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EXPERIMENTAL

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Inhaled nitric oxide during partial liquid ventilation shifts pulmonary blood flow to the non-dependent lung regions

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Abstract *Objective*: To elucidate the change in pulmonary blood flow brought about by nitric oxide (NO) inhalation during partial liquid ventilation (PLV).
Design: Prospective, controlled study.
Setting: A research laboratory at a university medical center.
Subjects: Fourteen Japanese white rabbits (3.2 ± 0.05 kg body weight).
Interventions: Animals were mechanically ventilated in the right decubitus position. Following saline lung lavage, PLV was started with perflubron (15 ml/kg). In the NO group (n = 7), PLV was supplemented by a 30-min challenge of NO inhalation (10 ppm) from 30 min after the initiation of PLV. In the control group (n = 7), PLV was continued for 60 min.
Measurements and main results: For the pulmonary blood flow analysis, colored microspheres were administered from the right atrium at 30 min (T_{PLV1}) and 60 min (T_{PLV2}) after the initiation of PLV. The percentage of the left lung blood flow in the total pulmonary blood flow ($\%Q_L/Q_T$) was significantly increased by NO inhalation in the NO group (p = 0.0164), while that in the control group was significantly decreased during the same period (p = 0.0107). PaO_2 in the NO group was significantly increased by NO inhalation (p = 0.0153), but not in the control group (p = 0.7911).
Conclusion: Inhaled NO during PLV shifted the pulmonary blood flow to the non-dependent region and improved pulmonary gas exchange. This result suggested that inhaled NO took effect predominantly in the non-dependent region during PLV.

Key words Liquid ventilation · Perfluorocarbon · Inhaled nitric oxide · Pulmonary blood flow · Colored microsphere · Ventilation-perfusion relationship

Introduction

Partial liquid ventilation (PLV) is the ventilatory method performed by conventional gas ventilation in the perfluorocarbon (PFC)-filled lung [1], and it is one of the therapeutic approaches for acute respiratory failure [2, 3 , 4, 5, 6, 7]. Because of its high density and low surface tension, PFC enhances recruitment of atelectatic lung regions and reduces lung damage [7]. In addition, PFC liquid distribution is gravity-dependent [8], and pulmonary blood flow is redistributed to the non-dependent regions because of PFC's high density [9, 10]. As a result, PLV increases the blood flow in relatively ventilated alveoli in the non-dependent area and ventilation-perfusion matching can be improved.

Inhaled nitric oxide (NO) is another choice for improving pulmonary gas exchange due to its selective pulmonary vasodilating effect. Inhaled NO dilates vessels responsible for ventilated alveoli and improves the ventilation-perfusion relationship in the lung. Recently, several reports have demonstrated the efficacy of the combination of these two therapeutic approaches [11,

12, 13, 14, 15, 16]. The supplementation of inhaled NO to PLV improved pulmonary gas exchange more than PLV alone did. One possible explanation for this cumulative effect is that alveolar recruitment by PLV augments NO delivery to its site of action [17]. Another possibility is that PFC contains dissolved NO gas, which improves pulmonary gas exchange. Unfortunately, it has not been elucidated yet whether the gas phase or the liquid phase is the dominant effective site of inhaled NO during PLV, because the solubility of NO in PFC liquid is not known. However, the change in the pulmonary blood flow distribution caused by NO inhalation reflects the distribution of NO in the lung. NO dissolved in the PFC liquid would shift the blood flow to the dependent regions because of its gravity-dependent distribution. By contrast, NO in the gas phase would shift the blood flow to the non-dependent regions because gas is predominantly distributed to the non-dependent regions during PLV. The purpose of the current study, therefore, was to investigate the change in pulmonary blood flow caused by NO inhalation, and to estimate the dominant effective site of inhaled NO during PLV.

Materials and methods

The following protocol was approved by the institutional animal ethics committee. All animals were handled according to the guidelines set out in the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health.

Animal preparation

Fourteen Japanese white rabbits (3.2 ± 0.05 kg body weight) were anesthetized with intramuscular ketamine (100 mg) and xylazine (12.5 mg). Tracheostomy was established under local anesthesia and an endotracheal tube (internal diameter: 4.0 mm) (Lo-contour; Mallincrodt Medical, Athlone, Ireland) was inserted. Ketamine (10 mg), xylazine (12.5 mg) and pancuronium (1.0 mg) were administered intravenously and volume-controlled mechanical ventilation was started with an animal ventilator (model SN-480–6; Shinano, Tokyo, Japan). Tidal volume (V_T) was 40 ml and respiratory rate was 30 breaths/min (bpm). FIO_2 was 0.99 and 6 ml/kg · h of lactate Ringer's solution was continuously infused. Anesthesia was maintained with continuous infusion of ketamine (10 mg/h), xylazine (25 mg/h) and pancuronium (1 mg/h).

A central venous catheter was inserted via the right jugular vein and the right carotid artery was cannulated with a 20-gauge Teflon cannula (Surflow; Terumo, Tokyo, Japan). Airway pressure and mean arterial pressure (MAP) was continuously monitored using a monitoring system (Lifescope 12, Nihonkohden, Tokyo, Japan). Arterial blood was sampled and analyzed using a pH/blood gas analyzer (IL1306A; Instrumentation Laboratory, Milan, Italy).

Nitric oxide inhalation

Nitric oxide was supplied from a cylinder containing 800 ppm of NO balanced with nitrogen. It was mixed with 99% oxygen by a flow meter (FLO-MS-33 C; Tokyo Ryuki Kogyo, Tokyo, Japan). The gas mixture was supplied to the animal ventilator via a soda lime filter. At the level of fresh gas supply of the ventilator, the gas mixture was sampled and the NO concentration was monitored continuously by a chemiluminescence NO/NO_2 analyzer (CLV-500; Shimadzu, Kyoto, Japan). Then NO concentration was adjusted to 10 ppm by titrating the flow rate of NO gas mixture from the cylinder.

Study protocol

After the preparation period, the position of the animal was changed to the right decubitus position and all the experimental procedures were performed in this position.

After the baseline measurement, the lungs were lavaged several times with 40 ml of normal saline at 37 °C until PaO_2 decreased to less than 100 mmHg, using a modification of the technique described by Lachmann et al. [18]. After 1-h stabilization of lung injury, PLV was started with 15 ml/kg of perflubron (PFOB; Nippon Mektron, Tokyo, Japan). During instillation of perflubron, the lung was ventilated with 99% of oxygen every 3 ml of instillation. During PLV, V_T was 40 ml, RR was 30 bpm and FIO_2 was 0.99. This ventilator setting was unchanged throughout the study. Then animals were randomly divided into the NO group and the control group. In the NO group, PLV was supplemented with a 30-min challenge of NO inhalation (10 ppm) from 30 min after the start of PLV. In the control group, PLV without NO inhalation was continued until the end of the protocol.

Arterial blood gas, peak inspiratory pressure (PIP) and hemodynamic data were measured at the following time points: (1) T_{BS}: before saline lung lavage (as baseline); (2) T_{LI}: 60 min after the completion of lung lavage; (3) T_{PLV1}: 30 min after the initiation of PLV; (4) T_{PLV2}: 30 min after the initiation of NO inhalation under PLV (or 60 min after the initiation of PLV in the control group).

Pulmonary blood flow analysis

To compare the pulmonary blood flow distribution between the dependent and the non-dependent lung regions, animals were positioned in the right decubitus position and the number of microspheres was compared between the right lung (dependent lung) and the left lung (non-dependent lung). Pulmonary blood flow was evaluated using the dye-extraction colored microsphere technique adapted from Hakkinen et al. [19] with some modifications. White, red and yellow dye extraction microsphere solutions (Dye-Trak; Triton technology, San Diego, Calif.) were infused via central venous catheter at T_{LI}, T_{PLV1} and T_{PLV2}, respectively. The diameter of the microsphere was 15.5 ± 0.33 μm and the concentration of microsphere solution was approximately 3×10^6 spheres/ml (yellow 3.1×10^6 spheres/ml; red 3.0×10^6 spheres/ml; white 3.0×10^6 spheres/ml). The infused volume of each solution was 0.05 ml. Thirty minutes after the last microsphere infusion, the animals were deeply anesthetized, heparinized and killed by the injection of a large dose of pentobarbital. Following a sternotomy, large-bore catheters were inserted into the pulmonary artery and left atrium, and the lungs were perfused with normal saline to clear blood.

The lungs were removed from the chest, and the left and the right lungs were separated. The tissue of each lung was broken down for 72 h by adding 20 ml of 4 N KOH containing 0.05% Tween 80 (Sigma Chemical, St. Louis, Mo.). The solution of dissolved tissue was filtered with a polyester filter (Triton 31079; Triton technology, San Diego, Calif.) to recover the microspheres trapped in each tissue sample. After the filters had been dried for

Table 1. Physiological data at T_{BS}

	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	pH	HR (bpm)	MAP (mmHg)	PIP (cmH_2O)
NO	536 ± 13	36.7 ± 1.4	7.404 ± 0.024	217 ± 19	93 ± 5	9.1 ± 0.5
Control	531 ± 17	34.6 ± 1.2	7.453 ± 0.025	212 ± 10	88 ± 4	8.5 ± 0.7

Data are shown as mean ± SEM (*HR* heart rate, *MAP* mean arterial pressure, *PIP* peak inspiratory pressure)

24 h, the dye was extracted from the filtered microspheres by adding 1 ml of dimethyl formamide. Then the extracted solution was centrifuged at 2000 g for 10 min. The absorbance of the supernatant was determined by a spectrophotometer (UV1600 Shimadzu, Kyoto, Japan). The composite spectrum of each dye solution was resolved into the spectrum of the single constituents by a matrix inversion technique [20]. The pulmonary blood flow to the non-dependent lung region was evaluated with the percentage of the left lung blood flow in the total pulmonary blood flow ($\%Q_L/Q_T$), calculated from the following equation:

$$\%Q_L/Q_T = A_L/(A_L + A_R) \times 100$$

where Q_L and Q_T represent the blood flow into the left lung and the total lung, respectively, and A_L and A_R represent the absorbance of the sample of the left and the right lung, respectively.

Statistical analyses

All data are expressed as mean ± SEM. All statistical analyses were performed with software (Stat View 4.5; Abacus Concepts, Berkeley, Calif.). The significant level was 0.05 in each statistical analysis. Inter-group difference in the baseline data was tested with unpaired *t*-test. From T_{LI} to T_{PLV2}, the effect of PLV or inhaled NO was analyzed independently. The effect of PLV was tested with two-factorial repeated measure analysis of variance (rmANOVA) for the data from T_{LI} to T_{PLV1}. The effect of inhaled NO during PLV was tested with two-factorial rmANOVA for the data from T_{PLV1} to T_{PLV2}. The effect of NO was evaluated by a significant interaction between group and time course. For intra-group comparison, paired *t*-test was performed.

Results

The average body weight of the animals was 3.2 ± 0.06 kg in the NO group, and 3.3 ± 0.08 kg in the control group. Therefore V_T was 12.5 ± 0.2 ml/kg in the NO group, and 12.4 ± 0.3 ml/kg in the control group. The physiological data at T_{BS} are shown in Table 1. There were no statistically significant differences in these parameters between the two groups at T_{BS}. Neither the total volume of saline used for lung lavage nor the recovery rate was significantly different between the two groups (data not shown).

Effect of partial liquid ventilation

The data from T_{LI} to T_{PLV1} were shown in Table 2. Saline lung lavage resulted in severe hypoxia and hypercapnia at T_{LI}. The result of rmANOVA showed significant intra-group (time course) differences in PaO_2 ($p = 0.0004$), $PaCO_2$ ($p = 0.0003$), HR ($p = 0.0034$), PIP ($p = 0.0103$) and $\%Q_L/Q_T$ ($p < 0.0001$). The interaction between group and time course was not significant in any variable, so that the effect of PLV was equal between the NO and the control groups. PLV increased PaO_2 (from 44 ± 6 to 194 ± 52 mmHg in the NO group, from 42 ± 3 to 185 ± 31 mmHg in the control group), while it decreased $PaCO_2$ (from 61.4 ± 5.2 to 56.7 ± 5.3 mmHg in the NO group, from 56.6 ± 3.1 to 51.9 ± 3.5 mmHg in the control group). In addition, $\%Q_L/Q_T$ was increased by PLV (from 35.4 ± 3.1 to 42.7 ± 2.2 % in the NO group, from 37.4 ± 2.6 to 41.7 ± 3.5 % in the control group). PLV showed a slight but significant decrease in PIP (from 23.3 ± 0.8 to 21.8 ± 0.8 cmH_2O in the NO group, from 23.3 ± 0.8 to 22.0 ± 1.1 cmH_2O in the control group), and significant increase in HR (from 184 ± 17 to 220 ± 16 bpm in the NO group, from 184 ± 17 to 220 ± 16 bpm in the control group).

Effect of nitric oxide inhalation during partial liquid ventilation

The data from T_{PLV1} to T_{PLV2} are shown in Fig. 1 and Table 2. Significant interaction between NO inhalation and time course was observed in $\%Q_L/Q_T$ ($p = 0.0004$) and PaO_2 ($p = 0.0065$).

Nitric oxide inhalation significantly increased $\%Q_L/Q_T$ in the NO group (from 42.7 ± 2.2 to 46.4 ± 1.4 %, $p = 0.0164$ in paired *t*-test), while $\%Q_L/Q_T$ in the control group was significantly decreased during the same period (from 41.7 ± 3.5 to 37.2 ± 2.8 %, $p = 0.0107$ in paired *t*-test). In addition, NO inhalation significantly increased PaO_2 in the NO group (from 194 ± 52 to 224 ± 55 mmHg, $p = 0.0153$ in paired *t*-test), while PaO_2 in the control group was not significantly changed during the same period (from 185 ± 31 to 178 ± 27 mmHg, $p = 0.7911$ in paired *t*-test). $PaCO_2$, HR, MAP, pH and PIP were not significantly changed from T_{PLV1} to T_{PLV2}.

Table 2. Physiologic variables from T_{LI} to T_{PLV2} (*NS* not significant, *HR* heart rate, *MAP* mean arterial pressure, *PIP* peak inspiratory pressure, $\%Q_L/Q_T$ the percentage of the non-dependent lung blood flow in the total pulmonary blood flow, T_{LI} 60 min after the completion of the lung lavage, T_{PLV1} 30 min after the initiation of PLV, T_{PLV2} 30 min after the initiation of NO inhalation under PLV (or 60 min after the initiation of PLV in the control group)

	Group	T_{LI}	T_{PLV1}	T_{PLV2}	Effect of PLV*	Effect of NO**
PaO_2 (mmHg)	NO	44 ± 6	194 ± 52	224 ± 55	0.0004	0.0065
	Control	42 ± 3	185 ± 31	178 ± 27		
$PaCO_2$ (mmHg)	NO	61.4 ± 5.2	56.7 ± 5.3	53.8 ± 3.8	0.0003	NS
	Control	56.6 ± 3.1	51.9 ± 3.5	51.7 ± 2.7		
pH	NO	7.238 ± 0.048	7.194 ± 0.067	7.219 ± 0.076	NS	NS
	Control	7.223 ± 0.059	7.207 ± 0.074	7.220 ± 0.076		
HR (bpm)	NO	184 ± 17	220 ± 16	223 ± 14	0.0034	NS
	Control	171 ± 18	217 ± 9	214 ± 8		
MAP (mmHg)	NO	94 ± 4	94 ± 5	92 ± 6	NS	NS
	Control	91 ± 3	90 ± 3	89 ± 2		
PIP (cmH_2O)	NO	23.3 ± 0.8	21.8 ± 0.8	21.4 ± 0.9	0.0103	NS
	Control	23.3 ± 0.8	22.0 ± 1.1	22.0 ± 1.1		
$\%Q_L/Q_T$	NO	35.4 ± 3.1	42.7 ± 2.2	46.4 ± 1.4	< 0.0001	0.0004
	Control	37.4 ± 2.6	41.7 ± 3.5	37.2 ± 2.8		

Data are shown as mean ± SEM

* Effect of PLV was evaluated by two factorial repeated measure ANOVA for the data from T_{LI} to T_{PLV1}. The *p* value was calculated for the intra-group difference between T_{LI} and T_{PLV1}

** Effect of NO was evaluated by two factorial repeated measure ANOVA for the data from T_{PLV1} to T_{PLV2}. The *p* value was calculated for the interaction between group and time course

Discussion

The results of this study demonstrated that inhaled NO shifted the pulmonary blood flow into the non-dependent lung regions and improved pulmonary gas exchange.

Effect of partial liquid ventilation on the pulmonary blood flow

The distribution of the pulmonary blood flow in the PFC-filled lung has been investigated in several studies [9, 10, 21]. Lowe et al. reported the result of an ex vivo study using isolated cat lungs filled with 30 ml/kg or 90 ml/kg PFC [21]. They showed that the blood flow in the dependent regions was shifted into more non-dependent sites by the PFC filling according to dosage. Doctor et al. also demonstrated redistribution of pulmonary blood flow into the non-dependent regions in the in vivo PLV model, and the perfusion pattern remained stable over a 2-h period after the instillation of 30 ml/kg PFC [10]. These results were explained by the theory that the dense PFC liquid raised the transalveolar pressure in the dependent regions and shifted pulmonary blood flow to the non-dependent regions. In the present study, PFC instillation shifted the pulmonary blood flow into the non-dependent regions at T_{PLV1}. However, this blood flow redistribution was transient in the control group and $\%Q_L/Q_T$ decreased to the same level as T_{LI} (Table 2). The true mechanism responsible for this transient effect is unknown. However, there was a possibility that the dose of perflubron in this study (15 ml/kg) was insufficient to keep the perfusion pattern stable.

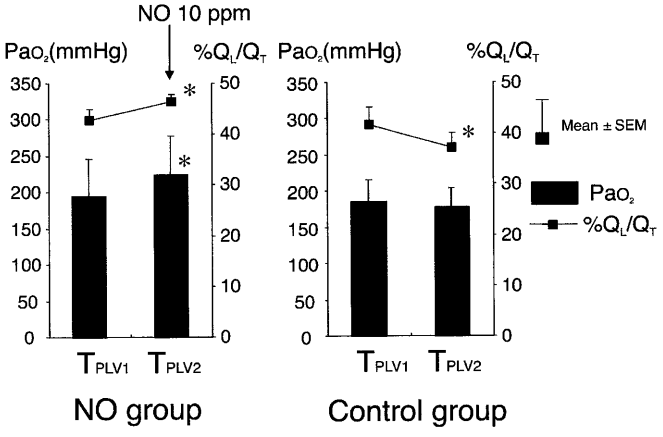

Fig. 1 Effect of nitric oxide inhalation during partial liquid ventilation on PaO_2 and the pulmonary blood flow to the non-dependent lung ($\%Q_L/Q_T$) (T_{PLV1} 30 min after the initiation of PLV, T_{PLV2} 30 min after the initiation of NO inhalation under PLV (or 60 min after the initiation of PLV in the control group) * $p < 0.05$ vs T_{PLV1}

Effect of inhaled nitric oxide on the pulmonary blood flow during partial liquid ventilation

Several studies demonstrated a cumulative effect between inhaled NO and PLV using different models, such as a congenital diaphragmatic hernia model [11], a saline lung lavage model [12, 13], an oleic acid lung injury model [14], a meconium aspiration model [15] and an extremely premature animal model [16]. They showed that inhaled NO was effectively delivered to reduce pulmonary hypertension and enhanced oxygenation during PLV. These reports showed relatively rapid response to a change in inhaled NO concentration. Houmes et al. demonstrated a sharp on-off response using online blood gas monitoring, and suspected the total amount of NO dissolved in PFC liquid was low [12]. However, it has not been elucidated yet whether the gas phase or the liquid phase is the effective site of inhaled NO during PLV, because the solubility of NO in PFC liquids is not known. The purpose of the present study was estimation of the distribution of NO during PLV via the change in pulmonary blood flow by NO inhalation. The result showed NO inhalation shifted the pulmonary blood flow into the non-dependent area and improved pulmonary gas exchange. This result suggested that inhaled NO took effect predominantly in the non-dependent region.

Quintel et al. demonstrated with computer tomographic assessment that PFC liquid distributed predominantly to the dependent regions and more gas than PFC liquid went to the non-dependent regions in each inspiration [8]. From the view point of inhaled NO, NO in the gas phase was distributed mainly to the non-dependent region and NO dissolved in the liquid was predominantly distributed to the dependent region. Therefore the result of this study suggested that NO in the gas phase had a stronger effect than NO dissolved in the PFC liquid. And this result was compatible with the rapid on-off response of inhaled NO during PLV [12].

Relationship between pulmonary blood flow distribution and gas exchange during partial liquid ventilation

Improvement in pulmonary gas exchange during PLV was explained by several mechanisms. Firstly, liquid PFC recruits collapsed alveolar units and increases end-expiratory lung volume [22]. Secondly, PFC instillation increases trans-alveolar pressure in the dependent lung region and shifts the pulmonary blood flow to the non-dependent region where lung injury is less severe [9, 10, 21]. In this study, 30 min PLV improved pulmonary gas exchange and increased the pulmonary blood flow in the non-dependent lung region (Table 2). These results were compatible with the hypothesis that blood flow redistribution contributed to the improvement in pulmonary gas exchange during PLV. However, in the control group, 60 min PLV returned $\%Q_L/Q_T$ to the T_{LI} level at T_{PLV2} without significant decrease in PaO_2 (Table 2). This was probably because the oxygenated PFC liquid in the dependent lung region contributed to the pulmonary gas exchange and blood flow redistribution to the dependent regions did not result in a decrease in PaO_2. Furthermore, there was a possibility of lung injury in the non-dependent lung regions. Injured lung units in the non-dependent lung region would restrain the effect of blood flow redistribution between the dependent and the non-dependent regions on pulmonary gas exchange. Concerning these factors, PLV itself would improve pulmonary gas exchange by alveolar recruitment, rather than by blood flow redistribution in this study.

On the other hand, inhaled NO improves pulmonary gas exchange by blood flow redistribution. In this study, NO inhalation improved pulmonary gas exchange and increased the pulmonary blood flow in the non-dependent lung region (Fig. 1, Table 2). This improvement in gas exchange was because NO was delivered predominantly into the non-dependent region and redirected, or "stole", the blood flow from injured lung units to more ventilated areas. Furthermore, because NO does not dilate vessels in injured lung units, the negative effect of injured units in the non-dependent lung regions would be less during NO inhalation. In other words, increased blood flow in the non-dependent regions was responsible for the ventilated area, not for the injured lung units. As a result, this steal phenomenon contributed to the improvement in pulmonary gas exchange during NO inhalation.

Study limitation

The blood flow was evaluated with the fraction of the blood flow to the right or the left lung divided by the total pulmonary blood flow, not the absolute blood flow value calculated from the reference blood flow and tissue weight in this study. In this sense, the absolute vasodilation by NO inhalation in each region could not be elucidated. However, concerning the view that NO inhalation increases total pulmonary blood flow by pulmonary vasodilating effect [14], inhaled NO increased absolute blood flow into the non-dependent lung region. On the other hand, the possibility of vasodilation in the dependent regions could not be excluded in this study. Nevertheless, this could not affect our conclusion that inhaled NO predominantly dilated vessels in the non-dependent regions and shifted the pulmonary blood flow into those areas.

Even if the gas phase is the dominant site of effect of inhaled NO, interaction between NO and oxygen in PFC has not been elucidated yet. Our preliminary data

showed PO_2 in the PFC is relatively lower than in the inspiratory gas during PLV [23]. This result suggests the interaction between NO and oxygen in the liquid phase could be less than in the gas phase. However, further studies about the toxicity of NO inhalation during PLV are needed to establish the safety of this combination therapy.

In conclusion, inhaled NO during PLV shifted the pulmonary blood flow into the non-dependent regions and improved pulmonary gas exchange. These results suggested that inhaled NO took effect predominantly in the non-dependent region during PLV, and NO in the gas phase had a stronger effect than NO dissolved in the PFC liquid.

References

1. Fuhrman BP, Paczan PR, DeFrancisis M (1991) Perfluorocarbon-associated gas exchange. Crit Care Med 19: 712–722
2. Tutuncu AS, Faithful NS, Lachmann B (1993) Intratracheal perfluorocarbon administration combined with mechanical ventilation in experimental respiratory distress syndrome: dose-dependent improvement of gas exchange. Crit Care Med 21: 962–969
3. Leach CL, Fuhrmann BP, Morin III FC, Rath MG (1993) Perfluorocarbon-associated gas exchange (partial liquid ventilation) in respiratory distress syndrome: a prospective, randomized, controlled study. Crit Care Med 21: 1270–1278
4. Hirschl RB, Tooley R, Parent AC, Johnson K, Bartlett RH (1995) Improvement of gas exchange, pulmonary function and lung injury with partial liquid ventilation: a study model in a severe respiratory failure. Chest 108: 500–508
5. Overbeck MC, Pranikoff T, Yadao CM, Hirschl RB (1996) Efficacy of perfluorocarbon partial liquid ventilation in a large animal model of acute respiratory failure. Crit Care Med 24: 1208–1214
6. Hirschl RB, Pranikoff T, Wise C, Overbeck MC, Gauger P, Schreiner RJ, Dechert R, Bartlett RH (1996) Initial experience with partial liquid ventilation in adult patients with the acute respiratory distress syndrome. JAMA 275: 383–389
7. Quintel M, Heine M, Hirschl RB, Tillmanns R, Wessendorf V (1998) Effects of partial liquid ventilation on lung injury in a model of acute respiratory failure: a histologic and morphmetric analysis. Crit Care Med 26: 833–843
8. Quintel M, Hirschl RB, Roth H, Loose R, Ackern K (1998) Computed tomographic assessment of perfluorocarbon and gas distribution during partial liquid ventilation for acute respiratory failure. Am J Respir Crit Care Med 158: 249–255
9. Gauger PG, Overbeck MC, Koeppe RA, Shulkin BL, Hrycko JN, Weber ED, Hirschl RB (1997) Distribution of pulmonary blood flow and total lung water during partial liquid ventilation in acute lung injury. Surgery 122: 313–323
10. Doctor A, Ibla JC, Grenier BM, Zurakowski D, Ferretti ML, Thompson JE, Lillehei CW, Arnold JH (1998) Pulmonary blood flow distribution during partial liquid ventilation. J Appl Physiol 84: 1540–1550
11. Wilcox DT, Glick PL, Karamanoukian HL, Morin FC III, Fuhrman BP, Leach C (1995) Perfluorocarbon-associated gas exchange improves pulmonary mechanics, oxygenation, ventilation and allows nitric oxide delivery in the hypoplastic lung congenital diaphragmatic hernia lamb model. Crit Care Med 23: 1858–1863
12. Houmes RJM, Hartog A, Verbrugge SJC, Bohm S, Lachmann B (1997) Combining partial liquid ventilation with nitric oxide to improve gas exchange in acute lung injury. Intensive Care Med 23: 163–169
13. Zobel G, Urlesberger B, Dacar D, Rodl S, Reiterer F, Friehs I (1997) Partial liquid ventilation combined with inhaled nitric oxide in acute respiratory failure with pulmonary hypertension in piglets. Pediatr Res 41: 172–177
14. Uchida T, Nakazawa K, Yokoyama K, Makita K, Amaha K (1998) The combination of partial liquid ventilation and inhaled nitric oxide in the severe oleic acid lung injury model. Chest 113: 1658–1666
15. Barrington KJ, Singh AJ, Etches PC, Finer NN (1999) Partial liquid ventilation with and without inhaled nitric oxide in a newborn piglet model of meconium aspiration. Am J Respir Crit Care Med 160: 1922–1927
16. Kinsella JP, Parker TA, Galan H, Sheridan BC, Abman SH (1999) Independent and combined effects of inhaled nitric oxide, liquid perfluorochemical and high frequency oscillatory ventilation in premature lambs with respiratory distress syndrome. Am J Respir Crit Care Med 159: 1220–1227
17. Kaisers U, Rossaint R (1997) Nitric oxide in partial liquid ventilation: better matching ventilation to perfusion in ARDS? Intensive Care Med 23: 139–140
18. Lachmann B, Robertson B, Vogel J (1980) In vivo lung lavage as an experimental model of the respiratory distress syndrome. Acta Anaesth Scand 24: 231–236
19. Hakkinen JP, Miller MW, Smith AH, Knight DR (1995) Measurement of organ blood flow with coloured microspheres in the rat. Cardiovasc Res 29: 74–79
20. Schosser R, Arfos KE, Messmer K (1979) MIC-II A program for the determination of cardiac output, arterio-venous shunt and regional blood flow using the radioactive microsphere method. Comput Programs Biomed 9: 19–38
21. Lowe CA, Shaffer TH (1986) Pulmonary vascular resistance in the fluorocarbon-filled lung. J Appl Physiol 60: 154–159
22. Gauger PG, Overbeck MC, Chambers SD, Cailipan CI, Hirschl RB (1998) Partial liquid ventilation improves gas exchange and increases EELV in acute lung injury. J Appl Physiol 84: 1566–1572
23. Uchida T, Yokoyama K, Nakazawa K, Makita K (1999) PO_2 of the perfluorocarbon liquid during partial liquid ventilation. Anesthesiology 91: A1342