Beneficial Effects of Hydralazine in Severe Mitral Regurgitation

BARRY H. GREENBERG, M.D., BARRY M. MASSIE, M.D., BRUCE H. BRUNDAGE, M.D., ELIAS H. BOTVINICK, M.D., WILLIAM W. PARMLEY, M.D., AND KANU CHATTERJEE, M.B., M.R.C.P.

SUMMARY The severity of mitral regurgitation is, in part, determined by aortic impedance to left ventricular outflow. Sodium nitroprusside acutely decreases regurgitant flow, but the importance of its dual vasodilating effects, the lowering of peripheral vascular resistance and increasing of venous capacitance, is unclear. We studied the hemodynamic response to intravenous hydralazine, which selectively acts on the arteriolar resistance bed, in 10 patients with severe mitral regurgitation. Hydralazine produced a 50% increase in forward stroke volume (22 ± 2 to 33 ± 3 ml/m², P < 0.001) and a 33% reduction in regurgitant stroke volume (40 ± 6 to 27 ± 6 ml/m², P < 0.001), with a resultant fall in pulmonary capillary wedge wave and mean pressures. Unlike nitroprusside, it did not alter left ventricular end-diastolic volume or pressure. Oral hydralazine maintained this hemodynamic improvement for at least 48 hours and, in three patients, provided more sustained clinical improvement. We conclude that hydralazine, by virtue of its selective lowering of aortic impedance, reduces the amount of mitral regurgitation and thus may be a useful mode of interim or chronic therapy in selected patients.

IN PATIENTS WITH mitral regurgitation, the balance between forward cardiac output and regurgitant flow is strongly influenced by aortic impedance to left ventricular outflow. When impedance is increased by vasopressors or aortic constriction, regurgitant flow increases and forward cardiac output falls.4-8 Impedance reduction with vasodilators would be expected to have the opposite effect. Indeed, several groups have demonstrated that sodium nitroprusside, a potent vasodilator, produces a reduction in regurgitant volume, with an increase in forward stroke volume.6-7 However, the precise mechanism of this favorable hemodynamic response to nitroprusside is uncertain, since this agent produces vasodilation of both the venous and arteriolar beds, causing an increase in venous capacitance and a reduction of impedance to left ventricular outflow.9-11 As a result, the reduction in mitral regurgitation and improvement in cardiac performance produced by nitroprusside may reflect a decrease in left ventricular stroke volume as well as reduced aortic impedance. In addition, the clinical utility of sodium nitroprusside is limited, since it must be given intravenously and its use requires intensive monitoring.

Hydralazine is an agent which has a direct relaxant effect on arteriolar smooth muscle, producing a marked fall in systemic vascular resistance with little effect on the venous bed.12-14 As a result, it has been used to improve forward cardiac output in patients with congestive heart failure, but it has little effect on ventricular filling.15-17 We undertook the present study to determine the hemodynamic effects of this predominant arteriolar dilator in a group of patients with severe mitral regurgitation who were studied at the time of cardiac catheterization. Several patients were then continued on oral hydralazine to determine whether its acute hemodynamic effects could be maintained, and thus whether it might be a potential mode of therapy in selected patients with mitral regurgitation.

Methods

Patient Population

Ten patients with clinically severe mitral regurgitation undergoing diagnostic catheterization were studied. All were limited by dyspnea, with mild exertion in five patients and at rest in five. All patients had severe mitral regurgitation documented at the time of catheterization. Regurgitation was due to a defect at the valvular level in four, at the subvalvular level in five and due to an undetermined defect in the last. Patients with additional valvular lesions were excluded from the study. The clinical profile of the patient group is shown in table 1.

Cardiac Catheterization

Cardiac catheterization was performed in the fasting state, using light premedication with either diazepam 10 mg, or demerol 50 mg intramuscularly. Right heart catheterization was performed with a #7 French triple lumen balloon tipped thermodilution catheter. Left heart catheterization was performed by the Seldinger technique using a #7 French pigtail catheter. Systemic arterial, right atrial, pulmonary artery, pulmonary capillary wedge and left ventricular end-diastolic pressures were measured and mean pressures were determined electronically. Cardiac output was measured in triplicate by the thermodilution technique using an analog computer (Santa Barbara Technology, Inc., Model 1700), with a variation of less than 10%.18
Biplane left ventricular angiography was performed in the 30° right anterior oblique and 60° left anterior oblique projections, alternatively filming each projection at a speed of 60 frames/sec. Renografin-76 at a dose of 0.8 ml/kg was injected over 3 to 4 seconds.

Volume Determination and Calculations

Ventricular volumes were determined from perimeter drawings of the left ventricle at end-diastole and end-systole. The earliest beat in which the left ventricle was visualized was used in patients in normal sinus rhythm. In the two patients in atrial fibrillation, the average of the first five visualized beats was used. Both premature and post-premature beats were excluded. In five patients ventricular volumes were calculated from the biplane orthogonal projections by the method of Goerke and Carlsson.19 In the remaining five patients in whom the outline of the left ventricle could be distinguished only in the right anterior oblique projection, volumes were calculated using the area length method of Sandler and Dodge.20 None of these patients had segmental wall motion abnormalities. All volumes were indexed for body surface area (BSA) and are expressed in ml/m² BSA. Derived parameters were calculated as follows:

1) Systemic vascular resistance (SVR) = MAP - RAP / F.C.O. × 80 where MAP = mean systemic arterial pressure in mm Hg, RAP = mean right atrial pressure in mm Hg, F.C.O. = forward cardiac output in l/min and 80 is the factor for converting resistance units to dyne-sec-cm⁻².

2) Total left ventricular stroke volume was obtained by subtracting angiographically derived end-systolic volume from end-diastolic volume.

3) Ejection fraction was calculated as the ratio of total left ventricular stroke volume to end-diastolic volume and was expressed as a percentage.

4) Forward left ventricular stroke volume was calculated by dividing the thermodilution cardiac output by the heart rate.

5) Regurgitant stroke volume was calculated as the difference between the total left ventricular stroke volume and the forward left ventricular stroke volume.21 The correlation between angiographic and thermodilution measurements of stroke volume in patients without regurgitant lesions in our laboratory is high (r = .92), with SVangio = 0.88 SVthermo - 0.4 ml.

6) Regurgitant fraction was calculated as the regurgitant stroke volume divided by the total stroke volume and was expressed as a percentage.

Statistical analysis was accomplished by paired t tests.

Hydralazine Administration

Acute studies were performed in the cardiac catheterization laboratory using intravenous hydralazine. After baseline pressure measurements and determination of cardiac output, left ventricular angiography was performed. Patients were then given hydralazine, 0.3 mg/kg (up to a maximal total dose of 20 mg), intravenously over 5 minutes. After 30 minutes, at a time when blood pressure and heart rate had stabilized, repeat pressure measurements, cardiac

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>NYHA Functional class</th>
<th>Angio grade MR</th>
<th>Etiology of MR</th>
<th>Duration of MR</th>
<th>Associated cardiac disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78</td>
<td>M</td>
<td>IV</td>
<td>4+</td>
<td>Ruptured chordae</td>
<td>12 years</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
<td>M</td>
<td>IV</td>
<td>4+</td>
<td>Ruptured chordae</td>
<td>18 months</td>
<td>CAD</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>M</td>
<td>III</td>
<td>4+</td>
<td>Papillary muscle dysfunction</td>
<td>3 years</td>
<td>CAD</td>
</tr>
<tr>
<td>4</td>
<td>62</td>
<td>M</td>
<td>IV</td>
<td>4+</td>
<td>Ruptured chordae</td>
<td>4 months</td>
<td>CAD</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>F</td>
<td>III</td>
<td>3-4+</td>
<td>Papillary muscle dysfunction</td>
<td>1 week</td>
<td>CAD; recent inferior MI</td>
</tr>
<tr>
<td>6</td>
<td>41</td>
<td>F</td>
<td>III</td>
<td>4+</td>
<td>Rheumatic</td>
<td>&gt; 5 years</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
<td>F</td>
<td>III</td>
<td>4+</td>
<td>Lupus erythematosus</td>
<td>2 years</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>55</td>
<td>F</td>
<td>III</td>
<td>3+</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Hypertensive cardiomyopathy</td>
</tr>
<tr>
<td>9</td>
<td>59</td>
<td>F</td>
<td>III</td>
<td>3-4+</td>
<td>Prolapse</td>
<td>&gt;14 years</td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>10</td>
<td>61</td>
<td>F</td>
<td>IV</td>
<td>4+</td>
<td>Prosthetic valve dysfunction</td>
<td>3 months</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: Angio = Left ventricular angiography; CAD = Coronary artery disease; MR = Mitral regurgitation; NYHA = New York Heart Association.
output determinations and left ventricular angiograms were performed.

In five patients the balloon tipped catheter was left in place and hydralazine was continued at a dose of 75 mg orally every 6 hours for 48 hours. Measurements of pressures and cardiac output were made periodically, and the final hemodynamic determination was made after 48 hours of continuous oral hydralazine. During this period, no other changes in therapeutic management were made.

In patients maintained on oral hydralazine left ventricular volumes were measured noninvasively by technetium-99m albumin gated blood pool scintigraphy, using a modification of the method of Strauss et al.22 prior to catheterization and at the time of the final hemodynamic measurement, 2 to 3 hours after the previous dose of hydralazine. Outline drawings at end-diastole and end-systole were taken from the microdot images of the left ventricle at equilibrium in the 30° right anterior oblique and 60° left anterior oblique projections. Ventricular volumes were calculated from the outline drawings using the method of Goerke and Carlsson.19 As previously reported from this laboratory, the calculated left ventricular volumes obtained by radionuclide angiography are comparable to those obtained from standard contrast angiography.23

Total stroke volume, regurgitant volume and regurgitant fraction were calculated using the radionuclide determined left ventricular volumes by the methods outlined above.

**Results**

**Acute Hydralazine Administration**

The acute hemodynamic effects of intravenous hydralazine are shown in tables 2 and figures 1–5. In general, patients showed similar directional changes for all parameters. Heart rate did not change significantly and mean arterial pressure fell slightly, but significantly (fig. 1). Hydralazine reduced systemic vascular resistance by an average of 44%, and produced a 50% increase in cardiac index. Total left ventricular stroke volume did not change. However, forward stroke volume increased by 50%, while regurgitant stroke volume fell by 34% (fig. 2). Although there was no change in left ventricular end-diastolic pressure, mean pulmonary capillary wedge pressure decreased by 24%, due mostly to a 31% reduction in the amplitude of the regurgitant v wave (fig. 3). A dramatic example of the effect of hydralazine on the amplitude of the regurgitant wave in the pulmonary capillary wedge pressure tracing is...
Table 3. Hemodynamic Changes After 48 Hours on Oral Hydralazine

<table>
<thead>
<tr>
<th>Patient</th>
<th>HR beats/min</th>
<th>MAP mm Hg</th>
<th>PAP mm Hg</th>
<th>PCW mm Hg</th>
<th>PCW V wave</th>
<th>FCI l/min/m²</th>
<th>FSVI ml/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>H</td>
<td>C</td>
<td>H</td>
<td>C</td>
<td>H</td>
<td>C</td>
</tr>
<tr>
<td>1</td>
<td>78</td>
<td>86</td>
<td>85</td>
<td>74</td>
<td>55</td>
<td>38</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>77</td>
<td>92</td>
<td>110</td>
<td>97</td>
<td>60</td>
<td>67</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>76</td>
<td>85</td>
<td>94</td>
<td>16</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>98</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>64</td>
<td>60</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>116</td>
<td>96</td>
<td>110</td>
<td>80</td>
<td>68</td>
<td>40</td>
<td>45</td>
</tr>
<tr>
<td>Mean</td>
<td>88</td>
<td>88</td>
<td>96</td>
<td>87</td>
<td>53</td>
<td>44</td>
<td>35</td>
</tr>
<tr>
<td>SEM</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>9</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

Abbreviations: HR = heart rate; MAP = mean arterial pressure; PAP = pulmonary artery pressure; PCW = mean pulmonary capillary wedge pressure; FCI = forward cardiac index; FSVI = forward stroke volume index; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; TSVI = total systolic volume index; RSVI = regurgitant stroke volume index; EF = ejection fraction.

Figure 3. Effect of intravenous hydralazine on left ventricular end-diastolic pressure (LVEDP), pulmonary capillary wedge mean (PCW) and v wave pressures and mean pulmonary artery pressure (PAP). LVEDP showed little change, but there was a marked decrease in v wave amplitude (58-35 mm Hg) with less prominent, but still significant, reduction in PCW and pulmonary arterial (PA) pressures.

Figure 4. Marked decrease of pulmonary capillary wedge v wave amplitude following intravenous hydralazine in patient 3.
shown in figure 4. Left ventricular volume did not change significantly. Consequently, overall left ventricular ejection fraction was not altered, but the regurgitant fraction fell significantly (fig. 5).

Effects of Oral Hydralazine

The data from the five patients maintained for 48 hours on oral hydralazine are shown in table 3 and figure 6. Hemodynamic improvements similar, and in some cases even greater, to those produced by intravenous hydralazine, were found. Systemic vascular resistance, mean pulmonary capillary wedge pressure and v wave amplitude were significantly decreased. Total left ventricular stroke volume was again unchanged, but forward stroke volume rose by a mean of 80%, while regurgitant stroke volume fell by 39%, with a resultant fall in regurgitant fraction. Left ventricular volumes and ejection fraction were unchanged.

Three patients (1, 5, 8) who were not considered good candidates for valve replacement because of poor left ventricular function were continued on hydralazine. All showed marked clinical improvement. Figure 7 illustrates the marked radiographic improvement in the signs of congestive heart failure manifested by patient 1 after two weeks of continuous vasodilator therapy. This patient, however, became symptomatic again three months later and underwent successful mitral valve replacement. Patient 8, whose mitral regurgitation essentially disappeared during the acute study, has remained improved, with findings suggesting diminished mitral regurgitation. The clinical course of patient 5, who presented in pulmonary edema with severe mitral regurgitation following an acute myocardial infarction, has been the most impressive. Hydralazine was initially started as an interim measure before surgery. However, she has done so well over a five-month period that surgery no longer appears indicated.

Discussion

In patients with mitral regurgitation, forward cardiac output decreases with the onset of decompensation. This decrease in forward output is associated with an increase in systemic vascular resistance. Such a rise in peripheral resistance may have deleterious consequences, since the balance between forward cardiac output and regurgitant flow is strongly influenced by the level of aortic impedance to left ventricular outflow. Reduction in systemic vascular resistance, on the other hand, should increase forward cardiac output, reduce regurgitant volume and thus should be beneficial in the management of such patients.

The present study demonstrates that hydralazine, an arteriolar dilator which predominantly decreases systemic vascular resistance, produces a beneficial hemodynamic response in patients with severe mitral regurgitation. Following the administration of intravenous hydralazine, systemic vascular resistance fell markedly (2110 ± 170 to 1290 ± 90 dyne-sec-cm⁻², \( P < 0.001 \)) and cardiac index rose by 50% (2.0 ± 0.1 to 3.0 ± 0.2 l/min/m², \( P < 0.001 \)). Since total left ventricular stroke volume did not change, the major effect of hydralazine was redistribution of the left ventricular output, so that a greater proportion was directed forward. As a result of the significant fall in regurgitant stroke volume (40 ± 6 to 27 ± cc/min/m², \( P < 0.001 \)), the pulmonary capillary \( v \) wave amplitude fell markedly, with lesser but still

---

**Table 3. Continued**

<table>
<thead>
<tr>
<th>SVR (dynes sec/cm²)</th>
<th>PVR (dynes sec/cm²)</th>
<th>EDVI (ml/m²)</th>
<th>ESVI (ml/m²)</th>
<th>TSVI (ml/m²)</th>
<th>RSVI (ml/m²)</th>
<th>RF (%)</th>
<th>EF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>H</td>
<td>C</td>
<td>H</td>
<td>C</td>
<td>H</td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td>2834</td>
<td>1082</td>
<td>378</td>
<td>267</td>
<td>233</td>
<td>199</td>
<td>141</td>
<td>114</td>
</tr>
<tr>
<td>1380</td>
<td>743</td>
<td>312</td>
<td>383</td>
<td>148</td>
<td>130</td>
<td>53</td>
<td>49</td>
</tr>
<tr>
<td>1580</td>
<td>1067</td>
<td>60</td>
<td>150</td>
<td>155</td>
<td>172</td>
<td>92</td>
<td>102</td>
</tr>
<tr>
<td>1470</td>
<td>1043</td>
<td>670</td>
<td>413</td>
<td>107</td>
<td>98</td>
<td>51</td>
<td>41</td>
</tr>
<tr>
<td>1652</td>
<td>753</td>
<td>400</td>
<td>176</td>
<td>116</td>
<td>145</td>
<td>72</td>
<td>89</td>
</tr>
<tr>
<td>1780</td>
<td>940</td>
<td>360</td>
<td>280</td>
<td>152</td>
<td>149</td>
<td>83</td>
<td>79</td>
</tr>
<tr>
<td>270</td>
<td>78</td>
<td>98</td>
<td>53</td>
<td>22</td>
<td>17</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Figure 5.** Overall ejection fraction (EF) did not change, but regurgitant fraction (RF) decreased from 61% to 39%.
significant decreases in mean pulmonary capillary wedge and pulmonary artery pressures.

One methodological limitation of this study should be noted. Regurgitant stroke volume was calculated by subtracting thermodilution stroke volume from angiographic stroke volume, as described by Sandler et al. While the correlation between these methods is high in our laboratory, our angiographic determinations are consistently lower than those by thermodilution. Thus, it is likely that regurgitant stroke volume and regurgitant fraction have been somewhat underestimated. This discrepancy, however, does not affect the validity of the comparison between the control and the post-hydralazine measurements, since the angiographic stroke volume was unchanged.

Our findings are, in some ways, similar to those previously reported after intravenous sodium nitroprusside in patients with mitral regurgitation, both of valvular and subvalvular origin. Our present study demonstrates that important differences exist between the acute hemodynamic effects of the two agents. Forward stroke volume index increased and regurgitant stroke volume decreased with both drugs. However, end-diastolic volume usually fell after nitroprusside infusion, but was not altered by hydralazine. Thus, although pulmonary capillary wedge and pulmonary artery pressures fell with both agents, the change observed with sodium nitroprusside was greater and probably reflects both a decrease in left ventricular end-diastolic pressure and in the regurgitant \( v \) wave, while it reflected primarily the change in regurgitant wave amplitude in those given hydralazine. Since both medications had similar effects on the degree of mitral regurgitation, it is likely that the changes in left ventricular end-diastolic volume and end-diastolic pressure produced by nitroprusside resulted from its additional vasodilating action on the venous bed and the consequent increase in venous capacitance.

The reduction of left ventricular volume might be of considerable importance in mitral regurgitation, particularly when it is due to dysfunction of the subvalvular apparatus. Indeed, left ventricular volume has been suggested to be a major determinant of the severity of mitral regurgitation. A decrease in left ventricular size might improve valvular competence either directly, by improving coaption of the valve leaflets during systole, or indirectly, by reducing myocardial ischemia. However, since hydralazine administration did not acutely change left ventricular volume, the resultant improvement in mitral regurgitation must be ascribed directly to the reduction in aortic impedance.

While sodium nitroprusside must be given intravenously under close monitoring, hydralazine can be given chronically with relative ease and safety. Our results in the patients studied after 48 hours of oral hydralazine indicate that its acute hemodynamic effects can be maintained and that forward stroke volume may, in fact, rise further. This cumulative

![Figure 6](http://circ.ahajournals.org/)

**Figure 6.** The significant changes in forward and regurgitant stroke volume indices (F-SVI and R-SVI) and regurgitant fraction (RF) persisted on oral hydralazine in the five patients studied. This figure illustrates the change from control after 48 hours on oral hydralazine.

![Figure 7](http://circ.ahajournals.org/)

**Figure 7.** PA chest films before (left) and 14 days after (right) the institution of oral hydralazine therapy in patient 5. Heart size decreased and other radiographic signs of heart failure improved. No other changes in medical regimen were made during this period.
effect from multiple doses of hydralazine has been demonstrated previously.15

Although mitral valve replacement is the treatment of choice for severe symptomatic mitral insufficiency, there are some clinical situations in which surgery could be delayed, or possibly, avoided. Patients with mitral regurgitation in the setting of acute myocardial infarction, those with chronic mitral regurgitation and poor left ventricular function, or those with associated medical problems might temporarily or chronically benefit from vasodilator therapy. Hydralazine has, in fact, been shown to be an effective modality of therapy in chronic heart failure without mitral regurgitation.15-17

The three patients maintained chronically on oral hydralazine in the present study are examples of such suboptimal surgical candidates. One developed severe mitral regurgitation during the course of an acute inferior myocardial infarction and has subsequently been well without surgery. The two others had severely depressed left ventricular function and both responded well to hydralazine, although one eventually required surgery. Each of these patients manifested a reduction of heart size on chest x-ray over a period of weeks or months on oral hydralazine (fig. 7), raising the possibility of a gradual reduction of left ventricular volume which was not observed during acute hydralazine administration.

The availability of a drug such as hydralazine which may chronically reduce the amount of regurgitant flow in patients with mitral incompetence clearly has important clinical implications which require further investigation. The subgroup of patients with symptomatic, severe mitral insufficiency who might benefit from temporary or chronic medical therapy requires further definition, and the chronic efficacy of such therapy needs further evaluation. In addition, the effect of chronic impedance reduction in patients with less severe, asymptomatic mitral regurgitation on the natural history of this disorder is an intriguing and potentially important area of study.

References
Beneficial effects of hydralazine in severe mitral regurgitation.
B H Greenberg, B M Massie, B H Brundage, E H Botvinick, W W Parmley and K Chatterjee

_Circulation._ 1978;58:273-279
doi: 10.1161/01.CIR.58.2.273

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1978 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/58/2/273

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/