EFFECTS OF PROSTACYCLIN (PGI₂) ON HYPOXIC PULMONARY VASOCONSTRICTION IN THE CONSCIOUS ADULT SHEEP

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The effects of prostacyclin (PGI₂) on alveolar hypoxic pulmonary vasoconstriction were investigated in the conscious adult sheep. In our model, hypoxia also produced increases in pulmonary arterial pressure (P_{PA}) and pulmonary vascular resistance (PVR), indicating pulmonary vasoconstriction. PGI₂ was injected rapidly as a 0.5 µg/kg bolus via the right atrium in five sheep during normoxia and hypoxia. During normoxia, PGI₂ increased P_{PA} and cardiac output, and decreased systemic arterial pressure (P_{SA}), systemic vascular resistance (SVR) and PVR. Left atrial pressure did not change. During hypoxia following PGI₂ administration, P_{PA} decreased, CO increased, and PVR decreased, suggesting dilator action on the pulmonary resistance vessels. As the same time P_{SA} and SVR decreased, suggesting dilator action on the systemic resistance vessels. However, the degree of the decline in PVR caused by PGI₂ was much greater during hypoxia than during normoxia. The decreases in P_{SA} and SVR induced by PGI₂ were not significant between hypoxia and normoxia. These findings confirm that PGI₂ decreases pulmonary and systemic vascular resistances in normoxic and hypoxic sheep. Moreover, during hypoxia, associated with the increased P_{PA} and PVR, the administration of PGI₂ appears to be particularly effective in "normalizing" these parameters.

IT is known that alveolar hypoxia elicits pulmonary vasoconstriction although the mechanism of this vasoconstriction remains unsolved^{1,2}. There are multiple studies on the role of prostaglandin (PG) in hypoxic pulmonary vasoconstriction. Vasodilator PGs, especially prostacyclin (PGI₂), are generated from the lungs of the anesthetized dog³ or the isolated rat⁴ during hypoxia, and modify the degree of vasoconstriction. Lock et al⁵ have reported that

in conscious newborn lambs, PGI₂ is a more effective vasodilator on the pulmonary rather than the systemic vascular bed under hypoxic conditions. Prostaglandin metabolism in the lungs differs as the cases of PGE₁ depending on the drug used for general anesthesia⁶. General anesthesia may significantly depress the pulmonary vasoconstrictor response to hypoxia⁷. Thus general anesthesia or other anesthetics used may possibly alter the organism's response to hypoxia or PGI₂. Furthermore, since PGI₂ is the major product of arachidonic acid metabolism in the fetal and neonatal pulmonary vessel walls^{8,9} it is possible that there is a difference in the pulmonary response to PGI₂ between the newborn

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TABLE I HEMODYNAMIC RESPONSES TO HYPOXIA IN CONSCIOUS SHEEP

	Mean pressure (mmHg)			Cardiac output (L/min)	Pulmonary vascular resistance (mmHg/L/min)	Systemic Vascular resistance (mmHg/L/min)
	Left atrium	Pulmonary artery	Systemic artery			
Baseline	5.4 ± 0.5	15.5 ± 0.5	88.4 ± 2.8	2.92 ± 0.27	3.71 ± 0.26	31.8 ± 3.3
Hypoxia						
5 min	4.3 ± 0.5	18.4 ± 0.5*	89.5 ± 4.0	3.51 ± 0.28*	4.29 ± 0.27*	26.8 ± 2.7*
10 min	4.0 ± 0.4*	19.9 ± 0.6*	88.3 ± 4.9	3.78 ± 0.35*	4.58 ± 0.37*	24.9 ± 3.0*
15 min	3.8 ± 0.5*	20.8 ± 0.9*	86.2 ± 4.2	3.85 ± 0.35*	4.74 ± 0.45*	23.2 ± 2.6*
20 min	3.8 ± 0.5*	20.5 ± 1.0*	86.2 ± 4.3	3.89 ± 0.34*	4.71 ± 0.47*	22.9 ± 2.7*
25 min	3.8 ± 0.5*	20.4 ± 0.8*	85.8 ± 2.8	4.07 ± 0.51*	4.58 ± 0.49*	22.5 ± 2.9*
30 min	3.7 ± 0.7*	20.3 ± 1.0*	84.5 ± 2.8	4.00 ± 0.50*	4.81 ± 0.50*	22.6 ± 2.8*
45 min	3.7 ± 0.4*	20.4 ± 0.9*	84.0 ± 2.2	4.12 ± 0.56*	4.65 ± 0.42*	22.2 ± 2.7*
60 min	3.6 ± 0.6*	21.0 ± 0.9*	85.2 ± 1.8	3.86 ± 0.47*	5.00 ± 0.51*	23.6 ± 2.8*

Values are means ± SE; n = 6. *p < 0.05 compared with baseline.

TABLE II HEMODYNAMIC RESPONSES TO PGI₂ IN NORMOXIC CONSCIOUS SHEEP

	Mean pressure (mmHg)			Cardiac output (L/min)	Pulmonary vascular resistance (mmHg/L/min)	Systemic vascular resistance (mmHg/L/min)	Heart rate (beats/min)
	Left atrium	Pulmonary artery	Systemic artery				
Baseline	4.4 ± 0.4	14.9 ± 0.7	92.5 ± 5.0	2.97 ± 0.34	3.49 ± 0.62	30.4 ± 4.4	126 ± 10
PGI ₂	4.1 ± 0.6	17.9 ± 0.9*	76.0 ± 4.8*	4.85 ± 0.61*	2.91 ± 0.54*	17.8 ± 3.1*	168 ± 6*

Values are means ± SE; n = 5. PGI₂ (0.5 µg/kg) was injected rapidly as a bolus into the right atrium.

*p < 0.05 compared with baseline.

lamb's and adult sheep. The effects of PGI₂ administration during hypoxia has not been reported for the conscious adult sheep.

Thus, we designed this study to investigate the effects of PGI₂ administration on pulmonary and systemic hemodynamics under hypoxic conditions using the conscious adult sheep. We used the male sheep, since the hypoxic pulmonary vasomotor response is more attenuated in the female.¹⁰

METHODS

Surgical Preparation

Sheep weighing 29–40 (average 33.8) kg were used. All animals were adult (postpubertal) males and over 8 months of age. They were anesthetized with pentobarbital sodium, intubated with an endotracheal tube, and maintained with halothane using a positive pressure ventilator (Harvard type). The preparations were performed as described previously.¹¹ Briefly, silicon tubes were inserted directly into the left atrium and

the pulmonary artery through a left thoracotomy. An electromagnetic flow probe was fixed around the trunk of the pulmonary artery. The same tubes were placed in the thoracic aorta and in the right atrium via the vessels of the neck. A tracheotomy was done and a tracheal window was prepared.

Measurements

Left atrial pressure (P_{LA}), systemic (P_{SA}) and pulmonary arterial pressures (P_{PA}) were measured continuously with pressure transducers (MPU-0.5, Nihon Koden Co., Tokyo, Japan) defining the left atrial levels as zero point. Cardiac output (CO) was determined with a Narco RT-500 electromagnetic flowmeter. Mean vascular pressures and CO were obtained by an electrical averaging of the pulsatile signals. Heart rate (HR) was measured with a heart rate recorder (AT-600 G, Nihon Koden Co.) triggered by the electrical signals from the flow curves. All vascular pressures, flow signal and HR were recorded on an 8-channel recorder (WT-685 G,

TABLE III HEMODYNAMIC RESPONSES TO PGI₂ IN HYPOXIC CONSCIOUS SHEEP

	Mean pressure (mmHg)			Cardiac output (L/min)	Pulmonary vascular resistance (mmHg/L/min)	Systemic vascular resistance (mmHg/L/min)	Heart rate (beats/min)
	Left atrium	Pulmonary artery	Systemic artery				
Baseline	4.1 ± 0.5	14.7 ± 0.7	91.6 ± 4.9	3.21 ± 0.34	3.48 ± 0.60	30.2 ± 4.1	125 ± 10
Hypoxia	2.9 ± 0.3*	22.7 ± 0.5*	87.5 ± 4.4	4.32 ± 0.46*	4.88 ± 0.50*	21.7 ± 2.9*	179 ± 12*
Hypoxia + PGI ₂	3.0 ± 0.3	18.6 ± 0.4†	71.9 ± 5.0†	5.32 ± 0.52†	3.34 ± 0.96†	14.0 ± 4.8†	211 ± 9†

Values are means ± SE; n = 5. PGI₂ (0.5 µg/kg) was injected rapidly as a bolus into the right atrium.

*p < 0.05 compared with baseline. †p < 0.05 compared with hypoxia.

Fig.1. A record illustrating the effects of PGI₂ on mean left atrial ($\bar{P}_{LA}$) and pulmonary arterial pressures ($\bar{P}_{PA}$), mean systemic arterial pressure ($\bar{P}_{SA}$), cardiac output (CO) and heart rate (HR). Left tracing: hemodynamic responses to PGI₂ in one normoxic sheep. Right tracing: hemodynamic responses to PGI₂ in same sheep under hypoxic condition. At the arrow, PGI₂ was injected rapidly as a 0.5 µg/kg bolus into the right atrium.

Nihon Koden Co.). Systemic (SVR) and pulmonary vascular resistances (PVR) were calculated by mean $\bar{P}_{SA}/CO$ and (mean $\bar{P}_{PA}$ - mean $\bar{P}_{LA}$)/CO, respectively. Arterial blood gas tensions and pH were measured consecutively with ABL-2 (Radiometer Co., Copenhagen, Denmark).

PGI₂, which was preserved at -70°C in the form of sodium salt, was dissolved just before use

on 0.5 ml ethanol and 20 mM of tris (hydroxymethyl) aminomethane (Tris) buffer, pH 8.5, and then diluted to 20 µg/ml with cooled saline. The vehicles used had no responses to hemodynamic parameters in the preliminary study.

Experimental Protocol

After about one week of recovery, when the

appetite had returned, the animal appeared well and the all hemodynamic parameters were stable, we performed the following two experiments on sheep that were in the conscious state and standing position.

A. Effect of hypoxia on hemodynamics. We used six sheep to assess the hemodynamic

Fig. 2. Time course of hemodynamic responses to PGI₂ in one hypoxic sheep. Cardiac output (CO), systemic vascular resistance (SVR), mean systemic arterial pressure (P_{sa}), pulmonary vascular resistance (PVR), and mean pulmonary arterial (P_{pa}) and left atrial pressures (P_{la}) are shown. At the arrow, PGI₂ was injected rapidly as a 0.5 μg/kg bolus into the right atrium.

responses to hypoxia and to decide the appropriate time for the administration of PGI₂. After measurements were made in room air (normoxia) sheep breathed a gas mixture of 10% oxygen and 90% nitrogen (hypoxia) for 1 hour through the tracheal window. Measurements were then done every 5 minutes during the first 30 minutes, and again 45 and 60 minutes.

B. Effects of PGI₂ on hemodynamics during normoxia and hypoxia. Five sheep were used to test the effects of PGI₂ on hemodynamics during normoxia and hypoxia. PGI₂ in a dose of 0.5 μg/kg was injected rapidly as a bolus through the tube placed in the right atrium, and followed by a 3 ml saline flush. After a baseline period of over 30 minutes, PGI₂ was administered during normoxia and observations were continued until all parameters returned to the baseline levels. After a successive waiting period of at least 30 minutes, the same sheep inhaled hypoxia. PGI₂ was administered after 20 minutes of hypoxia, and measurements were continued until all parameters returned to the values at 20 minutes of hypoxia. The maximal change of each parameter is reported in Tables II and III as the response to PGI₂.

Statistical Analysis

For the effects of hypoxia on hemodynamics and the PGI₂ injection data during normoxia, we used the Student's t-test for paired comparison between the baseline and experimental values. For the PGI₂ injection data during hypoxia, we compared the values at 20 minutes of hypoxia with those following PGI₂, using Student's t-test. The PGI₂ injection data obtained during normoxia and hypoxia were also compared using unpaired t-test. Values were shown as means ± SE. We accepted $p < 0.05$ as statistically significant.

TABLE IV COMPARISON OF HEMODYNAMIC RESPONSES TO PGI₂ BETWEEN NORMOXIC AND HYPOXIC SHEEP

	$\bar{P}_{PA}$ (%)	$\bar{P}_{SA}$ (%)	CO (%)	PVR (%)	SVR (%)	HR (%)
Normoxia	$+14.2 \pm 2.7$	-17.9 ± 1.7	$+63.9 \pm 6.2$	-16.7 ± 2.5	-42.2 ± 2.2	$+35.1 \pm 6.4$
Hypoxia	$-17.9 \pm 2.1^*$	-19.1 ± 2.8	$+23.7 \pm 4.4^*$	$-31.8 \pm 3.6^*$	-34.7 ± 2.7	$+19.4 \pm 7.7^*$

Values are means ± SE; $n = 5$. * $p < 0.05$ compared between both groups. $\bar{P}_{PA}$ and $\bar{P}_{SA}$ = mean pulmonary and systemic arterial pressures, respectively; CO = cardiac output; PVR and SVR = pulmonary and systemic vascular resistances, respectively; HR = heart rate. The data reported in normoxia and hypoxia are the percentage changes from the base-line values and from the values at 20 min of hypoxia, respectively.

RESULTS

A. Effect of hypoxia on hemodynamics.

Table I shows the effects of hypoxia on pulmonary and systemic hemodynamics in six conscious sheep. For the first 15 or 20 minutes of hypoxia, P_{LA} , P_{SA} and SVR decreased, and P_{PA} , PVR and CO increased. Thereafter, these changes remained constant. PaO_2 , $PaCO_2$ and pH were 82.9 ± 4.0 torr, 27.3 ± 1.8 torr and 7.56 ± 0.03 , respectively, during normoxia and were 31.6 ± 1.6 torr, 22.6 ± 1.4 torr and 7.64 ± 0.02 , respectively, during hypoxia.

B. Effects of PGI₂ on hemodynamics during normoxia and hypoxia.

Hemodynamics responses to PGI₂ injection in one normoxic sheep are illustrated in the left tracing of Fig. 1. During a baseline period, we were able to obtain stable values for all parameters, except for slight changes due to respiration and swallowing. Immediately after the injection of PGI₂, P_{SA} fell, while P_{PA} , CO and HR increased. These changes lasted for about 5 minutes. P_{LA} did not change. The effects of PGI₂ on hemodynamics during normoxia are summarized in Table II. PGI₂ produced significant decreases in P_{SA} , SVR and PVR, and significant increases in P_{PA} , CO and HR. At 20 minutes of hypoxia when hemodynamic responses to hypoxia seemed to remain stable, PGI₂ was administered. The immediate hemodynamic responses to PGI₂ in one hypoxic sheep are illustrated in Fig. 1. The typical time course of the effects of PGI₂ on CO, SVR, P_{SA} , PVR, P_{PA} and P_{LA} in another sheep is shown in Fig. 2. During hypoxia PGI₂ decreased P_{SA} and increased CO and HR. However, PGI₂ produced a drop in P_{PA} . P_{LA} did not change. SVR and PVR were decreased. The effects of PGI₂ on hemodynamics during hypoxia are summarized in Table III.

Hemodynamic responses to PGI₂ during hypoxia were compared with those during normoxia (Table IV). After PGI₂ administration, P_{PA} was increased during normoxia but decreased during hypoxia. Although PGI₂ caused a significant decrease in PVR during both conditions, the decrease in PVR during hypoxia was much greater than that during normoxia. P_{SA} and SVR showed similar decreases between both conditions. The increases in CO and HR were smaller during hypoxia than during normoxia.

DISCUSSION

In the present study, rapid injection of PGI₂ as a 0.5 μ g/kg bolus during normoxia resulted in remarkable drops in systemic arterial pressure and systemic vascular resistance in the conscious sheep. Such vasodilation in the systemic vascular beds has been a characteristic effect of this compound.¹²⁻¹⁴ Fitzpatrick et al.¹³ reported that PGI₂ had no effects on the pulmonary circulation during normoxia in the anesthetized dog. However, several investigators have shown that PGI₂ decreases pulmonary vascular resistances in experimental animals.^{5,14,15} We¹¹ indicated previously that PGI₂ had a pulmonary vasodilator activity during normoxia in the conscious sheep.

Our present study showed that alveolar hypoxia caused significant elevations of pulmonary arterial pressure and pulmonary vascular resistance in the conscious sheep, suggesting pulmonary vasoconstriction. During hypoxia, rapid injection of PGI₂ as a 0.5 μ g/kg bolus produced a significant drop in pulmonary arterial pressure or pulmonary vascular resistance. This finding indicates that PGI₂ also has a vasodilator action in the pulmonary vessels during hypoxia. Because the PGI₂-induced decrease in pulmonary vascular resistance is much greater during hypoxia ($31.8 \pm 3.6\%$ from baseline of hypoxia) than during normoxia ($16.7 \pm 2.5\%$ from baseline), the pulmonary vasodilator activity of PGI₂ may be enhanced under hypoxic condition. However, in contrast to the pulmonary circulation, the systemic vasodilation following PGI₂ seems to be almost equal between normoxic and hypoxic conditions, since the degrees of the declines in systemic vascular resistances are similar during both conditions. Our present results may support the studies of Gerber et al.³ and Voelkel et al.⁴ who suggested that PGI₂ was generated from the lungs during hypoxic pulmonary vasoconstriction to prevent the excessive vasoconstriction and maintain the normal vascular tone.

Lock et al.⁵ described that rapid injection of PGI₂ in conscious newborn lambs decreased pulmonary vascular resistance from 9.5 ± 0.9 units of baseline to 7.8 ± 0.6 of experiments during normoxia, and from 14.8 ± 1.4 units of baseline to 10.2 ± 1.2 of experiments during hypoxia. The decrements of pulmonary vascular resistance following PGI₂ during normoxia and hypoxia were 17.9% and 31.0%, respectively, and

those data are approximately equal to our PGI₂ findings in the conscious adult sheep. They⁵ also concluded that hypoxia augmented the pulmonary vasodilation of PGI₂ in conscious newborn lambs. On the other hand, the decrements of systemic vascular resistance following PGI₂ in conscious newborn lamb⁵ were 40.0% during normoxia and 37.3% during hypoxia. These values also are approximately equal to our PGI₂ findings in the conscious adult sheep (Table IV).

Although the doses of PGI₂ administered were 2.0 µg/kg in the conscious newborn lambs reported by Lock et al.⁵ and 0.5 µg/kg in the conscious adult sheep in this present study, these different doses between the newborn lambs and the adult sheep showed similar responses to hemodynamics during normoxia and hypoxia. This discrepancy is not clear. In the conscious newborn lambs PGI₂ of 0.5 µg/kg produced no changes in hemodynamics,⁵ but in the conscious adult sheep PGI₂ of 0.05–1.0 µg/kg caused significant agitations to hemodynamic parameters with a dose-dependent manner.¹¹ Because there are reports that a greater release of dilator prostagandins, especially PGI₂, occurs in the perinatal lungs of goats,⁸ bovines⁹ and lambs¹⁶ in order to lower pulmonary vascular resistance, the smaller exogenous PGI₂ such as 0.5 µg/kg may have no obvious responses to hemodynamics in the newborn lambs.

Hintze et al.¹⁷ recently reported that administration of PGI₂ produced a reflex bradycardia in the conscious dogs. However, our previous¹¹ and present data have shown that PGI₂ increases heart rate markedly in conscious sheep, and Szczeklik et al.¹⁸ reported that intravenous infusions of PGI₂ (10 ng/kg/min) led to the acceleration of heart rate in man. The cause of this discrepancy is unclear. Hitze et al. described that PGI₂-induced bradycardia was mediated by the activation of Bezold-Jarish effect.¹⁹ In our previous study,¹¹ the tachycardia induced by PGI₂ was blocked by pretreatment with propranolol. Thus this tachycardia caused by PGI₂ in the conscious sheep is probably due to an increase in the sympathetic tone. It may be likely that administration of PGI₂ does not stimulate the Bezold-Jarish effect in conscious sheep or in man.

In summary, our present findings indicate that PGI₂ has a vasodilator effect on the pulmonary as well as the systemic vascular beds during both normoxia and hypoxia in the conscious adult sheep. However, the pulmonary vasodilating

effect of PGI₂ is most clearly seen when the pulmonary vascular tone has been increased by alveolar hypoxia.

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