Beneficial Effects of Hydralazine on Rest and Exercise Hemodynamics in Patients with Chronic Severe Aortic Insufficiency

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

SUMMARY We studied the effects of afterload reduction in chronic severe aortic insufficiency by measuring the hemodynamic response to oral hydralazine in 10 consecutive patients. Hemodynamics were also measured during maximal exercise in eight of these patients. At rest, hydralazine reduced pulmonary artery wedge pressure from 14 to 9 mm Hg (p < 0.01), and increased cardiac index by 70% and stroke volume index by 35% (both p < 0.001). Before hydralazine, pulmonary artery wedge pressure exceeded 20 mm Hg in five patients during maximal exercise; with hydralazine, at identical levels of exercise, pulmonary artery wedge pressure remained below 20 mm Hg in all patients. For the group, hydralazine reduced pulmonary artery wedge pressure from 21 to 12 mm Hg (p < 0.05) and increased cardiac index by 31% (p < 0.05) during exercise; changes in stroke volume index were more variable and there was no significant increase for the group, although several patients increased stroke volume substantially and the overall increase was 34%.

These data show that afterload reduction has beneficial effects on cardiac performance in chronic severe aortic insufficiency both at rest and during exercise. Hydralazine may be of use in such patients either in preparation for valve replacement or as interim therapy.

THE USEFULNESS of vasodilators in the treatment of patients with congestive heart failure has been demonstrated.14 By virtue of their ability to unload the heart, vasodilators improve pump function at rest and appear to have beneficial effects on exercise performance and functional class.10-12 Depending on their site of action, vasodilators may result in a reduction in preload or afterload or both.

Nitroprusside, a drug that reduces both preload and afterload,13 has been shown to improve cardiac performance in patients with aortic insufficiency.14,15 Because nitroprusside requires continuous monitoring, its use is limited to the intensive care unit setting. Although oral afterload-reducing agents are available, the effects of isolated afterload reduction in aortic insufficiency are uncertain.

To assess the potential of afterload reduction in the management of patients with aortic insufficiency, we evaluated the effects of oral hydralazine on cardiac performance at rest and during exercise in a group of patients with chronic severe aortic insufficiency.

Methods

Patient Population

Ten consecutive patients with chronic severe aortic insufficiency were evaluated. All patients had undergone cardiac catheterization at our institution within 1 month of the study and had chronic severe aortic insufficiency on the basis of angiographic and hemodynamic measurements. The clinical and hemodynamic profile of the patient group is given in table 1. Regurgitant fraction averaged 63% (range 40-75%) while regurgitant volume index averaged 66 ml/m² (range 23-107 ml/m²). Left ventricular end-diastolic volume was increased in all patients and averaged 191 ml/m² (range 149-240 ml/m²). No patient had evidence of mitral stenosis; however, patient 1 had mild mitral regurgitation and patient 3 had moderate mitral regurgitation. Patient 9 had mild aortic stenosis with a mean gradient of 25 mm Hg at catheterization. Total left ventricular stroke volume was determined angiographically and the aortic valve area index was calculated to be 2.3 cm²/m².

Hemodynamic Measurements

Measurements of right atrial, pulmonary artery and pulmonary artery wedge pressures were obtained using a Swan-Ganz triple-lumen, balloon-tipped catheter (Edwards Laboratory). Cardiac output was measured through the same catheter using a bedside computer (9520 Thermodilution Computer, Edwards Laboratory). Arterial pressure was measured directly by means of a small catheter in the brachial artery in eight patients and electronically measured, and by sphygmomanometer in two patients and mean arterial pressure (MAP) derived from the formula:

\[ \text{MAP} = D + \frac{(S - D)}{3} \]

where S is the peak systolic and D the diastolic pressure. Systemic vascular resistance (SVR, dyn-sec-cm⁻¹) was derived from the formula:

\[ \text{SVR} = \frac{\text{MAP} - \text{RAP}}{\text{CO}} \times 80 \]

From the Division of Cardiology, Department of Medicine, University of Oregon Health Sciences Center, and the Portland Veterans Administration Hospital, Portland, Oregon.

Address for correspondence: Barry H. Greenberg, M.D., Division of Cardiology, OPC 7304, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, Oregon 97201.

Received August 20, 1979; accepted December 21, 1979.

TABLE 1. Clinical and Hemodynamic Information

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>NYHA functional class</th>
<th>Etiology of AI</th>
<th>Associated cardiac disease</th>
<th>EDVI (ml/m²)</th>
<th>EF</th>
<th>LVSVI (ml/m²)</th>
<th>RVI (ml/m²)</th>
<th>RF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57</td>
<td>F</td>
<td>III</td>
<td>Rheumatic</td>
<td>Mild MR</td>
<td>172</td>
<td>0.74</td>
<td>127</td>
<td>94</td>
<td>0.74</td>
</tr>
<tr>
<td>2</td>
<td>54</td>
<td>F</td>
<td>IV</td>
<td>Rheumatic</td>
<td>None</td>
<td>149</td>
<td>0.40</td>
<td>60</td>
<td>34</td>
<td>0.57</td>
</tr>
<tr>
<td>3</td>
<td>57</td>
<td>F</td>
<td>IV</td>
<td>Aortic dissection</td>
<td>Moderate MR</td>
<td>237</td>
<td>0.27</td>
<td>65</td>
<td>43</td>
<td>0.72</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>M</td>
<td>II</td>
<td>Congenital</td>
<td>None</td>
<td>207</td>
<td>0.27</td>
<td>125</td>
<td>82</td>
<td>0.66</td>
</tr>
<tr>
<td>5</td>
<td>59</td>
<td>M</td>
<td>III</td>
<td>Congenital</td>
<td>CAD</td>
<td>151</td>
<td>0.38</td>
<td>58</td>
<td>23</td>
<td>0.40</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>M</td>
<td>II</td>
<td>Ankylosing spondylitis</td>
<td>None</td>
<td>166</td>
<td>0.54</td>
<td>89</td>
<td>56</td>
<td>0.63</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>M</td>
<td>III</td>
<td>Congenital</td>
<td>None</td>
<td>152</td>
<td>0.66</td>
<td>99</td>
<td>66</td>
<td>0.66</td>
</tr>
<tr>
<td>8</td>
<td>36</td>
<td>M</td>
<td>III</td>
<td>Congenital</td>
<td>None</td>
<td>240</td>
<td>0.35</td>
<td>90</td>
<td>68</td>
<td>0.75</td>
</tr>
<tr>
<td>9</td>
<td>22</td>
<td>F</td>
<td>II</td>
<td>Congenital AS</td>
<td>AS</td>
<td>226</td>
<td>0.65</td>
<td>65</td>
<td>107</td>
<td>0.73</td>
</tr>
<tr>
<td>10</td>
<td>25</td>
<td>M</td>
<td>III</td>
<td>Unknown</td>
<td>None</td>
<td>211</td>
<td>0.61</td>
<td>128</td>
<td>84</td>
<td>0.66</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>191</td>
<td>0.52</td>
<td>99</td>
<td>66</td>
<td>0.65</td>
</tr>
<tr>
<td>SEM</td>
<td>±12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>±0.05</td>
<td>±10</td>
<td>±9</td>
<td>±0.03</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NYHA = New York Heart Association; AI = aortic insufficiency; EDVI = end-diastolic volume index; EF = ejection fraction; LVSVI = left ventricular stroke volume index; RVI = regurgitant volume index; RF = regurgitant fraction; MR = mitral regurgitation; CAD = coronary artery disease; AS = aortic stenosis.

where MAP = mean systemic arterial pressure (mm Hg), RAP = right atrial pressure (mm Hg), CO = cardiac output (1/min) and 80 is the conversion factor.

Hydralazine Protocol

Rest

During the study, all patients were clinically stable, and digitalis and diuretics were continued without change.

After stable and reproducible measurement of heart rate, pressures and cardiac output during the control state, oral hydralazine was begun at an initial dose of 50–75 mg. Measurements were repeated hourly and over the next 24 hours the dose of hydralazine was increased to a level where maximal beneficial effects were obtained using methods previously described.3 The optimal dose of hydralazine ranged from 50–150 mg every 8–12 hours. Patients were maintained on maximal dose therapy for an additional 24 hours before final resting measurements were obtained 2–3 hours after a dose of hydralazine.

Exercise

Eight of the 10 patients also performed maximal supine exercise using a bicycle ergometer before and after hydralazine administration. Exercise was begun at a level of 200 kilopond-meters (kpm) and subsequently increased by 100–200-kpm increments until maximal exercise performance was achieved. Each level of exercise was maintained for 4 minutes and a 5–10-minute rest was allowed between stages. Control state measurements of pressures, cardiac output and body oxygen consumption (VO₂) were obtained at each level of exercise. All patients were limited by symptoms of shortness of breath or fatigue; no patients were limited by orthopedic problems or claudication. No patient experienced angina during exercise. Two hours after the maximal dose of oral hydralazine, exercise was repeated to identical levels as during control using the same protocol. Measurements of cardiac output, pressures and oxygen consumption were repeated.

Statistical Analysis

The paired t test was used to compare values before and after hydralazine for the resting and exercise states. Exercise values were compared for the same external work load. Linear regression analysis was used to evaluate the relationship between control period systemic vascular resistance during maximal exercise and reduction in pulmonary artery wedge pressure after hydralazine.

Results

Rest

The effects of oral hydralazine on resting pressures and flow are shown in table 2 and figure 1. Heart rate, mean arterial pressure and right atrial and pulmonary artery pressures did not change significantly with hydralazine, although heart rate tended to increase and arterial pressure and pulmonary artery pressure tended to decrease. Pulmonary artery wedge pressure decreased significantly, from 14 to 9 mm Hg. The largest reduction in both pulmonary artery and pulmonary artery wedge pressures occurred in patients in whom control values were most markedly elevated (table 2, patients 3, 6 and 8). As a conse-
TABLE 2. Effects of Oral Hydralazine on Resting Hemodynamics

<table>
<thead>
<tr>
<th>Pt</th>
<th>HR (beats/min)</th>
<th>BP (mm Hg)</th>
<th>RA (mm Hg)</th>
<th>PA (mm Hg)</th>
<th>PAW (mm Hg)</th>
<th>CI (l/min/m²)</th>
<th>SVI (ml/m²)</th>
<th>SVR (dyn-sec-cm⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C H</td>
<td>C H</td>
<td>C H</td>
<td>C H</td>
<td>C H</td>
<td>C H</td>
<td>C H</td>
<td>C H</td>
</tr>
<tr>
<td>1</td>
<td>70 105</td>
<td>96 82</td>
<td>4 5</td>
<td>16 12</td>
<td>9 4</td>
<td>2.4 5.0</td>
<td>34 48</td>
<td>1963 768</td>
</tr>
<tr>
<td>2</td>
<td>88 96</td>
<td>85 80</td>
<td>5 8</td>
<td>20 22</td>
<td>12 10</td>
<td>2.7 4.3</td>
<td>31 44</td>
<td>1254 711</td>
</tr>
<tr>
<td>3</td>
<td>140 130</td>
<td>85 83</td>
<td>10 13</td>
<td>47 35</td>
<td>35 30</td>
<td>2.1 3.0</td>
<td>15 23</td>
<td>1875 1217</td>
</tr>
<tr>
<td>4</td>
<td>72 99</td>
<td>89 91</td>
<td>4 4</td>
<td>12 12</td>
<td>8 5</td>
<td>2.8 4.8</td>
<td>39 48</td>
<td>1283 782</td>
</tr>
<tr>
<td>5</td>
<td>60 69</td>
<td>85 94</td>
<td>6 —</td>
<td>16 15</td>
<td>9 7</td>
<td>2.4 3.7</td>
<td>40 54</td>
<td>1344 975</td>
</tr>
<tr>
<td>6</td>
<td>78 106</td>
<td>102 111</td>
<td>9 3</td>
<td>34 16</td>
<td>19 3</td>
<td>2.7 4.0</td>
<td>35 37</td>
<td>1488 1184</td>
</tr>
<tr>
<td>7</td>
<td>70 72</td>
<td>79 78</td>
<td>4 3</td>
<td>24 25</td>
<td>8 7</td>
<td>2.8 2.8</td>
<td>40 38</td>
<td>1111 1111</td>
</tr>
<tr>
<td>8</td>
<td>103 115</td>
<td>102 84</td>
<td>9 4</td>
<td>44 32</td>
<td>26 17</td>
<td>2.3 4.7</td>
<td>22 41</td>
<td>1550 653</td>
</tr>
<tr>
<td>9</td>
<td>84 75</td>
<td>78 70</td>
<td>3 1</td>
<td>9 10</td>
<td>6 3</td>
<td>3.3 4.1</td>
<td>39 55</td>
<td>1111 824</td>
</tr>
<tr>
<td>10</td>
<td>78 78</td>
<td>92 89</td>
<td>2 4</td>
<td>14 13</td>
<td>12 8</td>
<td>3.6 5.2</td>
<td>46 67</td>
<td>1116 734</td>
</tr>
<tr>
<td>Mean</td>
<td>84 94</td>
<td>89 86</td>
<td>6 5</td>
<td>24 19</td>
<td>14 9</td>
<td>2.7 4.6</td>
<td>34 46</td>
<td>1409 896</td>
</tr>
</tbody>
</table>

SEM ±7 ±6 ±3 ±4 ±1 ±4 ±3 ±3 ±3 ±0.1 ±0.3 ±3 ±4 ±103 ±71

p NS NS NS NS < 0.01 < 0.001 < 0.001 < 0.001

Abbreviations: HR = heart rate; BP = mean systemic blood pressure; RA = mean right atrial pressure; PA = mean pulmonary arterial pressure; PAW = mean pulmonary artery wedge pressure; CI = cardiac index; SVI = stroke volume index; SVR = systemic vascular resistance; C = control; H = hydralazine.

Figure 1. Effect of hydralazine on cardiac performance. Pulmonary artery wedge (PAW) pressure fell and cardiac index (CI) increased in most patients at rest (closed circles) and during exercise (open circles).

Consequence of a 36% reduction in systemic vascular resistance, cardiac index increased by 70% and stroke volume index increased by 35%. The beneficial effects of hydralazine on cardiac performance are illustrated in figure 1.

Exercise

The effects of hydralazine on pressures and flow during maximal exercise are shown in table 3 and figure 1. Heart rate tended to increase, but not significantly. Arterial pressure fell slightly but significantly, from 125 to 108 mm Hg. Pulmonary artery pressure was reduced by 36%; however, paired measurements were obtained in only six patients (p < 0.1). After hydralazine, pulmonary artery wedge pressure fell significantly, from 21 to 12 mm Hg. At maximal exercise during the control period, pulmonary artery wedge pressure exceeded 20 mm Hg in five of the eight patients (table 3, patients 1, 5, 6, 7 and 8). At identical levels of exercise after hydralazine, pulmonary artery wedge pressure remained below 20 mm Hg in all patients. Patients with the highest pulmonary artery and pulmonary artery wedge pressure measurements during control (table 3, patients 1, 6, 7 and 8) showed the greatest reduction in pressure with hydralazine.

Although a significant improvement of 31% was noted in cardiac index, changes in stroke volume were more variable. The average increase of 34% was heavily biased by a greater than sixfold increase in stroke volume index in patient 8 (table 3). For the group, no significant change in stroke volume index...
The relationship during exercise between systemic vascular resistance during the control period and the reduction in pulmonary wedge pressure after hydralazine is shown in figure 2. Patients who maintained the highest resistance during control exercise showed the greatest reduction in wedge pressure after treatment.

There was no significant difference in VO₂ during exercise between control and posthydralazine levels (table 3).

**Discussion**

This study shows that in patients with chronic severe aortic insufficiency, afterload reduction with hydralazine improves cardiac performance both at rest and during exercise. At rest, hydralazine resulted in a decrease in pulmonary artery and pulmonary artery wedge pressures. Although pulmonary artery wedge pressure fell in all 10 patients, the most striking changes were seen in patients whose control values were initially the highest (table 2, patients 3, 6 and 8). A similar trend was noted in pulmonary artery pressures, although changes for the group were not significant. Cardiac index increased 70% above control measurements. Stroke volume index also increased significantly; however, the magnitude of change was not as great as with cardiac index due to a tendency for heart rate to increase after hydralazine. Only two of 10 patients did not have an appreciable increase in stroke volume index in response to hydralazine. In patient 7 (table 2), hydralazine had no appreciable effect on resting flow, but during exercise, stroke volume index increased by 41% (from 44 to 62 ml/m²) above control exercise levels. In patient 6, stroke volume index increased from 35 to 37 ml/m². Because pulmonary artery wedge pressure was reduced from 19 to 3 mm Hg by hydralazine it is conceivable that augmentation of forward flow by afterload reduction was compromised by a reduction in filling pressure (presumably due to a reduction in regurgitant flow). A reduction in end-diastolic fiber stretch would result in a reduction in cardiac output by the Starling mechanism.

**TABLE 3. Effects of Oral Hydralazine on Exercise Hemodynamics**

<table>
<thead>
<tr>
<th>Pt</th>
<th>HR (beats/min)</th>
<th>BP (mm Hg)</th>
<th>PA (mm Hg)</th>
<th>PAW (mm Hg)</th>
<th>CI (l/min/m²)</th>
<th>SVI (ml/m²)</th>
<th>SVR (dyne-sec-cm⁻¹)</th>
<th>Body O₂ consumption (ml/min)</th>
<th>Exercise load (kpm)</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>
<td>H</td>
<td>C</td>
</tr>
<tr>
<td>1</td>
<td>100</td>
<td>138</td>
<td>130</td>
<td>85</td>
<td>41</td>
<td>16</td>
<td>27</td>
<td>7</td>
<td>4.3</td>
</tr>
<tr>
<td>4</td>
<td>114</td>
<td>132</td>
<td>103</td>
<td>107</td>
<td>17</td>
<td>16</td>
<td>10</td>
<td>8</td>
<td>7.9</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>93</td>
<td>120</td>
<td>132</td>
<td>—</td>
<td>21</td>
<td>22</td>
<td>15</td>
<td>4.5</td>
</tr>
<tr>
<td>6</td>
<td>140</td>
<td>137</td>
<td>170</td>
<td>135</td>
<td>73</td>
<td>28</td>
<td>37</td>
<td>12</td>
<td>4.9</td>
</tr>
<tr>
<td>7</td>
<td>110</td>
<td>95</td>
<td>123</td>
<td>97</td>
<td>65</td>
<td>50</td>
<td>21</td>
<td>17</td>
<td>4.8</td>
</tr>
<tr>
<td>8</td>
<td>123</td>
<td>136</td>
<td>130</td>
<td>104</td>
<td>59</td>
<td>44</td>
<td>35</td>
<td>19</td>
<td>2.4</td>
</tr>
<tr>
<td>9</td>
<td>132</td>
<td>145</td>
<td>109</td>
<td>98</td>
<td>16</td>
<td>17</td>
<td>12</td>
<td>8</td>
<td>6.9</td>
</tr>
<tr>
<td>10</td>
<td>107</td>
<td>129</td>
<td>114</td>
<td>106</td>
<td>14</td>
<td>—</td>
<td>6</td>
<td>6</td>
<td>6.2</td>
</tr>
</tbody>
</table>

Mean 113 126 125 108 45 29 21 12 5.2 6.8 47 63 1105 644 600 621

SEM ±7 ±7 ±7 ±6 ±4 ±6 ±4 ±2 ±6 ±0.6 ±0.3 ±6 ±5 ±9 ±166 ±56 ±112 ±92

Abbreviations: HR = heart rate; BP = mean systemic blood pressure; PA = mean pulmonary arterial pressure; PAW = mean pulmonary artery wedge pressure; CI = cardiac index; SVI = stroke volume index; SVR = systemic vascular resistance; C = control; H = hydralazine.
During exercise, left ventricular filling pressure was markedly reduced by hydralazine therapy. Several patients had shown an increase in pulmonary artery wedge pressure from either normal (tables 2 and 3, patients 1, 5, and 7) or mildly elevated levels (patient 6) at rest to levels above 20 mm Hg during control exercise. In patient 8, pulmonary artery wedge had risen from 26 to 35 mm Hg during exercise. After treatment with hydralazine pulmonary artery wedge pressure did not rise above 19 mm Hg in any patient. In the eight patients undergoing exercise studies, mean pulmonary artery wedge pressure was significantly reduced from 21 to 12 mm Hg by hydralazine. Mean pulmonary artery pressure was also reduced from 45 to 29 mm Hg ($p < 0.10$), and substantial reductions occurred in patients 1, 6, 7 and 8 (table 3). Cardiac index increased significantly with hydralazine, but because individual changes were more variable, stroke volume index did not differ significantly from control exercise values. As noted in table 3, patients with lower control values for cardiac index and stroke volume index (patients 5, 6, 7 and 8) tended to show an increase with hydralazine, whereas patients with higher control values (patients 4, 9 and 10) tended to have a more equivocal response. Patient 8 improved his stroke volume index from a control of 20 ml/m² to 125 ml/m² after hydralazine.

Hydralazine probably improves cardiac performance in aortic insufficiency by a combination of mechanisms. By virtue of a direct relaxant effect on arteriolar smooth muscle and reduction in systemic vascular resistance, ventricular emptying is facilitated. In addition, total left ventricular stroke volume is most likely redistributed in response to the reduction in vascular resistance so that forward flow increases while regurgitant flow declines. Such changes in the distribution of flow have been noted in patients with aortic insufficiency treated with nitroprusside, a drug whose effect on arteriolar resistance is similar to that of hydralazine. Unlike nitroprusside, hydralazine has little or no effect on venous capacitance, so the reduction in left ventricular filling pressure seen in our patients was most likely due to a reduction in regurgitant flow; however, other factors need to be considered. Because increases in heart rate alone can reduce left ventricular diastolic volume and pressure, hydralazine-induced changes in heart rate may have contributed to the beneficial response seen in our patients. However, the changes in heart rate after hydralazine tended to be small and were somewhat variable. In patients 3 and 9 (table 2), stroke volume index increased and pulmonary artery wedge fell despite a decrease in rate. Improved ventricular emptying with hydralazine might also have contributed to the reduction in filling pressure seen in our patients. However, data from previous studies suggest that when afterload reduction alone is used to treat patients with congestive heart failure, left ventricular filling pressure changes little despite significant improvement in cardiac output. In the presence of mitral regurgitation, filling pressure can be reduced by afterload reduction alone because of a significant reduction in regurgitant flow. Only patients 1 and 3 (table 1) had evidence of mitral regurgitation on left ventricular angiography. In patient 1, the lesion was trivial. Patient 3 had moderate mitral regurgitation, so reduction in filling pressure may have been due at least in part to reduced mitral regurgitation.

For all these reasons we conclude that the beneficial effects of hydralazine in reducing left ventricular filling pressure were largely the result of a reduction in regurgitant flow. Preliminary data from our laboratory in other patients treated with intravenous hydralazine suggest that afterload reduction in aortic insufficiency results in a consistent reduction in regurgitant flow (Greenberg BH, Murphy E, DeMots H, Rahimtoola SH: unpublished observations).

The changes in pressures and flow during exercise in this group of patients probably resulted from the interplay of multiple factors. Whether or not a patient would develop an abnormal elevation of pulmonary artery wedge pressure could not be determined from hemodynamic and angiographic data at catheterization or from control data obtained during rest. Previous reports have shown that in patients with aortic insufficiency, exercise may result in a reduction in the volume overload faced by the left ventricle. A decrease in diastolic flow period due to an increase in heart rate and a reduction in systemic vascular resistance due to increased muscle demands have been suggested as possible mechanisms whereby regurgitant flow is reduced. During exercise, however, patients with chronic severe aortic insufficiency may have impaired left ventricular function that was not apparent at rest. Although this factor was not assessed in our patients, exercise-induced abnormalities of ventricular function probably contributed to the hemodynamic deterioration in several of our patients. In addition, Zelis et al. pointed out that peripheral vasodilation may be defective in patients with congestive heart failure. This factor may also have played a role in our patients. Despite the fact that systemic vascular resistance was substantially reduced by exercise, from a resting level of 1442 to 1150 dyn-sec-cm⁻⁵ during the control period, further reduction of systemic vascular resistance during exercise to 673 dyn-sec-cm⁻⁵ by hydralazine appeared to have beneficial effects in reducing filling pressure and increasing forward flow. Perhaps the usual autoregulatory responses that control vasodilation were either not optimal for the hemodynamic burden imposed by severe aortic insufficiency or were defective in our patients.

Goldberg et al. noted the importance of systemic vascular resistance as a determinant of the response to vasodilators in patients with valvular regurgitation. These workers found that nitrates have an increasingly important effect in reducing afterload as the level of systemic vascular resistance increases. In our patients with aortic insufficiency, the higher the level of resistance initially, the greater the effect of afterload reduction in improving cardiac performance (fig. 2, tables 2 and 3).
Results undertaken set and flushing exercise tolerance, Maintenance therapy may be useful in chronic severe aortic hydralazine resulted in improved cardiac performance in patients with impaired left ventricular function to prepare some patients with impaired left ventricle to correct for hypotension and reduced ventricular performance. Am J Cardiol 38: 564, 1976.


Clinical Implications

In this study, afterload reduction with oral hydralazine resulted in improved cardiac performance at rest and during exercise. Short-term therapy with hydralazine may be useful in chronic severe aortic insufficiency to prepare some patients with impaired left ventricular function for valve replacement, or as interim therapy when valve replacement is best deferred because of other problems.

In patients with aortic insufficiency, impaired pump function may or may not improve when the volume overload faced by the left ventricle is corrected by valve replacement. Because afterload reduction also reduces volume overload, the response of a patient to afterload reduction therapy may be useful in predicting the improvement that can be expected after valve replacement.

The long-term effects of afterload reduction on ventricular performance and functional status should be determined by clinical trials.

Acknowledgments

The authors gratefully acknowledge the help of Madelyn Triplett in the preparation of the manuscript and the assistance of David Clark, M.D., John Greves, M.D., and Thomas Kovaric, M.D. in the evaluation and management of these patients.

References


CARDIAC TRANSPLANT EXERCISE RESPONSE/Savin et al. 55

Cardiorespiratory Responses of Cardiac Transplant Patients to Graded, Symptom-limited Exercise

WILLIAM M. SAVIN, M.A., WILLIAM L. HASKELL, PH.D., JOHN S. SCHROEDER, M.D., AND EDWARD B. STINSON, M.D.

SUMMARY The electrocardiographic and ventilatory responses of 15 denervated heart patients who had undergone cardiac transplantation and 14 age-matched, normally innervated men were compared to assess the pattern of response to graded treadmill exercise. A 5-minute postexercise venous lactate sample was also obtained. Respiratory exchange ratio and ventilation (VE) were higher in denervated patients than in normals during submaximal exercise. Peak values (normals vs denervated) for heart rate (172 vs 159 beats/min), blood pressure (189 vs 167 mm Hg), oxygen uptake (37 vs 25 ml/kg/min), oxygen pulse (0.22 vs 0.16 ml/kg/beat) and work time (26.2 vs 18.0 minutes) were higher in normals than in cardiac transplant recipients. Peak ventilatory equivalent (2.14 vs 3.13 l/min/kg) and lactate values were higher for transplants than for normal subjects, but there were no significant intergroup differences in peak VE or in the respiratory exchange ratio. In cardiac transplant recipients, work time correlated inversely with a measure of rejection history (r = −0.59, p < 0.01). The response of cardiac transplant recipients to treadmill work differs from that of normal men and reflects a diminished ability to meet the oxygen demands of the exercising periphery.

NUMEROUS INVESTIGATORS have reported the effects of chronic denervation on the exercise response of laboratory animals1–5 and men.6–12 During dynamic exercise, the denervated dog has cardiac output and oxygen consumption responses similar to those before denervation,1 though the capacity for maximal exercise is slightly diminished.2 In the normal dog, cardiac output during exercise is increased largely through elevation of heart rate, while in the denervated dog, an equivalent increase in cardiac output is achieved through a gradual and attenuated increase in heart rate and an increase in stroke volume subsequent to an increased venous return.13 This ability to increase heart rate gradually persists in the denervated, adrenalectomized dog,1 bringing to mind Blinks’s report of a positive chronotropic effect of increased right atrial pressure (i.e., venous return).14

Supine exercise studies in human cardiac transplant recipients have shown a pattern of response similar to that seen during submaximal exercise in animals. Cardiac output is increased during exercise by an initial elevation of stroke volume followed by a gradual rise in heart rate.6, 7, 9, 10 Clarke et al.10 reported that during dynamic exercise in the denervated human, cardiac output increases, first by stroke volume augmentation due to the Starling mechanism and later by enhancement of contractility by circulating catecholamines. In the innervated heart these two mechanisms occur simultaneously. Reports of a diminished cardiac output response for a given level of work accompanied by an elevated arteriovenous oxygen difference suggest that maximal oxygen uptake and exercise tolerance after transplantation may be restricted.9 To document the cardiorespiratory response and exercise capacity of cardiac transplant recipients during symptom-limited treadmill exercise, the following study was performed.

Methods

Subjects

To assess the effect of cardiac transplantation upon exercise capacity, 15 cardiac transplant recipients (12 men and three women) and 14 normal men performed graded, symptom-limited treadmill exercise. The transplant recipients were patients returning to Stanford for their annual evaluation, while the controls were volunteers, similar in age to the cardiac transplant patients, who were asymptomatic for car-
Beneficial effects of hydralazine on rest and exercise hemodynamics in patients with chronic severe aortic insufficiency.
B H Greenberg, H DeMots, E Murphy and S Rahimtoola

Circulation. 1980;62:49-55
doi: 10.1161/01.CIR.62.1.49

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1980 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/62/1/49

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/