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The Effects of Prostaglandin E_1 on Fetal Pulmonary Vascular Resistance[1] (38588)

S. CASSIN, T. TYLER, AND R. WALLIS

Department of Physiology, College of Medicine, University of Florida, Gainesville, Florida 32601

Prostaglandin E_1 (PGE_1) decreases pulmonary vascular resistance in several mammalian species (1–3) including man (4). Since 90% of PGE_1 entering the lung is inactivated in single transit through pulmonary circulation (3, 5, 6), the effects of PGE_1 on the extrapulmonary circulation are subject to route of administration (6, 7) and metabolism by lung. PGE_1 which is present in lung and can be released by the lung may be involved in matching perfusion to ventilation (8, 9). Perfusion–ventilation imbalance with increased pulmonary vascular resistance in the newborn has been reported in cases of severe respiratory distress (10, 11), persistent pulmonary hypertension (12), progressive pulmonary hypertension (13), and persistent fetal circulation (14).

The effects of PGE_1 on the vascular resistance of any fetal lung have not been studied previously. Thus, the following study was undertaken to determine effects of PGE_1 on the pulmonary vascular resistance of fetal goats.

Methods. Ten fetuses (average wt = 2.8 kg) ranging in age from 135 to 140 days gestation were delivered by cesarean section with umbilical circulation intact from goats anesthetized with Chloralose (50 mg/kg iv). A saline filled rubber bag was placed over the fetal head; the cord was protected by cotton soaked with warm saline. Colonic temperature was monitored and maintained between 37° and 39°. A polyethylene cannula filled with saline was introduced into the fetal trachea and the bag over the head removed. The left femoral artery was cannulated for monitoring systemic blood pressure (FAP). The chest was opened on the left side and the fourth through seventh rib removed to give access to the left pulmonary artery and the left lung. Venous drainage and arterial supply to the upper and middle lobes of the left lung were isolated and ligated. Fetal blood was anticoagulated with Heparin (2000 unit/kg iv). The pulmonary vein from the lower lobe of the left lung was cannulated via the left atrium. Pulmonary venous effluent was directed into a reservoir which could be raised or lowered to control pulmonary venous pressure. Blood from this reservoir was returned by means of a pump (Cole–Parmer Master-Flex Model 7016 Pump) through a heat exchanger into the right femoral artery. Pulmonary venous pressure (PVP) was monitored by a catheter threaded through the effluent cannula with its tip at the level of the pulmonary vein. The pulmonary venous reservoir was placed below the level of the lung to insure a zero reference pressure at some fixed point in the pulmonary vein. Blood was withdrawn from the inferior vena cava at approximately the level of the liver through a cannula introduced through the left femoral vein and was pumped (Cole–Parmer) into the distal end of the left pulmonary artery. Pulmonary arterial pressure (PAP) and pulmonary arterial flow ($\dot{Q}$) were monitored in this circuit.

Flows and pressures were recorded on a Grass Model 5C six channel Polygraph. Statham P23AC pressure transducers and *in vivo* Metric Model FT2C Flow Probes were utilized for this purpose. PGE_1 (Upjohn) was infused (Harvard Pump) at variable rates for a fixed time through a catheter threaded into the pulmonary artery circuit. PAP versus $\dot{Q}$ (15) was plotted on a Houston Model HR98 X-Y Plotter. The pH, P_{CO_2}, and P_{O_2} of the mother and fetus were monitored on a Radiometer blood gas analyzer (mean values ± SE for 10 fetuses during the experiments were: pH = 7.25 ± 0.04, P_{CO_2} = 44.0 ± 2.2 mmHg, P_{O_2} = 20.4 ± 1.1 mmHg).

Results. Figure 1 shows the effects of infusing PGE_1 (11.0 μg/kg/min) directly into the pulmonary artery of an unventilated

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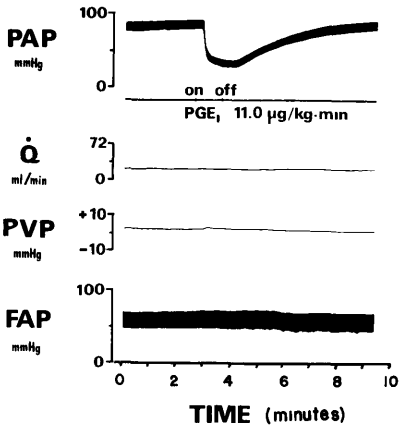

FIG. 1. Effect of intrapulmonary PGE$_1$ infusion (11.0 μg/kg/min) on pulmonary arterial pressure (PAP), pulmonary venous pressure (PVP), and femoral arterial pressure (FAP) during conditions of controlled pulmonary arterial flow (Q̇) in the unventilated fetal goat.

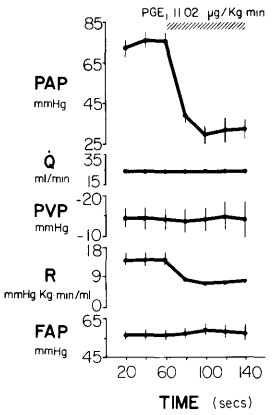

FIG. 2. Effect of intrapulmonary PGE$_1$ infusion (11.0 μg/kg/min) on pulmonary arterial pressure (PAP), calculated pulmonary vascular resistance (R = PAP − PVP/Q̇), and femoral arterial pressure (FAP) in 10 unventilated fetal goats. Q̇ was held constant. The pulmonary venous reservoir was placed below the level of the lung to insure a zero reference pressure at some fixed point in the pulmonary vein. Results are means ± SE.

fetus. Mean PAP was reduced from 87.5 to 34.2 mmHg. A significant decrease in pulmonary vascular resistance (61%) occurred while Q̇, PVP and FAP were constant.

The mean decrease in pulmonary vascular resistance (R) for all fetuses receiving an average dose of 11.02 μg/kg/min for one minute is given in Fig. 2. Q̇, PVP and FAP

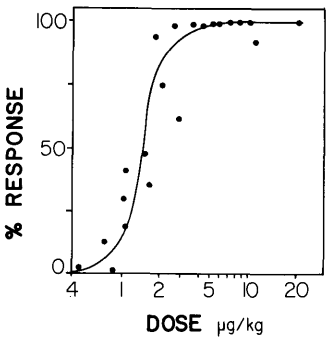

FIG. 3. Effect of intrapulmonary PGE$_1$ infusion at varied doses (for 1 min) on pulmonary arterial pressure (PAP) in four unventilated fetal goats (log scale).

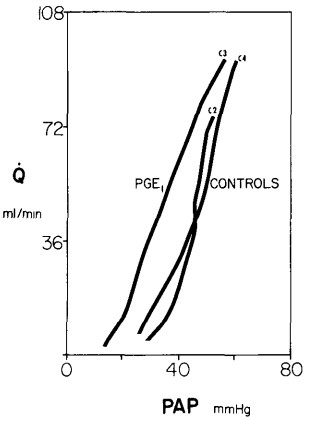

FIG. 4. Pulmonary arterial pressure-flow curves prior to (C$_2$), during (C$_3$), and following (C$_4$) PGE$_1$ infusion (11.0 μg/kg/min) in the unventilated fetal goat.

remained constant. R decreased 51.1% with PGE$_1$ infusion.

A dose response curve generated in four fetuses is shown in Fig. 3. Half of the maximal decrease in PAP at constant flow was achieved at a dose of 1.6 μg/kg (infused for 1 min).

Figure 4 demonstrates a shift in the pressure–flow curve during an infusion of PGE$_1$. The pulmonary inflow for the same pressure (40 mmHg) during infusion of PGE$_1$ is 96% higher than in the control state (PVP remained constant). The response is reversible as seen from the second control curve in the figure.

Discussion. With flow held constant, infusion of PGE$_1$ into the left pulmonary artery of fetal goats decreased perfusion pressure and pulmonary vascular resistance in an isolated unventilated lobe. In unventilated

fetal lungs, decreases in vascular resistance reflect a reduction in tonic contraction of vascular wall smooth muscle and resultant vasodilatation (15). These results are consistent with reports of active vasodilatation and decreased pulmonary vascular resistance with PGE$_1$ in other species (1–3).

PGE$_1$ infusions (for 1 min) in doses as high as 25 μg/kg/min into the left pulmonary artery did not alter femoral arterial pressure. This is consistent with reports in which intravenous infusion of E series prostaglandins in sheep had no effect on blood pressure and heart rate (1, 16). Since inactivation occurs by lung (3, 5, 6), the failure of PGE$_1$ to alter systemic blood pressure in these cited investigations may be due to route of administration (6, 7) and not simply differences in response of pulmonary and systemic circulations (in preliminary studies we found that 25 μg PGE$_1$/kg/min produced a systemic hypotension when infused directly into the left ventricle of a 2-day old goat). In man, differences in response of pulmonary and systemic circulations to infusion of PGE$_1$ are clearly a function of route of administration as well as dose. Intravenous PGE$_1$ infusion (0.1 μg/kg/min) generally decreases pulmonary vascular resistance without changing systemic systolic, diastolic, or mean arterial pressure. Infusions of greater concentrations of PGE$_1$ (0.18 μg/kg/min) produce a decrease in both pulmonary vascular resistance and systemic arterial pressures (4, 7).

Systemic cardiovascular effects with intravenous PGE$_1$ infusion may be due to saturation of pulmonary inactivation mechanisms and consequent delivery of noninactivated PGE$_1$ to the left heart. However, in our preparation pulmonary venous blood from the left lung is not returned to the left heart but to a reservoir, heat exchanger, and pumped into descending aorta. This circuitry may decrease effects of PGE$_1$ on the systemic circulation. Inactivation of PGE$_1$, itself, may be quantitatively greater in fetal lung (17). With these considerations, this study demonstrates that intrapulmonary PGE$_1$ infusion decreases pulmonary vascular resistance without a reduction in femoral artery pressure.

Since PGE$_1$ infused intravenously or directly into the pulmonary artery vasodilated pulmonary circulation without systemic effects it may be of therapeutic value in perfusion–ventilation imbalances with elevated pulmonary vascular resistance, particularly in instances where ventilatory assistance fails to improve blood gases.

Summary. The effects of PGE$_1$ on pulmonary vascular resistance were investigated in fetal goats using an isolated perfusion technique on otherwise intact unventilated lobes. PGE$_1$ decreased perfusion pressure in the left pulmonary artery under conditions of controlled flow reflecting a decrease in pulmonary vascular resistance by vasodilatation of tonically contracted vascular smooth muscle. In our preparation, intrapulmonary PGE$_1$ infusion did not alter femoral arterial pressure which suggests that PGE$_1$ is inactivated in the fetal lung. Implications for PGE$_1$ in the newborn with respiratory distress and increased pulmonary vascular resistance are discussed.

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