Hemodynamic Effects of Hydralazine in Infants with a Large Ventricular Septal Defect

ROBERT H. BEKKAMAN, M.D., ALBERT P. ROCCHINI, M.D., AND AMNON ROSENTHAL, M.D.

SUMMARY To evaluate the effects of acute afterload reduction, hydralazine, 0.2 mg/kg, was administered at cardiac catheterization to seven infants who had a large ventricular septal defect (VSD). The infants were 2.5-11 months old (mean 5.1 months). Before and 5, 15, 25 and 35 minutes after hydralazine, aortic, pulmonary capillary wedge, pulmonary artery, right atrial and superior vena cava pressures and saturations, heart rate and oxygen consumption were measured. Hemodynamic effects were noted after 5 minutes but were most pronounced 35 minutes after hydralazine. Prehydralazine baseline data were therefore compared with values 35 minutes after hydralazine. Pulmonary flow did not change, but systemic flow increased significantly (4.5 ± 0.2 to 6.7 ± 0.5 liters/min/m^2 [mean ± SEM], p < 0.001). The pulmonary-to-systemic flow ratio decreased by 32% (3.4 ± 0.4 to 2.3 ± 0.2, p < 0.001) and the absolute left-to-right shunt decreased by 24% (10.8 ± 1.3 to 8.2 ± 1.2 liters/min/m^2, p < 0.01). Hydralazine caused a significant decrease in systemic resistance (13.9 ± 0.7 to 9.5 ± 0.7 U, p < 0.001). Pulmonary resistance, aortic, pulmonary artery and pulmonary capillary wedge pressures, heart rate and oxygen consumption did not change after hydralazine. Right atrial pressure decreased slightly (4.0 ± 0.6 to 2.4 ± 0.6 mm Hg, p < 0.05). In conclusion, hydralazine caused a significant increase in systemic blood flow and a significant decrease in both pulmonary-to-systemic flow ratio and absolute left-to-right shunt in seven infants with a large VSD. These effects appear to be related to the decrease in systemic resistance that occurred with hydralazine. Although limited to the acute setting, these findings suggest that hydralazine may be beneficial in the management of infants with a large VSD.

VASODILATOR THERAPY is beneficial in the medical management of various hemodynamic disturbances, including mitral regurgitation, aortic regurgitation and primary or ischemic cardiomyopathy.1-14 In the pediatric age group, vasodilators have been used successfully in children with depressed ventricular function either postoperatively or due to cardiomyopathy.15-18 Experimental animal studies18-21 have shown that the magnitude of a left-to-right shunt across a ventricular septal defect (VSD) is responsive to changes in systemic resistance. This finding has piqued interest in the study of vasodilators in children with left-to-right shunts. We documented hemodynamic deterioration in infants with a large VSD during nitroprusside infusion.22 These effects were attributed to the marked decrease in ventricular preload that occurred with nitroprusside. The present study was therefore designed to evaluate the hemodynamic effects of hydralazine, a vasodilator with minimal influence on venous capacitance vessels,23 in infants with a large VSD.

Methods

Seven infants with a large VSD who underwent diagnostic cardiac catheterization at our institution were the subjects of this investigation. The relevant clinical and hemodynamic data are presented in table 1. There were three females and four males, ages 2.5-11 months (mean 5.1 months). Each infant manifested clinical findings consistent with the presence of a large VSD, including a loud holosystolic murmur and mid-diastolic rumble. Five infants were in congestive heart failure and all had cardiomegaly and increased pulmonary vasculature on chest x-ray. M-mode echocardiograms disclosed a mean left atrium-to-aorta (LA/Ao) ratio of 1.4 ± 0.1. Five infants received anticongestive therapy, consisting of digoxin and diuretics, before cardiac catheterization, although not within 12 hours before the study.

Informed consent was obtained. Six infants received morphine sulphate, 0.15 mg/kg, and diphenydramine, 1 mg/kg, and one infant received chloralhydrate, 20 mg/kg, for sedation. After right- and left-heart catheterization had confirmed the presence of a large VSD (pulmonary-to-systemic flow ratio ≥ 2.5, and pulmonary-to-aortic systolic pressure ratio > 0.50), and before angiography, hydralazine, 0.2 mg/kg i.v., was administered as a bolus over 1 minute. Before and 5, 15, 25 and 35 minutes after hydralazine administration, data were collected on aortic, pulmonary capillary wedge, pulmonary artery and right atrial pressures, aortic, pulmonary artery, right atrial and superior vena cava oxygen saturation, heart rate and oxygen consumption (using a continuous flow-through system24). Prehydralazine control data were measured over 20 minutes and did not vary significantly. Pulmonary and systemic blood flows, shunts and resistances were calculated in accordance with the Fick principle. Finally, left ventricular cineangiography confirmed the presence of a single large subaortic VSD in each infant. One infant also had a moderate-sized patent ductus arteriosus.

The data were evaluated by the two-tailed t test for paired observations. All values are expressed as mean ± SEM.

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TABLE 1. Clinical and Hemodynamic Data in Seven Infants Receiving Hydralazine

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (mo.)</th>
<th>Diagnosis</th>
<th>RR</th>
<th>Liver</th>
<th>LA/Ao ratio</th>
<th>Qp/Qs ratio</th>
<th>RV/LV pressure ratio</th>
<th>PA pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5</td>
<td>VSD PDA</td>
<td>80</td>
<td>4</td>
<td>1.3</td>
<td>5.2</td>
<td>1.00</td>
<td>77/27 (43)</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>VSD CHF</td>
<td>72</td>
<td>4</td>
<td>—</td>
<td>3.0</td>
<td>0.67</td>
<td>50/15 (26)</td>
</tr>
<tr>
<td>3</td>
<td>3.0</td>
<td>VSD CHF</td>
<td>64</td>
<td>5</td>
<td>1.6</td>
<td>4.0</td>
<td>1.00</td>
<td>85/25 (49)</td>
</tr>
<tr>
<td>4</td>
<td>3.5</td>
<td>VSD CHF</td>
<td>52</td>
<td>3</td>
<td>1.2</td>
<td>3.3</td>
<td>1.00</td>
<td>90/30 (51)</td>
</tr>
<tr>
<td>5</td>
<td>6.0</td>
<td>VSD CHF</td>
<td>65</td>
<td>4</td>
<td>1.2</td>
<td>3.6</td>
<td>0.94</td>
<td>75/30 (50)</td>
</tr>
<tr>
<td>6</td>
<td>7.0</td>
<td>VSD</td>
<td>35</td>
<td>1</td>
<td>1.5</td>
<td>2.5</td>
<td>0.67</td>
<td>53/13 (28)</td>
</tr>
<tr>
<td>7</td>
<td>11.0</td>
<td>VSD</td>
<td>35</td>
<td>2</td>
<td>1.7</td>
<td>2.5</td>
<td>0.51</td>
<td>46/19 (28)</td>
</tr>
</tbody>
</table>

Mean ± SEM 5.1 ± 1.2 1.4 ± 0.1 3.4 ± 0.4 0.83 ± 0.08

Abbreviations: VSD = ventricular septal defect; PDA = patent ductus arteriosus; CHF = congestive heart failure; RR = respiratory rate; Liver = centimeters below right costal margin; LA = left atrium; Ao = aorta; Qp = pulmonary blood flow; Qs = systemic blood flow; RV = right ventricle; LV = left ventricle; PA = pulmonary artery.

Results

Significant hemodynamic effects occurred as early as 5 minutes after hydralazine administration. The changes occurred gradually, and the most pronounced effects were noted at 35 minutes (fig. 1). Pulmonary blood flow did not change, but systemic blood flow increased progressively, which resulted in a gradual decrease in both the pulmonary-to-systemic flow ratio and the absolute left-to-right shunt. Pulmonary resistance was unaffected, whereas systemic resistance decreased after hydralazine. The pulmonary-to-systemic resistance ratio increased gradually, varying inversely with the pulmonary-to-systemic flow ratio.

Prehydralazine control data were compared with data obtained 35 minutes after hydralazine administration (table 2). Pulmonary blood flow did not change, but systemic blood flow increased (4.5 ± 0.2 to 6.7 ± 0.5 liters/min/m², p < 0.001) (fig. 2). The left-to-right shunt decreased significantly in every infant after hydralazine. The pulmonary-to-systemic flow ratio decreased (3.4 ± 0.4 to 2.3 ± 0.2, p < 0.001), as did the absolute left-to-right shunt (10.8 ± 1.3 to 8.2 ± 1.2 liters/min/m², p < 0.01). Pulmonary resistance was unaffected by hydralazine, whereas systemic resistance decreased markedly (13.9 ± 0.7 to 9.5 ± 0.7 U, p < 0.001) (fig. 3). Thus, hydralazine caused a significant increase in the pulmonary-to-systemic resistance ratio (0.13 ± 0.02 to 0.19 ± 0.03, p < 0.01). Aortic and pulmonary arterial mean pressures were unchanged. Mean pulmonary capillary wedge pressure decreased slightly in most patients, but this was not statistically significant. A small decrease in the right atrial mean pressure (4.0 ± 0.6 to 2.4 ± 0.6 mm Hg, p < 0.05) was also observed. Heart rate and oxy-

TABLE 2. Hemodynamic Effects of Hydralazine in Seven Infants with a Large Ventricular Septal Defect

<table>
<thead>
<tr>
<th>Pt</th>
<th>Qp (l/min/m²)</th>
<th>Qs (l/min/m²)</th>
<th>Qp/Qs ratio</th>
<th>L-R shunt (l/min/m²)</th>
<th>Rp (mm Hg/l/min/m²)</th>
<th>Rs (mm Hg/l/min/m²)</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>
</tr>
<tr>
<td>1</td>
<td>13.0 12.1</td>
<td>5.1 8.1</td>
<td>2.5 1.5</td>
<td>7.9 4.0</td>
<td>1.2 0.8</td>
<td>13.1 6.9</td>
</tr>
<tr>
<td>2</td>
<td>19.4 16.6</td>
<td>3.7 4.8</td>
<td>5.2 3.5</td>
<td>15.7 11.8</td>
<td>1.5 1.4</td>
<td>15.1 11.3</td>
</tr>
<tr>
<td>3</td>
<td>11.8 11.4</td>
<td>3.9 5.4</td>
<td>3.0 2.1</td>
<td>7.9 6.0</td>
<td>1.5 1.6</td>
<td>16.2 11.9</td>
</tr>
<tr>
<td>4</td>
<td>19.1 15.5</td>
<td>4.8 6.8</td>
<td>4.0 2.3</td>
<td>14.3 8.7</td>
<td>2.0 2.8</td>
<td>11.9 10.0</td>
</tr>
<tr>
<td>5</td>
<td>18.0 20.5</td>
<td>5.0 8.0</td>
<td>3.6 2.6</td>
<td>13.0 12.5</td>
<td>2.2 1.8</td>
<td>12.2 8.4</td>
</tr>
<tr>
<td>6</td>
<td>12.7 12.7</td>
<td>5.1 6.7</td>
<td>2.5 1.9</td>
<td>7.6 6.0</td>
<td>1.4 1.3</td>
<td>12.2 8.8</td>
</tr>
<tr>
<td>7</td>
<td>12.9 15.0</td>
<td>3.9 6.8</td>
<td>3.3 2.2</td>
<td>9.0 8.2</td>
<td>3.0 2.9</td>
<td>16.4 9.1</td>
</tr>
<tr>
<td>Mean</td>
<td>15.3 14.8</td>
<td>4.5 6.7</td>
<td>3.4 2.3</td>
<td>10.8 8.2</td>
<td>1.8 1.8</td>
<td>13.9 9.5</td>
</tr>
<tr>
<td>± SEM</td>
<td>±1.3 ±1.2</td>
<td>±0.2 ±0.5</td>
<td>±0.4 ±0.2</td>
<td>±1.3 ±1.2</td>
<td>±0.2 ±0.3</td>
<td>±0.7 ±0.7</td>
</tr>
</tbody>
</table>

p NS <0.001 <0.001 <0.01 NS <0.001

Abbreviations: L–R = left to right; Qp = pulmonary blood flow; Qs = systemic blood flow; Rp = pulmonary resistance; Rs = systemic resistance; Ao = aortic mean pressure; PA = pulmonary artery mean pressure; PCW = pulmonary capillary wedge mean pressure; RA = right atrial mean pressure; VO₂ = oxygen consumption; C = prehydralazine control data; H = data obtained 35 minutes after hydralazine.
tion in seven infants who had a large VSD. Systemic blood flow increased and the left-to-right shunt decreased significantly. The pulmonary-to-systemic flow ratio decreased by 32% and the absolute left-to-right shunt decreased by 24%. These effects appear to be related to the decrease in systemic resistance and to the increase in pulmonary-to-systemic resistance ratio that occurred with hydralazine. Pulmonary blood flow did not change, as the increase in systemic blood flow and venous return appear to have offset the decrease in left-to-right shunt.

Previous work in dogs with a VSD has shown that the left-to-right shunt is responsive to changes in systemic vascular resistance. Tanenbaum and Pfaff\textsuperscript{20} demonstrated an increase in left-to-right shunting after the infusion of pressor amines. Synhorst et al.\textsuperscript{19} showed that α-blockade, by dilating systemic resistance vessels, can markedly diminish the shunt across an experimental VSD. After administration of phenolamine or phenoxybenzamine, systemic resistance declined by 42% and the pulmonary-to-systemic flow ratio decreased by 32%. More recently, Boucek et al.\textsuperscript{21} studying lambs with a surgically created VSD, documented a significant increase in systemic flow and decrease in pulmonary-to-systemic flow ratio after administration of hydralazine or prazosin.

Several studies\textsuperscript{16–12} in human subjects have documented the beneficial effects of vasodilators in mitral regurgitation. With mitral insufficiency, as with a VSD, the balance between forward and regurgitant flow is strongly influenced by impedance to aortic flow. Vasodilator therapy, by reducing peripheral vascular resistance, significantly decreases regurgitant flow and increases forward cardiac output. Greenberg et al.,\textsuperscript{13} for example, observed a 50% increase in forward stroke volume and a 33% reduction in regurgitant stroke volume after administration of hydralazine to adults who had severe mitral insufficiency. These hemodynamic benefits persisted during a 48-hour course of oral therapy.

Hydralazine has also been shown to cause hemo-

**Discussion**

The present study has documented acute hemodynamic improvement after hydralazine administration.
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**Figure 2.** Effect of hydralazine on pulmonary flow, systemic flow, and left-to-right shunting in seven infants with a large ventricular septal defect. Values were measured before and 35 minutes after hydralazine administration. Abbreviations as in figure 1.

**Figure 3.** Effect of hydralazine on pulmonary and systemic resistance in seven infants with a large ventricular septal defect. Values were measured before and 35 minutes after hydralazine administration. Abbreviations are as in figure 1.

dynamic improvement in adults with congestive heart failure. These patients have been characterized by depressed ventricular function, low cardiac output and elevated systemic resistance. Under these circumstances, hydralazine increases cardiac output by decreasing aortic impedance to left ventricular ejection and reducing the work of myocardial contraction, thereby promoting more complete ventricular emptying. It is unlikely that these mechanisms play a major role in the response to hydralazine of infants with a large VSD, as these patients typically exhibit normal ventricular performance, cardiac output and systemic resistance. Nevertheless, in the present study hydralazine did cause a significant reduction in systemic resistance, which in turn significantly decreased the left-to-right shunt. Such an effect is not unexpected, as the magnitude of left-to-right shunting across a large VSD is determined by the relative resistance to flow across the pulmonary and systemic vascular beds. A larger pulmonary-to-systemic resistance ratio will promote a smaller shunt and a greater systemic blood flow, all other factors being equal. This relationship is evident in several clinical settings — for example, the diminished shunt that follows pulmonary artery banding or the development of pulmonary vascular obstructive disease — and has been borne out by the present study.

We previously documented hemodynamic deterioration during nitroprusside infusion in a similar group of infants with a large VSD. Although pul-
monary flow remained unchanged, systemic blood flow decreased and the pulmonary-to-systemic flow ratio therefore increased significantly. These effects were attributed to the decrease in both right and left ventricular filling pressures that occurred with nitroprusside. In contrast, hydralazine, a vasodilator with actions that are confined to arteriolar resistance vessels, has little effect on ventricular preload. Therefore, given adequate ventricular filling, a decrease in systemic vascular resistance apparently promotes an increase in forward flow and a corre-
spanding decrease in left-to-right flow across a large VSD. Nevertheless, Lindsay et al. \(^{38}\) failed to detect such improvement after hydralazine in five children with left-to-right shunts. However, they evaluated a diverse group of children with shunts at a variety of levels, which may explain why their findings differ from ours and from results of animal studies.

The small decrease in right atrial and pulmonary capillary wedge pressures observed in this study were unexpected because hydralazine is reported to have minimal effects on venous capacitance vessels. \(^{39}\) These changes in ventricular filling pressure may be due to afterload reduction and perhaps to improved contractility. \(^{34,35}\)

In conclusion, we documented acute hemodynamic improvement after hydralazine in infants with a large VSD. In response to decreased systemic resistance, systemic blood flow increased and the left-to-right shunt decreased significantly. The pulmonary-to-
 systemic flow ratio decreased by 32% and the absolute left-to-right shunt decreased by 24%. These data indicate that hydralazine, in contrast to conventional therapy, \(^{31}\) may act specifically to diminish a fundamental hemodynamic disturbance in these patients: the left-to-right shunt. We did not observe an acute change in pulmonary blood flow, because the increase in systemic flow and venous return compensated for the decrease in left-to-right shunt. However, such a redistribution of left ventricular output may prove beneficial in the management of infants with a large VSD.

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Effects of Hydralazine on Coronary Blood Flow and Myocardial Energetics in Congestive Heart Failure

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SUMMARY The acute effects of oral hydralazine, 1 mg/kg, on coronary vascular resistance, coronary blood flow (estimated using the coronary sinus thermodilution technique), and myocardial oxygen consumption were evaluated in 10 patients with chronic (New York Heart Association class III and IV) nonischemic congestive heart failure. Central hemodynamic responses demonstrated a modest decrease in mean arterial pressure, pulmonary capillary wedge pressure and systemic vascular resistance (12%, 15% and 29%, respectively), while the cardiac index increased from 2.3 ± 0.1 to 3.1 ± 0.3 and left ventricular stroke work index from 24 ± 3.7 to 28 ± 3.4 (p < 0.01). Heart rate and diastolic filling time did not change. Coronary blood flow increased approximately 50%, from 144 ± 17 to 218 ± 30 ml/min, and coronary vascular resistance decreased from 0.55 ± 0.09 to 0.36 ± 0.08 mm Hg/ml/min (both p < 0.01). Oral hydralazine increased myocardial oxygen consumption by 33%, from 15 ± 1.6 to 20 ± 2.7 ml/min. Despite this moderate augmentation in myocardial oxygen consumption, the arterial–coronary sinus oxygen difference decreased from 104 ± 6.2 to 94 ± 7.5 and the myocardial oxygen extraction ratio decreased from 71% to 64% (both p < 0.05). The ratio of coronary vascular resistance to systemic vascular resistance decreased with hydralazine therapy, while coronary blood flow increased from 3.5% to 4.3% of total cardiac output. In this group of patients with nonischemic cardiomyopathy, hydralazine had a favorable effect on the coronary circulation and improved the critical myocardial oxygen supply-demand ratio.

HYDRAZLINE induces peripheral circulatory vasodilation through direct relaxation of the arteriolar smooth muscle.1,2 Early studies3,4 suggested nonuniformity of vasodilation in systemic circulation. In the setting of congestive heart failure, recent reports have demonstrated augmentation of renal and forearm blood flow with little effect on the hepatic circulation.4,4 This study was designed to assess the effects of oral hydralazine on the coronary vascular system in patients with chronic severe nonischemic congestive heart failure.

Patients and Methods

Ten patients with congestive heart failure (New York Heart Association functional class III and IV) were studied. The group consisted of five females and five males, mean age 48 years (range 23–58 years). Each patient had nonischemic cardiomyopathy documented by cardiac catheterization performed within 6 weeks of the study. The left ventricular ejection fraction of all patients was less than 35% and eight patients had resting left ventricular end-diastolic filling pressure greater than 20 mm Hg. The patients had been maintained on conventional cardiac medications — 10 were taking digitalis, nine diuretics, four nitrates, and four antiarrhythmics. Diuretics and nitrates were discontinued 48 hours before the beginning of the study. Exclusion criteria included anemia, primary hepatic dysfunction, uremia, primary valvular heart disease or evidence of active myocarditis.

Protocol

Each patient gave written informed consent before study. Before the control period, a balloon-tipped, triple-lumen thermodilution catheter was placed in the pulmonary artery to measure central hemodynamic
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