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Treatment of Pulmonary Hypertension and Hypoxia Due to Oleic Acid Induced Lung Injury with Intratracheal Prostaglandin E_1 during Partial Liquid Ventilation

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Background: **Partial liquid ventilation using perfluorocarbon liquids may be of therapeutic benefit in patients with acute respiratory failure. This study investigated the effects of prostaglandin E_1 (PGE_1) delivered intratracheally during partial liquid ventilation on lung function and pulmonary circulation in rabbits with acute respiratory distress syndrome.**

Methods: **Lung injury was induced by intravenous oleic acid in adult Japanese white rabbits, 1 h after which they were divided into four groups of 10 animals. Group 1 received mechanical ventilation alone, group 2 received aerosolized PGE_1 (5 μg followed by 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) under mechanical ventilation combined with 5 cm H_2O positive end-expiratory pressure, and groups 3 and 4 received partial liquid ventilation with 15 ml/kg perflubron. Group 4 received a 5-μg bolus followed by 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ PGE_1 instilled intratracheally (not by aerosol) in combination with partial liquid ventilation. Measurements were performed at 30-min intervals for 120 min after lung injury.**

Results: **After lung injury, hypoxemia, hypercapnia, acidosis, and pulmonary hypertension developed in all animals and were sustained in groups 1 and 2 throughout the experiment. The partial pressure of oxygen in arterial blood of animals in group 3 improved with initiation of treatment, with statistical significance achieved at the 30 and 60 min time points as compared with controls. Group 4 animals had immediate and sustained increases in the partial pressure of oxygen in arterial blood that were significant compared with all other groups during the experiment. Statistically significant reductions in mean pulmonary artery pressure were seen only in group 4 animals compared with all other groups.**

Conclusions: **These results suggest that PGE_1 delivered intratracheally during partial liquid ventilation may be a useful therapeutic strategy for patients with the acute respiratory distress syndrome. (Key words: Acute lung injury; artificial respiration; vasodilators.)**

CLINICAL study has shown that the presence of severe pulmonary hypertension in patients with the acute respiratory distress syndrome is associated with a poor prognosis.[1] Accordingly, vasodilators have been used to reduce pulmonary vascular tone in such patients. Intravenous drugs such as PGE_1[2,3] and prostacyclin[4,5] reduce pulmonary artery pressure (PAP) and pulmonary vascular resistance, but they inhibit hypoxic pulmonary vasoconstriction and sometimes worsen pulmonary oxygenation. Inhalation of nitric oxide or aerosolized prostacyclin have been used successfully[6–8] and appear to improve both pulmonary circulation and the ventilation:perfusion ratio.

The clinical use of liquid ventilation with perflubron for children with respiratory failure[9,10] and adults with respiratory distress syndrome[11] was recently reported. It is speculated that partial liquid ventilation prevents alveolar collapse and provides better ventilation distribution to diseased lungs than does conventional gas ventilation. Subsequently, partial liquid ventilation improves both pulmonary oxygenation and lung compliance, not only in lung disease of prematurity but also in patients with acute respiratory distress syndrome. Partial liquid ventilation with perflubron may ventilate the lungs more homogeneously than conventional gas ventilation does.[12] Therefore we hypothesized that any drugs administered with the perflubron during partial liquid ventilation would be more efficiently delivered to the alveolar units than they would if they were aerosolized. This study was designed to investigate the effects of intratra-

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cheally administered PGE_1 during partial liquid ventilation and aerosolized PGE_1 during conventional gas ventilation on gas exchange and circulation in rabbits with oleic acid–induced acute respiratory distress syndrome.

Materials and Methods

Surgical Preparation

The experiments were reviewed and approved by the Animal Care and Use Committee of Tokyo Medical and Dental University and were carried out according to the National Institutes of Health guidelines. Fifty-five mature Japanese white rabbits, weighing 3.1 ± 0.1 kg, were anesthetized with 30 mg/kg ketamine and 0.3 mg/kg xylazine given intramuscularly. With the animals supine, a midline cervical incision was made after subcutaneous infiltration with 0.5% (wt/vol) lidocaine and a tracheostomy was established. The trachea was intubated with a 4-mm (inner diameter) endotracheal tube. A 22-gauge polyethylene catheter was secured inside the lumen of the tracheal tube so that its tip was positioned at the distal end of the endotracheal tube. Mechanical ventilation (tidal volume, 15 ml/kg; respiratory frequency, 30/min; inspiratory:expiratory ratio, 1:2; fractional concentration of oxygen in inspired gas, 1.0) was initiated (SN-480-6, Shinano Co., Tokyo, Japan). A 4-French double-lumen central venous catheter (CS-15402, Arrow International Inc., Reading, PA) was introduced through a jugular vein to measure central venous pressure and to infuse fluids and drugs. Hydroxyethylstarch (6% wt/vol) in lactated Ringer's solution (Hespander: Kyorin Pharmaceutical Co., Tokyo, Japan) was infused intravenously at a rate of 10 ml · kg^{-1} · h^{-1} throughout the study. Anesthesia was maintained by administering 2 mg · kg^{-1} · h^{-1} ketamine, 6 mg · kg^{-1} · h^{-1} propofol, and 0.05 mg · kg^{-1} · h^{-1} pancuronium through the central venous line. The incremental infusion rate of ketamine and propofol was given as necessary when inadequate anesthesia was observed. Inotropic support was not instituted in any of the animals. The left carotid artery was cannulated to measure the mean arterial pressure and to sample blood. A median sternotomy after local subcutaneous infiltration with 0.5% (wt/vol) lidocaine was performed without damaging the pleura, and catheters were inserted directly into the left atrium to measure the left atrial pressure, and into the pulmonary arterial trunk to measure the PAP and to sample blood. An electromagnetic flow probe (6-mm inner diameter; model MFV 1100; Nihon Kohden Co., Tokyo, Japan) was attached around the ascending aorta to measure the cardiac output. The flow probe was calibrated before use, and the expected error of the probe was within ±15% (published data from Nihon Kohden Co.). The arterial pressure, PAP, left atrial pressure, central venous pressure, cardiac output, and airway pressure were recorded simultaneously using a polygraph (142–8; San-ei Instrument Co., Tokyo, Japan), and blood gases were analyzed using a blood gas analyzer (1306A, Instrumentation Laboratory, Milan, Italy). Blood hemoglobin levels were measured using a blood cell analyzer for animals (MEK-6108, Nihon Kohden Co.). Each animal's chest was kept open and its body temperature was maintained at approximately 37°C throughout the study.

Experimental Design

Approximately 60 min after the experimental preparation, baseline measurements, including hemodynamics, blood gas parameters, and pulmonary compliance were obtained, after which 0.08 ml/kg oleic acid mixed with 5 ml heparinized blood was infused through the central venous catheter during a period of 20 min. Sixty minutes after completion of the oleic acid infusion, control measurements were taken, after which the animals were assigned to one of four groups. Control group animals (group 1) were ventilated at the aforementioned settings throughout the experiment. Group 2 received aerosolized PGE_1 (Prostandin 500; Ono Pharmaceutical Co., Osaka, Japan) by an ultrasonic nebulizer (Soniclizer 305, Atom Co., Tokyo, Japan) that was connected to the inspiratory limb of the ventilator circuit. The diameter of aerosolized particle was 1 or 2 μm (published data from Atom Co.). The PGE_1 was diluted with normal saline (100 μg/25 ml) and introduced into the bottom of the nebulizer chamber through a catheter, using a syringe pump (model 1235N; Atom Co.). The nebulizer chamber was filled with 5 μg PGE_1 beforehand, and PGE_1 was administered at a dosage of 0.1 μg · kg^{-1} · min^{-1}. The ventilator settings were not changed except that 5 cm H_2O positive end-expiratory pressure was added after the initiation of aerosolized PGE_1 administration. Groups 3 and 4 received 15 ml/kg perflubron ($CF_3(CF_2)_6CF_2Br$, Nippon Mektron Ltd., Tokyo, Japan) intratracheally in combination with mechanical ventilation. The perflubron was instilled in three divided doses. First the animals were tilted to the left decubitus position and 5 ml/kg perflubron was administered into the trachea through the endotracheal tube, followed by administration of the same dose with the animals in the right lateral decubitus and then in the supine position. Positive end-

expiratory pressure was not applied in groups 3 and 4. After the perflubron administration was complete, group 4 received a 5-μg bolus followed by 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ PGE_1 continuously instilled intratracheally through the catheter attached to the tip of the endotracheal tube. PGE_1 was diluted with normal saline (100 μg/5 ml).

Measurements were repeated every 30 min for 2 h after recording control data. Additional doses of perflubron were not administered during the 2 h of the study period after the initial dose. If animals died or experienced pneumothorax before the experiment was completed, they were excluded from the data analysis. The experiments were done until 10 complete sets of data were obtained for each group.

Data Analysis and Statistics

The physiologic shunt fraction during gas ventilation ($\dot{Q}s/\dot{Q}t$) was calculated using the arterial oxygen content (Ca_{O_2}), mixed venous oxygen content ($C\bar{v}_{O_2}$), and alveolar capillary oxygen content (Cc_{O_2}) and the following equations:

$$\dot{Q}s/\dot{Q}t = Cc_{O_2} - Ca_{O_2}/Cc_{O_2} - C\bar{v}_{O_2}$$

where $Cc_{O_2} = 1.34 \times Hb + 0.003 \times P_{A_{O_2}}$, $Ca_{O_2} = 1.34 \times Hb \times Sa_{O_2} + 0.003 \times Pa_{O_2}$, $C\bar{v}_{O_2} = 1.34 \times Hb \times S\bar{v}_{O_2} + 0.003 \times P\bar{v}_{O_2}$, $P_{A_{O_2}}$ = (barometric pressure − 47) × 1 − Pa_{CO_2}. The vapor pressure of perflubron used in this experiment was 10.5 mmHg at 37°C, so when we calculated $\dot{Q}s/\dot{Q}t$ during partial liquid ventilation, $P_{A_{O_2}}$ was calculated as (barometric pressure −47 − 10.5) × 1.0 − Pa_{CO_2}. Dynamic compliance was calculated using the formula tidal volume/end-inspiratory pressure − end-expiratory pressure.

The data are expressed as mean ± SD. All statistical analyses on recorded data were performed using the statistical software package StatView (J 4.5, Abacus Concepts, Berkeley, CA). The intragroup comparisons of control data and data obtained at 30, 60, 90 and 120 min, and the intergroup comparisons at each time interval were performed using repeated-measures analysis of variance. When a significant difference was noted, *post hoc* analysis using Bonferroni's method was performed within and between groups. Overall statistical significance was assumed at $P < 0.05$.

Results

Administration of oleic acid caused hypoxia and hypercapnia, decreased compliance, increased PAP, and decreased cardiac output in each group (table 1). Fifteen of 55 animals were excluded from the study: 12 died of severe hypoxia or right ventricular failure (7 before control measurements, 3 in group 1, and 2 in group 2), and 3 developed pneumothorax (2 in group 1 and 1 in group 3). The control data after lung injury were not different among the groups.

Changes in Hemodynamics after Lung Injury

Table 1 shows hemodynamic changes. The mean PAP was not altered in groups 1 and 2 after injury. The mean PAP of group 3 decreased 30 min after partial liquid ventilation ($P = 0.0012$ *vs.* control data), but the difference was no longer significant after 60 min. The mean PAP of group 4 was reduced significantly after partial liquid ventilation with PGE_1 ($P < 0.0001$ at 30 min and $P = 0.0026$ at 120 min *vs.* control data). The mean PAP values of group 4 after partial liquid ventilation and PGE_1 were significantly less than the corresponding group 1 values ($P = 0.0014$ at 30 min and $P = 0.0025$ at 120 min). They were also less than those of group 2 30, 60, and 90 min after partial liquid ventilation and PGE_1 ($P = 0.004$ at 30 min and $P = 0.0063$ at 90 min).

Changes in Blood Gas Parameters and Pulmonary Mechanics after Lung Injury

End-inspiratory pressure and compliance were not altered after lung injury was established in all groups (table 2). The increase in $\dot{Q}s/\dot{Q}t$ and decrease in Pa_{O_2} were sustained throughout the study in groups 1 and 2. The $\dot{Q}s/\dot{Q}t$ values decreased after initiation of partial liquid ventilation in groups 3 and 4 ($P < 0.005$ *vs.* control data) and they were less than those of groups 1 and 2 ($P < 0.006$). The Pa_{O_2} of group 3 increased 30 min after partial liquid ventilation ($P = 0.003$ *vs.* control data), but the difference was no longer significant 60 min after partial liquid ventilation, whereas the increase in Pa_{O_2} was sustained in group 4 ($P < 0.0001$ at 30 min, $P = 0.0024$ at 120 min *vs.* control data; fig. 1). Compared with groups 1 and 2, the Pa_{O_2} values were significantly greater in group 3 at 30 and 60 min ($p < 0.006$) and also higher in group 4 throughout the experiment after partial liquid ventilation and PGE_1 ($P < 0.0001$). The Pa_{O_2} values of group 4 at 30, 60, and 120 min after partial liquid ventilation and PGE_1 was higher than the corresponding value of group 3 ($P = 0.005$, $P = 0.0033$, and $P = 0.0016$, respectively).

Table 1. Hemodynamic Data of Animals at Baseline, after Injury (Control), and during Treatment

	Baseline	Control (after injury)	After Treatment			
			30 min	60 min	90 min	120 min
MAP (mmHg)						
Group 1	81 ± 11	72 ± 17	61 ± 17	64 ± 18	63 ± 6	60 ± 18*
Group 2	82 ± 23	79 ± 17	74 ± 23	71 ± 24	71 ± 19	71 ± 19
Group 3	79 ± 11	74 ± 28	68 ± 20	67 ± 20	63 ± 20	68 ± 17
Group 4	88 ± 15	75 ± 21	82 ± 19	80 ± 21	82 ± 17	78 ± 16
CVP (mmHg)						
Group 1	3 ± 2	5 ± 2	6 ± 3	6 ± 2	6 ± 2	6 ± 2
Group 2	3 ± 2	5 ± 2	5 ± 2	6 ± 2	6 ± 1	6 ± 1
Group 3	4 ± 2	5 ± 1	5 ± 1	5 ± 2	5 ± 2	6 ± 2
Group 4	3 ± 1	5 ± 2	4 ± 2	4 ± 1	4 ± 1	5 ± 1
LAP (mmHg)						
Group 1	4 ± 2	4 ± 2	4 ± 2	4 ± 2	4 ± 2	4 ± 2
Group 2	4 ± 1	4 ± 1	5 ± 1	4 ± 1	4 ± 1	4 ± 1
Group 3	3 ± 1	4 ± 2	4 ± 2	4 ± 2	4 ± 2	4 ± 2
Group 4	2 ± 1	3 ± 2	5 ± 2	5 ± 3	4 ± 3	4 ± 2
Mean PAP (mmHg)						
Group 1	14 ± 2	23 ± 3	21 ± 2	22 ± 2	23 ± 3	23 ± 3
Group 2	12 ± 2	24 ± 3	21 ± 3	22 ± 3	21 ± 3	21 ± 4
Group 3	13 ± 3	22 ± 4	19 ± 3*	20 ± 3	20 ± 3	20 ± 4
Group 4	13 ± 3	22 ± 3	16 ± 3*†‡	17 ± 3*†‡	18 ± 3*†‡	18 ± 3*†‡
Cardiac output (ml/min)						
Group 1	389 ± 90	253 ± 56	224 ± 68	229 ± 66	200 ± 64	178 ± 64
Group 2	370 ± 60	240 ± 82	229 ± 104	226 ± 94	214 ± 94	208 ± 90
Group 3	377 ± 83	261 ± 102	268 ± 84	253 ± 66	233 ± 72	230 ± 63
Group 4	386 ± 84	229 ± 78	299 ± 121*	279 ± 87	281 ± 102	254 ± 102

Values are mean ± SD.

Group 1 = gas ventilation; Group 2 = aerosolized PGE_1; Group 3 = partial liquid ventilation; Group 4 = partial liquid ventilation + intratracheal PGE_1; MAP = mean arterial pressure; CVP = central venous pressure; LAP = left atrial pressure; PAP = pulmonary artery pressure.

* $P < 0.0125$ *versus* control data after Bonferroni correction.

† $P < 0.0083$ *versus* corresponding data of group 1 after Bonferroni correction.

‡ $P < 0.0083$ *versus* corresponding data of group 2 after Bonferroni correction.

Discussion

Intratracheal administration of PGE_1 combined with partial liquid ventilation improved gas exchange and pulmonary circulation without causing systemic hypotension or reducing cardiac output, whereas aerosolized PGE_1 combined with conventional gas ventilation failed to improve oxygenation or reduce PAP. The results suggest that PGE_1 delivery during liquid ventilation augments the improvement in oxygenation and decreased PAP seen with liquid ventilation alone. Treatment of severe acute respiratory distress syndrome should be directed to recruitment of atelectasis, improvement of oxygenation without compromising the systemic circulation, and reduction of pulmonary vascular resistance. Among the four treatments in the current study, intratracheal PGE_1 combined with partial liquid ventilation achieved those purposes most successfully.

The administration doses of PGE_1 in those two groups were not equivalent. The dose of PGE_1 in group 4 was larger than the intravenous dose used clinically in acute respiratory distress syndrome,[2,3] whereas in group 2 it was probably much less because some aerosolized PGE_1 was lost through expired gas. In addition, it is possible that our aerosol delivery system failed to deliver particles to the lung, especially in small animals. Because no rabbit developed hypotension or low cardiac output in response to intratracheal PGE_1 during partial liquid ventilation, it did not seem that the dose of PGE_1 in group 4 was extremely large. There may be some other possible mechanisms by which aerosolized PGE_1 failed to im-

Table 2. Blood Gas Parameters and Pulmonary Mechanics of Animals at Baseline, after Injury (Control), and during Treatment

	Baseline	Control (after injury)	After Treatment			
			30 min	60 min	90 min	120 min
Arterial *p*H						
Group 1	7.46 ± 0.07	7.23 ± 0.08	7.18 ± 0.11	7.14 ± 0.12*	7.1 ± 0.14*	7.01 ± 0.14*
Group 2	7.52 ± 0.08	7.32 ± 0.09	7.20 ± 0.12	7.24 ± 0.14	7.23 ± 0.11	7.24 ± 0.12
Group 3	7.44 ± 0.07	7.29 ± 0.09	7.26 ± 0.1	7.26 ± 0.08	7.25 ± 0.07†	7.25 ± 0.08†
Group 4	7.49 ± 0.08	7.25 ± 0.14	7.22 ± 0.09	7.25 ± 0.07	7.24 ± 0.05†	7.25 ± 0.06†
Pa_{CO_2} (mmHg)						
Group 1	31 ± 4	54 ± 10	58 ± 10	61 ± 10	65 ± 12	66 ± 14
Group 2	31 ± 4	51 ± 7	56 ± 12	58 ± 10	59 ± 10	59 ± 10
Group 3	34 ± 7	53 ± 9	52 ± 6	57 ± 6	57 ± 6	56 ± 5
Group 4	31 ± 5	52 ± 11	51 ± 10†	50 ± 11†	51 ± 9†	50 ± 8†
Pa_{O_2} (mmHg)						
Group 1	530 ± 29	78 ± 22	76 ± 18	66 ± 11	62 ± 15	62 ± 16
Group 2	582 ± 52	65 ± 18	75 ± 53	64 ± 34	60 ± 33	57 ± 19
Group 3	516 ± 61	73 ± 41	187 ± 45*†‡	133 ± 56†‡	124 ± 68	112 ± 46
Group 4	537 ± 34	64 ± 14	283 ± 87*†‡§	204 ± 75*†‡§	205 ± 109*†‡	206 ± 112*†‡§
$P\bar{v}_{O_2}$ (mmHg)						
Group 1	47 ± 5	36 ± 11	32 ± 12	30 ± 8	26 ± 8	22 ± 8*
Group 2	50 ± 11	31 ± 6	29 ± 10	27 ± 11	25 ± 10	24 ± 10
Group 3	50 ± 4	35 ± 7	45 ± 8*†‡	41 ± 7†‡	37 ± 8‡	37 ± 7†‡
Group 4	47 ± 8	31 ± 8	45 ± 7*†‡	41 ± 7*†‡	39 ± 11†‡	35 ± 11†‡
$\dot{Q}s/\dot{Q}t$ (%)						
Group 1	10.4 ± 2.5	42.9 ± 5	41.3 ± 6.1	44.7 ± 8.1	44.5 ± 9.2	43.2 ± 10.1
Group 2	9 ± 5.6	46 ± 9.1	47 ± 9.4	49.7 ± 8.9	49.2 ± 9.5	50.1 ± 9
Group 3	12.6 ± 4	47.1 ± 12.5	28.5 ± 4.7*†‡	31.1 ± 6.1*†‡	30.2 ± 5.8*†‡	31.4 ± 7.2*†‡
Group 4	11.3 ± 2.9	43.2 ± 6.5	22.4 ± 6.1*†‡	26.1 ± 8.4*†‡	25.2 ± 4*†‡	25.6 ± 7*†‡
End-inspiratory pressure (cmH_2O)						
Group 1	7 ± 2	16 ± 5	16 ± 6	18 ± 6	18 ± 6	19 ± 6
Group 2	7 ± 2	15 ± 3	16 ± 3	17 ± 4	17 ± 3	17 ± 3
Group 3	7 ± 1	14 ± 4	13 ± 4	13 ± 3	13 ± 4	13 ± 4
Group 4	8 ± 2	15 ± 4	14 ± 4	14 ± 4	15 ± 5	15 ± 5
Lung compliance (ml/cmH_2O)						
Group 1	6.9 ± 2.7	3 ± 1.4	3.2 ± 2	2.9 ± 1.7	2.8 ± 1.6	2.8 ± 1.7
Group 2	6.8 ± 2	3.3 ± 0.6	3 ± 0.6	2.9 ± 0.6	2.9 ± 0.5	2.9 ± 0.5
Group 3	6.9 ± 2	3.6 ± 1.5	4.1 ± 1.9	3.7 ± 1.4	3.8 ± 1.5	3.8 ± 1.5
Group 4	5.8 ± 1.8	3.4 ± 1.1	3.8 ± 1.6	3.7 ± 1.3	3.6 ± 1.4	3.5 ± 1.4

Values are mean ± SD.

Group 1 = gas ventilation; Group 2 = aerosolized PGE_1; Group 3 = partial liquid ventilation; Group 4 = partial liquid ventilation + intratracheal PGE_1.

* $P < 0.0125$ *versus* control data after Bonferroni correction.

† $P < 0.0083$ *versus* corresponding data of group 1 after Bonferroni correction.

‡ $P < 0.0083$ *versus* corresponding data of group 2 after Bonferroni correction.

§ $P < 0.0083$ *versus* corresponding data of group 3 after Bonferroni correction.

prove oxygenation in our lung injury model. We assume that the distribution of PGE_1 during partial liquid ventilation and gas ventilation was different. Aerosolized PGE_1 may not be delivered to the alveoli because the positive end-expiratory pressure level might be inadequate to recruit collapsed alveoli in our study. Some of the aerosolized PGE_1 seemed to dissolve in edema fluid, which subsequently increased the shunt fraction. Those two factors might offset any favorable effects of PGE_1 on gas exchange and circulation in lung injury. On the other hand, intratracheally administered PGE_1 during partial liquid ventilation could be delivered to alveolar units by conductive transport of perflubron. Partial liquid ventilation improves gas exchange by several mechanisms: pulmonary blood flow redistribution, recruitment of atelectatic alveoli, and displacement of alveolar edema fluid by perflubron.[11,13] A recent study using isolated piglet lungs showed that partial liquid ventilation abated

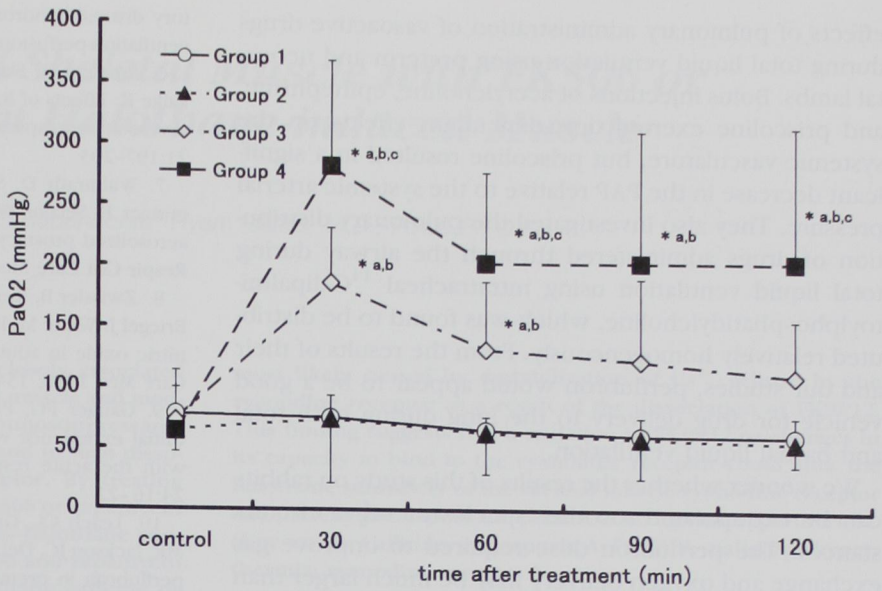

Fig. 1. Changes in partial pressure of oxygen in arterial blood after oleic acid administration. Values are mean ± SD. ○, group 1 (gas ventilation); ▲, group 2 (aerosolized PGE_1); ◇, group 3 (partial liquid ventilation); ■, group 4 (partial liquid ventilation plus intratracheal PGE_1). *$P < 0.0125$ *versus* control data after Bonferroni correction. [a]$P < 0.0083$ *versus* corresponding data of group 1 after Bonferroni correction. [b]$P < 0.0083$ *versus* corresponding data of group 2 after Bonferroni correction. [c]$P < 0.0083$ *versus* corresponding data of group 3 after Bonferroni correction.

oleic acid–induced elevation in pulmonary vascular resistance when given therapeutically after lung injury.[14] We also showed a transient reduction of PAP without decreasing cardiac output soon after partial liquid ventilation. Increased vasodilation of well-ventilated areas that received both oxygen-rich perflubron and PGE_1 may account for improved oxygenation and decreased pulmonary vascular resistance in group 4.

Few reports describe the effect of aerosolized PGE_1 on oxygenation and pulmonary circulation in acute respiratory distress syndrome. Keenan *et al.*[15] reported that inhaled PGE_1 improved the Pa_{O_2}/FI_{O_2} ratio from 78 to 107 in seven patients with severe acute respiratory distress syndrome. However, there were no significant changes in PAP or cardiac output. It seems that aerosolized drugs are more efficiently delivered to the distal airways in large animals or humans than they are in small animals. From the conflicting results of Keenan *et al.*'s and our current investigation, more studies are needed to determine the effects of inhalational PGE_1 on gas exchange and pulmonary circulation in acute respiratory distress syndrome.

In the current study, we used an open-chest preparation, which obviously differs physiologically from a closed-chest preparation. First, in an open-chest model under mechanical ventilation, the formation of atelectasis may be more extensive than in the closed chest, especially without suitable positive end-expiratory pressure. Second, larger doses of perflubron (15 ml/kg) were needed in this open-chest model to observe the presence of a perflubron meniscus in the tracheal tube compared with previous studies using rabbits.[12,16] Tütüncü *et al.*[12] investigated the effects of lesser doses (3, 6, 9, and 12 ml/kg) of perflubron in rabbits with acute lung injury induced by alveolar lavage. They observed that the groups treated with 9 or 12 ml/kg perflubron showed a significantly higher Pa_{O_2} level at the end of a 6-h study (without additional doses) compared with pretreatment values. On the other hand, the improvement of Pa_{O_2} by partial liquid ventilation in our study was only transitory. However, the improvement of Pa_{O_2} in the experiments of Tütüncü *et al.*[12] also seemed time dependent. According to a recent study by Mates *et al.*[17] using healthy piglets, estimation of evaporative losses of perflubron during partial liquid ventilation were calculated to be approximately 2 $ml \cdot kg^{-1} \cdot h^{-1}$ (assuming a ventilatory rate of 20 breaths/min, a tidal volume of 15 ml/kg, and a dead space of 3 ml/kg). In the current study, the loss of perflubron was estimated to be about 9 ml/h, provided that the ventilatory rate was 30 breaths/min, the rabbit weighed 3 kg, and the expired gas was fully saturated with perflubron (10.5 mmHg at 37°C), and this might affect the gas exchange.

Recently, the combination of perflubron and nitric oxide for ventilating surfactant-depleted lungs[18] or oleic acid–injured lungs[19] was found to have an additive effect, improving gas exchange and reducing PAP. It was proposed that the amount of perflubron used for partial liquid ventilation could be reduced by concomitant administration of nitric oxide. Other authors have investigated the efficacy of pulmonary administration of drugs during liquid ventilation.[20] Wolfson *et al.*[20] showed the

effects of pulmonary administration of vasoactive drugs during total liquid ventilation using preterm and neonatal lambs. Bolus injections of acetylcholine, epinephrine, and priscoline exerted dose-dependent effects on the systemic vasculature, but priscoline resulted in a significant decrease in the PAP relative to the systemic arterial pressure. They also investigated the pulmonary distribution of drugs administered through the airway during total liquid ventilation using intratracheal ^{14}C-dipalmitoylphosphatidylcholine, which was found to be distributed relatively homogeneously. From the results of their and our studies, perflubron would appear to be a good vehicle for drug delivery to the lung during both total and partial liquid ventilation.

We wonder whether the results of this study on rabbits can be extrapolated to other species or other circumstances. The perflubron dose required to improve gas exchange and oxygen delivery may be much larger than that for rabbits, especially for large animals.[18,21] Incremental dosing of perflubron may increase the PAP, and a few studies have shown this phenomenon. The PAP tended to increase in response to cumulative doses of perflubron in large-animal models of acute respiratory failure, although the increases were not significant.[18] Studies that evaluate the effects of intratracheal vasodilators during partial liquid ventilation on gas exchange and pulmonary circulation in large-animal models should be performed before this technique is used clinically.

In conclusion, intratracheal PGE_1 combined with partial liquid ventilation not only improved Pa_{O_2} and cardiac output but also reduced PAP in a rabbit model of acute respiratory distress syndrome. Intratracheal administration of PGE_1 during partial liquid ventilation may offer an alternative treatment for acute respiratory distress syndrome with pulmonary hypertension.

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