LABORATORY INVESTIGATION
CONGENITAL HEART DISEASE

Comparative circulatory effects of isoproterenol, dopamine, and dobutamine in conscious lambs with and without aortopulmonary left-to-right shunts

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ABSTRACT We studied the effect on the circulation of the catecholamines isoproterenol, dopamine, and dobutamine in chronically instrumented lambs with aortopulmonary left-to-right shunts (ages 11 to 87 days) and without shunts (ages 8 to 97 days). Infusion of 0.1 μg/kg/min isoproterenol or 10 μg/kg/min dobutamine markedly increased heart rate and systemic and pulmonary blood flows, while stroke volume and the left-to-right shunt flow did not change. Since pulmonary blood flow increased and the left-to-right shunt flow did not change, the left-to-right shunt fraction decreased with the infusions of isoproterenol and dobutamine. The hemodynamic changes during the infusion of isoproterenol and dobutamine occurred immediately after the start of infusion and stabilized within a few minutes. The pattern of hemodynamic changes was not influenced by the presence of an aortopulmonary left-to-right shunt or by age. Infusion of 10 μg/kg/min dopamine caused only small hemodynamic changes. This study shows that heart rate and systemic blood flow in the lamb are closely related. Furthermore, it demonstrates that despite an increased systemic blood flow, left-to-right shunt flow does not change after infusion of isoproterenol and dobutamine. Any decision as to which positive inotropic agent might be preferred at an early age should await experimental work concerning the effect of these agents on the myocardial oxygen demand and on the distribution of the systemic blood flow. Circulation 75, No. 6, 1222–1228, 1987.

CATECHOLAMINES are potent positive inotropic agents and are therefore often used temporarily in the management of cardiovascular dysfunction in children and adults. In adults, dobutamine and dopamine are considered superior to isoproterenol in the treatment of cardiogenic shock because, unlike isoproterenol, they do not elicit significant chronotropic or peripheral vascular responses.1-3 It is questionable, however, whether the same would apply to younger patients, since their heart rates might have a greater potential effect on left ventricular output than the other three determinants of myocardial performance: contractility, preload, and afterload.4 Moreover, isolated heart preparations have shown that the inotropic response to dopamine in perfused ventricles increased with advancing age in contrast to the response to isoproterenol, which was equal at all ages.5,6

Not only these age-related differences but also the different response of newborn and adult vessels to adrenergic stimuli7 suggest that different catecholamines should be used in children and adults. Therefore we infused dobutamine, dopamine, and isoproterenol into conscious lambs with and without aortopulmonary left-to-right shunts. Little is known about the hemodynamic effects of catecholamines in the presence of a left-to-right shunt lesion8 despite the fact that these lesions are the most common of all congenital heart diseases and often result in circulatory congestion, for which proper treatment should be instituted.

The objectives of this study were to compare the hemodynamic changes caused by the infusion of dopamine, dobutamine, and isoproterenol into conscious lambs with and without aortopulmonary left-to-right shunts to establish differences in changes between the

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two groups and to examine the changes in pulmonary and systemic blood flows in the lambs with shunts. Because of its chronotropic effect, we expected isoproterenol to be superior in increasing systemic blood flow.

Materials and methods

Thirty-four lambs of mixed breed with documented dates of birth were studied. They were divided into two groups of 17 lambs each, one group with aortopulmonary left-to-right shunts and the other without shunts. On the day of the study the lambs with shunts ranged in age from 11 to 87 days and the control lambs from 8 to 97 days. Between surgery and the day of the study, lambs younger than 60 days remained with their mothers.

Surgical procedures. Anesthesia was induced by inhalation of 2% to 3% halothane in oxygen. The lamb was intubated with a cuffed endotracheal tube, placed on a warming pad, and ventilated with 0.5% to 1.0% halothane in oxygen by an Engström intermittent positive-pressure respiratory pump. Analgesia was maintained with 2 mg/kg/mipirritamide. By sterile techniques, a left thoracotomy was performed in the third or fourth intercostal space. Polyvinyl catheters (id 1.0 mm, od 1.5 mm) were passed from the internal thoracic artery and vein into the aorta and superior vena cava, respectively. The pericardium was incised over the main pulmonary artery to within 2 to 3 mm of the vagus nerve. A Goretex conduit (id 6 or 8 mm) was saturated between aorta and main pulmonary artery. Through purse-string sutures catheters were inserted into the right ventricle, pulmonary artery, and left atrium. Precalibrated electromagnetic flow transducers with an internal diameter of 10 to 15 mm (Skalar Medical, Delft, The Netherlands) were applied around the ascending aorta just above the coronary arteries and around the main pulmonary artery proximal to the conduit. A No. 8F polyvinyl catheter was placed in the left pleural cavity for chest drainage. The control lambs were instrumented in the same way, except for the conduit, the right ventricular catheter, and the flow transducer around the aorta. All vascular catheters were filled with heparin, led to the lamb’s left flank together with the chest tube and the flow transducer cable(s), and protected by a Teflon cloth pouch sewn to the skin. The chest was closed in layers to minimize the risk of air leakage. Measurements were started 4 days after surgery to allow normal cardiovascular function to return.

Experimental protocols. The lambs were allowed to feed until 2 hr before the measurements. At that time they were weighed and placed in a canvas sling, which supported them in the upright position. Data were collected only when the lambs were calm and resting. In the lambs with shunts, pulmonary and systemic blood flows were measured continuously during the experiments with the electromagnetic flow transducers around the aorta and pulmonary artery, respectively. Since the aortic flow transducer was applied above the coronary arteries, it measured pulmonary minus coronary blood flow. In the lambs without shunts, only pulmonary blood flow was measured with the flow transducer around the pulmonary artery. In both groups we measured aortic, pulmonary arterial, left atrial, and central venous pressures every 5 min. Since ambient temperature influences oxygen consumption and cardiovascular function both at rest and during stress, ambient temperature was kept constant between 22° and 23° C.

After taking measurements for 30 min, we infused 0.1 μg/kg/min isoproterenol into 17 lambs of each group, 10 μg/kg/min dopamine into 15 shunt and 13 control lambs, and 10 μg/kg/min dobutamine into 16 shunt and 10 control lambs. The drugs were infused on different days, with at least 1 day in between, during a 1 hr period. At the end of the infusion the measurements were continued for another 30 min.

Measurements and calculations. Aortic, pulmonary arterial, left atrial and systemic venous pressures were measured with Gould P23 ID pressure transducers referenced to atmospheric pressure with zero obtained at mid-chest position. The precalibrated electromagnetic flow transducers were connected to Skalar MDL 400 flowmeters. By application of the electromagnetic flow transducer around the pulmonary artery as proximal as possible to the pulmonary valves, the zero flow during diastole in the lambs with aortopulmonary left-to-right shunts was not disturbed by the left-to-right shunt through the conduit. Heart rate was obtained from a flow probe with the aid of a cardiotachometer. All variables were recorded on an Elema Mingograf 800 ink-jet recorder. The left-to-right shunt flow was calculated by subtracting systemic from pulmonary blood flow, whereas the left-to-right shunt fraction was obtained by dividing shunt flow by pulmonary blood flow.

Statistical analysis. Results are expressed as mean ± SE. Each separate variable was analyzed statistically. Two-way analysis of variance with replication and unequal sample sizes was done within each group to test the response to drug infusion, the effect of the different drugs used, and their interaction.11 The same analysis with equal or unequal sample sizes was done with data from shunt and control lambs to test the response to each drug, the effect of the presence of the shunt, and their interaction. If analysis of variance revealed significant differences, the Newman-Keuls test was used to localize these differences.12 A p value < .05 was considered significant.

Results

Preinfusion hemodynamic values in the lambs with shunts and in the control lambs are shown in table 1. Within each group there were no significant differences between the values obtained before the infusion of isoproterenol, dopamine, or dobutamine. Between the groups some resting cardiovascular variables were significantly different. Thus pulmonary blood flow, left ventricular stroke volume, pulmonary arterial and left atrial pressures were higher, whereas effective stroke volume was lower in the shunt lambs. Furthermore, heart rate was significantly higher and pulmonary vascular resistance was lower in the shunt lambs. This, however, was not true for heart rate before the infusion of dopamine and for pulmonary resistance before dobutamine.

Since the responses to isoproterenol, dopamine, and dobutamine were not dependent on age in the shunt as well as in the control lambs, the data within these two groups were pooled. The time sequence of the responses to isoproterenol, dopamine, and dobutamine was similar in the two groups (figures 1 to 3).

Isoproterenol. Shortly after the onset of infusion there was a marked increase in systemic blood flow and heart rate. Within 5 min both variables stabilized at this higher level until the end of the infusion period (figure 1). Since systemic blood flow and heart rate increased proportionally, the effective stroke volume remained the same. Systemic vascular resistance de-
creased significantly (table 1) in both groups. Left atrial pressure also decreased but only significantly so in the lambs with shunts. The absolute increases in systemic and pulmonary blood flows were similar among these animals. Thus left-to-right shunt flow remained the same, while the left-to-right shunt fraction decreased. At corresponding times before and during the infusion of isoproterenol, pulmonary blood flow, left ventricular stroke volume, pulmonary arterial pressure and left atrial pressure were significantly higher in the animals with shunts than in the control lambs, whereas the pulmonary vascular resistance was lower in the lambs with shunts. After the infusion of isoproterenol all hemodynamic variables returned to their preinfusion values.

**Dopamine.** After the onset of infusion there were moderate hemodynamic changes in both groups (figure 2). None of these changes was significant, however. At corresponding times before and during infusion of dopamine, the pulmonary blood flow, left ventricular stroke volume, and left atrial pressure were significantly higher in the lambs with shunts, whereas the effective stroke volume and the pulmonary vascular resistance were lower than in the control lambs (table 1).

In both groups, at 60 min after the start of the infusion, the heart rate and the systemic and pulmonary blood flows were significantly lower than at the corresponding time during infusion of isoproterenol, whereas in the control lambs the left ventricular stroke volume and systemic resistance were higher.

**Dobutamine.** The hemodynamic effects of dobutamine were similar to those of isoproterenol (figure 3). Systemic and pulmonary blood flows and heart rate increased significantly, whereas effective stroke volume did not change (figure 3, table 1). However, it took about 5 min more than during infusion of isoproterenol before these levels were reached, which from then on were maintained until the end of the infusion period. The changes were smaller than during infusion.

### Table 1

<table>
<thead>
<tr>
<th>Preinfusion</th>
<th>Isoproterenol (60 min)</th>
<th>Preinfusion</th>
<th>Dopamine (60 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S C</td>
<td>S C</td>
<td>S C</td>
</tr>
<tr>
<td>n</td>
<td>17 17</td>
<td>15 13</td>
<td>15 13</td>
</tr>
<tr>
<td>Age at study (days)</td>
<td>43 ± 5 49 ± 3</td>
<td>44 ± 5 55 ± 6</td>
<td>166 ± 9C 137 ± 15C</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>14.3 ± 0.5 14.2 ± 0.4</td>
<td>14.7 ± 1.1 14.3 ± 1.6</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>177 ± 8 146 ± 13A</td>
<td>272 ± 4B 260 ± 7B</td>
<td>172 ± 10 141 ± 16</td>
</tr>
<tr>
<td>Systemic blood flow (ml/min/kg)</td>
<td>145 ± 11 149 ± 9</td>
<td>222 ± 13B 227 ± 12B</td>
<td>136 ± 9 135 ± 10</td>
</tr>
<tr>
<td>Pulmonary blood flow (ml/min/kg)</td>
<td>274 ± 17 149 ± 9B</td>
<td>364 ± 20B 227 ± 12A, B</td>
<td>266 ± 17 135 ± 10A</td>
</tr>
<tr>
<td>Left-to-right shunt flow (ml/min/kg)</td>
<td>129 ± 11 141 ± 12</td>
<td>129 ± 14 121 ± 10</td>
<td></td>
</tr>
<tr>
<td>Left ventricular stroke volume (ml/kg)</td>
<td>1.56 ± 0.07 1.08 ± 0.07A</td>
<td>1.36 ± 0.07 0.90 ± 0.05A</td>
<td>1.63 ± 0.10 1.03 ± 0.06A</td>
</tr>
<tr>
<td>Effective stroke volume (ml/kg)</td>
<td>0.82 ± 0.04 1.08 ± 0.07A</td>
<td>0.82 ± 0.04 0.90 ± 0.05</td>
<td>0.80 ± 0.04 1.03 ± 0.06A</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>72 ± 2 78 ± 2</td>
<td>73 ± 2 81 ± 2</td>
<td>68 ± 2 78 ± 2</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mm Hg)</td>
<td>27 ± 1 19 ± 1A</td>
<td>24 ± 1 20 ± 1A</td>
<td>27 ± 2 20 ± 2A</td>
</tr>
<tr>
<td>Mean left atrial pressure (mm Hg)</td>
<td>14 ± 1 7 ± 2A</td>
<td>11 ± 1B 5 ± 2A</td>
<td>15 ± 1 7 ± 1A</td>
</tr>
<tr>
<td>Systemic resistance (mm Hg/l/min/kg)</td>
<td>472 ± 36 508 ± 32</td>
<td>305 ± 19B 349 ± 22B</td>
<td>458 ± 32 562 ± 36</td>
</tr>
<tr>
<td>Pulmonary resistance (mm Hg/l/min/kg)</td>
<td>51 ± 7 88 ± 12A</td>
<td>37 ± 5 70 ± 8A</td>
<td>52 ± 8 94 ± 12A</td>
</tr>
<tr>
<td>Left-to-right shunt percentage</td>
<td>47 ± 2 39 ± 2B</td>
<td>48 ± 3 44 ± 2</td>
<td></td>
</tr>
</tbody>
</table>

S = lambs with aortopulmonary left-to-right shunts; C = control lambs.

Two-way analysis of variance with replication and (un)equal samples and the Newman-Keuls test using rank sums:

A p < .05 vs shunt lambs; B p < .05 vs preinfusion value; C p < .05 vs corresponding time during isoproterenol infusion; 1B p < .05 vs corresponding time during dopamine infusion.
of saline results in only a moderate increase in systemic blood flow in the lamb as compared with the adult sheep,\textsuperscript{16, 17} whereas afterload reduction by infusion of sodium nitroprusside does not increase the systemic blood flow in the young lamb.\textsuperscript{18} Heart rate, on the other hand, may be the most important factor determining cardiac output at an early age and especially in the neonate.\textsuperscript{4, 13} Because of its chronotropic effect, we therefore expected isoproterenol to be superior to dobutamine and dopamine in increasing systemic blood flow.

In this study systemic blood flow increased substantially during infusion of isoproterenol and dobutamine. In both instances the increases were proportional to the increases in heart rate. Dobutamine was originally advocated to treat heart failure in adults because of its

| TABLE 1  |
|---|---|---|---|
| Preinfusion | Dobutamine (60 min) |
| | S | C | S | C |
| 16 | 10 | 16 | 10 |
| 41 ± 4 | 51 ± 8 | 243 ± 7\textsuperscript{B,D} | 248 ± 17\textsuperscript{B,D} |
| 13.9 ± 0.6 | 15.8 ± 1.8 | 149 ± 18\textsuperscript{A} | 143 ± 12 |
| 186 ± 9 | 258 ± 149 | 175 ± 13\textsuperscript{B} | 198 ± 14\textsuperscript{B,C} |
| 130 ± 11 | 186 ± 10 | 310 ± 19\textsuperscript{B,C} | 198 ± 14\textsuperscript{A,B,C,D} |
| 258 ± 17 | 128 ± 10 | 135 ± 13 |
| 1.41 ± 0.08 | 1.02 ± 0.08\textsuperscript{A} | 1.27 ± 0.07 | 0.83 ± 0.07\textsuperscript{A} |
| 0.71 ± 0.06 | 1.02 ± 0.08\textsuperscript{A} | 0.72 ± 0.05\textsuperscript{D} | 0.83 ± 0.07 |
| 68 ± 2 | 75 ± 2 | 68 ± 2 | 81 ± 3 |
| 28 ± 2 | 18 ± 1\textsuperscript{A} | 26 ± 2 | 18 ± 1\textsuperscript{A} |
| 13 ± 1 | 8 ± 1\textsuperscript{A} | 11 ± 1 | 6 ± 1\textsuperscript{A} |
| 404 ± 67 | 514 ± 46 | 300 ± 47 | 403 ± 31\textsuperscript{C} |
| 48 ± 9 | 80 ± 11 | 41 ± 7 | 69 ± 10 |
| 50 ± 3 | 43 ± 3 |

Discussion

In the perinatal period, changes in heart rate probably affect systemic blood flow more than changes in the other three determinants of myocardial performance.\textsuperscript{4, 13} Recently it has been shown that the newborn lamb has a limited reserve in contractility, which increases progressively with age.\textsuperscript{19} This is in agreement with the finding that the response to digoxin is blunted in the newborn as compared with the adult sheep.\textsuperscript{15} Moreover, an increase of the preload by rapid infusion

FIGURE 1. Sequential effects of a 1 hr infusion of 0.1 \( \mu \)g/kg/min isoproterenol, followed by a 0.5 hr recovery period, on heart rate, systemic blood flow, and effective left ventricular stroke volume in animals with shunts (○) and in control lambs (●) and on left-to-right shunt flow (□). Data are expressed as mean ± SE.
with data obtained in the newborn lamb during an infusion of dopamine of comparable concentration.4

Stroke volume remained constant during all three infusions in both groups of lambs in spite of the positive inotropic effects of the catecholamines infused and the tendency toward a decrease in afterload during the infusion of isoproterenol and dobutamine (table 1). However, since left atrial pressure decreased with infusion of catecholamines, it is likely that a possible increase in stroke volume as a consequence of an increased contractility and decreased afterload is neutralized by a decreased preload.

On the whole, the hemodynamic response to dopamine was poor. Recent studies have shown that the availability of releasable norepinephrine in isolated ventricular myocardium of puppies3 is lower than that

moderate chronotropic effects.19-21 In children, increased22 and unchanged heart rates23 have been reported during the infusion of dobutamine; increased heart rates, however, are more common. Our results demonstrate that heart rate increases substantially during infusion of dobutamine. The cause of the difference in chronotropic effects of dobutamine is unclear. The findings in humans suggest age-related differences. In the lambs, however, the hemodynamic responses to the infused drugs were quite uniform in the age range studied. The differences in chronotropic effects seen in humans and lambs could be related to species differences in adrenoceptor type, number, or sensitivity.20, 21, 24, 25

In contrast to isoproterenol and dobutamine, dopamine had no effect on heart rate. This is in agreement

FIGURE 2. Sequential effects of a 1 hr infusion of 10 μg/kg/min dopamine, followed by a 0.5 hr recovery period, on heart rate, systemic blood flow, and effective left ventricular stroke volume in animals with shunts (○) and in control lambs (□) and on left-to-right shunt flow (□). Data are expressed as mean ± SE.
in adult tissue. This augments the possibility that the dopamine response is attenuated in newborns but does not explain why uniformly moderate hemodynamic responses to dopamine were observed in all lambs in our studies, even though the lambs varied in age from 8 to 97 days. Moreover, the intact cardiovascular system was reported to be responsive to dopamine even in puppies. It should be kept in mind that the mode of action of dopamine is complex in the intact receptor because of the different types of receptors mediating dopaminergic responses, including adrenoceptors of the α- and β-types. In addition, the circulatory effects of dopamine are dose dependent. The dose used in our study was chosen because it is also applied clinically and because doses higher than 15 μg/kg/min are believed to produce predominantly α-adrenergic effects. The increases in pulmonary and systemic blood flow during the infusion of isoproterenol and dobutamine were such that the left-to-right shunt flow did not change significantly. On the one hand this is not surprising, since the pressure difference between aorta and pulmonary artery did not change either. On the other hand, this is contrary to the increase that could be expected as a consequence of the increase in heart rate during both infusions. Such an increase would expand the total systolic time during which most of the shunt flow might occur as a consequence of the largest pressure difference between aorta and pulmonary artery being present during this part of the cardiac cycle. It is possible that, despite the increased total systolic time, the left-to-right shunt flow did not increase because an increased turbulence during the tachycardia effectively increased the resistance across the conduit. The percentage of blood flow shunting from left to right tended to decrease during the infusion of all three catecholamines. This does not imply that the severity of the left-to-right shunt decreased, since there was no change in left-to-right shunt flow. The severity of a shunt may therefore be more appropriately expressed by actual flows rather than by the flow ratio. The increased systemic blood flow during infusion of isoproterenol and dobutamine is not necessarily a hemodynamic improvement, since the flow distribution may also change. Although part of the increase in cardiac output by dobutamine was shown to be diverted to the coronary vascular bed, this drug tended to cause a redistribution of cardiac output favoring the muscular beds at the expense of the kidney and visceral beds. Isoproterenol was also reported to dilate skeletal muscle vessels, thus an important part of the extra systemic blood flow may have been diverted to muscle tissue. In addition, as discussed above, the increase in systemic blood flow is probably mainly caused by the increased heart rate. Heart rate is also one of the important factors determining myocardial oxygen consumption, and therefore the infusion of these catecholamines into lambs with shunts, in which an increased heart rate is already present under resting conditions, may further increase myocardial oxygen demands, thus enhancing the risk of an imbalance between oxygen supply and demand. However, depending on the catecholamine, the infusion results not only in an increase in heart rate but also in a decrease of preload and afterload, which will decrease wall stress and therefore myocardial oxygen consumption.

In conclusion, our results provide evidence that (1) heart rate is a predominant factor in determining systemic blood flow in lambs, (2) the hemodynamic responses to isoproterenol, dopamine, and dobutamine are similar in lambs with and without left-to-right shunts, and (3) both isoproterenol and dobutamine are suitable to increase systemic blood flow in animals with shunts and in control lambs, but these agents leave the left-to-right shunt flow unchanged.

The present data do not yet favor any of the three inotropic agents for use at an early age. More experimental work has to be done to determine how the increase in systemic blood flow is distributed over the different vascular beds and what the consequences of the infusion of these catecholamines are for myocardial oxygen consumption.

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References

9. Sidi D, Kuipers JRG, Heymann MA, Rudolph AM: Recovery of
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