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

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

SUMMARY To evaluate the effects of acute vasodilator therapy, nitroprusside was administered at cardiac catheterization to five infants (ages 10 days to 6 months) with isolated ventricular septal defect and congestive heart failure. Intravenous nitroprusside was begun at a dose of 0.5 μg/kg/min and was increased by increments of 0.5 μg/kg. Hemodynamic measurements were made before nitroprusside, after 5 minutes at each dose, and 10 minutes after nitroprusside was discontinued. Baseline data were obtained before nitroprusside administration and compared with data obtained at maximal nitroprusside dose. The pulmonary-to-systemic flow ratio increased from 2.2 ± 0.2 to 3.4 ± 0.2 (mean ± SEM, p < 0.05) as a consequence of a marked decrease in systemic blood flow (5.3 ± 0.7 to 3.6 ± 0.51/min/m², p < 0.05). Pulmonary flow did not change significantly. Mean pulmonary capillary wedge and right atrial pressures decreased by 53% (10.2 ± 1.4 to 4.8 ± 1.4 mm Hg [p < 0.01] and 6.0 ± 1.4 to 2.8 ± 1.1 mm Hg [p < 0.05], respectively). Decreases in mean aortic (63.6 ± 3.0 to 54.6 ± 2.1 mm Hg, p < 0.05) and mean pulmonary artery pressure (41.4 ± 6.2 to 32.0 ± 6.7 mm Hg, p < 0.05) were also observed. An apparently paradoxical increase in systemic resistance occurred (11.7 ± 1.6 to 15.4 ± 2.4 U, p < 0.05).

Our data show that nitroprusside causes a marked decrease in systemic blood flow and an increase in the pulmonary-to-systemic flow ratio in infants with a large ventricular septal defect. These findings may be related to the hemodynamic profile of these infants, in whom ventricular function, cardiac output and systemic resistance are normal.

VASODILATOR THERAPY has assumed an important role in the medical management of many cardiovascular disorders. Agents that decrease smooth muscle tone in systemic arterioles, venous capacitance vessels, or both have been shown to produce significant hemodynamic improvement in patients with ischemic heart disease, primary cardiomyopathy, and mitral or aortic valve disease. Although the majority of these studies involved only adults, vasodilators have been used successfully in children who have poor cardiac function postoperatively or due to cardiomyopathy. In addition, experimental animal work has shown that α-blocking agents, by dilating systemic resistance vessels, can diminish the magnitude of left-to-right shunting across a ventricular septal defect (VSD). The present study was designed to evaluate the hemodynamic effects of nitroprusside in infants with a large VSD.

Methods

Five infants, three females and two males, who had a large VSD and congestive heart failure, form the basis of this report. The relevant clinical data are presented in Table 1. The mean age was 2.8 months (range 10 days to 6 months). One patient had Down's syndrome. All patients were in congestive heart failure...
as manifested by tachycardia, tachypnea, hepatomegaly, cardiomegaly and increased pulmonary blood flow on chest x-ray. M-mode echocardiograms documented a mean ratio of left atrial to aortic size of 1.5 ± 0.1, and a left ventricular shortening fraction of 0.35 ± 0.03. Therapy for congestive heart failure, which consisted of digoxin, chlorothiazide and spironolactone, was administered to each patient before catheterization, although not within 12 hours before the study.

Informed consent for participation in this study was obtained. Four infants received chloralhydrate (25 mg/kg) and one received morphine sulphate (0.15 mg/kg) and benadryl (1 mg/kg) for sedation. Routine right- and left-heart catheterization was performed. Once the presence of an isolated large VSD was confirmed, and before angiography, nitroprusside infusion was begun through the proximal port of a #5F double-lumen catheter. The initial dose of 0.5 μg/kg/min was increased by increments of 0.5 μg/kg every 5 minutes until either aortic systolic pressure dropped by 15% or the maximal dose of 2.0 μg/kg/min was reached. Before the nitroprusside infusion, after 5 minutes at each nitroprusside dose, and 10 minutes after the infusion was discontinued the following data were collected: aortic, pulmonary capillary wedge, pulmonary artery, and right atrial pressures; aortic, pulmonary artery, and superior vena cava oxygen saturations; heart rate; and oxygen consumption (using a continuous-flow system19). Control data were measured during the 20 minutes before nitroprusside infusion. Blood flows, shunts and resistances were calculated in accordance with the Fick principle. Finally, left ventricular cineangiography confirmed the presence of a large VSD in each patient. One patient also had a small patent ductus arteriosus.

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

### Results

Before administration of nitroprusside, each infant had hemodynamic data typical of a large VSD. The indexed pulmonary blood flow of 11.4 ± 1.3 1/min/m², and the pulmonary-to-systemic flow ratio of 2.2 ± 0.2 indicate the presence of a large left-to-right shunt. The ratio of right ventricular to left ventricular systolic pressure was 0.83 ± 0.07.

The dose-related effects of nitroprusside on several hemodynamic variables are shown in figure 1. Most values changed gradually and returned toward pre-nitroprusside baseline levels when the infusion was stopped. Significant hemodynamic effects were first observed at an infusion rate of 1 μg/kg/min, which was the maximal dose received by two infants. A further gradual increase to 2 μg/kg/min produced significant hemodynamic changes in the other three infants. Systemic blood flow and pulmonary-to-systemic flow ratio did not improve significantly at any dose. Instead, these variables deteriorated in each infant, although at different nitroprusside doses.

The maximal dose of nitroprusside varied (two patients 1.0 μg/kg/min, three patients 2.0 μg/kg/min), so control data were compared with data obtained at the maximal dose for each patient (table 2). Baseline values before and after nitroprusside infusion were not significantly different, with the exception of pulmonary capillary wedge pressure, which remained slightly decreased after nitroprusside (p < 0.05). Nitroprusside had a significant effect on arterial and venous pressures (fig 2). Aortic mean pressure decreased from 63.6 to 54.6 mm Hg (p < 0.05), while pulmonary artery mean pressure decreased from 41.4 to 32.0 mm Hg (p < 0.05). Left and right ventricular filling pressures also decreased with nitroprusside.

### Table 1. Pertinent Clinical Findings in Infants Receiving Nitroprusside

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (mos)</th>
<th>Diagnosis</th>
<th>Heart rate (beats/min)</th>
<th>Respiratory rate</th>
<th>Liver (cm below RCM)</th>
<th>Cardio-thoracic ratio</th>
<th>Echocardiogram</th>
<th>LV/Ao ratio</th>
<th>RV shortening fraction</th>
<th>Hemoglobin (g%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>VSD PDA (small) CHF</td>
<td>158</td>
<td>78</td>
<td>4</td>
<td>0.64</td>
<td>1.4</td>
<td>0.30</td>
<td>12.8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.3</td>
<td>VSD CHF</td>
<td>150</td>
<td>65</td>
<td>3</td>
<td>0.64</td>
<td>—</td>
<td>—</td>
<td>15.0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6.0</td>
<td>VSD CHF</td>
<td>145</td>
<td>48</td>
<td>4</td>
<td>0.64</td>
<td>1.3</td>
<td>0.44</td>
<td>11.2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5.0</td>
<td>VSD CHF Down's syndrome</td>
<td>140</td>
<td>45</td>
<td>2</td>
<td>0.63</td>
<td>1.4</td>
<td>0.29</td>
<td>11.8</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>VSD CHF</td>
<td>154</td>
<td>50</td>
<td>3</td>
<td>0.63</td>
<td>1.8</td>
<td>0.36</td>
<td>11.5</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SEM: 2.8 ± 1.1 149 ± 3 57 ± 6 3.2 ± 0.4 0.64 ± 0.01 1.5 ± 0.1 0.35 ± 0.03 12.5 ± 0.7

Abbreviations: VSD = ventricular septal defect; PDA = patent ductus arteriosus; CHF = congestive heart failure; LA = left atrium; Ao = aorta; LV = left ventricle; RCM = right costal margin.
**NITROPRUSSIDE AND VSD/Beekman et al. 555**

**FIGURE 1.** The dose-related effects of nitroprusside on several hemodynamic variables in five infants with a large ventricular septal defect. Values are mean ± SEM. The data at 0, 0.5 and 1.0 μg/kg/min are from five infants and at 1.5 and 2.0 μg/kg/min are from three infants (*p < 0.05; **p < 0.01 vs value before nitroprusside). HR = heart rate; AO = mean aortic pressure; PA = mean pulmonary artery pressure; PCW = mean pulmonary capillary wedge pressure; RA = mean right atrial pressure; Qs = systemic blood flow; Qp/Qs = pulmonary-to-systemic flow ratio.

Mean pulmonary capillary wedge and right atrial pressure both declined by 53%, from 10.2 to 4.8 mm Hg (p < 0.01), and from 6.0 to 2.8 mm Hg (p < 0.05), respectively. Figure 3 shows the effect of nitroprusside on systemic and pulmonary blood flows. Systemic blood flow decreased in every patient during nitroprusside infusion. Indexed systemic flow decreased by 32%, from 5.3 to 3.6 l/min/m². Pulmonary blood flow did not change significantly. The pulmonary-to-systemic flow ratio increased in each patient (2.2 to 3.4, p < 0.05). An apparently paradox-

**TABLE 2.** Hemodynamic Effects of Nitroprusside in Five Infants with a Large Ventricular Septal Defect

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before NP</th>
<th>Maximal dose</th>
<th>After NP</th>
</tr>
</thead>
<tbody>
<tr>
<td>AO (mm Hg)</td>
<td>63.6 ± 3.0</td>
<td>54.6 ± 2.1*</td>
<td>63.0 ± 1.8</td>
</tr>
<tr>
<td>PA (mm Hg)</td>
<td>41.4 ± 6.2</td>
<td>32.0 ± 6.7*</td>
<td>39.2 ± 8.1</td>
</tr>
<tr>
<td>PCW (mm Hg)</td>
<td>10.2 ± 1.4</td>
<td>4.8 ± 1.4†</td>
<td>8.4 ± 1.6*</td>
</tr>
<tr>
<td>RA (mm Hg)</td>
<td>6.0 ± 1.4</td>
<td>2.8 ± 1.1*</td>
<td>5.2 ± 1.4</td>
</tr>
<tr>
<td>Qp (l/min/m²)</td>
<td>11.4 ± 1.3</td>
<td>12.2 ± 1.5</td>
<td>9.8 ± 0.8</td>
</tr>
<tr>
<td>Qs (l/min/m²)</td>
<td>5.3 ± 0.7</td>
<td>3.6 ± 0.4*</td>
<td>4.2 ± 0.4</td>
</tr>
<tr>
<td>Qp/Qs ratio</td>
<td>2.2 ± 0.2</td>
<td>3.4 ± 0.2*</td>
<td>2.4 ± 0.2</td>
</tr>
<tr>
<td>Rp (Wood units)</td>
<td>3.1 ± 0.9</td>
<td>2.6 ± 1.0</td>
<td>3.4 ± 1.0</td>
</tr>
<tr>
<td>Rs (Wood units)</td>
<td>11.7 ± 1.6</td>
<td>15.4 ± 2.4*</td>
<td>14.1 ± 1.3</td>
</tr>
<tr>
<td>Rp/Rs</td>
<td>0.26 ± 0.05</td>
<td>0.16 ± 0.03</td>
<td>0.24 ± 0.06</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>140 ± 6</td>
<td>160 ± 4*</td>
<td>138 ± 6</td>
</tr>
<tr>
<td>VO₂ (ml/min/m²)</td>
<td>181 ± 13</td>
<td>170 ± 13</td>
<td>170 ± 13</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
* p < 0.05 vs value before nitroprusside.
† p < 0.01 vs value before nitroprusside.

Abbreviations: NP = nitroprusside; Qp = pulmonary flow; Rp = pulmonary resistance; Rs = systemic resistance; VO₂ = oxygen consumption. See figure 1 for other abbreviations.

**FIGURE 2.** The effect of nitroprusside (NP) on mean aortic (AO), pulmonary artery (PA), pulmonary capillary wedge (PCW) and right atrial (RA) pressures in five infants with a large ventricular septal defect. Values (mean ± SEM) were measured before and at the maximal dose of nitroprusside.
The effect of nitroprusside (NP) on pulmonary blood flow ($Q_p$), systemic blood flow ($Q_s$) and $Q_p/Q_s$ ratio. Values ($mean \pm SEM$) were measured before and at the maximal dose of nitroprusside.

The clinical finding is that systemic resistance increased significantly with nitroprusside, from 11.7 to 15.4 $U$ ($p < 0.05$). Pulmonary resistance did not change, while the decrease in the pulmonary-to-systemic resistance ratio approached statistical significance ($p = 0.07$). The heart rate increased from 140 to 160 beats/min with nitroprusside ($p < 0.05$). Measured oxygen consumption remained unchanged throughout each study.

To determine if the infants studied with nitroprusside were representative of the population of infants with a large VSD, clinical and hemodynamic data were reviewed for all infants with a large VSD and heart failure who were catheterized at this institution between April 1979 and May 1980 (table 3). Premedication, catheterization techniques, and oxygen consumption measurements were as described above. No statistical difference in any clinical or hemodynamic variable was found between the study group and the group of all infants who had a large VSD and congestive failure and were catheterized. It appears, therefore, that the study group adequately represents the larger group of infants with an isolated large VSD.

**Discussion**

This study shows an adverse hemodynamic response to nitroprusside in infants with a large VSD and congestive heart failure in that systemic flow decreases and the pulmonary-to-systemic flow ratio increases significantly. Although right atrial and pulmonary capillary wedge pressures decrease significantly in response to nitroprusside's venodilator effect, pulmonary...
monary blood flow remains elevated while systemic blood flow is depressed. These hemodynamic changes are probably due to increased left-to-right shunting across the VSD, as the pulmonary-to-systemic flow is significantly increased with nitroprusside.

Nitroprusside usually causes a decrease in systemic arterial resistance; however, in these infants an unexpected increase in systemic resistance was observed. Reflex sympathetic vasoconstriction and the marked decrease in systemic flow that occurred with nitroprusside probably explain this apparently paradoxical increase in systemic resistance. The increase in heart rate is additional evidence of increased sympathetic activity, which is probably baroreceptor-mediated in response to the decrease in aortic pressure.

These findings contrast with previous reports on the effects of vasodilator agents in animal and human subjects. Synhorst et al. documented a decrease in left-to-right shunting in response to phentolamine or phenoxybenzamine in dogs with an experimental VSD. These a-blocking drugs have little effect on venous capacitance vessels; in fact, before the experiment, each dog was volume loaded with an equivalent of 20% of its total blood volume. Because the infants in the present study were in congestive failure, no attempt was made to keep ventricular preload constant by means of volume infusion. A decline in ventricular performance during nitroprusside infusion has been well documented in adults with heart failure and is related to relatively low filling pressures. Optimal performance is attained only when ventricular preload is maintained at or just above normal levels. The present data suggest that as ventricular preload and, perhaps performance, decrease in response to nitroprusside, the presence of a large interventricular communication permits a greater portion of the total cardiac output to enter the lower resistance pulmonary circulation. The net effect is to increase the left-to-right-shunt at the expense of systemic blood flow.

Previous work in human subjects has clearly documented hemodynamic improvement with nitroprusside in patients with congestive heart failure. These studies, however, evaluated patients who were characterized by depressed ventricular function, low systemic flow, and elevated systemic resistance. The data in table 3 are consistent with previous reports that suggest that this classic profile of the patient with congestive heart failure may not apply to infants with a large, isolated VSD. These infants, with overt signs and symptoms of heart failure, have normal cardiac indexes and systemic resistance and only mildly elevated left ventricular end-diastolic pressure. In addition, left ventricular shortening fraction is normal or increased, as assessed by echocardiography. Thus, ventricular performance appears to be normal in infants with a large interventricular shunt and congestive failure and, despite clinical similarities, their hemodynamics differ considerably from those of patients with depressed ventricular function. That nitroprusside exerts very different effects in these two groups of patients is, therefore, not surprising. Depressed ventricular performance, low cardiac output and high systemic resistance may be prerequisites of a favorable response to nitroprusside.

In conclusion, nitroprusside exerts adverse hemodynamic effects in infants with a large VSD and congestive failure. It causes a marked decrease in systemic blood flow and an increase in the pulmonary-to-systemic flow ratio. These findings may be related to the hemodynamic profile of these infants, in whom ventricular performance, cardiac output and systemic resistance are normal. Under such circumstances the venodilator action of nitroprusside appears to predominate. Careful maintenance of ventricular preload by means of volume infusion may improve the response of such infants to administration of nitroprusside.

References

Tetralogy of Fallot:
An Angiographic–Pathologic Correlative Study

Benigno Soto, M.D., Albert D. Pacifico, M.D., Ricardo Ceballos, M.D., and Lionel M. Bargeron, Jr., M.D.

SUMMARY  The anatomic abnormalities observed by cineangiographic axial techniques of 12 patients with tetralogy of Fallot were correlated with anatomic details noted at necropsy. Right ventricular angiograms made in the right anterior oblique view best demonstrated the severity and type of infundibular obstruction and also permitted differentiation of the perimembranous, infundibular muscular and subarterial types of ventricular septal defects. The degree of aortic overriding was best displayed in the long-axis view. Comparison of the intracardiac anatomy of each postmortem specimen with the respective premortem cineangiogram has provided further clarification of the angiographic anatomy displayed by these axial techniques.

Ventricular Septal Defect (VSD), dextroposition of the aorta, infundibular stenosis and hypertrophy of the right ventricle were clinically described by Fallot1 in 1888. These cardiac abnormalities form a well-defined entity. Their anatomic characteristics were clarified by Van Rokitansky and further examined by others.2-4 Many angiographic studies of the tetralogy have been published since angiography was developed, and the majority focus on details obtained using standard frontal and lateral projections.5-8 The use of axial projections displays additional anatomic details not seen previously.9 In this report we show the angiographic anatomy of a group of patients with tetralogy of Fallot studied at the University of Alabama Hospitals using axial views and correlate this with the anatomic features seen at necropsy.

Material and Methods

Twelve postmortem specimens of patients with classic tetralogy of Fallot were studied. Each patient had undergone cardiac catheterization and axial angiographic studies a few weeks before death. Each had tetralogy of Fallot with concordant atrioventricular connections, a large VSD in the left ventricular outflow septal area, biventricular origin of the aorta, origin of the pulmonary artery from the right ventricle, infundibular pulmonary stenosis and right ventricular hypertrophy.11

The specimens were selected on the basis of availability of angiographic and anatomic correlation. They had been fixed in formalin and opened in the usual fashion. The right ventricular incision was always extended into the pulmonary artery and the aorta opened from the left ventricle. This allowed clear definition of the VSD and its relation with the arterial and atrioventricular valves from either ventricle. The surgically placed patches were removed in all cases. The amount of infundibular and anterior right muscle wall removed by the surgeons varied from case to case according to the need at operation.

The catheterization had been performed under general anesthesia and angiograms made after obtaining hemodynamic and saturation data. Biplane 35-mm cineangiograms were made with injection of Renografin-76 through a large NIH catheter with side holes. Hand injection was used routinely, although power injection was used in larger patients or when smaller catheters were necessary.

Angiograms were made simultaneously in the long-axis and elongated right anterior oblique views after injection into the right ventricle. Left ventriculo-
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