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Hypoxia Stimulates Prostacyclin Synthesis by Neonatal Lungs

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Summary

Inhibition of prostaglandin cyclooxygenase augments hypoxic pulmonary vasoconstriction. We used a neonatal lamb lung preparation perfused with Krebs' bicarbonate buffer to characterize and quantify prostanoids produced by the pulmonary vasculature from endogenous arachidonic acid in the absence of formed blood elements during ventilation with normoxic and hypoxic gas mixtures. Prostaglandin (PG) I_2 synthesis increased from 6.4 ± 2.7 ng/min (SEM) during normoxic ventilation to 14.3 ± 5.4 ng/min during hypoxia and returned to 4.7 ± 1.2 ng/min with resumption of normoxia. These data demonstrate that hypoxia stimulates pulmonary vascular synthesis of prostaglandin I_2 from endogenous substrate in neonatal lambs and suggest that the augmentation of hypoxic pulmonary vasoconstriction by prostaglandin cyclooxygenase inhibition is due, at least in part, to interference with the synthesis of this vasodilator prostanoid.

Abbreviations

PG, prostanoid
PGI_2, prostacyclin
TXB_2, thromboxane B_2

Inhibition of prostaglandin cyclooxygenase augments hypoxic pulmonary vasoconstriction in adult mammals of several species (1, 12, 24, 27, 28). A possible explanation for this observation is that hypoxia or hypoxic pulmonary vasoconstriction induces the synthesis of a vasodilator PG that reduces the vasoconstriction. Inhibition of PG synthesis would remove this vasodilator PG and, thus, increase the hypoxic constriction. Indirect evidence supporting this hypothesis in the neonate includes the observations that: 1) PGI_2 is the most abundant PG produced by fetal bovine pulmonary arterial slices (22); 2) under normoxic conditions, PGI_2 is the most abundant PG produced by the newly ventilated neonatal lamb lung (10, 11); 3) PGI_2 is a pulmonary vasodilator in the fetal and neonatal lamb (3, 9, 13), and its vasodilatory effect on the neonatal pulmonary vasculature is more evident during hypoxic pulmonary vasoconstriction (13); and 4) hypoxic pulmonary vasoconstriction in premature and term neonatal goats is augmented by indomethacin, an inhibitor of PG synthesis (23). In the present study, we used a neonatal lamb lung preparation perfused with Krebs' bicarbonate buffer to characterize and quantify prostanoids produced by the pulmonary vasculature from endogenous arachidonic acid in the absence of formed blood elements. Pulmonary perfusate was collected during ventilation with normoxic and hypoxic gas mixtures. Analysis of these perfusates allowed determination of the effect of hypoxic pulmonary vasoconstriction on pulmonary vascular prostanoid synthesis.

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MATERIALS AND METHODS

Animal preparation. Fourteen neonatal lambs [10.7 ± 2.0 days old (SEM); 5.5 ± 1.6 kg) were anesthetized with 50 mg/kg α-chloralose IV. A tracheostomy was performed, and ventilation with room air was begun using a constant volume ventilator. A left thoracotomy was performed and the left lung was removed, leaving the mediastinum intact. Consequently, the right lung, which was to be perfused, was not exposed to the environment. The tidal volume was reduced by approximately 40%, the ductus arteriosus was ligated, and the left atrium was cannulated with a Teflon catheter. A repeat dose of 10 mg/kg α-chloralose was administered, and the pulmonary artery was ligated and cannulated, thus sacrificing the animal. Perfusion of the lung with 37°C Krebs' bicarbonate buffer, pH 7.4, containing 2 g glucose/liter equilibrated with 3% O_2, 5% CO_2, 92% N_2 was then begun using

a roller pump. The ventilating gas mixture was changed to 20% O_2, 5% CO_2, 75% N_2. The heart was clamped at the atrioventricular valves so that all perfusate exited through the left atrial catheter. The perfusate was not recirculated. During an initial 15-min equilibration period, formed elements cleared from the perfusate. A constant flow was maintained so that changes in pressure reflected changes in resistance. Flow was monitored electromagnetically. Pressure was monitored with a fluid-filled pressure transducer connected to a side arm of the inflow circuit just proximal to the pulmonary arterial catheter. Both signals were amplified and recorded with a direct-writing recorder.

Experimental protocol. After the 15-min equilibration period, pulmonary venous effluent was collected for 10 min. The ventilator gas mixture was then changed to 3% O_2, 5% CO_2, 92% N_2 reducing the pulmonary venous P_{O_2} from 85 to 33 mm Hg. One minute after the initiation of hypoxic ventilation, a second 10-min collection was begun. At the conclusion of this collection, the ventilating gas mixture was returned to 20% O_2, 5% CO_2, 75% N_2, and 10 min were allowed for return to normoxic conditions. Then a third 10-min collection was performed. The collected perfusates were stored at −60°C for later analysis.

Prostanoid analysis. The methods used are a modification of those which have been described and verified previously (8, 10). Each sample was treated thusly. The pulmonary venous effluents were allowed to thaw and 600 ng PGA_2 were added to each as an internal standard. A sample containing 600 ng PGA_2 and known amounts of PGE_2, 6-keto-$PGF_{1\alpha}$, TXB_2, and 6,15-diketo-13,14-dihydro-$PGF_{1\alpha}$ (Upjohn) were processed with each set of samples. Following acidification to pH 3 with formic acid, each sample was applied to an octadecylsilyl cartridge (Sep-Pak, Waters Associates, Inc.) that previously had been washed and wetted with 30 ml acetone, 30 ml hexane, 60 ml methanol, and 60 ml of water. The Sep-Pak containing the sample was washed with 20 ml of water followed by 20 ml petroleum ether, both of which were discarded. The PGs were eluted with 10 ml of ethyl acetate [modified from Powell (16)]. Fifteen ml of toluene was added to the 10 ml of ethyl acetate and the mixture was applied to a silica column (Adsorbosil, 8 cm × 5 mm, Anspec, Inc.). PGs on the column were washed with 25 ml of 60:40 toluene:ethyl acetate (discarded). PGs were eluted with 15 ml of 60:40:5:1 toluene:ethyl acetate:methanol:formic acid. The eluant was evaporated under vacuum and the invisible residue was transferred to a reaction vial for derivatization prior to analysis by gas chromatography with electron capture detection. Derivatization to pentafluorobenzyloximes of PG methyl ester trimethylsilyl ethers was accomplished as described perviously (8, 10). Analyses were performed on a Perkin-Elmer Sigma 4, equipped with heated splitless injector and ^{63}Ni electron capture detector. Gas-liquid chromatography was performed using 0.5 mm × 25 m SCOT OV101 capillaries (Scientific Glass Engineering) at 250°C and a column pressure of 140 mm Hg, with helium as the carrier. Injector and detector temperatures were 375°C.

Details and verification of methods used for quantification and mass spectrometric confirmation of derivatized standard structures have been published elsewhere (8). Briefly, the relative detector responses to PGA_2 and other PGs were determined from simultaneous extraction plus derivatization of known quantities of each. For each PG, a factor (Σ) encompassing all differences between PGs with respect to extraction, derivatization, and detector response, was calculated: $\Sigma = (W_x \cdot H_A)/(H_x \cdot W_A)$, where W_x is the quantity of PG_x, H_x is the detector response to PG_x, W_A is the quantity of PGA_2, and H_A is the detector response to PGA_2. PGs were quantified in the samples by comparison to PGA_2 added as the internal standard: $W_x = H_x \cdot W_A \cdot \Sigma \cdot H_A^{-1}$.

This method (8, 10) is capable of quantifying as little as 5 ng of PGD_2, PGE_2, 6-keto-$PGF_{1\alpha}$, TXB_2, 6-keto-PGE_1, or 6,15-diketo-13,14-dihydro-$PGF_{1\alpha}$ in the initial fluid sample.

Statistics. Results are reported as the mean ± standard error of the mean for 14 animals. Hemodynamic data and PG production were analyzed using a two-way analysis of variance allowing partitioning of variation into that due to treatments (normoxia, hypoxia, normoxia), replications (14 animals), and residual variation. The F for the effect of treatments was defined as the mean square for treatments divided by the mean square for residuals with significance defined as $P < 0.05$. When the effect of treatments was significant, the mean value of a hemodynamic or PG variable during hypoxia was compared with the average of the pre- and posthypoxia means of that variable using the t-test for planned comparisons among means as described by Snedecor and Cochran (20).

RESULTS

The results of these experiments are illustrated in Figure 1. Constant flow was maintained throughout each experiment, the mean flow being 2.2 ± 0.3 ml/min·kg body weight or 11.2 ± 1.1 ml/min. Hypoxia resulted in a significant rise of pulmonary perfusion pressure from 10.0 ± 2.3 to 14.1 ± 3.8 mm Hg, with return to 10.9 ± 2.5 mm Hg with resumption of normoxic ventilation. Calculated pulmonary vascular resistance increased significantly from a baseline during normoxia of 4.7 ± 0.8 to 5.9 ± 0.9 mm Hg/(ml/kg·min) during hypoxia, returning to 4.9 ± 0.9 mm Hg/(ml/kg·min) with return to normoxia. PGI_2 synthesis, measured as 6-keto$PGF_{1\alpha}$ increased significantly from 6.4 ± 2.7 ng/min during normoxic ventilation to 14.3 ± 5.4 ng/min during hypoxia and returned to 4.7 ± 1.2 ng/min with resumption of normoxia. A metabolite of PGI_2, co-migrating on the gas chromatographic column with synthetic 6,15-diketo-13,14-dihydro $PGF_{1\alpha}$, was detected sporadically and in concentrations far less than that of 6-keto-$PGF_{1\alpha}$. Thromboxane A_2 (as thromboxane B_2) was the only other prostanoid detected, and its synthesis did not change significantly with alveolar hypoxia (2.8

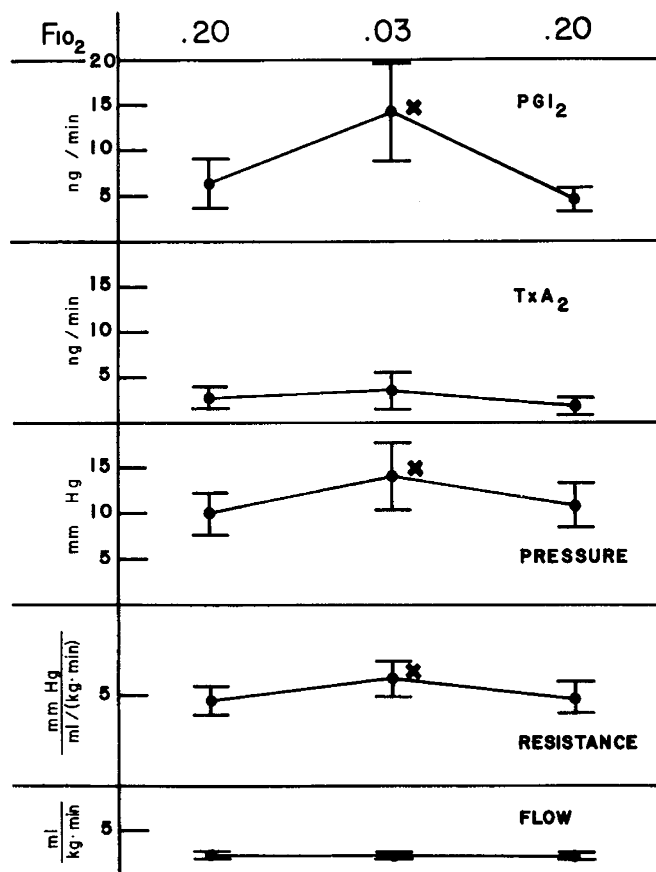

Fig. 1. Hypoxic pulmonary vasoconstriction and prostanoid synthesis in neonatal lambs. *Bars* indicate ±SEM. *Symbol* indicates significant difference between hypoxic period and average of pre- and posthypoxic control periods ($P < 0.05$; $n = 14$).

Table 1. *Analysis of variance tables for two-way classification*

Sources of variation	*df*	Sum of squares	Mean square	*F*	*P*
PGI_2					
Replications*	13	4060.30	312.33		
Treatments†	2	734.16	367.08	3.38	<0.05
Residuals	26	2820.58	108.48		
Total	41	7615.04			
TxA_2					
Replications	13	691.20	53.17		
Treatments	2	20.72	10.36	0.62	N.S.
Residuals	26	430.86	16.57		
Total	41	1142.78			
Pressure					
Replications	13	4321.37	332.41		
Treatments	2	126.70	63.35	3.66	<0.05
Residuals	26	450.34	17.32		
Total	41	4898.41			
Resistance					
Replications	13	400.81	30.83		
Treatments	2	11.34	5.67	6.16	<0.01
Residuals	26	23.87	0.92		
Total	41	436.02			

* Fourteen lambs.

† Three treatments: normoxia, hypoxia, normoxia.

± 1.1 ng/min prehypoxia; 3.6 ± 2.0 ng/min during hypoxia; 1.8 ± 0.9 ng/min posthypoxia). Analysis of variance tables for PGI_2, thromboxane A_2, pressure, and resistance are shown in Table 1.

DISCUSSION

The role of PGs in hypoxic pulmonary vasoconstriction has been of considerable interest since Said *et al.* (18) first suggested that alveolar hypoxia may induce PG synthesis. Since then, several groups have shown that inhibition of PG synthesis with a variety of cyclooxygenase inhibitors augments hypoxic pulmonary vasoconstriction (1, 12, 23, 24, 27, 28) in several species including newly ventilated and several-day-old neonatal goats (23). Augmentation of hypoxic pulmonary vasoconstriction following prostaglandin cyclooxygenase inhibition suggests that either alveolar hypoxia is associated with increased synthesis of a vasodilator PG by the pulmonary vasculature which blunts hypoxic pulmonary vasoconstriction or that cyclooxygenase inhibition diverts arachidonic acid to the lipoxygenase pathway causing increased synthesis of a vasoconstrictor leukotriene.

PGI_2 is a potent pulmonary vasodilator in the perinatal period (3, 9, 13) and is the major PG synthesized from endogenous arachidonic acid by the perinatal pulmonary vasculature under normoxic conditions (10, 11). The present study demonstrates that hypoxic pulmonary vasoconstriction is associated with an increased synthesis of PGI_2 from endogenous substrate in the neonatal lamb pulmonary vasculature. These data are consistent with previous studies showing that PG synthesis inhibition augments hypoxic pulmonary vasoconstriction, probably by inhibiting the synthesis of the vasodilator PG, PGI_2. Further, the ability of cyclooxygenase inhibitors to block the pulmonary vasoconstrictor response to exogenous arachidonic acid (6, 12) seems to argue against an important role of a vasoconstrictor leukotriene in the regulation of pulmonary vascular resistance.

Initial efforts by other workers at demonstrating the presence of and identifying a vasodilator PG employed classical tissue cascade bioassay techniques and radioimmunoassays of PGE and $PGF_{2\alpha}$ (19, 25, 29). Augmentation of PG synthesis by hypoxic pulmonary vasoconstriction was not detected in these studies. The radioimmunoassays used would not have detected PGI_2. Furthermore, although PGI_2 was first identified by bioassay, the small quantities of PGI_2 produced by the pulmonary vasculature and the spontaneous hydrolysis of PGI_2 to 6-keto-$PGF_{1\alpha}$ to which bioassay tissue respond poorly, may have hindered the detection of PGI_2 by the bioassay tissues. Supporting this idea are the observations of Mullane *et al.* (15) that infusions of arachidonic acid cause pulmonary vasodilation due to bioassayable PGI_2; infusion of arachidonic acid would allow for synthesis of considerably more PGI_2 by the pulmonary vasculature than could be produced from endogenous arachidonic acid and thus would facilitate detection of PGI_2 by bioassay.

The techniques employed in the present study were designed to allow detection and quantification of the small quantities of PGI_2 produced by the pulmonary vasculature from endogenous arachidonic acid by collecting all of the pulmonary perfusate over 10-min periods and concentrating the PGs thus collected.

Voelkel *et al.* (26) infused radioactively labeled arachidonic acid into perfused adult rat lungs, thus labeling the endogenous arachidonic acid pool. They subsequently measured increased release of the radioactive label with hypoxic pulmonary vasoconstriction and identified PGI_2 as the major labeled PG. Hamasaki *et al.* (4) found that hypoxia stimulates PGI_2 synthesis from endogenous arachidonic acid in homogenates of adult dog lung. These results are consistent with those of the present study performed on neonatal lamb lungs.

Effects of arachidonic acid, the precursor of PGI_2 and thromboxane A_2, on hypoxic pulmonary vasoconstriction have been variable with both dilation (2) and further constriction (6) described depending upon the experimental circumstances. Infusion of large quantities of exogenous arachidonic acid per unit time into the pulmonary circulation has a vasoconstrictor effect (5, 7, 12) and augments the constriction caused by alveolar hypoxia (6) or by 15-methyl-$PGF_{2\alpha}$ (21). On the other hand, Spannhake *et al.* (21) were able to produce pulmonary vasodilation by slowly infusing small quantities of arachidonic acid when pulmonary vascular tone was increased with either hypoxia or 15-methyl-$PGF_{2\alpha}$. Slow infusion of arachidonic acid may allow for more complete conversion of the precursor to PGI_2 without producing excessive vasoconstrictor cyclic endoperoxides and thromboxane A_2. Thus, Gerber *et al.* (2) reported that slow arachidonic acid infusion reduces hypoxic pulmonary vasoconstriction and identified PGI_2 in the pulmonary venous effluent. These observations are consistent with the results of the present study.

Rubin and Lazar (17) have reported recently that inhibition of hypoxic pulmonary vasoconstriction by hydralazine is prevented by indomethacin. Their data are consistent with ours but suggest that alveolar hypoxia alone does not stimulate prostacyclin synthesis maximally, since hydralazine appears to further reduce hypoxic pulmonary vasoconstriction by a PG-mediated mechanism.

Recently, Moon *et al.* (14) were able to reduce hypoxic pulmonary vasoconstriction in adult dogs by infusing arachidonic acid, and they detected an increase in the ratio of aortic to pulmonary arterial PGI_2 concentration. However, these workers were unable to detect a change in PGI_2 synthesis from endogenous substrate during alveolar hypoxia. This latter result differs from our own and could represent species or age differences.

In summary, the present study demonstrates that hypoxia stimulates pulmonary vascular synthesis of PGI_2 from endogenous substrate in neonatal lambs. These findings suggest that the augmentation of hypoxic pulmonary vasoconstriction by prostaglandin cyclooxygenase inhibition is due, at least in part, to interference with the synthesis of this vasodilator prostanoid.

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Vasopressin Concentration in Amniotic Fluid as an Index of Fetal Hypoxia: Mechanism of Release in Sheep

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Summary

Hypoxia is a potent stimulus to the release of vasopressin in fetal sheep, and plasma concentrations of the hormone correlate inversely with fetal oxygenation. Since the fetal kidney contributes to vasopressin clearance, we propose that measurement of increased amounts of vasopressin in amniotic fluid would be indicative of fetal hypoxia. Therefore, we measured concentrations of vasopressin in amniotic fluid under resting conditions, during and after fetal hypoxia, and with intravenous and intra-amniotic administration of vasopressin in 15 chronically instrumented fetal lambs between 111 and 141 days gestation. In the resting state, mean (±SE) vasopressin concentrations in amniotic fluid (1.6 ± 0.3 pg ml^{-1}) did not differ from those in maternal (1.4 ± 0.4 pg ml^{-1}) or fetal (1.8 ± 0.2 pg ml^{-1}) plasma. Following exposure of the ewe to 10% O_2 or partial occlusion of the umbilical cord, vasopressin concentrations in fetal plasma in-

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