The Effect of Alpha-Adrenergic Blockade on the Pulmonary Vascular Response to Dopamine in Neonatal Lambs

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Summary

The effect of alpha-adrenergic blockade by phentolamine on the pulmonary vascular response to dopamine was studied in chronically prepared newborn lambs. Dopamine was administered at doses of $2.7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, $27 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and $270 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ with and without alpha-adrenergic blockade. Dopamine infusion at $270 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ caused a rise in the mean pulmonary artery pressure from 22 ± 3.2 mmHg (mean $\pm$ S.E.) at baseline to 36 ± 4.1 mmHg ($P < 0.001$). This rise was unaffected by alpha-adrenergic blockade. Dopamine infusion alone did not change pulmonary blood flow, but, in the presence of alpha-adrenergic blockade, pulmonary blood flow rose from $190 \pm 12 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ at baseline to $280 \pm 13 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ at the maximum dopamine infusion rate ($P < 0.001$). Pulmonary vascular resistance was the same before and after alpha-adrenergic blockade and did not change from the baseline value during dopamine infusion.

Abbreviations

LAP, mean left atrial pressure

N.S., not significant

PAP, mean pulmonary artery pressure

PVR, pulmonary vascular resistance

QP, pulmonary blood flow

SAP, mean systemic arterial pressure

Neonates often have increased pulmonary vascular resistance and systemic hypotension complicating hyaline membrane disease, perinatal asphyxia, meconium aspiration syndrome, and diaphragmatic hernia. Dopamine has recently been used to improve systemic arterial pressure in newborns with pulmonary vasospasm (2, 5, 6, 11). Dopamine increases pulmonary artery pressure, presumably through alpha-adrenergic vasoconstriction (15). For this reason, some investigators have advised caution in the use of dopamine in patients with elevated pulmonary vascular resistance (3, 13).

For treatment of patients with elevated pulmonary vascular resistance, it would be beneficial if the alpha-adrenergic mediated pulmonary vasoconstriction could be eliminated while maintaining dopamine's positive inotropic cardiac effect and the renal and mesenteric vasodilating action. An alpha-adrenergic blocking agent such as phentolamine in combination with dopamine might offer a therapeutic advantage to neonates with pulmonary vasoconstriction and systemic hypoperfusion. To test this hypothesis, we studied the effect of alpha-adrenergic blockade on the response to dopamine in the pulmonary and systemic circulations of chronically prepared newborn lambs.

MATERIALS AND METHODS

Six lambs underwent surgery at ages 1-6 days using halothane anesthesia. Catheters were placed in hind leg vessels and advanced

into the abdominal aorta and inferior vena cava. Through a left thoracotomy, the ductus arteriosus was ligated and a pre-calibrated electromagnetic flow probe (C & C Instruments, Culver City, CA, and Howell Instruments, Camarillo, CA) was placed around the main pulmonary artery. Catheters were placed by direct puncture in the left atrium and in the main pulmonary artery distal to the flow probe. All catheter ends and the flow probe cable were exteriorized to the flank and were secured in a fabric pouch. The lambs were allowed to recover at least 2 days before being studied. They were studied in a conscious state, suspended upright in a canvas sling, spontaneously breathing room air.

Continuous recordings were made of SAP, PAP, LAP, mean QP corrected for weight, and heart rate, with Gould-Statham PB231D pressure transducers, a Gould-Statham SP2202 flowmeter and a Gould-Brush 2800 physiologic recorder. Flow measurements were made using end-diastolic flow as the zero reference (14). Before each measurement all transducers and the flowmeter were zeroed. Arterial blood gases were measured before each study using a Corning 165 blood gas analyzer.

In each lamb, the dose response to dopamine was determined on two successive days with and without alpha-adrenergic blockade. The order of studies was randomly assigned. Alpha-adrenergic blockade was achieved by rapid intravenous injection of 1 mg/kg phentolamine (CIBA Pharmaceutical Co., Summit, NJ). Methoxamine (Burroughs Wellcome Co., Research Triangle Park, NC), an alpha-adrenergic agonist, was used to test the blockade. Before blockade, administration of 0.05 mg/kg methoxamine produced a 15% rise in SAP 30 sec after injection. After alpha-adrenergic blockade by phentolamine, administration of methoxamine produced no change in SAP.

Dopamine (American Critical Care, McGraw Park, IL) was infused into the inferior vena cava using a Harvard pump for 5-min periods at each of three doses: $2.7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, $27 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, and $270 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. These doses, though not in the usual therapeutic range for humans, were chosen because of our experience with the dopamine dose response curve in neonatal lambs, which is shifted to the right compared to the dose response curve in adult humans (4).

PVR was calculated by dividing the difference between PAP and LAP by QP. Systemic vascular resistance was calculated by dividing SAP by QP making the assumptions that right atrial pressure is negligible and pulmonary blood flow is equal to systemic blood flow.

Results obtained with dopamine infusion before and after alpha-adrenergic blockade were statistically analyzed using the two-tailed paired *t* test. Differences at $P < 0.05$ were considered significant. The Bonferroni correction was used when multiple values were compared to a single baseline (16). The studies performed with dopamine infusion alone will be described as Group I. The studies with dopamine after alpha-adrenergic blockade will be referred to as Group II. Results are expressed as mean $\pm$ S.E.M.

Table 1. Comparison between the systemic circulation responses to dopamine with and without alpha-adrenergic blockade (mean $\pm$ S.E.M.)

Dose	Systemic arterial pressure (mmHg)		Systemic vascular resistance [mmHg/(ml·min ⁻¹ ·kg ⁻¹)]	
	Group I	Group II	Group I	Group II
Baseline	73 $\pm$ 1.8	66 $\pm$ 2.6	0.38 $\pm$ 0.029	0.37 $\pm$ 0.038
2.7 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$	74 $\pm$ 2.0	69 $\pm$ 3.0	0.38 $\pm$ 0.023	0.38 $\pm$ 0.041
27 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$	77 $\pm$ 4.1 ¹	62 $\pm$ 3.9 ¹	0.36 $\pm$ 0.095 ²	0.27 $\pm$ 0.026 ²
270 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$	143 $\pm$ 6.5 ¹	88 $\pm$ 6.1 ¹	0.69 $\pm$ 0.073 ¹	0.31 $\pm$ 0.026 ¹

¹ $P < 0.01$.

² $P < 0.02$.

Fig. 1. Pulmonary artery response (PAP) to dopamine infusion with and without alpha-adrenergic blockade by phentolamine. Both groups have significantly elevated PAP's over baseline at the two higher doses: $P < 0.014$ at 27 $\mu\text{g}/\text{kg}/\text{min}$ and $P < 0.001$ at 270 $\mu\text{g}/\text{kg}/\text{min}$ dopamine. Values are expressed as means $\pm$ S.E.M.

RESULTS

Table 1 shows the dopamine dose response in the systemic circulation with and without alpha-adrenergic blockade. Baseline SAP was similar in the two groups and no effect upon SAP was noted in either group at the lowest dopamine dose. At 27 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ dopamine, SAP fell in Group II to a level significantly lower than that of Group I ($P < 0.01$). SAP rose in both groups at the highest dopamine dose, with Group I being significantly higher ($P < 0.01$).

Systemic vascular resistance, also shown in Table 1, was the same in both groups at baseline. At 27 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ dopamine, systemic vascular resistance remained constant in the Group I animals but fell in Group II ($P < 0.02$). At the highest dopamine dose systemic vascular resistance rose in the unblocked animals to a level significantly higher than Group II ($P < 0.01$).

The PAP response is graphed in Figure 1. The baseline PAP in both groups was about 22 mmHg. The two groups had virtually identical PAP's at each dose. At 27 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ the PAP rose from baseline to 27 $\pm$ 3.9 mmHg ($P < 0.014$) in Group I and to 26 $\pm$ 3.1 mmHg in Group II ($P < 0.005$). At the highest dose the PAP rose further to 36 $\pm$ 4.1 mmHg in group I and to 35 $\pm$ 3.8 mmHg in Group II, significantly higher than baseline in both groups ($P < 0.001$).

Left atrial pressure, shown in Figure 2, rose slightly in the alpha-adrenergic blocked animals from 2.7 $\pm$ 0.82 mmHg at baseline to 5.5 $\pm$ 0.98 mmHg over the dosage range ($P < 0.005$). In contrast, in Group I, LAP rose markedly from 3.2 $\pm$ 0.49 mmHg at baseline to 16 $\pm$ 1.7 mmHg at the highest dopamine dose ($P < 0.001$). The LAPs of the two groups differed significantly

from one another at the middle dose ($P < 0.05$) and at the highest dose ($P < 0.01$).

Pulmonary blood flow (Fig. 3) remained constant at about 200 ml·min⁻¹·kg⁻¹ in Group I at all doses. After alpha-adrenergic blockade, QP rose from 190 $\pm$ 12 ml·min⁻¹·kg⁻¹ at baseline to 230 $\pm$ 12 ml·min⁻¹·kg⁻¹ at 27 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ dopamine ($P < 0.005$) and to 280 $\pm$ 5.3 ml·min⁻¹·kg⁻¹ at the highest dopamine dose ($P < 0.001$).

Pulmonary vascular resistance is shown in Figure 4. The baseline values were 0.095 $\pm$ 0.011 mmHg/(ml·min⁻¹·kg⁻¹) in the unblocked lambs and 0.10 $\pm$ 0.009 mmHg/(ml·min⁻¹·kg⁻¹) in Group II (N.S.). During the dopamine infusions no change in calculated PVR was seen in either group, and the two groups developed no between group differences in calculated PVR during the course of the experiment.

The lambs had normal arterial blood gases at the time they were studied. Neither group had a significant change in heart rate

Fig. 2. Left atrial pressure (LAP) response to dopamine infusion with and without alpha-adrenergic blockade by phentolamine. LAP was significantly higher with dopamine infusion alone than with dopamine infusion after alpha-adrenergic blockade at 27 $\mu\text{g}/\text{kg}/\text{min}$ ($P < 0.05$) and at 270 $\mu\text{g}/\text{kg}/\text{min}$ ($P < 0.01$). Values are expressed as means $\pm$ S.E.M.

Fig. 3. Pulmonary blood flow response to dopamine infusion with and without alpha-adrenergic blockade by phentolamine. Although QP remained constant with infusion of dopamine alone, after alpha-adrenergic blockade QP rose significantly over baseline at 27 $\mu\text{g}/\text{kg}/\text{min}$ ($P < 0.005$) and at 270 $\mu\text{g}/\text{kg}/\text{min}$ ($P < 0.001$). Values are expressed as means $\pm$ S.E.M.

Fig. 4. Effect of dopamine infusion with and without alpha-adrenergic blockade on pulmonary vascular resistance (PVR). There were no differences in PVR between groups and no significant changes during the infusions. Values are expressed as means $\pm$ S.E.M.

during the dopamine infusion, although the baseline heart rate in Group I was lower at 230 ± 12 beats per min, compared to 280 ± 18 after alpha-adrenergic blockade ($P < 0.02$). At the highest dopamine dose, one-third of the lambs developed an irregular heart beat, but no electrocardiographic trace was available to characterize the arrhythmia.

DISCUSSION

Dopamine, an endogenous catecholamine, has complex cardiovascular actions. There are specific dopamine-receptor mediated effects, which are vasodilatory in the mesenteric, renal, and coronary circulations (7). The beta-adrenergic effects of dopamine include positive chronotropic and positive inotropic myocardial actions with the inotropic effects predominating (8). At higher doses of dopamine, vasoconstricting alpha-adrenergic effects predominate in systemic vascular beds (8). Coronary artery resistance increases with larger doses of dopamine and myocardial oxygen consumption rises as the inotropic effects increase (7). Arrhythmias have been noted with dopamine administration in both lambs and children (4, 9).

Literature reports on effects of dopamine on pulmonary vascular resistance are variable, with some investigators reporting increases in PVR in response to dopamine, but others finding no change (10, 15). In our Group I lambs, dopamine caused a rise in PAP and LAP, but no change in QP. These findings are consistent with our previous observations in newborn lambs (4). Although PAP and LAP increased linearly and QP remained unchanged, the calculated PVR also remained unchanged.

Previous animal studies using the combination of dopamine and phentolamine have demonstrated a favorable effect on dopamine-induced pulmonary vasospasm. Mentzer *et al.* (15) studied the effect of $10\text{--}20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ dopamine on the pulmonary circulation in adult dogs using a controlled perfusion technique. He demonstrated an increase in PAP with dopamine. This response was reduced with phentolamine. Barer and McCurrie (1), using a similar method in cats, produced an increase in transpulmonary pressure with dopamine that was diminished with phentolamine. Hsieh and Goldberg (12) demonstrated a reduction in pulmonary and systemic artery pressure when acutely prepared adult dogs were given phentolamine while receiving a constant infusion of $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ dopamine; however, left atrial pressure and pulmonary blood flow were not measured and thus pulmonary vascular resistance could not be calculated.

In contrast to these literature reports, our study did not demonstrate a reduction in the pulmonary vasopressor effect of dopamine by alpha-adrenergic blockade. PAP increased proportionately to QP while LAP remained constant; thus, calculated PVR remained unchanged. Alpha-adrenergic blockade appeared to unmask the beta-adrenergic cardiac action of dopamine with a

positive inotropic effect. The lack of change in SAP at $27 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ dopamine after alpha-adrenergic blockade demonstrates adequate alpha-adrenergic blockade. Yet, PAP rose significantly at that dopamine dose despite previous phentolamine administration.

The difference in effect of alpha-adrenergic blockade on the pulmonary vascular response to dopamine seen between our study and the previous experiments may involve the methods utilized. In animals, which are acutely prepared, the stresses of anesthesia and surgery may cause significant changes in the levels of circulating endogenous catecholamines or in alpha-adrenergic tone. These changes alter the response to subsequently administered blockers and exogenous amines. Two of the previously cited animal studies were performed with the thorax open (1, 15), and all three studies were performed with the animals under general anesthesia and being mechanically ventilated (1, 12, 15). Barer and Mentzer both utilized techniques which did not allow interaction between the pulmonary circulation and the systemic circulation, thus ignoring simultaneous changes in cardiac output, in afterload, and in left atrial pressure which were prominent in our chronically catheterized animals during alpha-adrenergic blockade and dopamine administration.

The differences observed may be due to species differences in distribution and number of receptors or to differences in response to drugs. Alpha-adrenergic immaturity in our newborn animals does not explain the difference between our findings and previous works because the fetal sheep has been demonstrated to have developed maximal response to alpha-adrenergic blockade by 120 days gestation (17). But dopamine receptors may be dissimilar in adult and newborn animals. The effects of dopamine may have been exaggerated at the highest dose in our study. Yet, even at $27 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ dopamine, a dose which is comparable to the doses used in other studies, the mean pulmonary artery pressure was elevated despite alpha-adrenergic blockade by phentolamine.

Our experiment indicates that dopamine acts as a pressor in the normal pulmonary circulation and suggests that it should be used with caution in the presence of elevated pulmonary artery pressure. The increased systemic blood flow seen at high doses of dopamine after alpha-adrenergic blockade might be of theoretical benefit in a low cardiac output state; however, this benefit must be weighed against the disadvantage of increased myocardial oxygen consumption and the risk of cardiac arrhythmias. The combination of dopamine and phentolamine does not appear to offer a therapeutic advantage to the newborn requiring systemic vasopressor support in the face of elevated pulmonary artery pressure. Alternative pharmacologic agents with less pulmonary vasopressor effect should be sought for use in these infants.

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 19. Supported by Grant #HD12987 from the National Institute of Child Health and Human Development.
 20. Received for publication September 4, 1981.
 21. Accepted for publication September 14, 1982.