0031-3998/86/2006-0565$02.00/0
PEDIATRIC RESEARCH

Vol. 20, No. 6, 1986
Printed in U.S.A.

Effects of Prostaglandin H2 on Perinatal Pulmonary Circulation

MARY L. TOD,[1] SIDNEY CASSIN, DENNIS B. McNAMARA, AND PHILIP J. KADOWITZ

Departments of Physiology and Pediatrics, College of Medicine, University of Florida, Gainesville, Florida 32610 and Department of Pharmacology, Tulane Medical School, New Orleans, Louisiana 70112

ABSTRACT. A pivotal intermediate in prostaglandin (PG) biosynthesis is the endoperoxide PGH2. This endoperoxide is capable of eliciting direct responses in biological systems without undergoing conversion to other PGs. Effects of PGH2 include stimulation of platelet aggregation and vascular smooth muscle contraction *in vitro*; injections of PGH2 *in vivo* cause increases in pulmonary arterial pressure. The response of the pulmonary vasculature of perinatal lambs to PGH2 was measured using an *in situ* pump-perfused left lower lung preparation. Intrapulmonary injections of PGH2 (0.24–0.61 μg/kg) into six unventilated fetal lambs (0.93–0.97 gestation) produced decreases in pulmonary vascular resistance (PVR) of 10–21%. The fall in PVR was rapid in onset, reached a peak at 10 s after injection, and returned to baseline within 35 s. Following ventilation (F_{IO_2} = 0.21) of fetal lambs, injections of PGH2 (0.24–0.61 μg/kg) caused increases in PVR (ave increase = 50% over control PVR). The pulmonary pressor response to PGH2 in ventilated fetal lambs was depressed almost 50% by inhibition of thromboxane synthetase. Injections of a "heat-inactivated" PGH2 did not affect PVR in ventilated fetuses. We did not observe any effects on systemic blood pressure or heart rate of intrapulmonary arterial injections of PGH2. These findings suggest a metabolism of PGH2 to dilator PGs before ventilation and constrictor PGs and thromboxanes after ventilation, and/or direct effects of PGH2 on vascular smooth muscle that are dependent on existing vascular tone. (*Pediatr Res* 20: 565–569, 1986)

Abbreviations

PG, prostaglandin
PVR, pulmonary vascular resistance
SAP, systemic arterial pressure
TX, thromboxane
PAP, pulmonary arterial pressure
LAP, left atrial pressure
$\dot{Q}$, pulmonary arterial flow

PGH2 functions as the key intermediate in PG synthesis from which the stable products, PGD2, PGE2, and $PGF2_{\alpha}$, as well as the unstable compounds, PGI2 and TXA2, are derived. The terminal enzymes that yield these various products are present in varying amounts and activities in different organs, and this distribution contributes to the wide range of responses of individual systems to release of PGs (1–6). There is evidence that PGH2 is capable of eliciting direct responses to biological systems without undergoing conversion to other PGs (7, 8). Kadowitz *et al.* (9) demonstrated the ability of PGH2 to contract isolated segments of canine intrapulmonary vein. Additionally, bolus injections of PGH2 caused increases in lobar arterial and small vein pressures in pump-perfused canine lungs (9). Unanesthetized adult sheep responded to infusions of PGH2 with dose-related increases of pulmonary arterial pressure (10). In both of these studies, a stable analog of PGH2 also produced pulmonary vasoconstriction (9, 10). Endoperoxide analogs have been shown to cause dose-dependent increases in PVR and SAP in perinatal goats (11). Recently it was demonstrated that increases in PVR produced by infusions of arachidonic acid in perinatal lambs were not abolished by TX synthetase inhibition (12). It was proposed that a portion of the arachidonate-induced increase in PVR was due to PG endoperoxides. Thus, the effects of PGH2 were studied in pump-perfused lungs of perinatal lambs in the present study.

MATERIALS AND METHODS

Surgical preparation. Complete details of the surgical procedure for the *in situ* pump-perfused lower left lung preparation in perinatal lambs have been described previously (13, 14). Mothers of seven fetal lambs (0.93–0.97 gestation, weight = 3.6 ± 0.1 kg) were anesthetized with chloralose, and fetuses were delivered by cesarean section. Exteriorized fetuses were placed on a warmed table adjacent to the ewe with umbilical circulation undisturbed. A saline-filled rubber bag was placed over the fetal head to prevent breathing, and the fetal abdomen was sutured to the maternal skin to minimize exposure of the umbilical cord. A tracheal cannula filled with warm saline was placed in the fetal trachea, and the head cover was removed. Colonic temperature was monitored (Yellow Springs Instrument) and maintained between 38 and 40° C by infrared lamp and heating pad. Fetuses were prepared surgically so that left PAP, LAP, SAP, and heart rate were monitored continuously under conditions of constant left $\dot{Q}$. Flow through the ductus arteriosus and to the right lung was not disturbed. Pulmonary flow was set at a level at which PAP was equal to or slightly greater than mean SAP. By maintaining $\dot{Q}$ constant, changes in PAP reflected changes in PVR, calculated as the pressure drop from PAP to LAP divided by left pulmonary blood flow per kg body weight.

Experimental procedure. PGH2 was prepared from arachidonic acid, isolated and purified as described by Egan *et al.* (15) and She *et al.* (16). Immediately before injection of PGH2, an aliquot of the stock solution, which was stored in hexane:ether (4:6) solution at −85° C, was dried under a stream of nitrogen, diluted with cold saline, and drawn into a chilled Hamilton

Received October 23, 1985; accepted February 4, 1986.
Correspondence Dr. Sidney Cassin, Department of Physiology, Box J-274, JHMHC, College of Medicine, University of Florida, Gainesville, FL 32610.
This study was supported in part by National Institutes of Health Grant HL10834, and by Cooperative Funds of the Florida Heart Association and its chapters (AG 156).
[1] Present address The Johns Hopkins Medical Institutions at the Francis Scott Key Medical Center, Division of Pulmonary Medicine, 4940 Eastern Avenue, Baltimore, MD 21224.

syringe. PGH2 dissolved in water decomposes rapidly with a half-life of 5 min at 37° C or 10 min at 20° C in buffer at pH 7–8. An injection of 0.1 ml of various concentrations of PGH2 was performed within 15 s of dilution with saline. The concentrations of PGH2 used were 1.0, 10.0, 20.0, and 40.0 μg/ml. OKY-1581 (Ono Pharmaceutical Co.), a pyridine derivative, or UK 37,248-01 (Pfizer Chemical Co.), an imidazole derivative, was used to inhibit TX synthesis. OKY-1581 was diluted with saline to a concentration of 50 mg/ml and 1.0 ml was injected into the pulmonary arterial circuit. UK 37,248-01 was diluted with saline to a concentration of 6.0 or 10.0 mg/ml, so that 1.0 ml of solution gave a dose of approximately 2 mg/kg. These doses were greater than the effective doses in rabbits (17).

Following the surgical preparation, baseline values for pressures and flow in fetuses were established, and arterial blood gases and pH were analyzed. (Criteria for rejection of hemodynamic data in unventilated fetuses were arterial blood samples with pH < 7.20, PO_2 < 15 mm Hg, or PCO_2 > 60 mm Hg.) After baseline values were obtained (Table 1), bolus injections of PGH2 were made into the pulmonary arterial circuit. Doses were administered in random order. After several doses were given to fetuses, ventilation (FIO_2 = 0.21) was initiated with a Harvard respirator or a Healthdyne infant ventilator, and the umbilical cord was occluded. Following the ventilation-induced fall in PAP, $\dot{Q}$ was increased to reflect the normal increase in pulmonary perfusion occurring at birth. Control values were observed (Table 1), and bolus injections of PGH2 were administered to ventilated fetuses. (Criteria for rejection of hemodynamic data in ventilated fetuses were arterial blood samples with pH < 7.30, PO_2 < 75 mm Hg, and PCO_2 > 50 mm Hg.) After several injections, a TX synthetase inhibitor was injected into the pulmonary arterial circuit, and doses of PGH2 were repeated. One animal received two doses of OKY-1581 (separated by 40 min and two injections of PGH2), two received only UK 37,248-01, and one received a dose of OKY-1581, followed by an injection of PGH2 and then by a dose of UK 37,248-01, followed by a second injection of PGH2 (separated by at least 30 min). Due to deterioration of animal preparations after several injections, some animals did not receive all doses of PGH2, and each of the ventilated fetuses did not receive a TX synthesis blocker.

The following variables were sampled 60 s before injection, at 5-s intervals for the 1st min, and also at 120 s: PAP, LAP, $\dot{Q}$, mean SAP, and heart rate. The readings at 0 and −60 s were averaged to give a control value for the variables PVR and mean SAP. The control values were set to 100%, and the values at the remaining time intervals were expressed as a percentage of the control value. Each of the treatments within a group (fetus, ventilated fetus, and ventilated fetus with TX synthetase inhibition) was analyzed using a one-way analysis of variance with repeated measures, and differences between means were tested with the Newman-Keuls test (18). Differences between ventilated fetuses with and without TX synthetase inhibition were tested using the unpaired Student's *t* test. Differences cited were statistically significant at $p < 0.05$.

RESULTS

The average responses of the pulmonary circulation of six fetal unventilated lambs to 10 bolus injections of PGH2 are shown in Figure 1 and Table 2. Doses of PGH2 ranged from 0.24–0.61 μg/kg (average dose = 0.43 ± 0.06 μg/kg); however, there was not a dose-dependent relationship over this range of doses. Injections of PGH2 consistently produced decreases in PVR of 10–21%. The fall in PVR was rapid in onset, reached a peak at 10 s after injection, and returned to baseline within 35 s. Values at 5, 10, 15, 20, and 25 s were significantly ($p < 0.01$) different from the value at 0 s. The peak response was 1.03 PVR units less than the control PVR. At the doses of PGH2 injected, there was no effect on SAP.

Figure 2 and Table 2 show the results of 10 bolus injections of PGH2 in seven ventilated fetal lambs. The range of doses was 0.24–0.61 μg/kg (average dose = 0.39 ± 0.05 μg/kg). Within this dose range, injections of PGH2 caused significant pulmonary vasoconstriction (no significant change in LAP, Table 3), without producing a systemic blood pressure effect (Table 3). Increases in PVR were significantly different from control PVR at 10, 15, and 20 s (all $p < 0.01$). The peak pressor response occurred at

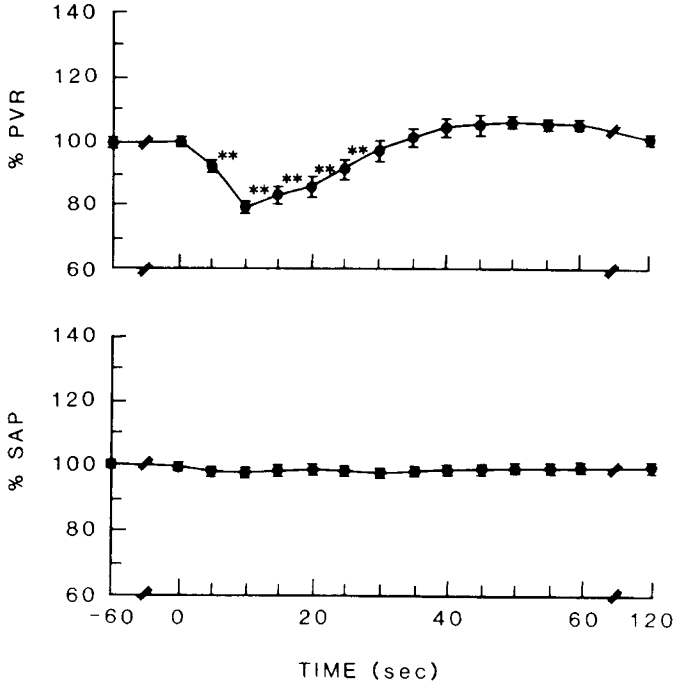

Fig. 1. Average pulmonary and systemic responses to bolus injections of PGH2 are shown for six unventilated fetal lambs (10 injections, average dose = 0.43 ± 0.06 μg/kg). Data are expressed as mean ± SEM. *Points* marked with *asterisks* are significantly different from the value at 0; ** $p < 0.01$.

Table 1. *Control values in unventilated and ventilated fetal lambs**

A. Hemodynamic data	PAP (mm Hg)	SAP (mm Hg)	$\dot{Q}$ (ml/kg min)	PVR (mm Hg kg min/ml)
1. Unventilated fetuses (n = 10)	70.9 ± 2.0	60.4 ± 1.9	16.5 ± 2.0	4.77 ± 0.52
2. Ventilated fetuses (n = 10)	27.4 ± 1.4	42.3 ± 3.0	24.00 ± 1.95	1.12 ± 0.12

B. Arterial blood samples	pH	PO_2 (mm Hg)	PCO_2 (mm Hg)
1. Unventilated fetuses (n = 10)	7.31 ± 0.01	25.9 ± 0.6	52.7 ± 1.4
2. Ventilated fetuses (n = 10)	7.44 ± 0.02	112.1 ± 7.6	33.2 ± 2.0

* Data are control values for mean PAP, mean SAP, $\dot{Q}$, PVR, and arterial blood gases and pH in six unventilated and seven ventilated fetal lambs. Data are expressed as mean ± SEM. The number of observations for the control values is indicated by n.

Table 2. *Mean values (± SEM) for PVR (mm Hg·kg·min/ml) before, during, and after PGH_2*

Time (s):	−60	0	5	10	15	20	25	30	35	40	45	50	55	60	120
Unventilated (n = 10)	4.75	4.78	4.39*	3.73*	3.92*	4.04*	4.30*	4.56	4.78	4.93	4.95	4.99	4.95	4.95	4.75
	±0.51	±0.52	±0.49	±0.36	±0.42	±0.42	±0.43	±0.44	±0.46	±0.49	±0.49	±1.62	±1.61	±0.52	±0.50
Ventilated (n = 10)	1.11	1.12	1.14	1.60*	1.65*	1.42*	1.31	1.27	1.24	1.20	1.18	1.12	1.14	1.11	1.10
	±0.11	±0.11	±0.10	±0.13	±0.16	±0.16	±0.14	±0.13	±0.13	±0.10	±0.11	±0.31	±0.31	±0.10	±0.11
Ventilated post-TSI† (n = 7)	1.04	1.04	1.07	1.31*	1.19*	1.07	1.05	1.05	1.05	1.03	1.02	1.00	1.00	1.00	1.00
	±0.08	±0.08	±0.08	±0.07	±0.06	±0.06	±0.07	±0.08	±0.07	±0.08	±0.07	±0.07	±0.07	±0.07	±0.07

* Significantly different from −60 and 0, $p < 0.01$.
† Tx synthetase inhibition.

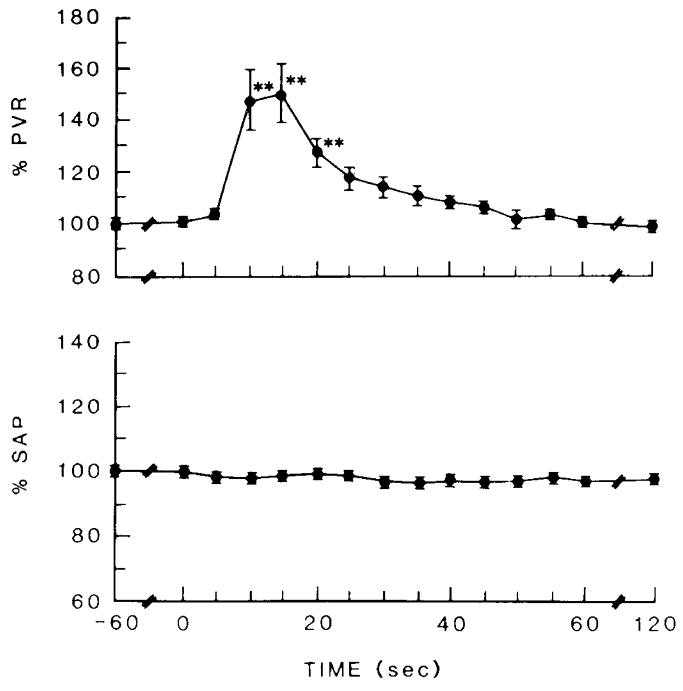

Fig. 2. Average pulmonary and systemic responses to bolus injections of PGH2 are shown for seven ventilated fetal lambs (10 injections, average dose = 0.39 ± 0.05 μg/kg). *Symbols* are as in Figure 1.

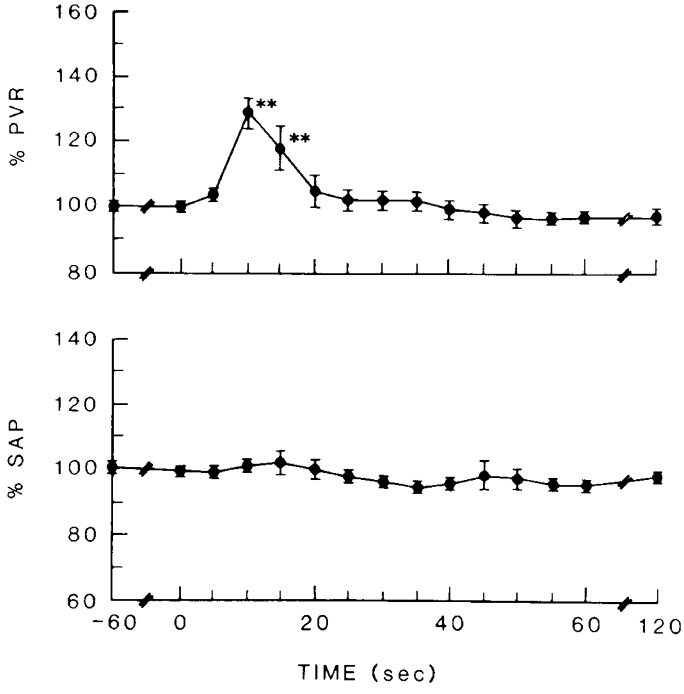

Fig. 3. Average pulmonary and systemic responses to bolus injections of PGH2 following TX synthetase inhibition (*TSI*) are shown for four ventilated fetal lambs (seven injections, ave dose = 0.31 ± 0.03 μg/kg). *Symbols* are as in Figure 1.

15 s, and it was 150% of the baseline value. PVR remained elevated above control values until 50 s after injection.

Four ventilated fetal lambs were treated with either OKY-1581 (50 mg) or UK 37,248-01 (2–3 mg/kg) to inhibit TX synthesis. There was no difference between the two blockers in the pulmonary response to PGH2; therefore, the data for the two drugs were combined (Fig. 3 and Table 2). Injections of PGH2 (average dose = 0.31 ± 0.03 μg/kg) following TX synthetase inhibition were able to cause significant ($p < 0.01$) increases in PVR at 10 and 15 s. The maximal response at 10 s was 128% of control PVR. This peak increase in PVR was 56% of the maximal increase in PVR in the lambs without the inhibitors. There were significant differences in the increases in PVR in response to PGH2 in ventilated fetal lambs with and without TX synthetase inhibition. In the group treated with inhibitors, the PGH2-induced increases in PVR were significantly depressed in comparison with the untreated group at 15, 20, 25, 30, 40, 45, and 55 s ($p < 0.05$ by unpaired t tests). There were no differences between the treated and untreated lambs in response of the systemic blood pressure to intrapulmonary injections of PGH2 (Table 3).

Control injections of ice-cold saline (0.1 ml) were given to two fetal lambs before ventilation and two different lambs after ventilation. These injections did not elicit any changes in PVR or mean SAP. In three fetal lambs before and after ventilation, injections were given of an "inactivated" PGH2. The endoperoxide was prepared in the same manner as for an injection, but the syringe containing the PGH2 in saline was allowed to sit on a warmed surface under light for at least 15 min before injection. There was no response of the pulmonary circulation to "inactivated" PGH2 injections in ventilated fetal lambs. There was a slight, but significant ($p < 0.01$), decrease in PVR in unventilated fetal lambs to 94% of control PVR, perhaps due to degradation of PGH2 to PGE2. Systemic pressure was not affected by intrapulmonary injections of "inactivated" PGH2.

DISCUSSION

The finding that injections of PGH2 into the pulmonary circulation of ventilated fetal lambs produced increases in PVR confirms earlier reports on PGH2 and the adult lung (9, 10). Over the dose range used in this study, PGH2 did not exhibit a dose-dependent relationship with PVR. The range was small, primarily due to limited quantities of PGH2 available. The average dose of PGH2 in the present study (0.39 μg/kg) was approximately four times the dose used in adult dogs (9). The increase in PVR in ventilated fetal lambs was 50% above baseline, while the increase in lobar arterial pressure in adult dogs was 24% greater than control. Bowers et al. (10) reported a tripling of PVR at steady state during an infusion of 0.25 μg/kg·min PGH2 into the superior vena cava of unanesthetized adult sheep. The greater responsiveness of the pulmonary circulation

Table 3. *Mean values (± SEM) for PAP, SAP, and LAP (mm Hg) before, during, and after PGH_2*

Time		−60	0	5	10	15	20	25	30	35	40	45	50	55	60	120
Unventilated (n = 10)	PAP	70.62	71.09	65.37*	56.73*	58.79*	60.72*	65.10*	69.30	72.36	74.29	76.64	74.79	74.38	74.19	71.18
		±1.96	±2.13	±2.31	±2.35	±2.61	±2.91	±3.31	±3.51	±3.32	±3.14	±3.07	±2.86	±2.80	±2.73	±2.61
	SAP	60.61	60.17	59.51	59.34	59.31	59.63	59.39	59.09	59.40	59.69	59.62	59.88	59.74	59.91	60.11
		±1.81	±1.92	±1.95	±1.84	±1.71	±1.63	±1.59	±1.75	±1.73	±1.67	±1.72	±1.70	±1.75	±1.70	±1.93
	LAP	1.13	1.17	1.22	1.25	1.23	1.15	1.13	1.20	1.18	1.19	1.29	1.15	1.23	1.16	1.36
		±0.19	±0.26	±0.22	±0.17	±0.16	±0.17	±0.18	±0.17	±0.17	±0.17	±0.15	±0.19	±0.18	±0.20	±0.19
Ventilated (n = 10)	PAP	27.28	27.40	28.09	38.56*	39.12*	34.00*	31.66	31.05	30.12	29.32	28.86	27.82	27.89	27.5	26.58
		±1.35	±1.36	±1.32	±2.18	±2.14	±1.71	±2.01	±2.00	±2.06	±1.86	±1.69	±1.79	±1.57	±1.60	±1.34
	SAP	42.33	42.33	41.77	41.44	41.59	41.93	41.89	41.18	40.90	41.19	40.82	41.02	41.41	40.91	41.24
		±2.88	±3.14	±3.22	±3.03	±2.85	±2.99	±3.19	±3.10	±3.11	±3.17	±2.86	±3.02	±2.99	±3.00	±3.10
	LAP	2.08	2.05	2.07	2.05	2.09	2.14	2.05	2.16	2.14	1.93	2.04	2.06	1.84	2.1	1.89
		±0.30	±0.33	±0.36	±0.36	±0.34	±0.34	±0.38	±0.36	±0.33	±0.38	±0.35	±0.38	±0.37	±0.37	±0.37
Ventilated Post-TSI† (n = 7)	PAP	29.49	29.72	30.61	36.97*	33.76*	30.46	29.92	29.93	29.91	29.26	29.03	28.71	28.64	28.66	28.43
		±2.47	±2.52	±2.43	±2.09	±1.84	±2.01	±2.23	±2.52	±2.38	±2.47	±2.32	±2.33	±2.33	±2.26	±2.39
	SAP	34.45	33.97	33.87	34.38	34.55	34.03	33.23	32.78	32.11	32.42	33.15	32.9	32.59	32.62	33.49
		±3.01	±3.04	±3.08	±2.77	±2.46	±2.62	±2.58	±2.73	±2.69	±2.57	±2.37	±2.34	±2.61	±2.7	±2.85
	LAP	1.64	1.77	1.82	1.85	1.73	1.67	1.71	1.59	1.59	1.56	1.66	1.7	1.68	1.72	1.45
		±0.26	±0.42	±0.35	±0.28	±0.27	±0.3	±0.32	±0.28	±0.3	±0.29	±0.29	±0.27	±0.29	±0.29	±0.3

* Significantly different from −60 and 0 at $p < 0.01$.

† Tx synthetase inhibition.

of adult sheep as compared with ventilated fetal lambs could be due to lack of anesthesia in the adults. Also, in the adults the PGH2 was infused over a period of at least 15 min, and a steady state increase in PVR was observed. In the present study, PGH2 injections lasted approximately 3 s, so that comparisons with responses obtained during infusions are difficult.

Intrapulmonary injections of PGH2 produced decreases in PVR in fetal unventilated lambs and increases in PVR in ventilated fetuses. The doses of PGH2 administered to the two groups were similar; thus, there should be no differences in response due to differing substrate concentrations. Major differences which existed between the ventilated and unventilated fetal lambs were decreased PVR, increased $\dot{Q}$, increased PO_2 and decreased PCO_2 after ventilation (Table 1); changes reflecting the normal events which occur at birth (19). Decreased pulmonary vascular tone may be the most important factor in explaining the differing responses to PGH2. Studies in adult cat lung by Hyman *et al.* (20) demonstrated that infusion of the bisenoic PG precursor, arachidonic acid, produced pulmonary vasodilatation when pulmonary vascular tone was elevated. These investigators proposed that the pulmonary vascular response to exogenous arachidonate infusion was dependent in part on the preexisting level of PVR. This agreed with the finding by Gerber *et al.* (21) that PVR in dogs undergoing a hypoxic pressor response was returned toward prehypoxia baseline values by infusion of arachidonic acid.

In contrast, an earlier study (11) reported only pulmonary vasoconstriction when arachidonic acid was infused into the pulmonary circulation of fetal and neonatal goats. These findings were confirmed in ventilated fetal and neonatal lambs (14) which had low pulmonary vascular tone (comparable to that of the ventilated fetuses in the present study). However, when PVR was increased above baseline by 6% hypoxia, infusion of arachidonic acid at all doses produced only further increases in PVR (14). The use of OKY-1581 to inhibit TX synthetase prior to infusions of arachidonic acid did not prevent pulmonary vasoconstriction in ventilated fetal and neonatal lambs (12). Thus, the remaining pulmonary pressor response was attributed to formation and actions of PGH2. While the data in ventilated fetal lambs injected with PGH2 agree with the above studies, there are differing results from unventilated fetuses receiving PGH2 and arachidonic acid.

Histamine, a chemically different compound, also produces pulmonary vasoconstriction and vasodilatation in animals of differing ages (19, 22). In fetal lambs prior to ventilation, injection of histamine caused a very large increase in pulmonary blood flow; after ventilation, the same dose caused little or no increase in pulmonary blood flow (19). In adult dogs, histamine actively constricted small lobar veins (22). PGD2 has similar actions on the pulmonary circulation (23). Infusion of PGD2 into the pulmonary circulation of unventilated fetal goats caused dose-dependent decreases in PVR. In ventilated fetuses and newborn lambs, infusions of PGD2 at doses greater than 8.0 μg/kg·min resulted in increases in PVR (23). It is conceivable that PGD2 could be formed from the injections of PGH2 in the present study.

Freidman *et al.* (24) have shown that fetal microsomes are capable of producing PGE2, PGI2, and TXA2 enzymatically from PGH2. Prostacyclin synthetase exhibited enzyme saturation at low levels of PGH2, and formation of PGI2 was low throughout gestation. Thromboxane synthetase showed low activity when PGH2 concentrations were low, but at high PGH2 concentrations (400 ng PGH2/250 μg lung homogenate protein), TXs were a major product of PG synthesis in late term fetal lung. The product formed in greatest quantities by fetal lamb lung homogenates was PGE2 (24), and formation of PGE2 by fetal goat lung microsomes was enhanced by addition of GSH (25). Thus, levels of endogenous GSH in fetal lung may exert an important control over products of PGH2 metabolism, with greater amounts of TXs formed in the absence of GSH and more PGE2 formed in the presence of GSH (25). Factors involved in the regulation of GSH in fetal lung are unknown.

The above studies on PGH2 metabolism in fetal and neonatal lung microsomes do not indicate whether PGD2 production was assayed. It has been shown that there is a specific glutathione-S-transferase present in adult sheep lung which causes production of large amounts of $PGF2\alpha$ and PGD2 (26). Incubation of the purified enzyme with PGH2 resulted in three times more PGD2 than PGE2 produced (26). Thus, if this enzyme were present and active in fetal sheep lungs, formation of PGD2 could be a significant factor in the response to PGH2.

TXs are potent constrictors of vascular smooth muscle *in vitro* (7); PGE2 and PGI2 are vasodilators of fetal and neonatal pulmonary and systemic circulations (13, 27).

In summary, injections of PGH2 caused increases in PVR in

ventilated fetuses. This is consistent with 1) direct effect of PGH2 on vascular smooth muscle (7) and 2) formation of products with vasoconstrictor activity, such as TXA2, PGD2, and PGF2α. Inhibition of TX synthetase with either OKY-1581 or UK 37,248-01 resulted in a reduction of pulmonary vasoconstriction, but did not abolish the response completely (Fig. 3 and Table 2). In contrast, unventilated fetal lambs always responded to injections of PGH2 with decreases in PVR. These findings suggest metabolism of PGH2 to PGI2, PGD2, and/or PGE2, with little direct action of PGH2 on fetal pulmonary vessels. It is possible that ventilation of fetal lungs alters the end products of PGH2 metabolism, perhaps by limiting availability of GSH, so that after ventilation more TXs are formed in response to a bolus of PGH2. Alternatively, the pulmonary vascular response to PGH2 may depend in part on existing basal pulmonary vascular tone.

Acknowledgments. The authors acknowledge the excellent technical assistance of H. Kuck, T. Cupp, R. Shoup, and R. Su. The authors thank S. Jones and John Hatton for help in preparing the manuscript, and Dr. L. S. Berman for obtaining the Healthdyne infant ventilator.

OKY-1581 was the kind gift of Ono Pharmaceutical Company and UK 37,248-01 was a gift from Pfizer Chemical Company.

REFERENCES

1. Ferreira SH, Vane JR 1967 Prostaglandins: their disappearance from and release into the circulation. Nature 216:868–873
2. Gryglewski RJ, Bunting S, Moncada S, Flower RJ, Vane JR 1976 Arterial walls are protected against deposition of platelet thrombi by a substance (prostaglandin X) which they make from prostaglandin endoperoxides. Prostaglandins 12:685–713
3. Hensby CN 1974 The enzymatic conversion of prostaglandin D2 to prostaglandin F2alpha. Prostaglandins 8:369–375
4. Needleman P, Moncada S, Bunting S, Vane JR, Hamberg M, Samuelsson B 1976 Identification of an enzyme in platelet microsomes which generates thromboxane A2 from prostaglandin endoperoxides. Nature 261:558–560
5. Nugteren DH, Hazelhof E 1973 Isolation and properties of intermediates in prostaglandin biosynthesis. Biochim Biophys Acta 326:448–461
6. Sun FF, Chapman JP, McGuire JC 1977 Metabolism of prostaglandin endoperoxide in animal tissues. Prostaglandins 14:1055–1074
7. Hamberg M, Hedqvist P, Strandberg K, Svensson J, Samuelsson B 1975 Prostaglandin endoperoxides. IV. Effects on smooth muscle. Life Sci 16:451–462
8. Hamberg M, Svensson J, Samuelsson B 1974 Prostaglandin endoperoxides. A new concept concerning the mode of action and release of prostaglandins. Proc Natl Acad Sci USA 71:3824–3828
9. Kadowitz PJ, Gruetter CA, McNamara DB, Gorman RR, Spannhake EW, Hyman AL 1977 Comparative effects of endoperoxide PGH2 and an analog on the pulmonary vascular bed. J Appl Physiol 42:953–958
10. Bowers RE, Ellis EF, Brigham KL, Oates JA 1979 Effects of prostaglandin cyclic endoperoxides on the lung circulation of unanesthetized sheep. J Clin Invest 63:131–137
11. Tyler TL, Leffler CW, Cassin S 1978 Circulatory responses of perinatal goats to prostaglandin precursors. Prostaglandins Leukotrienes Med 1:213–229
12. Tod ML, Cassin S 1985 Thromboxane synthetase inhibition and perinatal pulmonary responses to arachidonic acid. J Appl Physiol 58:710–716
13. Cassin S, Tyler T, Leffler C, Wallis R 1979 Pulmonary and systemic vascular responses of perinatal goats to prostaglandins E1 and E2. Am J Physiol 236:H828–H832
14. Tod ML, Cassin S 1984 Perinatal pulmonary responses to arachidonic acid during normoxia and hypoxia. J Appl Physiol 57:977–983
15. Egan RW, Paxton J, Kuehl FA, Jr 1976 Mechanisms for irreversible self-deactivation of prostaglandin synthetase. J Biol Chem 251:7329–7335
16. She HS, McNamara DB, Spannhake EW, Hyman AL, Kadowitz PJ 1981 Metabolism of prostaglandin endoperoxide by microsomes from cat lung. Prostaglandins 21:531–541
17. Miyamoto T, Taniguchi K, Tanouchi T, Hirata F 1980 Selective inhibition of thromboxane synthetase: Pyridine and its derivatives. In: Samuelsson B, Ramwell PW, Paoletti R (eds). Advances in Prostaglandin and Thromboxane Research, Vol. 6. Raven Press, New York, pp 443–445
18. Winer BJ 1971 Statistical Principles of Experimental Design, 2 ed. McGraw-Hill Co., New York
19. Dawes GS, Mott JC 1962 The vascular tone of the foetal lung. J Physiol 164:465–477
20. Hyman AL, Spannhake EW, Kadowitz PJ 1980 Divergent responses to arachidonic acid in the feline pulmonary vascular bed. Am J Physiol 239(Heart Circ Physiol 8):H40–H46
21. Gerber JG, Voelkel N, Nies AS, McMurtry IF, Reeves JT 1980 Moderation of hypoxic vasoconstriction by infusion of arachidonic acid: Role of PGI2. J Appl Physiol 49:107–112
22. Hyman AL 1969 The direct effects of vasoactive agents on pulmonary veins. Studies of responses to acetylcholine, serotonin, histamine and isoproterenol in intact dogs. J Pharmacol Exp Ther 168:96–105
23. Cassin S, Tod M, Philips J, Frisinger J, Jordan J, Gibbs C 1981 Effects of prostaglandin D2 on perinatal circulation. Am J Physiol 240(Heart Circ Physiol 9):H755–H760
24. Friedman WF, Printz MF, Skidgel RA, Benson LN, Zednikova M 1982 Prostaglandins and the ductus arteriosus. In: Oates JA (ed). Prostaglandins and the Cardiovascular System. Raven Press, New York, pp 277–302
25. McNamara DB, Laird M, Hyman AL, Kadowitz PJ, Cassin S 1982 Prostaglandin H2 metabolism by fetal, newborn and adult goat lung. Fed Proc 41:1251
26. Christ-Hazelhof E, Nugteren DH, Van Dorp DA 1976 Conversions of prostaglandin endoperoxides by glutathione-S-transferases and serum albumin. Biochim Biophys Acta 450:450–461
27. Cassin S, Winikor I, Tod M, Philips J, Frisinger J, Jordan J, Gibbs C 1981 Effects of prostacyclin on fetal pulmonary circulation. Pediatr Pharmacol 1:197–207