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Effects of Vasoactive Drugs on Thromboxane A_2 Mimetic-Induced Pulmonary Hypertension in Newborn Lambs

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ABSTRACT. Isoproterenol, dobutamine, dopamine, and nitroprusside are four vasoactive drugs used to decrease pulmonary arterial pressure and increase cardiac output in newborns, infants, and children with sepsis. Thromboxane A_2 likely produces some of the hemodynamic changes in sepsis, and U46619, a thromboxane A_2 mimetic, produces similar changes in lambs. We studied the hemodynamic effects of these four vasoactive drugs in 10 spontaneously breathing newborn lambs during an infusion of U46619. After baseline hemodynamic measurements, U46619 (1–2 μg/kg/min) was infused to increase pulmonary arterial pressure and to decrease cardiac output. Then, either isoproterenol (0.05–1.0 μg/kg/min), dobutamine (5–20 μg/kg/min), dopamine (3–30 μg/kg/min), or nitroprusside (0.5–10.0 μg/kg/min) was infused. Every 10 min, measurements were repeated and the dose increased. U46619 significantly increased pulmonary arterial pressure by 182% and decreased cardiac output by 25% ($p < 0.05$). Isoproterenol decreased pulmonary arterial pressure by 30% ($p < 0.05$) and increased cardiac output by 25% ($p < 0.05$) at low doses, and increased cardiac output by 115% at the maximum dose ($p < 0.05$). Dobutamine decreased pulmonary arterial pressure by 11% ($p < 0.05$) and increased cardiac output by 28% ($p < 0.05$) at low doses, and increased cardiac output by 71% at the maximum dose ($p < 0.05$). Dopamine did not decrease pulmonary arterial pressure or increase cardiac output. Nitroprusside decreased pulmonary arterial pressure by 11% at the maximum dose ($p<0.05$). Isoproterenol and dobutamine may be more useful than dopamine and nitroprusside in the management of pulmonary hypertension and decreased cardiac output during sepsis. (*Pediatr Res* 29: 167–172, 1991)

The hemodynamic consequences of sepsis include pulmonary hypertension and decreased cardiac output. Newborns and infants with sepsis often require aggressive intensive care management, including the use of the vasoactive drugs isoproterenol, dobutamine, dopamine, or nitroprusside. Clinically, the hemodynamic effects of each vasoactive drug are difficult to assess because multiple therapies are used simultaneously and the patient's small size makes measuring pulmonary arterial pressure and cardiac output difficult. Although the hemodynamic effects of these vasoactive drugs have been studied in the adult, age-related differences in the cardiovascular system necessitate study in the newborn and infant.

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The hemodynamic consequences of sepsis, pulmonary hypertension and decreased cardiac output, appear to be mediated in part by thromboxane A_2, a cyclooxygenase metabolite of arachidonic acid (1–4). The infusions of *Escherichia coli* endotoxin or live or heat-killed group B β-hemolytic streptococci into dogs, piglets, and sheep cause a marked increase in pulmonary arterial pressure and a decrease in cardiac output, associated with an increase in the plasma concentration of thromboxane B_2, the stable metabolite of thromboxane A_2 (1, 4, 5). U46619, an endoperoxide compound (Upjohn Co., Kalamazoo, MI), causes contractions of smooth muscle strips similar to thromboxane A_2 (6, 7) and the infusion of U46619 in lambs produces a dose-dependent increase in pulmonary arterial pressure and a dose-dependent decrease in cardiac output (8). These hemodynamic effects are constant throughout the infusion of U46619, dissipate 1 min after the infusion is stopped, and are reproducible with subsequent infusions. These properties of infusions of U46619 allow for comparisons of the hemodynamic effects of other vasoactive drugs during steady state pulmonary hypertension and decreased cardiac output. Therefore, the purpose of our study was to determine the hemodynamic effects of four vasoactive drugs, isoproterenol, dobutamine, dopamine, and nitroprusside, in newborn lambs with pulmonary hypertension and decreased cardiac output caused by an infusion of U46619.

MATERIALS AND METHODS

Surgical preparation. Under local anesthesia, 10 newborn lambs from 3 to 5 d of age had polyvinyl catheters placed into the artery and vein of both hind legs and advanced to the descending aorta and inferior vena cava, respectively. Then, general anesthesia was induced by having the lamb breathe a mixture of oxygen and halothane. The lamb was intubated with a 4.5-mm endotracheal tube and mechanically ventilated. Anesthesia was maintained with 1–2% halothane.

A left lateral thoracotomy was performed in the 4th intercostal space. Polyvinyl catheters were placed into the internal thoracic artery and vein and advanced to the ascending aorta and right atrium, respectively. The pericardium was excised along the main pulmonary trunk. Three Teflon cannulas attached to polyvinyl catheters were inserted, two into the main pulmonary artery, and one into the left atrium. A precalibrated electromagnetic flow transducer was placed around the ascending aorta to measure cardiac output. A chest tube was placed into the pleural space. The catheters were filled with heparin sodium, plugged, and, along with the flow probe cable, brought to the skin and secured in a pouch on the lamb's flank. The lamb was weaned from mechanical ventilation, extubated, and returned to its mother. An intramuscular injection of 1 mL of penicillin G procaine and 1 mL of dihydrostreptomycin sulfate suspension was given daily. Three d were allowed for recovery. This protocol was approved

by the Committee on Animal Research, University of California, San Francisco.

Experimental protocol. With the lambs spontaneously breathing and resting quietly in a sling, the baseline hemodynamic variables (pulmonary and systemic arterial pressures, right and left atrial pressures, heart rate, and cardiac output) and systemic arterial pH and blood gases were measured. Then U46619 (1–2 μg/kg/min) was infused into the inferior vena cava to increase mean pulmonary arterial pressure to approximately two times baseline and decrease cardiac output. When this pulmonary arterial pressure was attained, the dose was not changed for the remainder of the study. After 10 min of stable pulmonary hypertension and decreased cardiac output, the hemodynamic variables and systemic arterial pH and blood gases were measured.

During the infusion of U46619, an i.v. infusion of a randomly selected vasoactive drug was started. The vasoactive drug was either isoproterenol (0.05, 0.1, 0.2, 0.4, and 1.0 μg/kg/min), dobutamine (5, 10, 15, and 20 μg/kg/min), dopamine (3, 5, 10, 15, and 30 μg/kg/min), or nitroprusside (0.5, 1, 2, 5, and 10 μg/kg/min). The infusions were started at the lowest dose and increased in a stepwise fashion. Each dose was infused for 10 min. Five min were allowed for the hemodynamic changes to occur. The hemodynamic variables and systemic arterial pH and blood gases were measured after 5 more min of a hemodynamic steady state. When necessary, warm 0.9% normal saline was infused to maintain left atrial pressure constant. Saline was only administered during the infusion of nitroprusside; no lamb received more than 3 mL/kg. After the maximum dose was infused, the infusion of U46619 was continued alone for 10 min. All measurements were repeated and the infusion of U46619 was then stopped. The lambs were allowed a minimum of 30 min to recover between drug studies. Only two vasoactive drugs were studied each day. The remaining two vasoactive drugs were studied 24 h later.

Drug preparation. All drugs were prepared immediately before use. U46619 in ethanol, stored at −20°C, was diluted in 0.9% normal saline. Isoproterenol, dobutamine, and dopamine were diluted in 0.9% normal saline; nitroprusside was diluted in 5% dextrose in water. Infusion rates varied between 0.3 and 1 mL/min.

Measurements and analysis. Pulmonary and systemic arterial and right and left atrial pressures were measured by Statham PDb23 pressure transducers (Hato Rey, Puerto Rico). Mean pressures were obtained by electrical integration. Cardiac output (left ventricular output minus coronary blood flow) was measured on a Statham SP2202 flowmeter. Heart rate was measured on a cardiotachometer triggered from the phasic systemic arterial pressure pulse wave. All hemodynamic variables were continuously recorded on a multichannel direct writing recorder. Rectal temperature was measured. Systemic arterial pH and blood gases (corrected for body temperature) were measured on a Corning 158 pH/blood gas analyzer (Corning Glass Works, Corning, NY).

Statistical analysis. Pulmonary and systemic vascular resistances and stroke volume were calculated using standard formulas. For each vasoactive drug, the means ± SD were calculated for the hemodynamic variables, pulmonary and systemic vascular resistances, stroke volume, and systemic arterial pH and blood gases during the baseline period, during the infusion of U46619 alone, and during the infusion of U46619 with each dose of the vasoactive drug. These were compared using analysis of variance for repeated measures and the Student-Newman-Keuls test for multiple comparisons. A $p < 0.05$ was considered statistically significant.

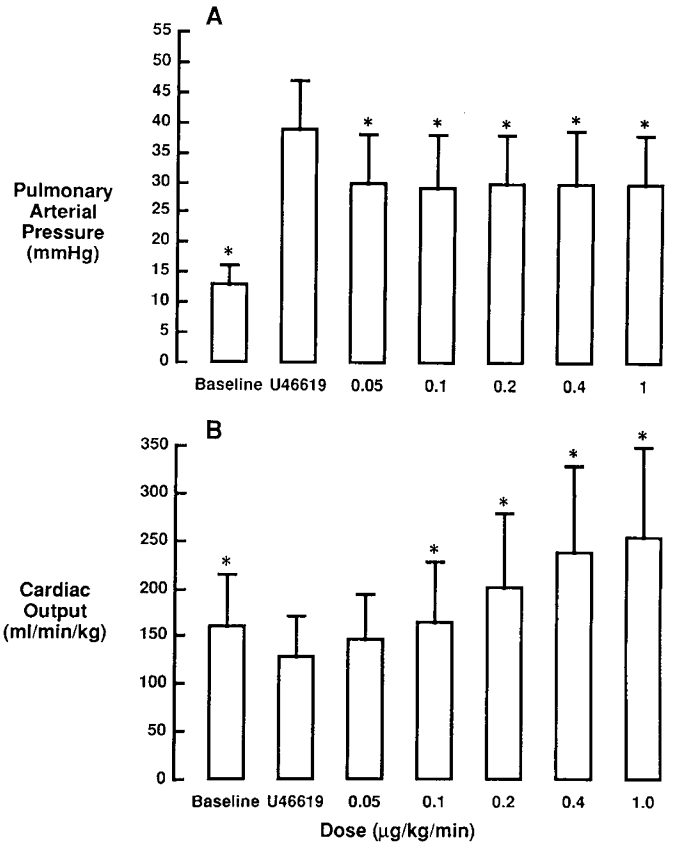
RESULTS

U46619, when infused alone, increased mean pulmonary arterial pressure by 182% ($p < 0.05$) and mean systemic arterial pressure by 18% ($p < 0.05$) and decreased cardiac output by 25% ($p < 0.05$) compared to baseline. Therefore, pulmonary and systemic vascular resistances increased ($p < 0.05$). In addition, heart rate decreased by 15% ($p < 0.05$). There were no differences in the hemodynamic effects of U46619 before or after the infusion of each vasoactive drug was stopped.

Isoproterenol decreased mean pulmonary arterial pressure by approximately 30% at all doses ($p < 0.05$) and increased cardiac output between 25 and 115% with increasing doses ($p < 0.05$) (Fig. 1). Therefore, pulmonary vascular resistance decreased between 38 and 62% ($p < 0.05$) (Table 1). At the maximum dose, with left atrial pressure held constant, stroke volume did not increase. Heart rate increased between 19 and 58% at doses greater than 0.05 μg/kg/min ($p < 0.05$). Mean systemic arterial pressure decreased by approximately 10% at doses greater than 0.1 μg/kg/min ($p < 0.05$). Systemic vascular resistance decreased between 15 and 53% ($p < 0.05$). Systemic arterial pH and P_{O_2} did not significantly change. Systemic arterial P_{CO_2} decreased by 10% at high doses ($p < 0.05$) (Table 2).

Dobutamine decreased mean pulmonary arterial pressure by approximately 11% at doses of 5 and 10 μg/kg/min ($p < 0.05$) (Fig. 2). There was no significant decrease at higher doses. Cardiac output increased between 28 and 71% with increasing doses ($p < 0.05$). Therefore, pulmonary vascular resistance decreased between 23 and 38% ($p < 0.05$) (Table 1). At the higher doses, with left atrial pressure held constant, stroke volume increased ($p < 0.05$). Heart rate increased between 22 and 33% with doses of 15 and 20 μg/kg/min, respectively ($p < 0.05$). Although there was no change in mean systemic arterial pressure, systemic vascular resistance decreased between 29 and 35% at the higher doses. Systemic arterial pH, P_{O_2}, or P_{CO_2} did not change (Table 2).

Dopamine produced no significant changes in mean pulmo-



N=10
* p<0.05 vs U46619 (ANOVA)

Fig. 1. Isoproterenol (*A*) decreases pulmonary arterial pressure and (*B*) increases cardiac output during the infusion of U46619 (values are mean ± SD).

Table 1. *Effects of isoproterenol, dobutamine, dopamine, and nitroprusside on heart rate, systemic arterial and left atrial pressures, vascular resistances, and stroke volume during the infusion of U44619**

			Isoproterenol (μg/kg/min)				
	Baseline	U46619	0.05	0.1	0.2	0.4	1.0
Heart rate (beats/min)	230 ± 27†	197 ± 18	207 ± 22	234 ± 44†	279 ± 49†	304 ± 33†	312 ± 30†
Systemic arterial pressure (mm Hg)	73 ± 5	83 ± 11	82 ± 14	82 ± 13	77 ± 11†	74 ± 12†	76 ± 10†
Left atrial pressure (mm Hg)	0.67 ± 0.58†	2.0 ± 1.0	0.67 ± 0.58	0.67 ± 0.58	0.0 ± 0.0	0.0 ± 0.0	0.33 ± 0.58
Pulmonary vascular resistance (mm Hg/mL/min/kg)	0.07 ± 0.02†	0.29 ± 0.10	0.18 ± 0.06†	0.17 ± 0.09†	0.13 ± 0.05†	0.12 ± 0.05†	0.11 ± 0.04†
Systemic vascular resistance (mm Hg/mL/min/kg)	0.42 ± 0.09†	0.59 ± 0.14	0.50 ± 0.16†	0.47 ± 0.18†	0.38 ± 0.12†	0.29 ± 0.12†	0.28 ± 0.12†
Stroke volume (mL/kg)	5.40 ± 0.70	4.93 ± 1.12	4.98 ± 0.82	4.43 ± 1.55	6.43 ± 2.84	5.55 ± 1.34	6.08 ± 1.36
			Dobutamine (μg/kg/min)				
			5	10	15	20	
Heart rate (beats/min)	230 ± 25†	190 ± 26	193 ± 23	209 ± 33	228 ± 36†	249 ± 34†	
Systemic arterial pressure (mm Hg)	74 ± 10†	85 ± 13	90 ± 18	88 ± 18	89 ± 18	90 ± 16	
Left atrial pressure (mm Hg)	1.60 ± 0.90†	3.60 ± 2.30	3.50 ± 1.70	2.80 ± 1.90	2.60 ± 1.50	3.00 ± 1.40	
Pulmonary vascular resistance (mm Hg/mL/min/kg)	0.07 ± 0.03†	0.26 ± 0.07	0.20 ± 0.07†	0.19 ± 0.06†	0.17 ± 0.06†	0.16 ± 0.07†	
Systemic vascular resistance (mm Hg/mL/min/kg)	0.39 ± 0.13†	0.58 ± 0.18	0.56 ± 0.18	0.50 ± 0.20	0.41 ± 0.15†	0.38 ± 0.14†	
Stroke volume (mL/kg)	5.26 ± 0.95	4.84 ± 0.72	5.24 ± 1.03	5.30 ± 0.90	6.04 ± 1.25†	6.04 ± 1.06†	
			Dopamine (μg/kg/min)				
			3	5	10	15	30
Heart rate (beats/min)	224 ± 17†	194 ± 19	190 ± 17	188 ± 27	179 ± 25	183 ± 30	184 ± 37
Systemic arterial pressure (mm Hg)	70 ± 11†	88 ± 12	86 ± 16	86 ± 17	90 ± 22	92 ± 22	98 ± 10†
Left atrial pressure (mm Hg)	0.40 ± 0.09	2.60 ± 1.10	2.40 ± 1.10	2.20 ± 1.30	2.60 ± 2.00	1.80 ± 1.50	2.40 ± 2.10
Pulmonary vascular resistance (mm Hg/mL/min/kg)	0.07 ± 0.03†	0.25 ± 0.11	0.26 ± 0.11	0.24 ± 0.10	0.25 ± 0.10	0.25 ± 0.11	0.26 ± 0.11
Systemic vascular resistance (mm Hg/mL/min/kg)	0.39 ± 0.14†	0.59 ± 0.14	0.59 ± 0.17	0.53 ± 0.14	0.58 ± 0.18	0.59 ± 0.12	0.59 ± 0.11
Stroke volume (mL/kg)	5.17 ± 1.17	4.60 ± 1.24	4.40 ± 0.85	5.03 ± 1.80	5.30 ± 1.72	5.50 ± 1.29	6.41 ± 2.30†
			Nitroprusside (μg/kg/min)				
			0.05	1	2	5	10
Heart rate (beats/min)	220 ± 20†	186 ± 20	184 ± 19	182 ± 15	180 ± 33	189 ± 39	206 ± 40
Systemic arterial pressure (mm Hg)	72 ± 11	86 ± 12	84 ± 11	84 ± 13	83 ± 13	79 ± 12	76 ± 14†
Left atrial pressure (mm Hg)	1.25 ± 0.96†	3.00 ± 0.82	3.00 ± 0.82	2.25 ± 0.50	1.50 ± 1.29	1.50 ± 1.91	1.25 ± 1.50
Pulmonary vascular resistance (mm Hg/mL/min/kg)	0.07 ± 0.03†	0.28 ± 0.12	0.26 ± 0.13	0.25 ± 0.12	0.29 ± 0.15	0.29 ± 0.10	0.25 ± 0.07
Systemic vascular resistance (mm Hg/mL/min/kg)	0.40 ± 0.13†	0.70 ± 0.25	0.70 ± 0.32	0.67 ± 0.28	0.87 ± 0.68	0.68 ± 0.26	0.57 ± 0.15
Stroke volume (mL/kg)	5.50 ± 1.35	4.79 ± 1.66	4.93 ± 1.81	4.96 ± 1.57	4.54 ± 1.78	4.40 ± 1.24	4.19 ± 1.16

* $n = 10$, mean ± SD.

† $p < 0.05$ *vs* U46619 (analysis of variance).

nary arterial pressure, cardiac output, vascular resistances, or heart rate at any dose; mean systemic arterial pressure increased at the highest dose ($p < 0.05$) (Fig. 3, Table 1). At the maximum dose, with left atrial pressure held constant, stroke volume increased ($p < 0.05$). Systemic arterial P_{O_2} decreased by 15% at all doses without changes in systemic arterial pH or P_{CO_2} ($p < 0.05$) (Table 2).

Nitroprusside decreased mean pulmonary arterial pressure by 11% at doses greater than 1.0 μg/kg/min without changing cardiac output ($p < 0.05$) (Fig. 4). Nitroprusside decreased systemic arterial pressure by 12% at the maximum dose ($p < 0.05$) (Table 1). There were no significant changes in vascular resistances, stroke volume, heart rate, or systemic arterial pH, P_{O_2}, or P_{CO_2} (Table 2).

DISCUSSION

Pulmonary hypertension and decreased cardiac output are two hemodynamic consequences of sepsis. In this study, by infusing U46619 rather than bacteria, the hemodynamic effects of four vasoactive drugs commonly used in the treatment of sepsis were assessed in the same newborn lambs with the same degree of pulmonary hypertension and decreased cardiac output. The results of our study demonstrate that these four vasoactive drugs have different hemodynamic effects. Isoproterenol and dobutamine decreased pulmonary arterial pressure and increased cardiac output more than dopamine or nitroprusside. Also, isoproterenol and dobutamine decreased pulmonary arterial pressure at doses that did not increase cardiac output, suggesting that these vasoactive drugs produce pulmonary vasodilation and decrease pulmonary vascular resistance. Cardiac output and heart rate increased with increasing doses of both vasoactive drugs. Dopamine did not significantly change pulmonary arterial pressure or cardiac output and increased systemic arterial pressure at the highest dose. Nitroprusside decreased pulmonary arterial pressures nonselectively without changing cardiac output. These differences in hemodynamic effects of the four vasoactive drugs are due to differences in their pharmacologic properties.

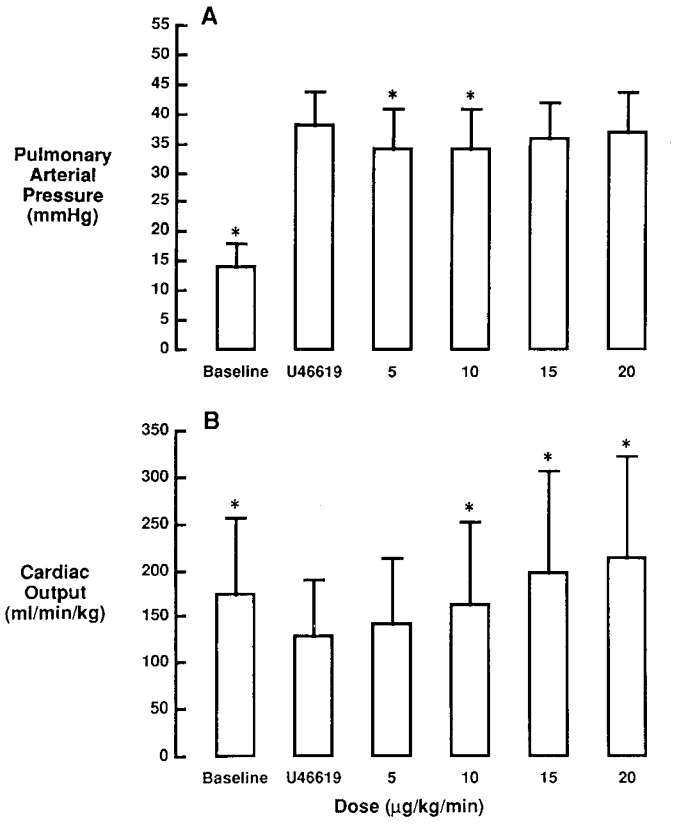
Table 2. *Effects of isoproterenol, dobutamine, dopamine, and nitroprusside on systemic arterial blood gases and pH during the infusion of U46619**

			Isoproterenol (μg/kg/min)				
	Baseline	U46619	0.05	0.1	0.2	0.4	1.0
P_aO_2							
kPa	10.8 ± 1.6	10.3 ± 1.5	10.3 ± 1.9	10.9 ± 2.1	10.9 ± 1.7	10.8 ± 1.6	11.3 ± 1.5
torr	80.8 ± 12.0	77.3 ± 11.3	77.6 ± 14.8	82.2 ± 15.9	82.3 ± 13.2	80.9 ± 12.3	84.9 ± 11.6
P_aCO_2							
kPa	6.1 ± 0.5	6.0 ± 0.5	5.7 ± 0.6	5.7 ± 0.5	5.6 ± 0.5	5.4 ± 0.6†	5.3 ± 0.7†
torr	45.9 ± 3.7	44.9 ± 3.8	43.1 ± 4.6	43.0 ± 3.6	42.1 ± 3.5	40.7 ± 4.3†	39.5 ± 5.2†
pH (units)	7.38 ± 0.04	7.38 ± 0.04	7.38 ± 0.04	7.38 ± 0.04	7.37 ± 0.03	7.37 ± 0.04	7.37 ± 0.05
			Dobutamine (μg/kg/min)				
			5	10	15	20	
P_aO_2							
kPa	10.7 ± 1.9	10.0 ± 1.5	9.4 ± 1.6	10.0 ± 1.4	10.2 ± 1.6	10.0 ± 1.6	
torr	80.5 ± 14.3	74.8 ± 11.4	70.4 ± 11.7	75.0 ± 10.4	77.0 ± 11.8	75.3 ± 12.1	
P_aCO_2							
kPa	5.9 ± 0.3	5.9 ± 0.6	5.9 ± 0.6	5.8 ± 0.5	5.7 ± 0.4	5.7 ± 0.5	
torr	43.9 ± 2.0	43.9 ± 4.0	44.4 ± 4.4	43.2 ± 3.4	42.8 ± 2.9	42.8 ± 3.6	
pH (units)	7.36 ± 0.04	7.36 ± 0.03	7.36 ± 0.04	7.37 ± 0.04	7.36 ± 0.04	7.36 ± 0.03	
			Dopamine (μg/kg/min)				
			3	5	10	15	30
P_aO_2							
kPa	10.1 ± 1.1	10.2 ± 2.6	8.8 ± 0.9†	8.3 ± 0.9†	8.3 ± 1.5†	8.2 ± 0.4†	8.5 ± 1.4†
torr	76.3 ± 7.9	76.8 ± 19.7	65.7 ± 6.5†	62.0 ± 6.4†	62.3 ± 11.2†	61.3 ± 3.3†	64.0 ± 10.6†
P_aCO_2							
kPa	6.1 ± 0.7	6.0 ± 0.6	6.2 ± 0.6	6.3 ± 0.5	6.5 ± 1.0	6.2 ± 1.1	6.5 ± 0.4
torr	45.6 ± 5.0	45.1 ± 4.2	46.2 ± 4.6	47.3 ± 4.1	49.0 ± 7.7	46.6 ± 8.0	49.0 ± 3.3
pH (units)	7.39 ± 0.03	7.39 ± 0.03	7.38 ± 0.02	7.51 ± 0.02	7.34 ± 0.09†	7.36 ± 0.03	7.35 ± 0.03
			Nitroprusside (μg/kg/min)				
			0.05	1	2	5	10
P_aO_2							
kPa	11.0 ± 1.3	10.8 ± 2.2	11.0 ± 2.1	10.8 ± 1.5	10.2 ± 1.5	11.2 ± 1.4	11.3 ± 1.6
torr	82.3 ± 9.4	81.1 ± 16.2	82.3 ± 15.6	81.4 ± 11.3	77.1 ± 11.3	83.9 ± 10.5	85.1 ± 12.0
P_aCO_2							
kPa	5.9 ± 0.4	5.5 ± 0.6	5.4 ± 0.6	5.5 ± 0.6	5.3 ± 0.5	5.3 ± 0.5	5.1 ± 0.6
torr	44.3 ± 2.8	41.4 ± 4.2	40.6 ± 4.7	41.1 ± 4.3	40.1 ± 4	39.9 ± 3.5	37.9 ± 4.6
pH (units)	7.38 ± 0.05	7.39 ± 0.07	7.39 ± 0.07	7.40 ± 0.08	7.40 ± 0.06	7.41 ± 0.07	7.41 ± 0.09

* $n = 10$, mean ± SD. P_aO_2, arterial O_2 pressure; P_aCO_2, arterial CO_2 pressure.
† $p < 0.05$ *vs* U46619 (analysis of variance).

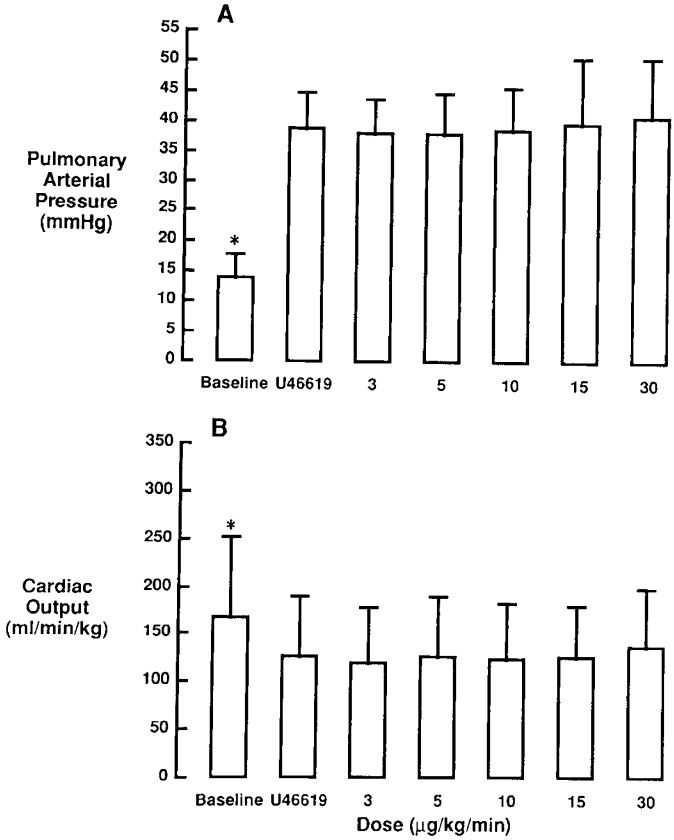
Isoproterenol, a β_1- and β_2-adrenergic agonist, and dobutamine, a β_1-, β_2-, and α_1-adrenergic agonist, are used in the treatment of children with pulmonary hypertension (9). Animal studies have shown that isoproterenol and dobutamine decrease pulmonary arterial pressure and pulmonary vascular resistance during hypoxic pulmonary vasoconstriction and during sepsis-induced lung injury (9–12). Similarly, in our study, isoproterenol and dobutamine decreased pulmonary arterial pressure and pulmonary vascular resistance. At the lowest dose of each vasoactive drug, cardiac output or atrial pressures did not change, suggesting that isoproterenol and dobutamine produced pulmonary vasodilation. Isoproterenol decreased pulmonary arterial pressure and vascular resistance more than dobutamine and also decreased systemic arterial pressure because it is a more potent β_2-adrenergic agonist than dobutamine and has no α_1-adrenergic activity (13). Inasmuch as isoproterenol did not decrease systemic arterial pressure at low doses, and it did decrease pulmonary vascular resistance more than systemic vascular resistance at each dose, isoproterenol has a greater effect on the pulmonary than on the systemic circulation in this model.

Isoproterenol and dobutamine are also used in the treatment of children with decreased cardiac output. In animal studies, isoproterenol and dobutamine did not increase cardiac output in normal newborns, but did increase cardiac output in older animals (14, 15). This age-related difference in the ability of these vasoactive drugs to increase cardiac output may be due to the higher resting cardiac output in the normal newborn whose heart functions at the maximum contractile state with little available contractile reserve (16). However, in hypoxic newborn lambs, isoproterenol and dobutamine increased cardiac output by 50% (17). Similarly, in our study in which cardiac output was decreased by the infusion of U46619, isoproterenol and dobutamine at the maximum dose increased cardiac output by 115 and 71%, respectively. Isoproterenol increased cardiac output more than dobutamine because it increased heart rate more than dobutamine. Because isoproterenol did not increase stroke volume when left atrial pressure or preload was held constant, there was likely no change in contractile state. However, inasmuch as dobutamine increased stroke volume when left atrial pressure or preload was held constant, contractile state likely increased. The increase in cardiac output produced by isoproterenol was likely due to a large increase in heart rate and a decrease in vascular resistance or afterload, whereas the increase in cardiac output produced by dobutamine was likely due to a smaller increase in



N=10
* p<0.05 vs U46619 (ANOVA)

Fig. 2. Dobutamine (*A*) decreases pulmonary arterial pressure and (*B*) increases cardiac output during the infusion of U46619 (values are mean ± SD).



N=10
* p<0.05 vs U46619 (ANOVA)

Fig. 3. The effects of dopamine on (*A*) pulmonary arterial pressure and (*B*) cardiac output during the infusion of U46619 (values are mean ± SD).

heart rate, an increase in contractile state, and a smaller decrease in afterload. These studies show that the newborn, when hemodynamically compromised, can significantly increase cardiac output in response to β_1-adrenergic stimulation by increasing heart rate (for isoproterenol and dobutamine) or by increasing contractile state (for dobutamine).

Dopamine, a β_1-, β_2, α_1-adrenergic, and dopaminergic agonist that also releases norepinephrine from myocardial stores, is used in the treatment of newborns, infants, and children with pulmonary hypertension and decreased cardiac output (18). However, in animal studies its effect on pulmonary arterial pressure has been inconsistent. For example, dopamine has increased, decreased, or had no effect on pulmonary arterial pressure during hypoxic pulmonary vasoconstriction (10, 11, 19, 20). In our study, dopamine had no effect on pulmonary arterial pressure at any dose and increased systemic arterial pressure at the highest dose because it is an α_1-adrenergic agonist. At low doses, the α_1-adrenergic activity offsets the vasodilation produced by dopamine's β_2-adrenergic activity and at higher doses it produces vasoconstriction. Similarly, dopamine's effect on cardiac output has also been inconsistent (19, 21). In our study, dopamine had no effect on cardiac output because it did not increase heart rate or decrease afterload. Dopamine is a less potent β_1- and β_2-adrenergic agonist than either isoproterenol or dobutamine (13). In addition, the newborn heart may have a decreased response to dopamine because it has decreased norepinephrine stores or decreased sympathetic innervation (22). Stroke volume did increase at the highest dose, whereas heart rate tended to decrease, suggesting that dopamine may have increased contractile state. However, the failure of dopamine to significantly increase heart rate or decrease afterload (systemic arterial pressure actually increased) prevented a significant increase in cardiac output. Dopamine also decreased arterial O_2 pressure at each dose due to a ventilation-perfusion mismatch. For example, in mechanically ventilated patients, dopamine increased blood flow to poorly ventilated alveoli and decreased blood flow to well-ventilated alveoli without changing the distribution of ventilation (23).

Nitroprusside, a direct arteriolar and venous dilator, is used to decrease pulmonary arterial pressure in neonates with persistent pulmonary hypertension and to increase cardiac output in infants and children with congenital heart disease (24, 25). However, in animal models of pulmonary hypertension, nitroprusside decreased pulmonary arterial pressure nonselectively (26, 27) and did not affect cardiac output (28, 29). We found similar results in our study. Nitroprusside did not increase cardiac output because unlike isoproterenol or dobutamine it did not increase heart rate, stroke volume, or contractile state. Therefore, a decrease in pulmonary arterial pressure (similar to dobutamine) and a decrease in systemic arterial pressure (similar to isoproterenol) alone are not enough to increase cardiac output. Alternatively, even though left atrial pressure was maintained constant during the infusion of nitroprusside by the administration of saline, in this range of left atrial pressure left ventricular end-diastolic volume may have changed because the heart is functioning on the flat portion of the diastolic pressure-volume curve, where the lack of change in left atrial pressure may not reflect true changes in left ventricular end-diastolic volume. Preload may have actually decreased during the infusion of nitroprusside and, therefore, cardiac output could not increase with the decrease in pulmonary and systemic arterial pressures.

In conclusion, in newborn lambs with pulmonary hypertension and decreased cardiac output induced by the infusion of U46619, a thromboxane A_2-mimetic, isoproterenol and dobutamine at low doses selectively decreased pulmonary arterial pressure and

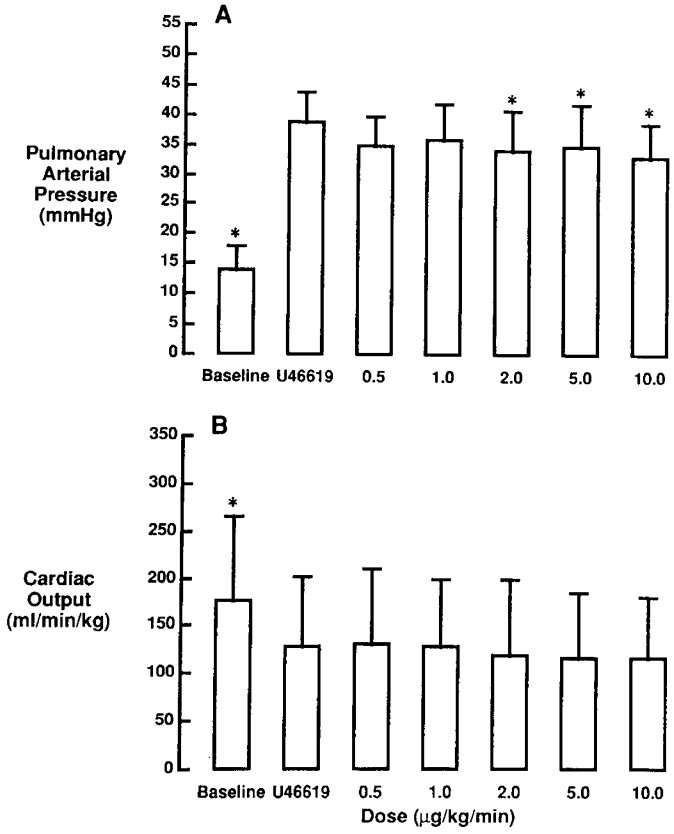


Fig. 4. The effects of nitroprusside on (*A*) pulmonary artery pressure and (*B*) cardiac output during the infusion of U46619 (values are mean ± SD).

at higher doses increased cardiac output. Dopamine did not decrease pulmonary arterial pressure or increase cardiac output but decreased systemic arterial Po_2. Nitroprusside decreased pulmonary arterial pressure nonselectively without changing cardiac output. The ability of isoproterenol and dobutamine to decrease pulmonary arterial pressure at low doses and increase cardiac output at higher doses may make these vasoactive drugs more useful than dopamine or nitroprusside in the treatment of newborns, infants, and children with pulmonary hypertension and decreased cardiac output during sepsis.

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REFERENCES

1. Brigham KL, Meyrick B 1986 Endotoxin and lung injury. Am Rev Respir Dis 133:913–927
2. Gibson RL, Truog WE, Redding GJ 1988 Thromboxane-associated pulmonary hypertension during three types of gram-positive bacteremia in piglets. Pediatr Res 23:553–556
3. Runkle B, Goldberg RN, Streitfeld MM, Clark MR, Buron E, Setzer ES, Bancalari E 1984 Cardiovascular changes in group B streptococcal sepsis in the piglet: response to indomethacin and relationship to prostacyclin and thromboxane A_2. Pediatr Res 18:874–878
4. D'Orio V, Halleux J, Rodriguez LM, Wahlen C, Marcelle R 1986 Effects of *Escherichia coli* endotoxin on pulmonary vascular resistance in intact dogs. Crit Care Med 14:802–806
5. Hœttemeier PC, Watkins WD, Peterson MB, Zapol WM 1982 Acute pulmonary hypertension and lung thromboxane release after endotoxin infusion in normal and leukopenic sheep. Circ Res 50:688–694
6. Coleman RA, Humphrey PPA, Kennedy I, Levy GP, Lumley P 1981 Comparison of the actions of U46619, a prostaglandin H_2-analogue, with those of prostaglandin H_2 and thromboxane A_2 on some isolated smooth muscle preparations. Br J Pharmacol 73:778–778
7. Wilson NH, Jones RL 1985 Prostaglandin endoperoxide and thromboxane A_2 analogs. In: Pike JE, Morton DR (eds) Advances in Prostaglandin, Thromboxane, and Leukotriene Research, Vol 14. Raven Press, New York, pp 393–425
8. Soifer SJ, Schreiber MD, Heymann MA 1989 Leukotriene antagonists attenuate thromboxane-inducible pulmonary hypertension. Pediatr Res 26:83–87
9. Zaritsky A, Chernow B 1984 Use of catecholamines in pediatrics. J Pediatr 105:341–350
10. Mentzer Jr RM, Alegre CA, Nolan SP 1976 The effects of dopamine and isoproterenol on the pulmonary circulation. J Thorac Cardiovasc Surg 71:807–814
11. Furman WR, Summer WR, Kennedy TP, Sylvester JT 1982 Comparison of the effects of dobutamine, dopamine and isoproterenol on hypoxic pulmonary vasoconstriction in the pig. Crit Care Med 10:371–374
12. Gnidec AG, Finley RR, Sibbald WJ 1988 Effect of dobutamine on lung microvascular fluid flux in sheep with "sepsis" syndrome. Chest 93:180–186
13. Robie NW, Nutter DO, Moody C, McNay JL 1974 *in vivo* analysis of adrenergic receptor activity of dobutamine. Circ Res 34:663–671
14. Driscoll DJ, Gillette PC, Fukushige J, Lewis RM, Contant C, Hartley CJ, Entman ML, Schwartz A 1980 Comparison of the cardiovascular action of isoproterenol, dopamine and dobutamine in the neonatal and mature dog. Pediatr Cardiol 1:307–314
15. Driscoll DJ, Gillette PC, Lewis RM, Hartley CJ, Schwartz A 1979 Comparative hemodynamic effects of isoproterenol, dopamine, and dobutamine in the newborn dog. Pediatr Res 13:1006–1009
16. Teitel DF, Sidi D, Chin T, Brett C, Heymann MA, Rudolph AM 1985 Developmental changes in contractile reserve in the lamb. Pediatr Res 19:948–955
17. O'Laughlin MP, Fisher DJ, Dreyer WJ, Smith EO 1987 Augmentation of cardiac output with intravenous catecholamines in unanesthetized hypoxemic newborn lambs. Pediatr Res 22:667–674
18. Drummond WH, Gregory GA, Heymann MA, Phibbs RA 1981 The independent effects of hyperventilation, tolazoline, and dopamine on infants with persistent pulmonary hypertension. J Pediatr 98:603–611
19. Drummond WH, Webb IA, Purcell KA 1981 Cardiopulmonary response to dopamine in chronically catheterized neonatal lambs. Pediatr Pharmacol 1:347–356
20. Lejeune P, Naeije R, Leeman M, Melot C, Deloof T, Delcroix M 1987 Effects of dopamine and dobutamine on hyperoxic and hypoxic pulmonary vascular tone in dogs. Am Rev Respir Dis 136:29–35
21. Feltes TF, Hansen TN, Martin CG, Leblanc AL, Smith S, Giesler ME 1987 The effects of dopamine infusion on regional blood flow in newborn lambs. Pediatr Res 21:131–136
22. Friedman WF 1973 The intrinsic properties of the developing heart. In: Friedman WF, Lesch M, Sooneblick EH (eds) Neonatal Heart Disease. Grune and Stratton, New York, pp 21–49
23. Renotte MT, Reynaert M, Clerbaux TH, Willems E, Roesler J, Verith C, Rodenstein O, Frans A 1989 Effects of two inotropic agents, dobutamine and dopamine, on pulmonary gas exchange in artificially ventilated patients. Intensive Care Medicine 15:160–165
24. Faraci PA, Rheinlander HF, Cleveland RJ 1980 Use of nitroprusside for control of pulmonary hypertension and repair of ventricular septal defects. Ann Thorac Surg 29:70–73
25. Benitz WE, Malachowski N, Cohen RS, Stevenson DK, Ariagno RL, Sunshine P 1985 Use of nitroprusside in neonates: efficacy and safety. J Pediatr 106:102–110
26. Prielipp RC, Rosenthal MH, Pearl RG 1988 Vasodilator therapy in vasoconstrictor-induced pulmonary hypertension in sheep. Anesthesiology 68:552–558
27. Rudinsky BF, Komar KJ, Strates E, Meadow WL 1987 Neither nitroglycerin nor nitroprusside selectively reduces sepsis-induced pulmonary hypertension in piglets. Crit Care Med 15:1127–1130
28. Mirro R, Milley JR, Holzman IR 1985 The effects of sodium nitroprusside on blood flow and oxygen delivery to the organs of the hypoxemic newborn lamb. Pediatr Res 19:15–18
29. Kuipers JRG, Sidi D, Heymann MA, Rudolph AM 1984 Effects of nitroprusside on cardiac function, blood flow distribution, and oxygen consumption in the conscious young lamb. Pediatr Res 18:618–626