Mechanism for Improved Cardiac Performance with Arteriolar Dilators in Aortic Insufficiency

BARRY H. GREENBERG, M.D., HENRY DEMOTS, M.D., EDWARD MURPHY, M.D., AND SHABUDIN H. RAHIMTOOLA, M.B.

SUMMARY To determine how arteriolar dilation improves cardiac performance in aortic insufficiency, we evaluated the acute effects of hydralazine in 10 patients with chronic severe aortic insufficiency. Control measurements of intracardiac and intravascular pressures, cardiac output and left ventricular volumes were obtained at cardiac catheterization. Hydralazine, 0.3 mg/kg i.v. (maximal dose 20 mg), was administered and all measurements were repeated 30 minutes later. A reduction in systemic vascular resistance from 1264 to 710 dyn-sec-cm⁻² was associated with significant increases in forward cardiac index (2.9 to 5.1 l/min/m²) and stroke volume index (37 to 55 ml/m²). Left ventricular end-diastolic pressure was reduced from 19 to 12 mm Hg. There was a significant reduction in mean arterial pressure (88 to 83 mm Hg) and a significant increase in heart rate (81 to 94 beats/min).

Regurgitant stroke volume was reduced by more than 10 ml/m² in seven patients and for the group was significantly reduced, from 65 to 53 ml/m². Regurgitant fraction was reduced in all patients; the overall reduction from 0.64 to 0.48 was highly significant. Ejection fraction increased more than 0.10 in four patients, by 0.08 in an additional patient and for the group increased significantly from 0.50 to 0.57. Left ventricular end-diastolic volume decreased by more than 25 ml/m² in four patients, by 19 ml/m² in an additional patient and was decreased significantly, from 208 to 190 ml/m², for the group.

Arteriolar dilators improve cardiac performance in aortic insufficiency by reducing the amount of aortic regurgitation and, in some patients, by substantially improving systolic pump function. These data suggest a role for arteriolar dilators in the management of selected patients with aortic insufficiency.

ARTERIOLAR DILATORS have beneficial effects on cardiac performance in a variety of clinical settings. In patients with congestive heart failure, reduced impedance enhances left ventricular emptying and increases stroke volume. In mitral regurgitation, the predominant effect of arteriolar dilation is to redistribute total left ventricular stroke volume in a manner favoring forward stroke volume at the expense of regurgitant flow. In patients with chronic severe aortic insufficiency, arteriolar dilation with hydralazine improves cardiac performance both at rest and during exercise. However, the mechanism responsible for the beneficial effects is uncertain. The present study was designed to evaluate the effects of hydralazine on left ventricular performance, volumes and regurgitant flow in patients with aortic insufficiency.

Methods

Patient Population

Ten consecutive patients with chronic severe aortic insufficiency were studied at diagnostic cardiac
Table 1. Hemodynamic Data

<table>
<thead>
<tr>
<th>Pt</th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>PA (mm Hg)</th>
<th>PAW (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>CI (l/min/m²)</th>
<th>SVI (ml/m²)</th>
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*p < 0.005 < 0.025 NS NS < 0.05 < 0.001 < 0.001

Abbreviations: HR = heart rate; MAP = mean arterial pressure; PA = mean pulmonary artery pressure; PAW = mean pulmonary artery wedge pressure; LVEDP = left ventricular end-diastolic pressure; CI = cardiac index; SVI = stroke volume index; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; EDV = end-diastolic volume index; ESV = end-systolic volume index; LVSVI = left ventricular stroke volume index; EF = ejection fraction; RSVO = regurgitant stroke volume index; RF = regurgitant fraction; C = control; H = hydralazine.

catheterization. Informed consent was obtained from all patients. The hemodynamic data for these 10 patients are given in table 1. Eight males and two females, ages 23–70 years, were studied. Aortic insufficiency was due to a congenital abnormality in patients 2, 4, 6, 7, 8 and 10 and to rheumatic fever in patients 3 and 9, was present as a residual lesion after valve commissurotomy for congenital aortic stenosis in patient 5 and was associated with ankylosing spondylitis in patient 1. All patients had had aortic insufficiency for at least 18 months. Patient 5 had mild aortic stenosis. A mean transvalvular gradient of 25 mm Hg was measured at catheterization. Left ventricular stroke volume was determined angiographically and the calculated aortic valve area was 2.3 cm²/m². Patient 9 had moderately severe mitral insufficiency. The other patients had no valvular disease. No patient had angina or ECG evidence of a previous myocardial infarction. All patients were clinically stable at the time of study.

Cardiac Catheterization

Cardiac catheterization was performed with the patients in the fasting state after light premedication with either diazepam, 10 mg orally, or demerol, 50 mg intramuscularly. Right-heart catheterization was performed using a #7F triple-lumen balloon-tipped thermodilution catheter (Swan-Ganz catheter, Edwards Laboratories). Left-heart catheterization was performed by the Seldinger technique using a #7F Gensini catheter. Systemic arterial, right atrial, pulmonary artery, pulmonary artery wedge and left ventricular pressures were measured and mean pressures were determined electronically. Cardiac output was measured in triplicate by the thermodilution technique using a balloon-tipped catheter and a thermodilution computer (9520A, Edwards Laboratories). In 18 consecutive patients studied in our laboratory, the correlation between duplicate thermodilution cardiac output measurements was TD₁ = 1.0 TD₂ + 0.01 (r = 0.98), where TD₁ and TD₂ represent two thermodilution output measurements. In 16 of these patients, thermodilution cardiac output was compared with values obtained by the Fick method and the indicator-dilution method. There were no significant differences between thermodilution output (5.2 ± 0.5 l/min) (mean ± SEM) and the Fick output (5.2 ± 0.6 l/min) or indicator-dilution output (5.1 ± 0.3 l/min). As described below, cardiac output measurements were also used to calculate regurgitant volume. These measurements were obtained within 30 seconds of ventriculography in all cases.

Left ventricular angiography was performed in the 30° right anterior oblique projection at a speed of 60 frames/sec. Renografin-76, 0.8 ml/kg, was injected over 3–4 seconds.

Volume Determination and Calculations

Ventricular volumes were determined from silhouette drawings of the left ventricle at end-diastole and end-systole. The earliest beat in which the left ventricle was visualized was used in all patients. All patients were in normal sinus rhythm. Both premature and postpremature beats were excluded from analysis. Ventricular volumes were calculated from the silhouette drawings using the area-length method of Sandler and Dodge.13 None of the patients had
Table 1. (Continued)

<table>
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<tr>
<th>SVR (dyn-sec-cm⁻²)</th>
<th>PVR (dyn-sec-cm⁻²)</th>
<th>EDVI (ml/m²)</th>
<th>ESVI (ml/m²)</th>
<th>LVSVI (ml/m²)</th>
<th>EF</th>
<th>RSVI (ml/m²)</th>
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<td>&lt; 0.025</td>
<td>NS</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>&lt; 0.001</td>
</tr>
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</table>

Segmental wall motion abnormalities. All volumes were indexed for body surface area (BSA) and are expressed in ml/m² BSA.

Systemic vascular resistance (SVR) was calculated as

\[
\text{MAP} - \text{RAP} \times 80
\]

where MAP = mean systemic arterial pressure (mm Hg), RAP = mean right atrial pressure (mm Hg), CO = cardiac output in (l/min) and 80 is the factor for converting resistance units to dyn-sec-cm⁻².

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

Ejection fraction was calculated as the ratio of total left ventricular stroke volume to end-diastolic volume.

Forward stroke volume was calculated by dividing the thermodilution cardiac output by the heart rate.

Regurgitant stroke volume was calculated as the difference between the total left ventricular stroke volume and the forward stroke volume.

Regurgitant fraction was calculated as the regurgitant stroke volume divided by the left ventricular total stroke volume.

Hydralazine Administration

After control measurement of pressures and cardiac output, left ventricular angiography was performed. Patients were then given hydralazine, 0.3 mg/kg i.v. (maximal dose 20 mg), over a 5-minute period with constant monitoring of blood pressure and heart rate. After 30 minutes, when blood pressure and heart rate had stabilized, pressure measurements, cardiac output determination and left ventricular angiography were repeated.

Statistical Analysis

The paired \( t \) test was used to compare values before and after hydralazine. An unpaired \( t \) test and linear regression analysis were used to evaluate the relationship between heart rate and changes in cardiac performance after hydralazine. Linear regression analysis was used to evaluate the relationship between control systemic vascular resistance and change in left ventricular end-diastolic volume after hydralazine.

Results

The acute effects of i.v. hydralazine are shown in table 1. Mean arterial pressure decreased from 88 to 83 mm Hg (\( p < 0.025 \)) and heart rate increased from 81 to 94 beats/min (\( p < 0.005 \)). Mean pulmonary artery pressure and mean pulmonary artery wedge pressure were reduced, but not significantly. Left ventricular end-diastolic pressure decreased from 19 to 12 mm Hg (\( p < 0.05 \)). A reduction in systemic vascular resistance from 1264 to 710 mm Hg resulted in a 76% increase in cardiac index (2.9 to 5.1 l/min/m²) and a 49% increase in stroke volume index (37 to 55 ml/m²).

Left ventricular end-diastolic volume decreased from 208 to 190 ml/m² (\( p < 0.05 \)) and end-systolic volume decreased from 101 to 82 ml/m² (\( p < 0.025 \)). The magnitude of change in end-diastolic volume index varied widely. In patients 1, 4, 9 and 10, end-diastolic volume was reduced by at least 25 ml/m² and in patient 6 it was reduced by 19 ml/m². The others showed a change of 15 ml/m² or less. There was a strong correlation between the reduction in end-diastolic volume resulting from hydralazine administration and the level of systemic vascular resistance during the control period (fig. 1). If the single outlying value is excluded, the correlation coefficient between change in end-diastolic volume and control resistance is \(-0.88 (p < 0.001)\).
TABLE 2. Hydralazine-induced Change in Key Variables in Patients Separated by Heart Rate Response

<table>
<thead>
<tr>
<th>Group 1</th>
<th>MAP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>CI (l/min/m²)</th>
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<tr>
<td>HR increase ≤ 10 beats/min</td>
<td>n</td>
<td>C</td>
<td>H</td>
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<tr>
<td>5</td>
<td>91 ± 4</td>
<td>85 ± 3</td>
<td>21 ± 8</td>
</tr>
<tr>
<td>Group 2</td>
<td>HR increase &gt; 10 beats/min</td>
<td>5</td>
<td>86 ± 6</td>
</tr>
<tr>
<td>p Group 1 vs 2</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
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</table>

Abbreviations: MAP = mean arterial pressure; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; CI = cardiac index; EDVI = end-diastolic volume index; EF = ejection fraction; RVSI = regurgitant stroke volume index; RF = regurgitant fraction; C = control; H = hydralazine.

After hydralazine, the mean ejection fraction increased from 0.50 to 0.57 (p < 0.05). Ejection fraction increased by more than 0.10 in patients 3, 4, 9 and 10, by 0.08 in patient 8 and by less than 0.05 in the others. Regurgitant stroke volume was reduced by more than 10 ml/m² in seven patients and for the group decreased from 65 to 53 ml/m². Regurgitant fraction was reduced in all patients, and for the group decreased from 0.64 to 0.48.

To determine whether the increased heart rate might be responsible for the improvement seen with hydralazine, changes in cardiac performance were evaluated as a function of change in heart rate. No significant correlation between the change in heart rate and changes in left ventricular filling pressure, cardiac index, end-diastolic volume index, ejection fraction, regurgitant stroke volume or regurgitant fraction was noted. When the patients were divided on the basis of the increase in heart rate (≤ 10 or > 10 beats/min), there was no significant difference in the response to hydralazine (table 2).

Discussion

These data demonstrate that the administration of hydralazine, an arteriolar dilator, acutely improves cardiac performance in patients with aortic insufficiency by redistributing total left ventricular stroke volume so that forward flow increases while aortic regurgitant flow is reduced. In addition, systolic pump function appears to improve substantially in selected patients.

Although systemic vascular resistance was reduced by an average of 44%, mean arterial pressure was only reduced from 88 to 83 mm Hg in our patients. Maintenance of arterial pressure was due to an increase (76%) in cardiac index. Although heart rate increased significantly, the changes varied widely and did not always appear to be related to a reduction in arterial pressure. Patients who experienced little change or even an increase in pressure often had substantially increased heart rate (table 1, patients 1, 7, 8 and 10). Increased automaticity of the sinus node after hydralazine has been reported and may have contributed to the increased heart rate in our patients. As discussed below, changes in heart rate may be of considerable importance in patients with aortic insufficiency. Both cardiac index and stroke volume index were increased in all 10 of our patients. Stroke volume index rose to a lesser degree than did cardiac index because of the tendency for heart rate to increase. Left ventricular filling pressure was significantly reduced, from 19 to 12 mm Hg after hydralazine.

These changes in cardiac performance appear to have two causes: reduced aortic regurgitation and, in some patients, increased ejection fraction. Analysis of control measurements revealed no variable that could be used to predict reliably the amount by which re-
gurgitation was reduced or the extent of improvement in ejection fraction after hydralazine. Improved systolic pump function has been reported in patients with congestive heart failure when afterload is reduced and ventricular emptying is enhanced.  

In addition, the increase in heart rate in our patients may have contributed to the improvement in cardiac performance. An increase in heart rate benefits patients with aortic insufficiency by reducing regurgitant stroke volume. 18 However, the correlation between changes in heart rate and changes in regurgitant stroke volume (or any other variable) was not significant in our patients. Patients with modest increases in heart rate and those with more substantial increases responded similarly to arteriolar dilation (table 2). Changes in heart rate alone would not be expected to increase forward stroke volume, as occurred in all of our patients. Patient 2 exemplifies improved cardiac performance despite minimal change in heart rate.

After hydralazine, left ventricular end-diastolic volume decreased significantly, from 208 to 190 ml/m². However, the magnitude of change varied considerably from patient to patient. The level of systemic vascular resistance during the control period appeared to be an important predictor of change in end-diastolic volume (fig. 1). When systemic vascular resistance was elevated, the use of an arteriolar dilator was more likely to result in a substantial reduction in left ventricular volume. Although the chronic effects of arteriolar dilator therapy on end-diastolic volume are unknown, the observation that an acute reduction in aortic regurgitation can reduce left ventricular dilation is encouraging. Recent reports have demonstrated that when aortic regurgitation is treated by valve replacement, significant regression of left ventricular dilation and hypertrophy is possible. 17-19

Indeed, we have seen a reduction in left ventricular end-diastolic volume and mass and an increase in ejection fraction in a patient with chronic severe aortic insufficiency who was maintained on long-term hydralazine therapy (unpublished observations).

In this study, ventricular volumes were obtained from single-plane ventriculograms performed in the 30° right anterior oblique projection. Volume measurements obtained from single-plane ventriculography have correlated well with both biplane angiography and with volumes obtained from left ventricular casts. 13, 20, 21 Abdulla et al. 22 showed that in patients with aortic insufficiency, there is a good correlation between single-plane and biplane ventriculography for both left ventricular volumes and ejection fraction.

Other investigators evaluating the effects of nitroprusside in aortic insufficiency have presented results similar to those obtained in this study. 23, 24 Whereas hydralazine is predominantly an arteriolar dilator, 25-28 nitroprusside is known to affect venous capacitance as well as arteriolar resistance vessels. 1, 2 As the effect on capacitance vessels would be expected to reduce venous return to the heart, the reduction in left ventricular end-diastolic volume and pressure with nitroprusside could be explained on the basis of venous pooling as well as arteriolar dilation. Our data show that arteriolar dilation is sufficient to reduce left ventricular end-diastolic volume and pressure acutely. In addition, the studies using nitroprusside were designed to reduce arterial pressure substantially. 23, 24 Such changes may result in adverse rather than beneficial effects because tissue perfusion may be compromised by a reduction in pressure. Data from this study suggest that with arteriolar dilators a reduction in arterial pressure is not necessary to achieve substantial improvement in cardiac performance.

Clinical Implications

In this study, arteriolar dilation using hydralazine in patients with aortic insufficiency resulted in reduced systemic vascular resistance, increased forward stroke volume and reduced regurgitant flow. In selected patients, ejection fraction may improve substantially. As a consequence of these changes, cardiac performance improves significantly and the volume overload of the left ventricle can be reduced.

The effects of chronic administration of hydralazine on regurgitant flow, cardiac performance, and left ventricular dilation are unknown. However, the beneficial effects noted in this study and in our previous report 19 suggest that further studies are appropriate.

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References
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