EFFECTS OF PROSTAGLANDIN E₁ AND ISOSORBIDE DINITRATE ON ACUTE HYPOXIC PULMONARY VASOCONSTRICTION IN CONSCIOUS SHEEP

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The pulmonary vascular effects of prostaglandin E₁ (PGE₁) and isosorbide dinitrate (ISD) on acute hypoxic pulmonary vasoconstriction in conscious sheep were studied. While the animals inhaled room air or hypoxic gas (O₂:N₂ = 1:9), PGE₁ (0.5 µg/kg/min) and ISD (10 µg/kg/min) were administered intravenously for 20 min, using an infusion pump.

The changes of pulmonary arterial pressure ($\bar{P}_{PA}$) or pulmonary vascular resistance (PVR) in room air due to PGE₁ were not significant, but in the hypoxic condition, PGE₁ decreased $\bar{P}_{PA}$ by 14.7% ($p < 0.05$) and PVR by 14.5% ($p < 0.05$). The effect of PGE₁ in room air on systemic arterial pressure ($\bar{P}_{SA}$) remained nearly constant, whereas slight decreases in systemic vascular resistance (SVR) were noticed. In hypoxic condition, $\bar{P}_{SA}$ levels were slightly decreased by PGE₁, but SVR indicated a slight degree of delayed rise.

When ISD in room air was administered, the values of $\bar{P}_{PA}$, PVR, $\bar{P}_{SA}$ and SVR decreased by 9% ($p < 0.05$), 10.4% ($p < 0.05$), 17.7% ($p < 0.05$) and 21.8% ($p < 0.05$), respectively. In hypoxic condition, ISD decreased the values of $\bar{P}_{PA}$, PVR, $\bar{P}_{SA}$ and SVR by 14.7% ($p < 0.05$), 15.8% ($p < 0.05$), 10.2% ($p < 0.05$) and 6.7% ($p < 0.05$), respectively.

In summary in hypoxic condition both PGE₁ and ISD cause similar decreases of $\bar{P}_{PA}$ and PVR. Furthermore, there was a very little decrease in $\bar{P}_{SA}$ during PGE₁ infusion in the hypoxic condition. These findings may suggest that the vasodilator actions of PGE₁ were not evident in the pulmonary vascular bed under resting conditions, but could be demonstrated in vessels with increased tone produced by hypoxia without a marked fall in the systemic arterial pressure.

PULMONARY hypertension due to hypoxic pulmonary vasoconstriction may develop in patients with chronic obstructive pulmonary disease and acute respiratory failure. It is necessary for these patients with severe pulmonary

hypertension to reduce effectively the pulmonary arterial pressure. The use of vasodilators, such as nifedipine, nitroprusside and nitroglycerine, has recently been shown to have some favorable pulmonary hemodynamic effects,¹⁻⁶ though the drugs have negative side-effects or cause excessive systemic vasodilation.

Isosorbide dinitrate (ISD), which is one of the most commonly used agents in the treatment of angina pectoris, may be thought to have vasodilating effects not only on systemic but also on

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pulmonary vascular beds^{2,3}

The hemodynamic responses to prostaglandin E_1 (PGE_1) have shown decreases in systemic and pulmonary arterial pressures and the vascular resistances.⁷⁻¹¹ However, the biological activity of PGE_1 is almost entirely lost during a single passage through the pulmonary circulation.^{12,13} In this respect, PGE_1 may be useful in treating pulmonary hypertension due to hypoxic pulmonary vasoconstriction without decreasing the systemic arterial pressure.

In this study, the hemodynamic effects of PGE_1 during hypoxic conditions were investigated and these effects were compared with those during normoxic conditions. In addition the hemodynamic effects of ISD during both normoxic and hypoxic conditions were studied and compared with the effects of PGE_1 .

MATERIALS AND METHODS

Sheep weighing 22 to 44 kg were anesthetized with intravenous pentobarbital sodium (20 mg/kg), and were ventilated at 15 ml/kg, 15 cycles per min with 0.5 to 1.0% halothane through a cuffed endotracheal tube using positive pressure ventilation. A left thoracotomy (3rd intercostal space) was performed under aseptic conditions, silicon catheters (ID 2 mm, OD 4 mm) were inserted and fixed directly into the left atrium and into the pulmonary artery. A probe of an electromagnetic flowmeter (Narco Co.) was fixed around the trunk of the pulmonary artery. The same catheters were placed in the thoracic aorta and the right atrium via the left carotid artery and right jugular vein respectively. A chronic tracheostomy was also performed to make insertion of a cuffed endotracheal tube possible at the time of experiment. Antibiotics were administered daily for five days post-operatively. The catheters were thoroughly flushed with saline and filled with heparin once a day. After about one week, the following experiments in the conscious state of sheep were performed.

The mean left atrial pressure ($\bar{P}_{LA}$), mean systemic ($\bar{P}_{SA}$) and pulmonary arterial pressures ($\bar{P}_{PA}$) were measured continuously using pressure transducers (Nihon Koden Co., Model MPU-0.5-290-III) defining the left atrial level as the zero point. Cardiac output (CO) was measured by an electromagnetic flowmeter (Narco Co., Narco RT-500). Heart rate was measured using a heart rate recorder (Nihon Koden Co., Model

Fig.1. The time course of hemodynamic responses to hypoxia (10% O_2) in conscious sheep.

$\bar{P}_{PA}$ = mean pulmonary arterial pressure; $\bar{P}_{SA}$ = mean systemic arterial pressure; CO = cardiac output; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance. Data show means $\pm$ SE (n = 6).

AT-600G) triggered by electrical signals from flow curves. These parameters were recorded on an 8-channel recorder (Nihon Koden Co., Model WT-685G). Systemic (SVR) and pulmonary vascular resistances (PVR) were calculated by $\bar{P}_{SA}/CO$ and $(\bar{P}_{PA}-\bar{P}_{LA})/CO$ respectively.

Control Study

The time course of hemodynamic responses to hypoxia in conscious sheep was studied for the hypoxic control study. Measurements of hemodynamics were obtained from six sheep breathing room air and hypoxic gas mixture (10% O_2) for 40 min.

Experiment I: Administration of PGE_1 in normoxic condition

The solution of PGE_1 (0.5 $\mu g/kg/min$), which was first dissolved in 95% ethanol and diluted in normal saline, was administered into the right

TABLE I HEMODYNAMIC RESPONSES TO PGE₁ DURING NORMOXIC (n = 5) AND HYPOXIC (n = 6) CONDITIONS IN CONSCIOUS SHEEP

		Mean pressure (mmHg)				Cardiac output (L/min)	Heart rate (beats/min)	Pulmonary vascular resistance ($\frac{\text{mmHg}}{\text{L/min}}$)	Systemic vascular resistance ($\frac{\text{mmHg}}{\text{L/min}}$)	pH	PO ₂	PCO ₂
		Pulmonary artery	Left atrium	Systemic artery								
Baseline		16.1 ± 1.1	5.3 ± 0.4	93.2 ± 6.9	2.89 ± 0.17	121 ± 11	3.86 ± 0.59	32.3 ± 1.5	7.53 ± 0.01	85.0 ± 8.8	28.3 ± 0.7	
PGE ₁	5 min	16.6 ± 1.2	4.9 ± 0.3	92.7 ± 6.7	3.06 ± 0.19*	125 ± 8	3.93 ± 0.60	30.4 ± 1.5				
	10 min	17.5 ± 1.3	4.8 ± 0.4	95.2 ± 6.7	3.24 ± 0.16*	130 ± 8*	3.97 ± 0.65	29.5 ± 2.2*	7.54 ± 0.01	78.3 ± 6.3	28.5 ± 0.8	
	15 min	17.7 ± 0.5	4.6 ± 0.7	96.6 ± 5.7	3.44 ± 0.27*	134 ± 8*	3.99 ± 0.41	28.6 ± 2.4				
	20 min	17.8 ± 0.6	4.6 ± 0.7	93.7 ± 5.8	3.45 ± 0.29*	141 ± 11*	3.95 ± 0.39	27.7 ± 2.3				
Baseline		16.4 ± 0.9	5.1 ± 0.4	86.5 ± 3.5	3.00 ± 0.19	119 ± 9	3.81 ± 0.44	29.2 ± 1.2	7.55 ± 0.03	98.2 ± 6.6	28.8 ± 1.9	
Hypoxia		23.5 ± 2.0*	2.5 ± 0.4*	87.2 ± 3.7	4.53 ± 0.38*	197 ± 7*	4.76 ± 0.53*	19.7 ± 1.2*	7.64 ± 0.02*	32.9 ± 1.4*	22.8 ± 0.9*	
Hypoxia +PGE ₁	5 min	21.8 ± 1.9#	2.4 ± 0.4	83.4 ± 2.7	4.55 ± 0.39	214 ± 9	4.37 ± 0.45#	18.8 ± 1.1				
	10 min	21.7 ± 1.4	3.1 ± 0.4	83.6 ± 2.7	4.48 ± 0.42	206 ± 9	4.27 ± 0.39#	19.3 ± 1.2	7.60 ± 0.04	28.2 ± 1.9#	21.0 ± 0.9#	
	15 min	20.2 ± 1.4#	3.3 ± 0.3	83.3 ± 3.3#	4.16 ± 0.37#	184 ± 9	4.19 ± 0.42#	20.8 ± 1.7				
	20 min	19.8 ± 1.3#	3.4 ± 0.3	83.1 ± 3.1	4.20 ± 0.45	188 ± 7	4.06 ± 0.44#	20.6 ± 1.7				

Values are means ± SE. Hypoxic values are at the 20th min of hypoxia.

* = statistically significant (p < 0.05) compared with baseline; # = statistically significant (p < 0.05) compared with hypoxic values

TABLE II HEMODYNAMIC RESPONSES TO ISD DURING NORMOXIC AND HYPOXIC CONDITIONS IN CONSCIOUS SHEEP (n = 6)

	Mean pressure (mmHg)				Cardiac output (L/min)	Heart rate (beats/min)	Pulmonary vascular resistance (mmHg/L/min)	Systemic vascular resistance (mmHg/L/min)	pH	PO ₂	PCO ₂
	Pulmonary artery	Left atrium	Systemic artery								
Baseline	16.5 ± 0.6	4.5 ± 0.6	90.6 ± 1.3		2.85 ± 0.16	129 ± 12	4.34 ± 0.46	32.2 ± 1.4	7.57 ± 0.02	91.4 ± 4.0	24.8 ± 2.1
ISD	5 min	15.0 ± 0.4*	3.1 ± 0.7*	84.5 ± 1.6*	3.05 ± 0.32	143 ± 11	4.17 ± 0.42	28.8 ± 2.2*			
	10 min	15.3 ± 0.6	2.8 ± 0.6*	82.3 ± 1.1*	3.15 ± 0.39	157 ± 13	4.18 ± 0.46	27.7 ± 2.6*	7.59 ± 0.02	85.0 ± 11.0	23.4 ± 0.8
	15 min	15.9 ± 0.8	2.7 ± 0.6*	82.5 ± 1.3*	3.37 ± 0.42	161 ± 17	4.13 ± 0.48	26.0 ± 2.5*			
	20 min	15.8 ± 0.7	2.9 ± 0.5	83.3 ± 1.8*	3.47 ± 0.45	166 ± 18	3.88 ± 0.42*	25.3 ± 2.6*			
Baseline	15.8 ± 0.6	5.1 ± 0.2	90.9 ± 1.4		2.82 ± 0.13	125 ± 8	3.84 ± 0.20	32.6 ± 1.5	7.52 ± 0.01	97.1 ± 17.1	28.0 ± 0.9
Hypoxia	24.8 ± 2.1*	4.3 ± 0.7	92.4 ± 4.7		4.05 ± 0.37*	187 ± 19*	5.09 ± 0.36*	23.8 ± 2.8*	7.63 ± 0.01*	33.9 ± 2.0*	21.6 ± 0.8*
Hypoxia + ISD	5 min	21.5 ± 2.0#	4.2 ± 1.1	84.2 ± 3.6#	3.78 ± 0.20	194 ± 18	4.54 ± 0.30#	22.7 ± 1.9			
	10 min	21.4 ± 1.4#	4.2 ± 0.8	84.2 ± 3.8#	3.94 ± 0.21	197 ± 21	4.43 ± 0.36#	21.9 ± 2.2	7.60 ± 0.03	30.6 ± 1.9#	21.4 ± 1.3
	15 min	21.0 ± 1.3#	3.8 ± 0.6#	85.3 ± 2.4#	3.79 ± 0.16	180 ± 16	4.57 ± 0.35#	22.7 ± 1.3			
	20 min	20.8 ± 1.4#	4.3 ± 0.6	82.5 ± 2.6#	3.84 ± 0.17	192 ± 17	4.31 ± 0.37#	21.8 ± 1.4			

Values are means ± SE. Hypoxic values are at the 20th min of hypoxia.

* = Statistically significant (p < 0.05) compared with baseline; # = Statistically significant (p < 0.05) compared with hypoxic values

Fig.2. Percent changes in the mean pulmonary arterial pressure ($\bar{P}_{PA}$) and the vascular resistance (PVR) due to PGE₁ infusion during normoxic and hypoxic conditions. Data show means $\pm$ SE. *p < 0.05 compared with baseline (Time 0).

atrium for 20 min (0.95 ml/min) using a Harvard type infusion pump (Truth II-A) in normoxic condition (n = 5). Infusion of 0.95 ml/min of normal saline produced no pressor response.

Experiment II: Administration of PGE₁ in hypoxic condition

To approximate an acute hypoxic condition, a mixture of 10% oxygen in nitrogen was force-inhaled through a cuffed endotracheal tube. At the 20th min after the beginning of the hypoxic condition, PGE₁ of the same amount as that of the normoxic condition was infused into the right atrium during the period of 20 min (n = 6).

Experiment III: Administration of ISD in normoxic condition

Solution of ISD (10 μ g/kg/min), which was dissolved in normal saline, was administered into the right atrium for 20 min under normoxic conditions in the same manner as Experiment I (n = 6).

Fig.3. Percent changes in the mean pulmonary arterial pressure ($\bar{P}_{PA}$) and the vascular resistance (PVR) due to ISD infusion during normoxic and hypoxic conditions. Data show means $\pm$ SE. *p < 0.05 compared with baseline (Time 0).

Experiment IV: Administration of ISD in hypoxic condition

Ten percent oxygen inhalation was performed as in Experiment II. At the 20th min after the beginning of hypoxic condition, ISD of the same amount as that of Experiment III was infused into the right atrium for 20 min (n = 6).

Arterial blood gas tensions were analyzed for pH, PO₂ and PCO₂ before and at 10 min of the drug infusion in the normoxic experiments. In the hypoxic experiments, they were measured before, at 10 min of hypoxia and at 10 min of the drug infusion by ABL₂ (Radiometer Co.).

STATISTICAL ANALYSIS

All data were shown as the means and standard errors. Responses to hypoxia and the effects of the drugs were statistically compared by Student's paired t-test. The differences of the pulmonary vascular responses between normoxic and hypoxic conditions were compared using the unpaired t-test. The data in hypoxic condition were also compared between the hypoxic values of the control study and PGE₁ or ISD, and the differences were evaluated by the unpaired t-test. The probability of less than 0.05 was considered statistically significant.

Fig. 4. Comparison of the percent changes in the mean pulmonary arterial pressure ($\bar{P}_{PA}$) and the vascular resistance (PVR) due to PGE_1 and ISD infusions in hypoxic condition with the hypoxic control study from 20 to 40 min. Each baseline (Time 0) reveal the 20th min of the respective hypoxic values. Data show means $\pm$ SE. $\circ-\circ = PGE_1$ (n = 6); $\bullet-\bullet = ISD$ (n = 6); $\blacksquare-\blacksquare =$ Hypoxic control study (n = 6). * $p < 0.05$ compared with baseline (Time 0). * $p < 0.05$ compared with the hypoxic control study.

RESULTS

The control study of the hemodynamic responses to hypoxia

The effects of continuous hypoxic gas inhalation on the hemodynamics of a group of six sheep are shown in Fig. 1. The mean pulmonary arterial pressure, cardiac output, heart rate and the pulmonary vascular resistance were significantly increased. These significant increases in the mean pulmonary arterial pressure and the vascular resistance during continuous hypoxic gas inhalation remained stable for 40 min. The mean left atrial pressure and the calculated systemic vascular resistance were significantly decreased. The mean systemic arterial pressure revealed a tendency to decrease, but it was not significant.

Hemodynamic responses to PGE_1 (0.5 $\mu\text{g/kg/min}$) and ISD (10 $\mu\text{g/kg/min}$) administered

into the right atrium in both normoxic and hypoxic conditions are summarized in Tables I and II.

Experiment I: Administration of PGE_1 in normoxic condition

The baseline measurements of all parameters were obtained after the sheep had rested for 15 to 20 min. PGE_1 infusion in normoxic condition resulted in a tendency to increase the mean pulmonary arterial pressure (Table I). Cardiac output and heart-rate values were increased significantly during the PGE_1 infusion. The mean left atrial, systemic arterial pressures and the calculated pulmonary vascular resistance remained unchanged, but the systemic vascular resistance was slightly decreased. Arterial blood gas tensions and pH level remained nearly constant.

Experiment II: Administration of PGE_1 in hypoxic condition

Hemodynamic changes induced by hypoxia were as follows: the mean pulmonary arterial pressure, cardiac output, heart rate and the calculated pulmonary vascular resistance were increased by 43.3, 51.0, 65.5 and 24.9%, respectively; while the mean left atrial pressure and the calculated systemic vascular resistance were decreased. The mean systemic arterial pressure was not altered. Hypoxia lowered arterial PO_2 to similar level of less than 40 mmHg (mean $PO_2 = 32.9$ mmHg).

The PGE_1 infusion in hypoxic condition significantly decreased the mean pulmonary arterial pressure from 23.5 ± 2.0 to 19.8 ± 1.3 mmHg and the vascular resistance from 4.76 ± 0.53 to 4.06 ± 0.44 mmHg/L/min (Table I). The mean left atrial pressure, heart rate and the systemic vascular resistance remained unchanged, but the mean systemic arterial pressure was shown to decrease slightly during the infusion of PGE_1 . Both arterial PO_2 and PCO_2 were decreased during the PGE_1 infusion.

Experiment III: Administration of ISD in normoxic condition

The ISD infusion resulted in tendencies to decrease both the mean pulmonary arterial pressure and the vascular resistance in normoxic condition. Similarly, ISD decreased the mean systemic arterial pressure from 90.6 ± 1.3 to 83.3 ± 1.8 mmHg and the vascular resistance from 32.2 ± 1.4 to 25.3 ± 2.6 mmHg/L/min

significantly. The cardiac output and heart rate showed tendencies to increase during the ISD infusion, but these increases were not so significant. Arterial blood PO₂, PCO₂ and pH were unchanged by the ISD administration.

Experiment IV: Administration of ISD in hypoxic condition

Hypoxia induced significant increase in the mean pulmonary arterial pressure, cardiac output, heart rate and the calculated pulmonary vascular resistance by 57.0, 43.6, 49.6 and 32.6%, respectively. When ISD in the hypoxic condition was administered, it followed that the values of the mean pulmonary arterial pressure and the vascular resistance were significantly decreased by 16.1 and 15.3%, respectively.

Further, ISD caused a significant decrease in the mean systemic arterial pressure (Table II). The mean left atrial pressure, cardiac output, heart rate and the calculated systemic vascular resistance were not altered. Arterial PO₂ was decreased during the ISD infusion.

Although the mean pulmonary arterial pressure tended to be increased by the PGE₁ infusion in normoxic condition, it was significantly decreased in the hypoxic condition (Fig. 2). Whereas ISD revealed the responses to decrease the mean pulmonary arterial pressure and the vascular resistance in both normoxic and hypoxic conditions (Fig. 3). Although the pulmonary pressor responses to hypoxia were stable for at least 40 min in the control study, infusion of PGE₁ or ISD after induction of hypoxic pulmonary vasoconstriction reversed the responses significantly (Fig. 4). Further, in hypoxic condition both PGE₁ and ISD could cause similar tendencies of the decreases for the mean pulmonary arterial pressures and the vascular resistances (Fig. 4).

DISCUSSION

In the patients with chronic obstructive pulmonary disease, pulmonary vasoconstriction caused by alveolar hypoxia secondary to airway obstruction serves the useful function of shunting blood away from poorly ventilated areas towards better ventilated portions of the lung.¹ However, it has the disadvantage of causing increased pulmonary vascular resistance and an increased load on the right ventricle. Pharmacologic pulmonary vasodilation in such patients could be expected to prevent the hypoxic pulmonary

vasoconstriction and to decrease the pulmonary arterial pressure, the vascular resistance and an afterload of the right ventricle.

Previous workers presented the effects of PGE₁ on the pulmonary vasculatures in anesthetized or sedated animals. Intravenous infusion of exogenous PGE₁ abolished the pulmonary vascular responses to hypoxia in anesthetized dogs¹¹ and newborn goats.⁹ Pulmonary arterial hypertension produced by hypobaric hypoxia (14,000 feet) was not inhibited by PGE₁ in sedated dogs.¹⁰ PGE₁ was demonstrated to have no effect on the pulmonary arterial pressure or resistance in normoxic condition, while in hypoxic condition, the pulmonary arterial pressure and the vascular resistance were reduced by PGE₁ in the intact anesthetized dogs.¹⁴ However, general anesthesia was reported to alter not only the baseline state but also the responses to physiologic and pharmacologic stimuli,¹⁵⁻¹⁸ and to increase level of vasodilator prostaglandins in the renal circulation.¹⁹ Further, it has been reported that the effects of PGE₁ on the pulmonary circulation are influenced by the drugs used for general anesthesia.⁸

Although the hypoxic pulmonary vasoconstrictor response seems to be similar in many kinds of adult mammals, species-specific adaptive mechanisms may come into play in some species but not in others.²⁰ In the case of mongrel dogs which are usually used in many kinds of experiments, the elevated pulmonary arterial pressure and the vascular resistance produced by alveolar hypoxia are not well sustained.²¹ This present model using conscious sheep indicates that the pulmonary pressor responses to hypoxia were well sustained (Fig. 1).

For the selection of the dose of PGE₁ for these experiments, the results of preliminary experiments in conscious sheep (Jpn Circ J 45: 975, 1981 abstr.) were used. According to these results, although PGE₁ revealed no effect on the systemic circulation in 0.02 to 1.0 µg/kg, the cardiovascular effects became remarkable in 1.5 to 5.0 µg/kg. Further, the dose of ISD was selected to approximate an effective clinical dose.^{22,23}

The present results in conscious sheep demonstrated that in normoxic condition, the infusion of PGE₁ caused a slight increase in the pulmonary arterial pressure, though it was not statistically significant. It is thought that this pressure rise due to PGE₁ infusion in normoxia was derived from the significant increase of

cardiac output. In addition, under normoxic conditions, PGE₁ increased the heart rate and cardiac output significantly without a marked fall of the systemic arterial pressure. It could be explained that PGE₁ has direct myocardial chronotropic and inotropic actions without involving peripheral vasodilation. During the hypoxic condition, however, the PGE₁ infusion inhibited the sustenance of the pulmonary arterial pressure and the vascular resistance produced by the hypoxic gas inhalation. Figure 2 shows the comparison of the responses of PGE₁ infusion to the pulmonary vascular bed during normoxic conditions with those values during hypoxic conditions. It would be considered that the vasodilator capacity of PGE₁ could not be demonstrate in the pulmonary vascular bed under resting conditions, but could be better demonstrated in vessels with increased tone induced by hypoxia.

Organic nitrates such as glyceryl trinitrate and isosorbide dinitrate (ISD) are well known to reduce the preload and the afterload of the left ventricle. The mode of their action could be explained by both dilatation of postcapillary capacitance vessels and precapillary resistance vessels. Pulmonary vasodilating effects of organic nitrates in human subjects and anesthetized animals were reported by previous investigators.²²⁻²⁴ Aviado et al. reported that pulmonary arterial injection of ISD (0.025–0.25 mg/kg) showed a reduction in perfusion pressure of the left lower lobe with and without prior infusion of serotonin.²⁴ Dresdale et al.²² and Ferrer et al.²³ presented clinical studies that organic nitrates decreased the pulmonary arterial pressure consistently in one female patient and other patients with secondary pulmonary hypertension regardless of the baseline levels.

In the present experiment, ISD produced decreases in the pulmonary arterial pressure and the vascular resistance in both normoxic and hypoxic conditions. Pulmonary vascular effects of the ISD infusion in hypoxic condition did not significantly differ from those values in the normoxic condition (Fig. 3). These results indicate that ISD has vasodilator actions in the pulmonary vascular bed during both normal condition and constricted state by alveolar hypoxia. ISD is effective in reducing the mean pulmonary arterial pressure and the vascular resistance; however, the drug has such unfavorable side-effects as systemic vasodilation and hypotension.

Similarly, PGE₁ also decreases systemic arterial pressure, mainly by decreasing peripheral vascular resistance. As has been previously reported, PGE₁ produced a greater response in intra-arterial infusion than in intravenous infusion.²⁵ It has also been presented that 80–95% of PGE₁ is inactivated during a single passage through the pulmonary circulation.¹²⁻¹³

In the present study, the effects of PGE₁ for systemic arterial pressure remained nearly constant under normoxic condition, whereas a slight decrease in the systemic vascular resistance was noticed. This decrease in the calculated systemic vascular resistance would be derived from the significant increase in the cardiac output. In the hypoxic condition, although there was a very little decrease in the systemic arterial pressure, the calculated systemic vascular resistance remained unchanged. Therefore, in both normoxic and hypoxic conditions, PGE₁ administered was considered to be almost inactivated during a single passage through the pulmonary circulation.

Pharmacologic pulmonary vasodilation in the presence of patchy vasoconstriction produced by alveolar hypoxia would increase the perfusion of poorly ventilated lung units and diminish the PO₂ in arterial blood gas. In the present study, both PGE₁ and ISD were shown to cause significant decreases in PO₂ during the hypoxic gas inhalation. These decreases of PO₂ in the experiments could be explained by both the increase in intrapulmonary shunt and the decrease in ventilation/perfusion ratio induced by PGE₁ or ISD.

Recently, PGE₁ was reported to reduce pulmonary hypertension in patients with chronic obstructive pulmonary disease.²⁶ The essential objective of vasodilator therapy for cor pulmonale or pulmonary hypertension secondary to hypoxic pulmonary vasoconstriction is a decrease in right ventricular work with both a reduction in pulmonary arterial pressure and an increase in cardiac output, further without systemic hypotension. These data suggest that the dose of PGE₁, which reduce the right ventricular afterload without severe systemic hypotension, might be beneficial to the patients with pulmonary hypertension, particularly in the early phase of acute exacerbation of chronic cor pulmonale.

However, positive conclusions as to the therapeutic values of PGE₁ for the patients with chronic obstructive pulmonary disease should

not be drawn unless well-controlled randomized clinical studies with PGE₁ are completed.

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