ACUTE HEMODYNAMIC EFFECTS OF DOPAMINE, DOBUTAMINE, AND ISOPROTERENOL IN CONGESTED INFANTS OR YOUNG CHILDREN WITH LARGE VENTRICULAR SEPTAL DEFECT

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We studied the acute hemodynamic effects of dopamine, dobutamine, and isoproterenol in infants and young children with large ventricular septal defect (VSD). Dopamine (5 μg/kg/min) had no significant hemodynamic effects. Dobutamine (5 μg/kg/min) administration resulted in modest increases in heart rate and systemic arterial pressure and a decrease in left atrial pressure. This drug decreased the pulmonary blood flow, and the pulmonary-to-systemic blood flow (Qp/Qs) ratio, although these changes were not statistically significant. Isoproterenol, infused at doses of 0.03 and 0.06 μg/kg/min, increased the heart rate and lowered left atrial pressure. Only the high dose of isoproterenol lowered systemic and pulmonary arterial pressure. The low dose infusion of this drug increased the pulmonary blood flow as well as the systemic flow, whereas the high dose infusion resulted in a decrease of the Qp/Qs ratio without an increase in the pulmonary blood flow. Right atrial pressure was lowered by dobutamine and the high dose of isoproterenol, but the mean change was only 1 to 2 mmHg. The difference of the effects among these catecholamines is due to their relative strength of action on the vascular bed and the myocardium. Although the doses and durations of the drug infusions were limited, these acute hemodynamic effects should be taken into account when they are to be given to congested infants and young children with large VSD.

Patients with large ventricular septal defect (VSD) present with clinical findings of congestive heart failure during early infancy. It has been generally believed that their signs and symptoms are mainly due to depressed ventricular function. Accordingly, such infants have been treated with digitalis because it has a positive inotropic effect. Recently, Berman et al. reported that digitalis did not necessarily improve left ventricular pump function even in patients who showed clinical improvement with this drug. White and Lietman published a commentary that “heart failure” in large VSD might not result from myocardial depression but might be due primarily to volume overload on the heart and lung. In fact, hemodynamic improvement was achieved by an afterload-reducing drug, hydralazine, which does not have a significant inotropic action. Thus, it is not clear whether positive inotropic drugs improve the congested state due to large VSD. Yet, catecholamines are

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often given for very severe cases to improve the hemodynamic state. However, the hemodynamic effects of catecholamines on large VSD have not been investigated precisely. Therefore, we studied the acute effects of dopamine, dobutamine, and isoproterenol in infants or young children with large VSD.

SUBJECTS AND METHODS

The subjects of this study were 16 patients with isolated VSD. The patients' ages ranged from 1 to 21 months with a mean of 8 ± 4 (SD) months, and 13 were less than 12 months old. All patients had been hospitalized for determination of operative indication because of poor weight gain, frequent respiratory infection, pulmonary hypertension, or other symptoms of intractable heart failure. All of them were on digitalis and 13 were also on diuretics (Table I). Informed consent was obtained for each patient before the study was started. All patients received pethidine HCl, 1 mg/kg, and hydroxyzine pamoate, 1 mg/kg, 30 minutes before the study. Right and left heart catheterization was done before and during infusion of dopamine (5 μg/kg/min), dobutamine (5 μg/kg/min), or isoproterenol (0.03 and 0.06 μg/kg/min). Oxygen consumption was measured by the flow-through method. Systemic and pulmonary blood flows (Qs and Qp, respectively) were obtained by the Fick method, then systemic and pulmonary vascular resistances were calculated and expressed in units normalized by body surface area (units·m² = mmHg/liter/min/m²).

Infusion of the catecholamines were continued for 5 to 10 minutes before we started data collection. In 9 patients, dopamine and dobutamine were given in an alternate manner where by one was started 10 or more minutes after the other was completely stopped. In the remaining 7 patients, isoproterenol was infused at the rate of 0.03 and 0.06 μg/kg/min, though in one patient data for the high dose infusion were not obtained because the baby cried during the procedure. At each rate, 5 or more minutes were allowed for stabilization before data collection. Clinical and basic hemodynamic data for the two groups did not differ (Table I). During the study, arrhythmias were evoked in only one of the patients in whom infrequent premature ventricular contractions were induced by dobutamine.

Data were analysed by the Student t test. All
values were expressed as mean ± SD. Statistical significance was accepted when p-value was less than 0.05.

RESULTS

Mean heart rate was increased by isoproterenol (+23 ± 16% for 0.03 µg/kg/min and +36 ± 23% for 0.06 µg/kg/min), but was not altered by dopamine. The increase in heart rate by dobutamine was very small (+6 ± 9%).

Mean systemic and pulmonary arterial pressure were altered only by the high dose of isoproterenol (−11 ± 7% and −31 ± 17%, respectively). Left atrial pressure decreased with dobutamine (−2 ± 1 mmHg) and isoproterenol (−3 ± 3 mmHg and −5 ± 2 mmHg for the high and low doses, respectively), but not with dopamine (Fig. 1).

Dopamine had no effect on systemic or pulmonary vascular resistance, systemic or pulmonary blood flow, or the pulmonary-to-systemic blood flow (Qp/Qs) ratio. On the dobutamine infusion, pulmonary blood flow changed from 9.0 ± 2.1 liter/min/m² to 8.0 ± 2.2 liter/min/m² and the Qp/Qs ratio from 3.2 ± 0.2 to 2.9 ± 0.4 (0.1 > p > 0.05) (Table II). Isoproterenol infusion resulted in a decrease in systemic vascular resistance (−30 ± 26% and −36 ± 9% for the low and high doses, respectively), and in an increase in systemic blood flow (+59 ± 57% and +42 ± 14% for the low and high doses, respectively). The low dose of isoproterenol decreased pulmonary vascular resistance by 29 ± 34% and increased pulmonary blood flow by 25 ± 34%, but the high dose did not bring about statistically significant changes of these parameters from the control. The Qp/Qs ratio was reduced from 3.4 ± 0.4 to 2.4 ± 0.8 by isoproterenol at 0.06 µg/kg/min (Table II).

DISCUSSION

The acute hemodynamic effects were different among the catecholamines used in large VSD. Dopamine had almost no effect. Matsuoka et al. demonstrated that there were no significant hemodynamic effects when dopamine was given at 5 µg/kg/min on an experimental model of VSD, but with higher doses, they showed an increase in cardiac output. This indicated that significant effects might have been induced with higher doses in the present subjects, although these were not allowed technically. Dobutamine had only modest effects which included an elevation in systemic arterial pressure, a reduction in
right and left atrial pressure, and a reduction in pulmonary blood flow and the Qp/Qs ratio. These results were quite similar to the experimental data reported by Matsuoka et al. On the other hand, isoproterenol showed remarkable effects; one favorable effect was that the high-dose infusion resulted in an increase in systemic blood flow without an increase in pulmonary blood flow, accompanied by a reduction in right and left atrial pressure.

Driscoll et al. reported that dopamine and dobutamine were effective in the treatment of heart failure or cardiogenic shock and the doses they used were similar to ours. Experimental studies have shown that the inotropic action of these two drugs is less prominent in the newborn than in mature subjects. Clinically, there are reports suggesting that the hemodynamic effects of dopamine and dobutamine are less in patients younger than 12 months than in older patients. These studies have indicated that the catecholamine treatment could be less effective in very young subjects. The subjects of the present study did not include newborns and we did not find any age difference in the hemodynamic response, which led us to believe that there must be other mechanisms to explain the lack of marked effects of dopamine and dobutamine in these patients.

In previous studies, the effectiveness of these two catecholamines was evaluated in non-shunt cardiac problems, in which the cause of congested state resulted primarily from myocardial failure. In contrast, in the case of large VSD, the congested state might not be primarily due to cardiac dysfunction but may well be secondary to volume and pressure overload on the heart and lung. The degree of volume overload is determined by the amount of left-to-right shunt which, in turn, is determined by the ratio of pulmonary-to-systemic vascular resistance in a large and non-restricted VSD. Dobutamine in a low dose and dopamine have an alpha-stimulating action. This vascular effect impedes an increase in systemic blood flow and increases the amount of ventricular shunt, which are disadvantageous. Therefore, it was possible that the positive inotropic effect of these drugs was masked by their alpha-stimulating action.

Isoproterenol is a potent agonist of beta 1 and 2 receptors. The experimental study of Robie et al. showed that isoproterenol at a dose that was 1/180 that of dobutamine had the same

<p>| TABLE II | HEMODYNAMIC EFFECTS OF DOPAMINE, DOBUTAMINE AND ISOPTROTERENOL IN LARGE VENTRICULAR SEPTAL DEFECT |
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<table>
<thead>
<tr>
<th></th>
<th>Qp/Qs ratio</th>
<th>Qp (L/min/m2)</th>
<th>Qs (L/min/m2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>control</strong></td>
<td><strong>response</strong></td>
<td><strong>control</strong></td>
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<td>response</td>
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<tr>
<td><strong>Dopamine</strong></td>
<td><strong>control</strong></td>
<td><strong>response</strong></td>
<td><strong>control</strong></td>
</tr>
<tr>
<td>(n = 9)</td>
<td>3.1 ± 0.5</td>
<td>2.9 ± 0.4</td>
<td>3.2 ± 0.8</td>
</tr>
<tr>
<td><strong>Dobutamine</strong></td>
<td>8.7 ± 2.2</td>
<td>8.0 ± 2.2</td>
<td>10.4 ± 2.0*</td>
</tr>
<tr>
<td>(n = 7)</td>
<td>3.4 ± 0.4</td>
<td>3.4 ± 0.4</td>
<td>2.4 ± 0.8*</td>
</tr>
<tr>
<td><strong>Isoproterenol</strong></td>
<td><strong>control</strong></td>
<td><strong>response</strong></td>
<td><strong>control</strong></td>
</tr>
<tr>
<td>(0.03* g)</td>
<td>2.9 ± 0.6</td>
<td>2.8 ± 0.6</td>
<td>2.9 ± 0.8*</td>
</tr>
<tr>
<td>(n = 7)</td>
<td>3.7 ± 0.7*</td>
<td>3.7 ± 0.7*</td>
<td>3.7 ± 0.8*</td>
</tr>
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Abbreviations: PVR = pulmonary vascular resistance; Qp = pulmonary blood flow; Qs = systemic blood flow; *: micrograms/kg/min; p < 0.05 vs control. Mean ± SD

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vascular effect as the latter drug and a dose that was 1/43 that of dobutamine had the same positive inotropic effect. This has indicated that isoproterenol has a relatively greater effect on the vascular system than on the myocardium, and that, with the dose used in the present study, its positive inotropic effect should have been less than that of dobutamine. Thus, the potent vasodilating action of isoproterenol was possibly the major mechanism of the effect shown in the present study. The hemodynamic effect, observed in the present study, was qualitatively the same as the results of an experimental study of Nakatsu et al.20

It should be noted that the present results of acute response can not be extrapolated directly to chronic effects in the management of these congested patients. In addition, it is also known that dopamine and dobutamine have different actions with different doses. These problems need to be clarified, but there are obvious technical and ethical limitations to the research that can be conducted in the human subject. Nevertheless, the present study indicated that these catecholamines did not necessarily bring about favorable acute hemodynamic effects, but that they could act adversely by increasing pulmonary blood flow and heart rate. The tachycardia due to isoproterenol infusion could possibly cause myocardial ischemia by excessive ventricular work with the lowered coronary perfusion pressure, although we have not experienced any electrocardiographic evidence of it.

The present study thus suggests the clinical applications of these catecholamines. Dopamine is not the drug of choice in infants with large ventricular shunt, although its selective effect on renal circulation may be helpful when diuresis is not sufficient by other diuretic agents. Dobutamine may be used in patients with severe systemic and/or pulmonary congestion because it lowers atrial pressures, but nitroprusside or other nitrous agents are clearly superior for that purpose.21-23 Isoproterenol is the most favorable among the drugs tested, thus it is the drug of choice for treatment of congested infants with large ventricular septal defect unless the patient is not hypotensive and its electrophysiologic effect does not become adverse.

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