>
<td>Prol</td>
<td>F</td>
<td>77</td>
<td>92</td>
<td>4</td>
<td>1</td>
<td>16</td>
<td>9</td>
<td>15</td>
<td>4</td>
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Mean: 84.886.13.92719.2113.3217.8871.179.222.72.71.526.016.4

S.E.M.: 3.64.90.70.62.72.41.71.93.31.91.22.11.61.20.20.20.710.363.31.7

P < 0.001 0.001 0.001 0.001 0.001 0.001 0.01 0.05

Abbreviations: Dx = diagnosis; R = rhythm; HR = heart rate; RA = right atrial mean pressure; PA = pulmonary artery mean pressure; PCW = pulmonary capillary wedge mean pressure; V = v wave peak pressure in the pulmonary capillary wedge phasic pressure tracing; MAP = mean arterial pressure; LVEDP = left ventricular end diastolic pressure; FCI = forward cardiac index; PVR = peripheral vascular resistance; SVR = systemic vascular resistance; R.U. = resistance units; C = control; NP = nitroprusside; RHD = rheumatic heart disease; R.C. = ruptured chordae tendineae; ABE = acute bacterial endocarditis; PMD/CAD = papillary muscle dysfunction due to coronary artery disease; Prol = prolapse of the mitral valve; NSR = normal sinus rhythm; AF = atrial fibrillation; S.E.M. = standard error of the mean.
Table 2

Summary of Hemodynamic Data on Left Volume Changes Due to Nitroprusside Infusion in 10 Patients

<table>
<thead>
<tr>
<th>Pt no.</th>
<th>Sex</th>
<th>Dr.</th>
<th>R</th>
<th>FCI L/min/m²</th>
<th>EDV ml</th>
<th>ESV ml</th>
<th>TSV ml</th>
<th>FSV ml</th>
<th>R.V. ml</th>
<th>RF</th>
<th>EF</th>
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</thead>
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<td></td>
<td>RHD</td>
<td>NSR</td>
<td>2.8</td>
<td>3.2</td>
<td>168</td>
<td>143</td>
<td>74</td>
<td>49</td>
<td>94</td>
<td>94</td>
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<tr>
<td>2/F</td>
<td></td>
<td>RHD</td>
<td>AF</td>
<td>2.7</td>
<td>4.2</td>
<td>269</td>
<td>239</td>
<td>117</td>
<td>104</td>
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<td>135</td>
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<tr>
<td>3/F</td>
<td></td>
<td>RHD</td>
<td>NSR</td>
<td>1.8</td>
<td>2.8</td>
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<td>151</td>
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<td>4/F</td>
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<td>R.C.</td>
<td>NSR</td>
<td>1.0</td>
<td>1.7</td>
<td>221</td>
<td>185</td>
<td>149</td>
<td>106</td>
<td>72</td>
<td>79</td>
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<td>AF</td>
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<td>1.7</td>
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<td>127</td>
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<tr>
<td>7/M</td>
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<td>3.0</td>
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<td>NS</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>NS</td>
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</table>

NOTE: Patients 8, 9, 10, and 12 were not evaluated.

Abbreviations: EDV = end-diastolic volume; ESV = end-systolic volume; TSV = total stroke volume; FSV = forward stroke volume; R.V. = regurgitant volume; RF = regurgitant fraction; EF = ejection fraction; other abbreviations as in Table 1.
Nitroprusside in Mitral Regurgitation

Repeated during nitroprusside infusion. The results are summarized in table 2. The end-systolic and end-diastolic volumes decreased by 15% and 10% respectively with an insignificant (−6%) change in the total ventricular stroke volume (fig. 4). This resulted in a small but insignificant increase in the ejection fraction of the ventricle (6%). Patient 13 differed somewhat from the rest of the patients by exhibiting a prominent increase in ventricular stroke volume, probably the result of a decreased ventricular rate response to atrial fibrillation following nitroprusside.

The 29% increase in forward stroke volume is almost entirely the result of a 30% reduction in regurgitant volume, with the regurgitant fraction decreasing by 29% (fig. 4). Patients 5 and 7, who did not exhibit declines in regurgitant fraction, showed relatively small nitroprusside induced declines in mean arterial pressure when compared to the rest of the patients. Two of the three patients who increased their ejection fraction during nitroprusside infusion by more than 10% had the lowest control values of 0.33 and 0.40. In all other patients the control ejection fraction was above 0.51. This may be related to the underlying myocardial disease in the two patients with a markedly decreased ejection fraction, while muscle function in the other patients was relatively normal. Representative left ventricular end-systolic and end-diastolic cineangiographic frames taken be-

![Figure 2](image)

**Figure 2**

Change in pulmonary capillary wedge mean pressure (left panel), left ventricular end-diastolic pressure (middle panel) and v wave peak pressure (right panel) during nitroprusside infusion. Individual values for the 14 patients are shown, as well as the mean (heavy bars) and standard error of the mean (lighter horizontal bars). A significant decrease in all three parameters is demonstrated. NP = nitroprusside.

![Figure 3](image)

**Figure 3**

Left ventricular and phasic pulmonary capillary wedge pressure tracing before (left panel) and during (right panel) nitroprusside infusion. As a result of drug infusion, there is a marked decrease in the peak v wave pressure, as well as a decrease in the left ventricular end-diastolic pressure.

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before and during nitroprusside infusion demonstrate these changes graphically (fig. 5).

Discussion
This study was undertaken to demonstrate that in patients with moderate degrees of mitral insufficiency, especially of long duration, vasodilator therapy can produce beneficial hemodynamic changes. Since the patients were not symptomatic at rest at the time of the catheterization, it was not possible to judge an effect on the patients' clinical status. The acute nitroprusside infusion resulted in a decreased afterload as judged by significant reductions in systemic arterial pressure and systemic vascular resistance. This was accompanied by a very significant increase in forward cardiac output, as well as by significant decreases in right and left ventricular filling pressure, pulmonary artery pressure, and pulmonary vascular resistance.

Of the seven patients whose heart rates increased during nitroprusside infusion, six had a control pulmonary artery wedge mean pressure less than 20, while five of the six whose heart rate fell during nitroprusside had a control pulmonary artery wedge mean pressure greater than 20. This may be related to abnormal autonomic function found in patients with cardiac decompensation.6, 7

Although forward cardiac index was increased, this was not done at the expense of an increase in heart rate or in the left ventricular stroke volume. The forward stroke volume index increased, not because of an increase in total left ventricular stroke volume (which decreased insignificantly), but due to a large decrease in the regurgitant volume and regurgitant fraction. This confirms the original hypothesis that by decreasing impedance to ejection through the aorta, one of the two avenues for ejection of left ventricular blood in mitral regurgitation, the volume of blood regurgitated through the mitral valve would be reduced. Recently, Chatterjee et al.3 have demonstrated beneficial hemodynamic effects of nitroprusside infusion in eight patients with very severe mitral insufficiency due to dysfunction of the subvalvar mitral apparatus. These authors postulated that the decrease in regurgitation was due not only to a decrease in aortic impedance, but also to an increased valvar competence resulting from improved function of the subvalvar structures related in turn to a decrease in left ventricular cavity size and relief of myocardial and papillary muscle ischemia. Examination of table 1, however, shows that even for patients with fibrotic and calcified valves resulting from rheumatic disease no simple relation exists between the decrease in mean arterial pressure or systemic vascular resistance and the reduction in regurgitant volume and regurgitant fraction.

While no complications occurred during this study, it is important to be aware of the extreme potency of nitroprusside and the occasional marked variation in subject response to the drug. Small changes in infusion rate, for example 5 µg/min, may result in a large and sudden fall in systemic blood pressure. In addition, some patients are apparently very sensitive to nitroprusside; even at the very small initial infusion rate of 15 µg/min their blood pressure reduction was...
Figure 5

Individual frames from a left ventricular cineangiogram exposed before (top panels) and during (bottom panels) nitroprusside infusion. Panels on the left were taken during end-systole, panels on the right during end-diastole. Note the decrease in chamber size, especially visible in end-diastole, and the marked decrease in mitral regurgitation, seen best in the end-systolic frames.
marked. Other patients respond to drug infusion with tachycardia, which may be deleterious in patients with associated cardiac disease. Therefore, while nitroprusside may be used safely in patients with mitral regurgitation and low cardiac output, it is necessary that caution be exercised with the use of nitroprusside. Continuous hemodynamic monitoring is essential at all times.

One of the important aims of this study was to demonstrate that vasodilator therapy would result in significant hemodynamic improvement in patients with only moderate mitral insufficiency. Indeed, no change in clinical status could be demonstrated in this acute situation because no patient was symptomatic at rest. In addition, 13 of the 14 patients studied had chronic valvar insufficiency, related to rheumatic heart disease in eight. Atrial fibrillation, an indication of chronicity, was present in five patients. It is interesting to speculate whether the beneficial hemodynamic effects produced during the acute administration of nitroprusside might be extended, in this type of patient, by the use of chronic afterload reduction using a more appropriate agent. Would it be possible to chronically maintain the decrease in ventricular volume and regurgitant fraction? If so, would this influence the natural history of the disease, delaying left ventricular dilatation and hypertrophy and preventing to some extent left atrial enlargement?

Acknowledgments

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References

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