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Hemodynamic Effects of Postpulmonary Administration of Prostaglandin D_2 in Fetal Animals[1] (42111)

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Abstract. Dose-response relationships in pulmonary vascular resistance (PVR), mean systemic arterial pressure (SAP), and heart rate (HR) to left atrial administration of prostaglandin D_2 (PGD_2) were determined in five fetal lambs. Fetuses were delivered by cesarean section from chloralose anesthetized ewes with the umbilical circulation maintained intact. Fetuses were prevented from breathing thus maintaining pulmonary vascular tone in the elevated fetal state. Blood was withdrawn from the inferior vena cava and pumped at constant flow into the lower left lobe of the fetal lung. Postpulmonary infusions of PGD_2 brought about dose-dependent decreases in pulmonary vascular resistance. Heart rate tended to increase in fetal lambs. Mean systemic arterial pressure increased in the fetal lambs at all doses tested except for the largest dose (44.14 $\mu g/kg \cdot min$), which produced slight hypotension. These data demonstrate that exposure to the systemic circulation prior to entering the pulmonary vasculature does not alter the preferential dilator action of PGD_2 on fetal pulmonary vessels nor does it produce significant systemic hypotension.

Age-specific differences in responses of the pulmonary vasculature to intrapulmonary infusions of prostaglandin D_2 (PGD_2) and their possible mechanisms have been reported previously. Cassin *et al.* (1) demonstrated that PGD_2, when infused directly into the pulmonary artery, dilates the fetal pulmonary circulation, produces a dose-dependent biphasic response in the newborn, and causes pulmonary vasoconstriction in the adult. Also demonstrated was the absence of a significant systemic hypotension by means of administration of PGD_2. These studies are in contrast to those of Lock *et al.* (2) who reported only a pulmonary pressor response to PGD_2 in newborn sheep (6–26 days of age) whether normoxic or hypoxic. However, the studies of Soiffer *et al.* (3) have corroborated our data showing a pulmonary dilator effect in ventilated near term fetal lambs. These and other studies (4–6) have confirmed the absence of systemic hypotension in fetal and newborn lambs treated with PGD_2 after being subjected to hypoxic pulmonary vasoconstriction. Preferential pulmonary vasodilation without systemic effects are significant findings in light of substantial systemic hypotension caused by other dilator prostaglandins (7–10). A recent paper by Soiffer *et al.* (3) on newborn lambs (1–30 days of age) chronically instrumented, made hypoxic, and treated with PGD_2 has provided further evidence of an age-related effect of PGD_2. Under these conditions (in contrast to our studies) a dose-related biphasic response in newborn lambs (1–8 days of age) was not observed. A clinical need still remains for a drug that can specifically increase pulmonary blood flow without creating a fall in systemic arterial pressure to be used in the treatment of newborns with persistent pulmonary hypertension. The purpose of the present study was to evaluate the effects of postpulmonary (left arterial) infusions of PGD_2 on the pulmonary and systemic circulations of unventilated perinatal lambs.

Materials and Methods. Five fetal lambs were delivered by cesarean section from chloralose anesthetized ewes (50 mg/kg iv, supplemented with 10 mg/kg · hr). Fetuses were positioned on a heating pad adjacent to the mother with the umbilical circulation maintained intact. The fetal abdomen was sutured to the uterus to prevent stretching and/or cooling of the cord. Fetal colonic temperature was maintained between 38 and 40°C. Fe-

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tuses were prevented from breathing by means of a saline-filled rubber bag placed over the head. Following tracheostomy and insertion of a saline-filled endotracheal tube closed to ambient air, the fetal head cover was removed. A catheter was placed in the descending aorta via a femoral artery for monitoring mean systemic arterial pressure ($\overline{SAP}$) and arterial blood gas analysis (Instrumentation Laboratory pH/blood gas analyzer 213). A left thoracotomy was performed and the left pulmonary artery isolated. After administration of heparin (2000 U/kg), a catheter was positioned in the inferior vena cava at a level cranial to the hepatic veins; the left atrium and left pulmonary artery were cannulated. A double lumen catheter was placed in the atrium to facilitate simultaneous drug infusion and pressure recording. Blood was withdrawn from the inferior vena cava and pumped (Cole-Parmer Masterflex Pump, No. 7016) into the left pulmonary artery at a constant flow rate. This technique, described in detail previously (7), perfuses approximately 35% of total lung mass and allows mean left pulmonary arterial perfusion pressure ($\overline{PAP}$), mean left atrial pressure ($\overline{LAP}$), and ventricular heart rate (HR) to be monitored (Statham P23DC transducers). Left pulmonary arterial blood flow ($\dot{Q}$) was also measured (Statham flowmeter with *in vivo* metric 3.0-mm cannulating electromagnetic flow probe). Perfusion rates were set so that $\overline{PAP} \geq \overline{SAP}$. All measurements were continuously recorded on a Gould Brush 480 eight-channel polygraph and periodically sampled and recorded by an Apple II plus microcomputer. From these variables, left pulmonary vascular resistance (PVR, mmHg·kg·min/ml) was calculated as pulmonary arterial pressure minus left atrial pressure divided by flow per unit body weight of animal. PGD_2 (Upjohn), diluted with saline, was infused (Harvard infusion pump) at several concentrations for 1 min at various rates into the left atrium. Values for PVR, $\overline{SAP}$, and HR, measured before an infusion (control) and at the peak responses to an infusion, were used to calculate maximum percentage changes evoked by a given dose of PGD_2. Regression analyses (method of least-squares) were performed on these data after log transformation of doses to evaluate the relationship between changes in PVR, $\overline{SAP}$, and HR and a range of doses of PGD_2.

Results. PGD_2 administered directly into the left atrium of fetal lambs resulted in dose-dependent decreases in left pulmonary arterial pressure. Figure 1A shows the relationship between various doses delivered as 1-min infusions to fetal lambs and the percentage change in PVR. Decreases in PVR varied from 2% at an infusion rate of 0.81 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to 66% at an infusion rate of 29·42 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The regression analysis for the 1-min infusion data resulted in a best-fit line (Fig. 1) having the equation $y = -1.117 - 34.01 \log X$ and a correlation coefficient (r) of 0.87 ($P < 0.05$). Analyses of arterial blood samples ($n = 19$) taken from the fetal lambs gave mean blood gas val-

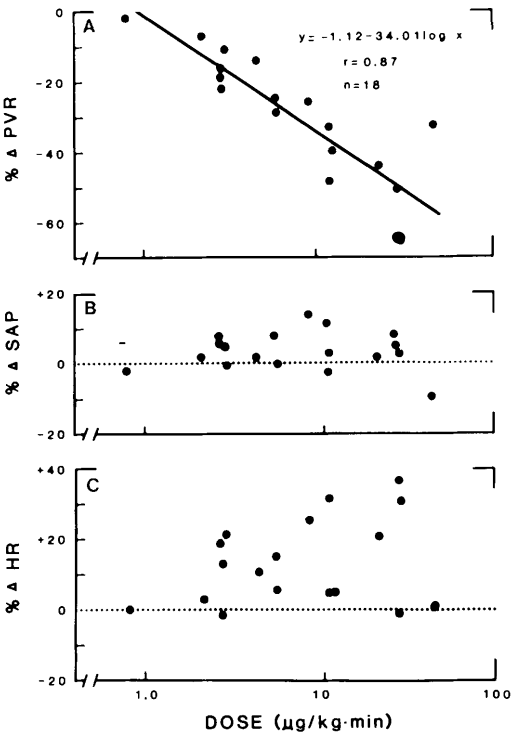

FIG. 1. (A) Relationship between the log dose (μg/kg·min) of PGD_2 infused for 1 min into the left atrium of fetal sheep and the maximum response in pulmonary vascular resistance (% change from control values). (B) Maximum responses in systemic arterial pressure (% change from control) for the various doses tested. (C) Maximum responses in ventricular heart rate (% change from control) for the various doses.

ues of pO_2 = 25.2 ± 0.96 torr and pCO_2 = 57.3 ± 2.16 torr and a mean pH = 7.289 ± 0.016 (±SE).

Figures 1B and C show percentage change in $\overline{SAP}$ and HR, respectively, for the various infusions of PGD_2. Baseline values for PVR, $\overline{SAP}$, and HR were 0.94 ± 0.07, 56.09 ± 1.86, 232 ± 11.21 (±SE), respectively. The usual response in fetal lambs was to increase $\overline{SAP}$ and HR. Heart rate increased (maximum increase 37% of control) or was unchanged in 89% of the experiments on fetal lambs; 11% of the experiments showed decreases of 1% of control. Heart rate responses were weakly related to dose (r = 0.3). $\overline{SAP}$ responses were not related to dose (r = 0). The largest dose tested in the fetal lamb (44.41 μg/kg • min) produced a $\overline{SAP}$ decrease of 10% of control.

Discussion. The concomitant production of systemic hypotension by most vasodilator agents has precluded their use in the treatment of persistent fetal circulation or persistent pulmonary hypertension of the neonate, a severe disease of the near term infant, characterized by cyanosis, elevated pulmonary vascular resistance, and right to left shunting at the ductus arteriosus and foramen ovale. Drugs which have been used as dilators to treat persistent pulmonary hypertension include tolazoline and prostacyclin (11). Unfortunately these agents lack specificity as pulmonary dilators and may have complicating side effects (11–14).

The results of this study demonstrate that the postpulmonary administration of PGD_2 produces dose-dependent dilatation of the fetal pulmonary circulation. Equally important is the finding that, except for the largest dose tested, this route of delivery may produce an increase in $\overline{SAP}$ and HR in the fetal lamb, rather than a systemic hypotension as seen with other dilators.

An earlier study carried out in this laboratory demonstrated similar responses in PVR, $\overline{SAP}$, and HR to 1-min infusions of PGD_2 into the left pulmonary artery of fetal goats (1). The major differences between the earlier and the present study are that larger doses of PGD_2 are required for threshold responses via intraatrial infusion; and intrapulmonary infusion of PGD_2, over a wide range of doses, tended to increase systemic blood pressure, whereas the largest dose (44.4 μg/kg • min) administered intraatrially caused a slight systemic hypotension. The reason(s) for these differences is not known. They may represent species-specific differences between goat and sheep. Alternatively, these differences may be due to the route of administration. PGD_2 has been shown to be enzymatically converted to $PGF_{2\alpha}$ (a vasoconstrictor) in the blood of sheep (15) and monkeys (16). Likewise, the lung is known to be metabolically active with regard to many prostanoid compounds and may contribute to the modification of vasoactive compounds affecting the systemic circulation. The different routes of administration used in the two studies, intrapulmonary vs postpulmonary, present the PGD_2 to the various body components in different sequences of exposure. Thus, the ratios of metabolite(s) to precursor presented to the various vascular beds may vary. Additionally, it has been shown that many exogenous vasoactive compounds elicit the release of other regulatory agents (17, 18). Regardless of the mechanism involved, these data further support the potential usefulness of PGD_2 as a specific dilator of the pulmonary circulation in the treatment of infants with persistent fetal circulation.

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