Short-term hemodynamic effects of hydralazine in infants with complete atrioventricular canal defects

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ABSTRACT We evaluated the acute hemodynamic responses to hydralazine during cardiac catheterization in eight infants (ages 1.0 to 5.5 months) with congestive heart failure due to complete atrioventricular canal defect. Hydralazine administered intravenously (0.5 to 1.0 mg/kg body weight) increased heart rate and systemic blood flow and decreased mean right atrial pressure, systemic and pulmonic arterial pressures, systemic arteriolar resistance, and the ratio of pulmonary to systemic blood flow (p < .05). The percentage of pulmonary flow contributed by shunted blood (percent left-to-right shunt; measured by indicator dilution) was decreased by hydralazine in six (mean = 85% before to 64% after hydralazine; p < .01), but remained unchanged (79%) in two infants. The two infants with no change in percent left-to-right shunt had higher pulmonary arteriolar resistances (Rp) before hydralazine (mean = 12.8 vs. 3.2 U/m²) and had greater declines in Rp (mean change = -5.1 vs + 0.3 U/m²) in response to hydralazine. Thus, if Rp does not fall, hydralazine reduces the percentage of left-to-right shunt over the short term and therefore might be useful for managing congestive heart failure in these infants. However, because the response varies, an evaluation of the short-term hemodynamic effects of hydralazine may be warranted in an attempt to select those infants who might respond favorably to long-term hydralazine therapy.


SUCCESSFUL MEDICAL MANAGEMENT of congestive heart failure can be difficult to achieve in infants with large systemic-to-pulmonary shunts.1 Recent reports suggest that treatment with digoxin, a principal therapeutic agent for this condition,2 may not benefit a substantial number of these infants.3 4 It would be helpful to identify additional drugs that might provide hemodynamic improvement, especially in cases in which surgical intervention is not feasible.

Vasodilators are commonly used to help control congestive heart failure in adults,5-9 but the experience in pediatric patients is mostly limited to children with depressed ventricular function either due to a congestive cardiomyopathy10,11 or occurring immediately after cardiac surgery.12-14 Experiments in animals have demonstrated that reduction of the systemic vascular resistance with a vasodilator will decrease the magnitude of a left-to-right shunt across a ventricular septal defect.15,16 Presumably a reduction in left-to-right shunting would benefit infants with congestive failure due to a systemic-to-pulmonary communication with high pulmonary blood flow. However, conflicting results have been reported regarding the short-term effects of vasodilators administered to infants with ventricular septal defects.17-20

Our study was designed to assess the short-term hemodynamic responses to hydralazine (an arteriolar dilator) in infants with left-to-right shunts and congestive heart failure. We chose to study infants with complete atrioventricular canal defects because many of these patients have heart failure that is refractory to conventional medical therapy.

Methods

Eight infants (four boys; four girls) with congestive heart failure and complete atrioventricular canal defects were the subjects of this study. Each infant was less than 6 months old and all had trisomy 21. Pertinent clinical characteristics of this group are summarized in Table 1.

All eight infants underwent cardiac catheterization to confirm the clinical diagnosis and to precisely define hemodynamic and anatomic abnormalities. The hemodynamic status was assessed before and after the intravenous administration of hydralazine. Informed consent was obtained from a parent or legal guardian. Digoxin and/or diuretics were not administered within 12 hr before catheterization. Six infants were sedated with 2 mg/kg meperidine, and 1 mg/kg hydroxyzine each given intramuscu-
TABLE 1
Clinical characteristics of eight infants with complete atroventricular canal defects

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (months)</th>
<th>Weight (kg)</th>
<th>PDA</th>
<th>MR</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>3.5</td>
<td>3.4</td>
<td>Small</td>
<td>Mild</td>
<td>Dig/diuretic</td>
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<td>2</td>
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<td>3</td>
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<tr>
<td>4</td>
<td>F</td>
<td>3.25</td>
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</tr>
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<td>6</td>
<td>M</td>
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<td>3.7</td>
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</tr>
<tr>
<td>7</td>
<td>M</td>
<td>2.5</td>
<td>3.3</td>
<td>None</td>
<td>Mild</td>
<td>Dig/diuretic</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>1.0</td>
<td>3.6</td>
<td>None</td>
<td>Mild</td>
<td>None</td>
</tr>
<tr>
<td>Mean</td>
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<td>3.0</td>
<td>3.5</td>
<td></td>
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</tr>
</tbody>
</table>

PDA = patent ductus arteriosus assessed angiographically; MR = mitral regurgitation assessed angiographically; Dig = digoxin.

Infants usually died in the first 45 min after catheterization. Two infants did not require sedation.

Angiography was not performed until after the effects of hydralazine were evaluated. The following measurements were obtained in each infant, usually in duplicate, both before and 30 min after the administration of hydralazine: blood oxygen saturations measured from the superior vena cava (selected as mixed venous blood), pulmonary artery, pulmonary vein or left atrium, and the femoral artery; pressures recorded from the right atrium, left atrium, pulmonary artery, and femoral artery; and the indicator dilution curves (obtained by injecting 0.2 mg/kg indocyanine green into the pulmonary artery and withdrawing blood from the femoral artery through a densitometer cuvette). Withdrawn blood was reinjected. Oxygen consumption was assumed to be maintained since hydralazine does not affect oxygen consumption under these conditions. Oxygen content was calculated by multiplying the product of the measured hemoglobin and oxygen saturation by 1.34.

Hydralazine, 0.5 mg/kg, was administered intravenously over 1 to 2 min. Thirty minutes later the aforementioned measurements were repeated. Five infants (Nos. 2 through 6) received a second dose of hydralazine (0.5 mg/kg; 1.0 mg/kg total) and the data obtained 30 min after the second dose are the results presented for those infants. The remaining three infants were not given the second dose because the first dose of hydralazine either increased heart rate by greater than 20 beats/min or reduced mean systemic blood pressure by more than 10 mm Hg. No adverse side effects of hydralazine were observed.

Pulmonary and systemic blood flows and arteriolar resistances were calculated in accordance with the Fick principle. Oxygen saturations were not routinely obtained from the inferior vena cava because of contamination by blood shunted through the atrial septal defect. Mixed venous blood saturation was therefore defined as the saturation in the superior vena cava. Systemic arteriolar resistance units were defined as the difference between mean aortic pressure and mean right atrial pressure divided by the systemic blood flow. Pulmonary arteriolar resistance units were defined as the difference between mean pulmonary arterial pressure minus mean left atrial pressure divided by the pulmonary blood flow. The percent age of pulmonary flow contributed by shunted blood (percent left-to-right shunt) was determined from the indicator dilution curves by standard formulas.

The prehydralazine and posthydralazine values were compared by a two-tailed t test for paired observations. Differences were considered to be statistically significant if p < .05. Results are expressed as mean ± SD.

Results
The short-term effects of hydralazine were evaluated by comparing the results obtained 30 min after hydralazine administration to the prehydralazine control data. Pertinent data for each infant are presented in table 2. Hydralazine increased heart rate from 128 ± 13 (mean ± SD) to 147 ± 15 beats/min (p < .005). Pulmonary arterial and venous oxygen saturations and aortic saturation were not affected by hydralazine. The prehydralazine and posthydralazine pulmonary venous (or left atrial) saturations were 94 ± 2% and 96 ± 1%, respectively. Saturation in the superior vena cava in-

TABLE 2
Hemodynamic effects of hydralazine in eight infants with complete atroventricular canal defects

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Ao (mm Hg)</th>
<th>PA (mm Hg)</th>
<th>LA (mm Hg)</th>
<th>Qp (l/min/m²)</th>
<th>Qs (l/min/m²)</th>
<th>Rp (U/m²)</th>
<th>Rs (U/m²)</th>
<th>% L to R (dye curve)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>Hz</td>
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<td>Hz</td>
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<tr>
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<td>70</td>
<td>60</td>
<td>50</td>
<td>38</td>
<td>9</td>
<td>4</td>
<td>13.5</td>
<td>12.0</td>
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<tr>
<td>3</td>
<td>75</td>
<td>65</td>
<td>28</td>
<td>20</td>
<td>10</td>
<td>11</td>
<td>6.5</td>
<td>6.5</td>
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<tr>
<td>4</td>
<td>65</td>
<td>55</td>
<td>63</td>
<td>50</td>
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<td>3</td>
<td>3.2</td>
<td>3.7</td>
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<tr>
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<td>40</td>
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<td>50</td>
<td>47</td>
<td>34</td>
<td>32</td>
<td>6</td>
<td>3</td>
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<td>6.7</td>
</tr>
<tr>
<td>Mean</td>
<td>68</td>
<td>52</td>
<td>50</td>
<td>37</td>
<td>8</td>
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<td>10.4</td>
<td>8.6</td>
</tr>
<tr>
<td>SD</td>
<td>11</td>
<td>9</td>
<td>15</td>
<td>9</td>
<td>2</td>
<td>3</td>
<td>4.8</td>
<td>3.2</td>
</tr>
</tbody>
</table>
p value      | <.005      | <.01       | NS         | NS            | <.025       | NS       | <.01     | NS               |                |                |              |                |              |                |

Ao = mean aortic pressure; PA = mean pulmonary arterial pressure; LA = mean left atrial pressure; Qp = pulmonary blood flow (Fick); Qs = systemic blood flow (Fick); Rp = pulmonary arteriolar resistance; Rs = systemic arteriolar resistance; % L to R = percent left-to-right shunt (indicator dilution technique); C = prehydralazine control values; Hz = values obtained after hydralazine administration.

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creased from a baseline of $56 \pm 5\%$ to $63 \pm 3\%$ ($p < .01$) after hydralazine administration.

Mean right atrial pressure fell after hydralazine was given. Right atrial pressure decreased from $7 \pm 2$ to $4 \pm 2$ mm Hg ($p < .05$). Prehydralazine left atrial pressure was $8 \pm 2$ mm Hg and that after hydralazine was essentially unchanged ($6 \pm 3$ mm Hg). Hydralazine reduced systemic and pulmonary arterial pressures. Mean aortic pressure decreased from the baseline value of $68 \pm 11$ mm Hg to a posthydralazine value of $52 \pm 9$ mm Hg ($p < .005$). Each infant had pulmonary hypertension and the initial mean pulmonary arterial pressure was $50 \pm 15$ mm Hg. Hydralazine reduced mean pulmonary pressure to $37 \pm 9$ mm Hg ($p < .01$).

Hydralazine increased systemic blood flow as assessed by the Fick method. Before hydralazine systemic blood flow for the group was $2.7 \pm 0.7$ l/min/m² and after hydralazine it increased to $3.2 \pm 0.5$ l/min/m² ($p < .025$). Hydralazine produced no significant change in pulmonary blood flow (prehydralazine value = $10.4 \pm 4.8$; posthydralazine value = $8.6 \pm 3.2$ l/min/m²).

The effects of hydralazine on systemic and pulmonary arteriolar resistances as calculated by the Fick method are illustrated in figure 1. Systemic resistance fell significantly from $24.3 \pm 7.2$ U/m² before hydralazine to $15.2 \pm 3.4$ U/m² after hydralazine administration ($p < .01$). In contrast, for these infants taken as a group, hydralazine had no significant effect on pulmonary resistance.

Figure 2 illustrates the effects of hydralazine on two independent assessments of the magnitude of the systemic-to-pulmonary shunt. With the use of the Fick method the pulmonary/systemic flow ratio was initially $4.0 \pm 1.7$ and hydralazine produced a significant drop in this parameter to $2.7 \pm 0.9$ ($p < .05$). Hydralazine also reduced the percentage of left-to-right shunt as measured by indicator dilution, a technique that does not require knowledge of the rate of oxygen consumption. Percentage of left-to-right shunt initially was $83 \pm 15\%$ and declined after hydralazine administration to $67 \pm 19\%$ ($p < .01$).

However, on an individual basis, two infants demonstrated no change in the percentage of left-to-right shunt despite a fall in systemic resistance in response to hydralazine (one infant was given $0.5$ mg hydralazine/kg body weight and the other received $1.0$ mg/kg). Prehydralazine systemic resistances in these two patients were $31.0$ and $34.1$ U/m² and hydralazine reduced systemic resistance more than $10$ U/m² in each infant (to $13.0$ and $22.6$ U/m², respectively). Despite this change in systemic resistance, the percentage of left-to-right shunt was essentially unchanged by hydralazine in these two infants. Before hydralazine their left-to-right shunts were $83\%$ and $74\%$; after hydralazine, these values were $82\%$ and $76\%$, respectively. These two infants also had the highest prehydralazine pulmonary resistances and the greatest declines in pulmonary resistance in response to hydralazine, as shown in figure 3. Figure 4 illustrates the relationship between the change in the percentage of left-to-right shunt and the prehydralazine pulmonary resistance. The two infants with an initial pulmonary resistance greater than $5.1$ U/m² were the individuals in whom the percentage of left-to-right shunt remained unchanged.
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In summary, six of the eight infants had normal or only mildly elevated prehydralazine pulmonary resistance. After hydralazine these infants had falls in systemic resistance with virtually no change in pulmonary resistance, and thus their left-to-right shunts decreased. In contrast, the two infants with the highest pulmonary resistances responded to hydralazine with declines in both pulmonary resistance and systemic resistance. The net effect of hydralazine in these two infants was such that the left-to-right shunt did not change.

Discussion

Our results document a short-term decrease in the left-to-right shunt fraction, as measured by the indicator dilution technique, after hydralazine administration to six of eight infants with congestive heart failure due to complete atrioventricular canal defects. We attribute this change to the systemic arteriolar dilation produced by hydralazine. Our findings are consistent with those of previous experimental studies in dogs\textsuperscript{15, 23} and lambs,\textsuperscript{16} which demonstrated that the magnitude of the systemic-to-pulmonary shunt across a ventricular septal defect was responsive to changes in systemic resistance; an increase in systemic resistance produced an increase in left-to-right shunting, whereas a decrease in systemic resistance reduced the left-to-right shunt. Beekman et al.\textsuperscript{19} reached similar conclusions after administering hydralazine to seven infants with large ventricular septal defects. In their study hydralazine increased systemic blood flow and decreased the left-to-right shunt by reducing systemic resistance. Each infant had a normal pulmonary resistance and hydralazine had no effect on pulmonary resistance.

Recently, Nakazawa et al.\textsuperscript{20} concluded that the pre-treatment systemic resistance is the primary determinant of the hemodynamic response to hydralazine in children with ventricular septal defects. They found that the ratio of pulmonary to systemic flow declined only in those patients with an initially high systemic resistance. In contrast, two of the eight infants we studied had no change in the percentage of left-to-right shunt despite high prehydralazine systemic resistances and large declines in this parameter after hydralazine administration. Compared with our remaining six patients, these two infants demonstrated a larger decline in pulmonary resistance in response to hydralazine. These results suggest that the effect of hydralazine on pulmonary resistance is also an important determinant of the net hemodynamic response to hydralazine in infants with systemic-to-pulmonary shunts. If hydralazine reduces systemic resistance, but pulmonary resistance is low (or does not react), then the left-to-right shunt decreases. Conversely, if hydralazine reduces systemic resistance but pulmonary resistance also falls, then the left-to-right shunt may not change (as was observed in two of our patients). Thus, our findings in humans verify results from previous animal experiments that indicated that the magnitude of the left-to-right shunt across a ventricular septal defect can be altered pharmacologically by ma-
manipulating the relative resistance to flow through the pulmonary and systemic circuits.\textsuperscript{15, 16, 23}

Potential concerns regarding the interpretation of portions of our results might arise from our use of assumed rates of oxygen consumption and to the difficulty in obtaining blood samples for measuring oxygen saturation that are representative of mixed venous blood and pulmonary venous blood. For these reasons, results of our calculations of flows and resistances may not be precise in an absolute sense. However, our major conclusions are not founded primarily on the absolute values for flows and resistances, but instead are derived from the changes we observed after hydralazine administration. Furthermore, the indicator dilution technique was also applied to the study of each of these infants. This method circumvents these concerns because it provides an independent assessment of the effects of hydralazine on the left-to-right shunt fraction and does not require knowledge of the rate of oxygen consumption or blood oxygen content. In the presence of very large shunts, small errors in measurement of the percentage of left-to-right shunt will magnify errors in calculating the ratio of pulmonary to systemic flow because the ratio and percentage of shunt are exponentially related. However, again our conclusions regarding the effects of hydralazine on the left-to-right shunt fraction are not based on absolute values, but rather on the changes we observed in response to hydralazine.

Beekman et al.\textsuperscript{17} found that the administration of nitroprusside produced deleterious hemodynamic effects in five infants with congestive heart failure due to ventricular septal defects. Nitroprusside decreased systemic blood flow and increased the left-to-right shunt in these patients. These effects were attributed to a nitroprusside-mediated increase in venous capacitance with resultant declines in ventricular filling and output. Lindsay et al.\textsuperscript{18} administered hydralazine to three children with ventricular septal defects and reported no decrease in the percentage of left-to-right shunt. This finding was not explained by a large fall in pulmonary resistance and the reasons that their results differ from those reported from the previous clinical and animal investigations are not entirely clear. However, compared with our subjects, their patients were older (ages 0.5, 1.8, and 7.5 years), one patient had a small shunt initially (27% left-to-right), and they each received a lower dose of hydralazine (0.15 or 0.30 mg/kg vs 0.5 or 1.0 mg/kg).

In our study hydralazine significantly increased heart rate and decreased systemic arterial pressure. These changes were less pronounced in previous studies of infants given lower doses of hydralazine.\textsuperscript{19, 20} The optimal dose of hydralazine would be one that produces the desired changes in blood flow without increasing heart rate or decreasing systemic pressure. However, the best single dose for testing the short-term hemodynamic response to hydralazine is not known at present.

Many infants in our study had mild mitral regurgitation, a common feature of atrioventricular canal defects. Vasodilators have been demonstrated to be of benefit in adults with mitral regurgitation because they reduce the impedance to aortic outflow.\textsuperscript{3-8} Hydralazine might provide additional hemodynamic improvement in infants with significant mitral regurgitation by reducing the regurgitant fraction and thereby increasing systemic output. However, the changes in the degree of left-to-right shunting produced by hydralazine cannot be attributed solely to the presence of mitral regurgitation in our patients. We evaluated two infants with no mitral regurgitation but in whom hydralazine reduced the degree of left-to-right shunting. Furthermore, both of the infants in whom the left-to-right shunt did not change had mitral regurgitation. None of the infants we studied showed angiographic evidence of a left ventricular-to-right atrial shunt, which may occur in infants with atrioventricular canal defects. In this situation, a decrease in systemic resistance after hydralazine could conceivably result in significant hypotension because the obligatory shunt might remain fixed and systemic flow may not increase to compensate for the fall in systemic resistance. This point should be considered prior to initiating hydralazine therapy in an infant with an atrioventricular canal defect.

Three infants we studied had patent ductus arteriosus with systemic-to-pulmonary shunting. As with a ventricular septal defect, the magnitude (and direction) of blood flow through the ductus arteriosus is determined by the relative pulmonary and systemic resistances.\textsuperscript{24} Therefore, ductal blood flow should also be decreased by hydralazine, provided systemic resistance falls and pulmonary resistance does not change. Of our three patients with patent ductus arteriosus, two were infants in whom hydralazine did not decrease the percentage of left-to-right shunt. However, it is difficult to accurately assess the relative contributions of ductal and ventricular shunting to the overall left-to-right shunt, and further investigation would be necessary to clarify the effect of patent ductus arteriosus on the response to hydralazine in infants with ventricular left-to-right shunts.

Although confined to an evaluation of the short-term
responses to hydralazine, our results suggest that some infants with congestive heart failure due to complete atrioventricular canal defect may respond favorably to hydralazine therapy. The net response appears to depend on the relative effects of hydralazine on the pulmonary and systemic vascular beds. A fall in systemic vascular resistance with no change in pulmonary vascular resistance will promote a decrease in the systemic-to-pulmonary shunt. Pulmonary blood flow may remain high, but the infant might improve symptomatically because of an increase in systemic output. Thus, in contrast to conventional therapies, hydralazine may provide a more direct approach to improving the hemodynamic status of these infants. However, the effects of hydralazine varied in our study and for this reason, evaluation of the short-term hemodynamic responses may be helpful in selecting those infants who might be more likely to benefit from long-term hydralazine therapy.

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